ANTIBACTERIAL STEWARDSHIP PRACTICES IN SOUTH AFRICA DURING THE COVID-19 ERA: A RETROSPECTIVE REVIEW

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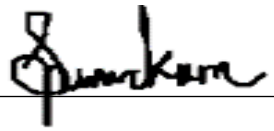
Johannesburg, 2024.

DECLARATION

I, Logan Jade Spinickum, declare that this dissertation is my own work. It is being submitted in fulfilment for the degree of Master of Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



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ABSTRACT

Background:

Several mechanisms may facilitate and steer the development of antibiotic resistance patterns. The most prominent driver associated with antibiotic resistance has been indicated as inappropriate use or consumption of antibiotics. The sudden emergence of Coronavirus Disease 2019 (COVID-2019) changed the conventional practices related to drug utilisation through the repurposing of antibiotics. Despite the implementation of antibiotic stewardship programs, the pressure that COVID-19 placed on healthcare systems resulted in poor prescribing and antibiotic review practices, potentially exacerbating antibiotic resistance. Moreover, the public health sector faces various challenges that make it difficult to consistently assess and quantify antibiotic usage; while providing quality review, feedback, and intervention, especially in low-and-middle-income countries like South Africa. As a result, there is a paucity of information concerning antibiotic utilisation in the public healthcare sector, even following the emergence of the COVID-19 pandemic. It is essential to determine the extent of antibiotic use to improve antibiotic utilisation, patient outcomes and stimulate viable policies and initiatives to strengthen public healthcare drug surveillance amidst the challenges of increased infectious diseases, resistance, and health personnel shortages.

Aim of study:

The aims of the study were to determine, analyse and compare antibiotic consumption amongst intensive care unit (ICU) patients admitted in a Gauteng public hospital during the pre-COVID-19 era and commencement of the COVID-19 era.

Methodology:

A retrospective cross-sectional data analysis of 335 medical files of ICU patients hospitalised in a Gauteng Provincial Tertiary Hospital (GPTH) between January 2017 and December 2021. Descriptive statistics were used to examine patient characteristics and antibiotic prescribing variables.

Results:

The study found that the more frequently prescribed antibiotics were amoxicillin/clavulanate (pre-pandemic = 31.99%; COVID-19 = 38.43%), followed by ceftriaxone (pre-pandemic = 15.44%; COVID-19 = 14.55%), piperacillin/tazobactam (pre-pandemic = 11.40%; COVID-19 = 8.58%) and azithromycin (pre-pandemic = 7.73%; COVID-19 = 19.78%). Common bacterial pathogens detected in both periods included *Acinetobacter baumannii* (pre-pandemic = 29.2%; COVID-19 = 20.9%), *Enterobacter cloacae* (pre-pandemic = 10.4%; COVID-19 = 14.0%), *Escherichia coli* (pre-pandemic = 22.9%; COVID-19 = 25.6%), and *Klebsiella pneumoniae* (pre-pandemic = 25.0%; COVID-19 = 18.6%). Resistance was predominantly observed in ciprofloxacin (pre-pandemic = 11.4%; COVID-19 = 12.9%), piperacillin/tazobactam (pre-pandemic = 12.7%; COVID-19 = 0.1%), cefotaxime (pre-pandemic = 13.2%; COVID-19 = 14.7%), and cefepime (pre-pandemic = 12.7%; COVID-19 = 11.2). Resistance to commonly prescribed antibiotics observed a decrease trend moving from the pre-pandemic period into the COVID-19 pandemic.

Conclusion:

The macrolide and penicillin (in combination with beta-lactamase inhibitor(s)), classes demonstrated an increase in prescribing and use across the pre-pandemic period transitioning into the COVID-19 pandemic. While overall resistance observed a decline moving into the COVID-19 pandemic. However, “Watch” category antibiotic resistance increased slightly. An increase in prescribing and use of macrolides coupled with an increase in “Watch” category antibiotic resistance, highlights the need for improved antibiotic stewardship programs in public healthcare and pathogen-directed prescribing, to combat inappropriate and unnecessary use of antibiotics.

DEDICATION

Psalm 90:17

"Let the kindness of the Lord our God be over us. Make the work of our hands last. Make the work of our hands last!"

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- Proverbs 16:3 " Commit your work to the lord, and your plans will succeed." I would like to foremost acknowledge and thank, my Heavenly father, who has been my guidance, counsellor, and strength, who has always been present from the conception of my dissertation to its completion.

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LIST OF PRESENTATION AND PUBLICATIONS ARISING FROM THIS STUDY

Publication:

Refer to Appendix A_1* and *A_2* *(Pg. 127-129)

1. Spinickum L.J., Booth Z. and De Rapper S.L. (2023) Pattern of antibiotic utilisation among ICU patients hospitalised in a Gauteng (South Africa) Tertiary Public Hospital: Comparing Pre- and Post-COVID-19 findings. *South African Medical Journal (SAMJ).* Accepted: 19 February 2024.

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Abbreviations

A

AARMS	Academic Affairs and Research management system
ABR	Antibiotic resistance
ACE	Angiotensin-converting enzyme
AMS	Antimicrobial stewardship
ASP	Antibiotic stewardship
AWaRe	Access, Watch, Reserve

B

BR	Brazil

C

CAP	Community acquired pneumonia
CDC	Centers for Disease Control and Prevention
CEO	Chief executive officer
CFR	Case-fatality ratio
CI	Confidence interval
COV	Coronavirus
COVID-2019	Coronavirus Disease 2019
CRP	C-reactive protein
CURB-65	Confusion, uraemia, respiratory rate, blood pressure, age≥65 years

D

DDD	Defined Daily Dose
DOT	Days of Therapy
DPP	Dipeptidyl Peptidase
DUR	Drug utilisation review

E

EML	Essential Medicines List
ESBL	Extended-spectrum beta-lactamases
ESKAPE	*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species.

G

GISAID	Global Initiative on Sharing All Influenza Data
GPTH	Gauteng Provincial Tertiary Hospital

H

HAP	Hospital acquired pneumonia
H1N1	Influenza A virus
HIV	Human Immunodeficiency Virus
HOD	Head of department
HREC	Health research ethics committee
HRV	Human rhinovirus

I

ICU	Intensive care unit

K

KS	Kolmogorov-Smirnov

L

LMIC	Low-and middle-income countries
LRTI	Lower respiratory tract infection

M

MDR	Multidrug-resistant
MERS-CoV	Middle East respiratory syndrome coronavirus
MICU	Main intensive care unit

MRSA	Methicillin-resistant *Staphylococcus aureus*

N

NdoH	National Department of Health
NHLS	National Health Laboratory Services
NICD	National Institute for Communicable Diseases
NPI	Non-pharmaceutical interventions
NR	No report

P

PCR	Polymerase chain reaction
PDD	Prescribed Daily Dose
PPL	Priority pathogens list

R

RBD	Receptor binding domain
RDD	Recommended Daily Dose
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RTI	Respiratory tract infection

S

SA	South Africa
SAASP	South African Antibiotic Stewardship Programme
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
STG	Standard treatment guideline

T

TPTH	Tembisa Provincial Tertiary Hospital

U

UK	United Kingdom
URTI	Upper respiratory tract infection
USD	United States Dollar

V

VRE	Vancomycin-resistant *Enterococci*

W

WHO	World Health Organization

CHAPTER 1

INTRODUCTION

Chapter Overview

This chapter provides insight into antibiotic resistance and the engagement of antibiotic utilisation metrics in the foreground of the Coronavirus Disease 2019 (COVID-19) in South Africa. In addition, this chapter will also discuss the involvement of the World Health Organization (WHO) in establishing antibiotic utilisation indicators and measures, therefore enabling, and supporting the growth of antibiotic surveillance and restraint of antibiotic resistance.

1.1 Antibiotic resistance

The term "antibiotics" was first coined by the American microbiologist Selman Waksman and his colleagues to describe chemical substances produced by microorganisms that exhibit antagonistic effects on the growth of other micro-organisms (Sengupta, Chattopadhyay and Grossart, 2013). Calhoun *et al*. (2022) further defines antibiotics as compounds that target bacteria and, therefore, are intended to treat and prevent bacterial infections.

Antibacterial pharmacotherapy has stimulated significant progress in modern medicine (Rossolini *et al.*, 2014). It has transformed and set the standard for healthcare through the reduction of morbidity and mortality rates attributed to bacterial infections for decades (Hollingworth and Kairuz, 2021). These drugs therefore play an essential role in the treatment, management, and prevention of bacterial infections (Sengupta, Chattopadhyay and Grossart, 2013; Christensen, 2021). However, inappropriate, and excessive use of antibiotics has led to the emergence of antibiotic resistance (Llor and Bjerrum, 2014; Aslam *et al.*, 2018a). Antibiotic resistance (ABR) refers to bacteria's ability to change and become less susceptible to antibacterial drugs overtime (MacGowan and Macnaughton, 2017).

The complexity of ABR can be attributed to the rapid acquisition and dissemination of genetic information by bacteria, resulting in antibiotic resistant micro-organisms. Moreover, the convolution of ABR is further compounded by gene expression alteration that enables bacterial

survival in the presence of antibiotics. Furthermore, bacteria can develop mechanisms to detoxify antibiotics, pump antibiotics out of and prevent antibiotics from entering the bacterial cell by biofilm production or the alteration of their cell surface structure. These resistance mechanisms promote the survival of bacterial organisms thus leading to a decrease in the efficacy of antibiotics and inadequate health outcomes (Santajit and Indrawattana, 2016).

The conception of antibiotic resistance dates to as early as the 1930s, during which salvarsan and sulphonamide resistance was first documented (Christensen, 2021). Thereafter, penicillin resistance was identified in the 1940s, preceding the identification of Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococci* (VRE), in the 1960s and 1980s, respectively(Hollingworth and Kairuz, 2021). Since then, antibiotic resistance has been an increasingly urgent issue attributed to the growing emergence of multidrug-resistant (MDR) bacteria (Hassoun, Linden and Friedman, 2017), deeming bacterial isolates non-susceptible to at least one agent in three or more antibiotic classes (Magiorakos *et al.*, 2012).

Several external factors may facilitate and steer developing resistance against antibacterial agents (Figure 1.1) (Aslam *et al.*, 2018a). The most prominent driver associated with ABR being inappropriate use or consumption (Anteneh *et al.*, 2021). Inappropriate use of antibiotics can be related to incorrect medical indication, antibiotic selection, dosing, route of administration and timing of antibiotic administration (Bailey *et al.*, 2015). Studies have shown that these factors are incorrectly implemented in 30% to 50% of cases (Ventola, 2015). This degree of error accelerates and exacerbates resistance resulting in poor patient outcomes, which is coupled with the lack of antibiotic choices available (Wang et al., 2022). Globally, antibiotic resistance has led to the death of approximately 700, 000 people each year (Wang et al., 2022). This estimate is expected to surge to ten million by the year 2050; paired with an increase in costs of up to USD100 trillion without any combative measures employed (Baekkeskov *et al.*, 2020).

The broader perspective of an expanding burden of infectious disease; resilient micro-organisms and the torpor of new antibiotic drug development, compounded on the on-going antibiotic resistance phenomenon, is concerning. It threatens the efficacy of antibiotics, which forms a cornerstone of modern healthcare and the treatment of infectious diseases (Aslam *et al.*, 2018b). Thus, many combative measures and initiatives have been proposed and considered with the aim of restraining the advancement of antibiotic resistance.

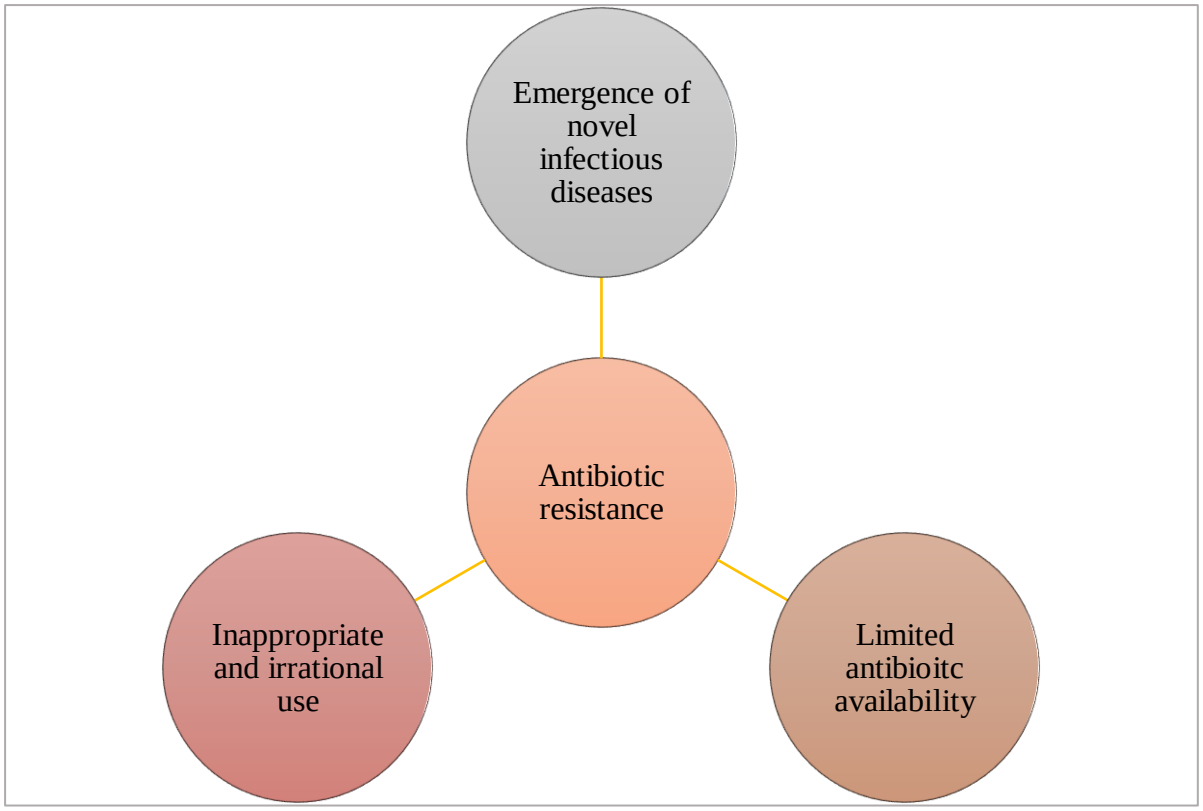

Figure 1.1 Overview of potential antibiotic resistances facilitators

1.2 Initiatives against resistance

1.2.1 Global pathogens list

In 2017, an appeal was made to the WHO by member states to develop a global priority pathogen list (PPL) of antibiotic resistant bacteria, to assist in prioritising the research and development of new and effective antibiotic treatments (WHO, 2017). The emergence of MDR bacteria has been highly provoked by "ESKAPE" pathogens, therefore, these pathogens are prominently featured in the global PPL of antibiotic resistant bacteria.

The global PPL stratifies these pathogens into three priority ranks: critical, high, and medium (Figure 1.2). The ranks catalogue 12 species of bacteria grouped under three priority tiers according to the severity of antibiotic resistance: critical (three species), high (six species), and medium (three species). In South Africa, many common infectious diseases are of bacterial origin and feature the "ESKAPE" *pathogens* (Ramsamy *et al.*, 2018). In the adult population, *Klebsiella pneumoniae*, *Acinetobacter* species (spp.), *Pseudomonas aeruginosa*, *Enterobacter*

spp., *Enterococcus faecium* and *Staphylococcus aureus* are some of the bacterial causative agents resulting in high morbidity and mortality rates (Mulani *et al*., 2019).

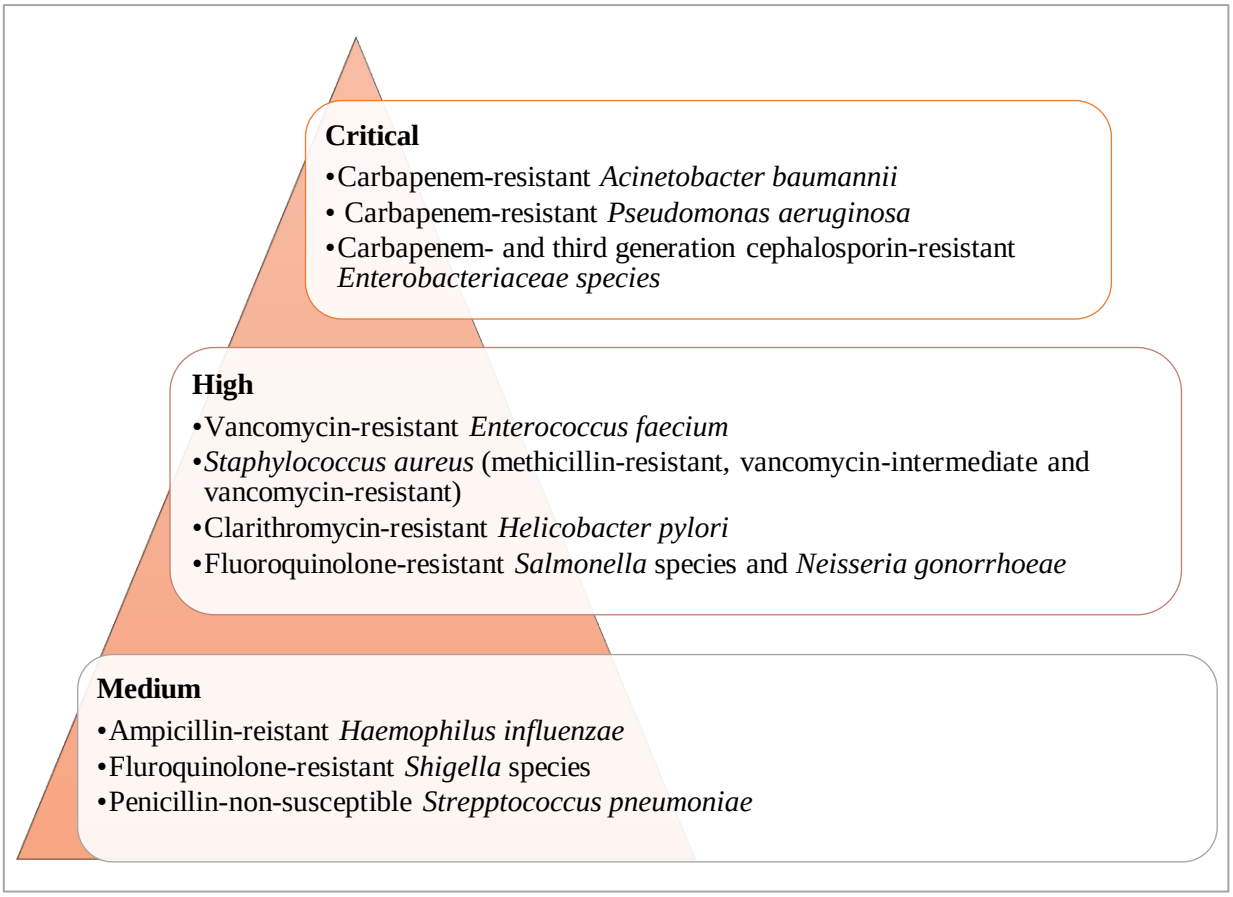

Figure 1.2 The global priority pathogens list hierarchical strata mapping (WHO, 2017)

Additionally, drug-resistant micro-organisms, predominantly carbapenem-resistant or polymyxin-resistant *P. aeruginosa*, extended-spectrum-beta-lactamases-producing (ESBL) or carbapenemase-producing *K. pneumoniae,* methicillin-resistant *S. aureus* and *Acinetobacter* spp. have become a survival threat (Ramsamy *et al.*, 2018). These findings are supported by figures released by the South African National Department of Health (NDoH) where it is reported that the total number of "ESKAPE" organisms in the public health sector in 2018, 2019 and 2020 were 26 481, 27 333 and 29 199, respectively (South African National Department of Health, 2021). Pathogens, *A. baumannii, E. coli, K. pneumoniae* and *S. aureus* were among the more common micro-organisms observed (Figure 1.3)(South African National Department of Health, 2021).

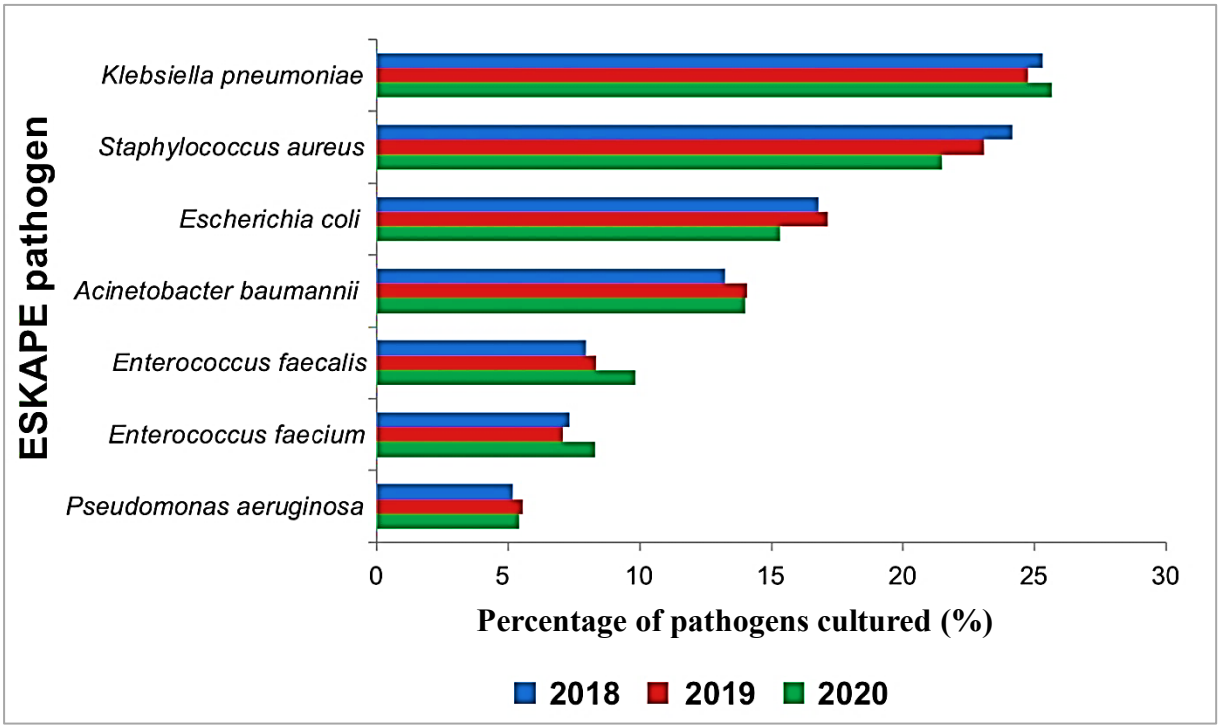

Figure 1.3 Proportion of cultured "ESKAPE" pathogens in the public health sector of South Africa between 2018 and 2020, adapted from the South African antimicrobial resistance national strategy framework (South African National Department of Health, 2021)

1.2.2 The classification of antibiotics (AWaRe)

In 2017, the WHO established the Access, Watch, and Reserve (AWaRe) antibiotic classification system in response to the persistent ABR pandemic (WHO, 2022). The “AwaRe” classification objectifies the promotion and importance of optimal antibiotic use within the “Watch” and “Reserve” antibiotic categories, with the intent to restrain further emergence and advancement of antibiotic resistance through surveillance of identified priority antibiotics. Furthermore, “AWaRe” advocates the availability and use of access category antibiotics as first-line agents for global health coverage (WHO, 2022). The classification system encompasses 180 antibiotics that are sorted into three stewardship categories (“Access” category = 48 antibiotics, “Watch” category = 110 antibiotics and “Reserve” category = 22 antibiotics), in accordance with the Essential Medicines List (EML) developed by the WHO, to accentuate rational use of antibiotics.

The “Access” category includes empiric first- or second- choice antibiotics with a narrow spectrum of antibacterial activity and a low potential for resistance (South African National Department of Health, 2021; WHO, 2022) (Table 1.1). Conversely, the “Watch” category includes antibiotics with a broader spectrum of antibacterial activity, however antibiotics within this category are susceptible to a greater likelihood of resistance in comparison to antibiotics in the “Access” category. Furthermore, “Watch” category antibiotics are used in patients with severe clinical manifestations that are characterised by micro-organism resistance and where antibacterial agents within the “Access” category cannot be considered for the treatment and management of infectious diseases (WHO, 2022). Lastly, the “Reserve” category constitutes antibiotics with the highest potential of resistance, which are “last choice or last resort.” This means that antibiotics within the “Reserve” category are only to be prescribed and used in multidrug-resistant infections and in clinical instances where “Access” and “Watch” category agents are deemed unsuitable. Figure 1.4 provides a summary of the definitions of the various WHO AwaRe classification.

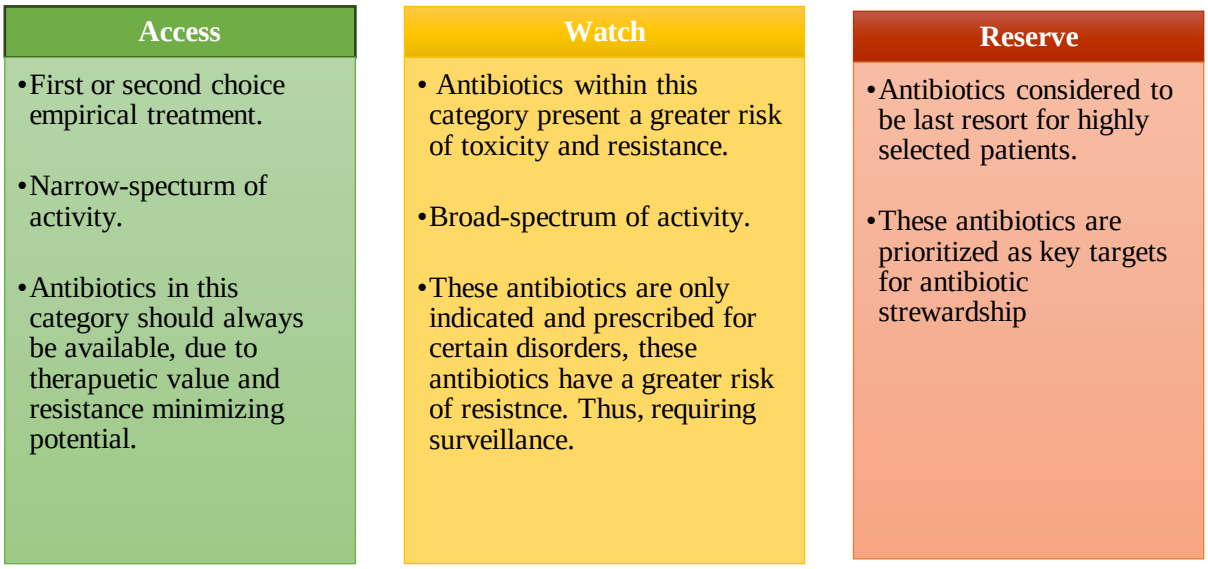

Figure 1.4 The World Health Organization Access, Watch and Reserve antibiotic classification system(South African National Department of Health, 2021; WHO, 2022)

Table 1.1. Antibiotics categorised in accordance with the Access, Watch and Reserve classification listed on the essential medicines list as per the WHO.

Antibiotic class		**WHO *"AwaRe"* categories**[1]		
		Access	**Watch**	**Reserve**
Aminocyclitols		Spectinomycin	-	-
Aminoglycosides		Amikacin; Gentamicin	-	Plazomicin
Amphenicols		Chloramphenicol	-	-
Beta-lactam/Extended Beta-lactam inhibitors		Amoxicillin/ Clavulanate	Piperacillin/ Tazobactam	-
Carbapenems		-	Meropenem	Meropenem/ Vaborbactam
Cephalosporins	1st	Cefazolin; Cefalexin	-	-
	2nd	-	Cefuroxime	-
	3rd	-	Cefixime, Cefotaxime, Ceftazidime, Ceftriaxone	*Ceftazidime/ Avibactam
	4th	-	-	Cefiderocol
Fluoroquinolones		-	Ciprofloxacin	-
Glycopeptides		-	Vancomycin (IV & O)	-
Imidazole		Metronidazole (IV & O)	-	-
Lincosamides		Clindamycin	-	-
Macrolides		-	Azithromycin; Clarithromycin	-
Nitrofuran-derivatives		Nitrofurantoin	-	-
Oxazolinones		-	-	*Linezolid
Penicillins		Ampicillin; Benzathine-Benzylpenicillin; Benzylpenicillin; Cloxacillin; Phenoxymethylpenicillin; Procaine-Benzylpenicillin	-	-
Phosphonics		-	-	Fosfomycin (IV)
Polymyxins		-	-	*Colistin (IV); *Polymyxins (IV)
Sulphonamides		Sulphonamide/ Trimethoprim	-	
Tetracyclines		Doxycycline	-	Tigecycline
Trimethoprim-derivatives		Trimethoprim	-	-

IV, intravenous; O; oral; WHO, World Health Organization; (*) indicates "Reserve" antibiotics that are registered in South Africa; Green= "Access" category; Yellow = "Watch" category and Red= "Reserve" category.

[1] WHO AWaRe list(WHO , 2022) available in in Appendix B

The “AWaRe” classification system is significant as it critically considers the impact of different antibiotics and antibiotic classes on antibacterial resistance, emphasising the importance of their appropriate use. Furthermore, probing conservative antibiotic utilisation, thus supporting the long-term effectiveness of antibiotics. Moreover, the classification system can be actively geared towards monitoring antibiotic utilisation with the aid of utilisation indicators, defining surveillance targets, and monitoring the effects of stewardship procedures and policies that aim to optimise and reduce antibacterial resistance (Sharland *et al.,* 2022).

1.3 The quantification of antibiotic utilisation

Pharmaco-epidemiology refers to the study of drug utilisation, additionally the risks and benefits associated with drug use in exposed populations (Montastruc *et al.*, 2019). In 1997, the WHO integrated and advocated for the use of drug utilisation indicators with the objective to ease irrational use while optimising access to essential medicines. Today, there is rising attentiveness to pharmaco-epidemiological studies in low- and middle-income countries (LMIC), including South Africa and the African continent at large, as these regions demonstrate a high prevalence of infectious disease and subsequently the increased potential for the development of ABR (Massele *et al.*, 2017; Montastruc *et al.*, 2019).

1.3.1 Data sources for antibiotic utilisation

Antibiotic utilisation data for pharmaco-epidemiology studies can be obtained from various sources, including sales (derived from drug imports, wholesalers, and manufacturers), dispensing (dispensing software and reimbursement/ claim systems), patient encounter-basis and healthcare facilities (derived from hospitals, clinics, and mobile facilities). In South Africa, antibiotic consumption data is commonly obtained from the procurement and supply sector (Figure 1.5) (South African National Department of Health, 2021). Utilisation data retrieved from the procurement and supply sector provides data that can be used to measure antibiotic health expenditure that entails drug sale aspects (Public Health Ontario (PHO), 2017; South African National Department of Health, 2021). However, there may be difficulties in retrieving actual consumption data as medication acquired does not surrogate the actual cost of patient pharmacotherapy, medication received and used by patients (Public Health Ontario (PHO, 2017). Though, the data remains useful in estimating the consumption of antibiotics and determining the level of antibiotic use in South Africa.

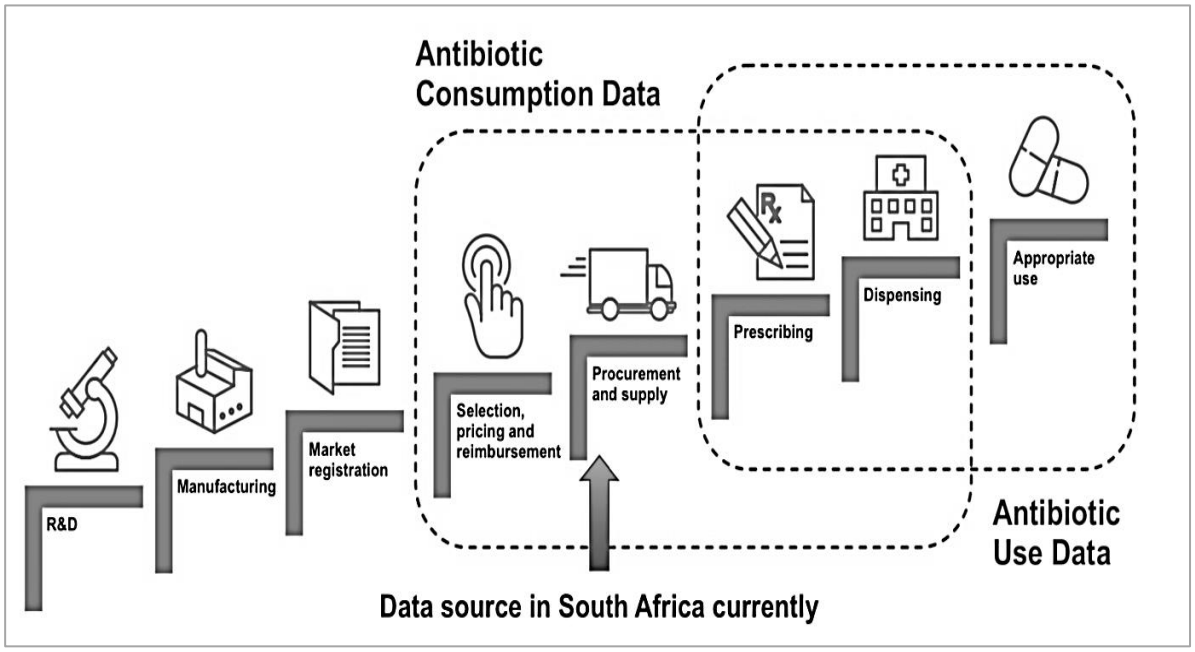

Figure 1.5 An overview of potential antibiotic utilisation data sources within the drug cycle (South African National Department of Health, 2021)

1.3.2 The quantification of antibiotic utilisation

Utilisation indicators commonly used in antibiotic pharmaco-epidemiological studies include Defined Daily Dose (DDD), Days of Therapy (DOT), and Prescribed Daily Dose (PDD) (Table 1.2). The DDD is defined by the WHO as the daily anticipated average maintenance dose for an adult patient for the drug's primary indication (WHO, 2023). While DOT is defined as the duration of antibiotic course, whereby one DOT is equivalent to a single antibiotic administered in 24 hours, regardless of the route of administration and partial day patient exposure (Moehring *et al.*, 2018). The PDD indicator measures the definite amount of a drug prescribed by health professionals, based on the amount of a drug recommended for a given indication in each population. The DDD, DOT, and PDD can be derived from a validated Recommended Daily Dose (RDD), which refers to the dose(s) specified in clinical practice or standard treatment guidelines (Först *et al.*, 2017). The RDD may not be reflected in utilisation metrics as utilisation indicators can vary across different indications, prescribing guidelines, and policies. These utilisation indicators can further differ based on individual characteristics such as age, weight, ethnic differences, diseases, and pharmacokinetic properties (World Health Organization, 2023).

Table 1.2 Comparison of common antibiotic dose utilisation indicators

Metric	Abbreviation	Advantages	Disadvantages
Defined Daily Dose	*DDD*	▪ Allows for standardised comparison on a local, regional, national, and international level (Public Health Ontario (PHO), 2017). ▪ Allows estimation in cases with restricted access to computerised systems (Public Health Ontario (PHO), 2017). ▪ The calculated DDD will change along with RDD amendments, but the WHO approved DDD will remain constant (Public Health Ontario (PHO), 2017).	▪ Inaccurate in certain populations (i.e. renal impairment, paediatrics) (Mimura *et al.*, 2023). ▪ Historic data confusion: DDD may change as new doses are established for existing drugs, which can create confusion when comparing use overtime (Public Health Ontario (PHO), 2017). ▪ Inaccurate when administered daily dose is inequivalent to the DDD. Therefore, DDD cannot be used to compare relative use between different antibiotic classes (Public Health Ontario (PHO), 2017).
Days of Therapy	*DOT*	▪ Suitable for use in paediatrics (Public Health Ontario (PHO), 2017). ▪ uninfluenced by amendments in recommended dosages (Public Health Ontario (PHO), 2017). ▪ Uninfluenced by discrepancies between the DDD and PDD (Public Health Ontario (PHO), 2017).	▪ Difficulty in measuring multiple simultaneous antibiotic agent administrations (Vallès *et al.*, 2020). ▪ Use overestimation for drugs that are administered in multiple doses per day (Public Health Ontario (PHO), 2017). ▪ Difficulty in measuring without computerised systems (Public Health Ontario (PHO), 2017). ▪ Difficulty in determining patient partial day exposure (less than 24 hours) (Public Health Ontario (PHO), 2017; Vallès *et al.*, 2020).
Prescribed Daily Dose	*PDD*	▪ Calculated on an individual level therefore considers patient characteristics (pharmacokinetics) and, making it suitable for drug use estimation in paediatrics (Mimura *et al.*, 2023).	▪ Non-standardised, therefore needs to be developed in each setting to account for variations in indications, recommendations, and formularies/policies (Mimura *et al.*, 2023).

1.4 Emergence of the Coronavirus Disease 2019

COVID-19 is a novel coronavirus caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The National Institute for Communicable Diseases (NICD) reported and confirmed the first positive cases of COVID-19 in South Africa on March 3, 2020, (NICD, 2020). Global efforts were made in repurposing of drugs and the navigation of pharmacotherapy approaches to manage and treat COVID-19 (Abelenda-Alonso, Padullés, *et al.*, 2020; Yacouba, Olowo-okere and Yunusa, 2021a; Khataniar *et al.*, 2022). In the scarcity of standard treatment guidelines, a prominent pharmacotherapy approach implemented was the use of antibiotics (Abelenda-Alonso, Padullés, *et al.*, 2020; Beović *et al.*, 2020; Vasireddy *et al.*, 2021; Yacouba, Olowo-okere and Yunusa, 2021a; Khataniar *et al.*, 2022).

The use of antibiotics in the management and treatment of COVID-19, delineated from the primary use of antibiotics which are indicated for bacterial infections (Abelenda-Alonso, Padullés, *et al.*, 2020). Calderon-Parra *et al* (2021) reported that despite a comparatively low bacterial co-infection rate, the prevalence of antibiotic usage in COVID-19 patients was still considerably high. The use of antibiotics in viral infection is not warranted in the absence of bacterial co-infections (Mahmoudi, 2020). This addresses the poor antibiotic stewardship (ASP) and selective pressure placed of antibiotics during the COVID-19 pandemic, therefore intensifying an on-going antibiotic resistance pandemic (Mahmoudi, 2020; Livermore, 2021; Gillies *et al.*, 2022). Inappropriate and irrational use of antibiotics is also a salient issue associated with antibiotic resistance in low- and middle-income countries (LMIC) (Aslam *et al.*, 2018a).

1.5 Problem Statement

The South African National Department of Health's (NDoH) Antibiotic Resistance National Strategic Framework (2014-2024) and 'A Pocket Guide to Antibiotic Prescribing for Adults in South Africa' by the South African Antibiotic Stewardship Programme (SAASP) were developed to optimise appropriate use of antibiotics and combat resistance (Wasserman, Boyles, and Mendelson, 2015; Departments of Health and Agriculture, 2017). Despite existing policies and procedures, the evolution of resistance is a continuous phenomenon requiring more collaborative efforts in public health (Salam *et al.*, 2023). This may be due to the integration of

the public healthcare system and ASP (Aslam *et al.*, 2018a). The public healthcare system is often overburdened. Consequently, the intricacies regarding drug utilisation and review are overlooked due to weak policy infrastructure as seen in COVID-19 and a lack of resources (Tattevin *et al.*, 2020).

In South Africa there is a paucity of information about antibiotic utilisation in the public healthcare sector (Paruk *et al.*, 2012), more so following the emergence of the COVID-19 pandemic that prompted pandemic drug repurposing. Furthermore, drug utilisation research integrating utilisation metrics in South African studies are scarce. In the last five years, only a few studies have reported antibiotic use (commonly employing the DDD metric) in adult hospital wards and that to in the pre-pandemic period (Mthombeni *et al.*, 2014; Brink *et al.*, 2016; Boyles *et al.*, 2017; Johnston *et al.*, 2018; Skosana *et al.*, 2021). Therefore, there is a need for exploration concerning pandemic antibiotic utilisation in South Africa. Pandemic antibiotic use and the lack of antibiotic utilisation data compounded on progressing antibiotic resistance; necessitates antibiotic utilisation research in the public health sector.

1.6 Research Question

What changes in antibiotic utilisation have occurred following the emergence of COVID-19?

1.7 Aims and Objectives

This study aimed to investigate, describe, and analyse changes in antibiotic utilisation and resistance across the pre-COVID-19 era and during the COVID-19 era, in the management of ICU patients in a Gauteng tertiary hospital.

This aim was met by the following objectives:

- To describe antibiotic utilisation amongst ICU patients admitted in a Gauteng tertiary hospital before and during the COVID-19 pandemic.
- To compare the prevalence of "Watch" category antibiotic use before and following the emergence of COVID-19.
- To describe and compare antibiotic resistance before and during the COVID-19 pandemic.

1.8 Study significance

The study will identify antibiotic uses and quantify antibiotic utilisation in the pre-pandemic period transitioning into the COVID-19 pandemic. Thus, enabling the evaluation of antibiotic utilisation trends across both periods of interest. Furthermore, the study will highlight the proportion of "Access" category antibiotics to "Watch" category antibiotics used during both periods; scrutinising whether antibiotics with a high potential of resistance prior to COVID-19 have shifted with regards to utilisation and resistance; simultaneously highlighting newer antibiotic agents that are at risk of resistance and require surveillance within the select setting. The study is valuable because it will provide ICU antibiotic utilisation data that will address gaps in antibiotic prescribing and justify the bacterial resistance trends leading up to the bridging of a pre-pandemic era to a pandemic era within a public hospital; thus, facilitating the stricter implementation of antibiotic stewardship, infection prevention control and stimulating parameters to sustain viable prescribing practices and antibiotic utilisation surveillance amidst future pandemics (Buckley and Palmer, 2022).

CHAPTER 2

LITERATURE REVIEW

Chapter Overview

This chapter will review and discuss antibiotic use and the upsurge of resistance concomitant with the use of these drugs. Furthermore, provide insight into the development of respiratory viral pandemics, such as Influenza, the Middle East Respiratory Syndrome Coronavirus, and the Coronavirus Disease 2019. This literature review further presents the pertinent aspects of the use of antibiotics in virulence, common etiologies, symptoms, and treatments associated with respiratory viral pandemics in the last decade.

2. ANTIBIOTICS IN VIRULENCE: TREATMENT OF RESPIRATORY TRACT INFECTIONS

2.1 An introduction to respiratory tract infections

The respiratory system is complex functionally and partitioned into two zones as described by Patwa & Shah (2015). The conducting zone (nasal passage to bronchioles) which forms a path for conduction of inhaled gases; and the respiratory zone (alveolar duct to alveoli) which allows for gaseous exchange to occur. Anatomically, the respiratory tract segments into an upper (extra-thoracic airway – nasal passage, pharynx, and larynx) and lower respiratory tract (intra-thoracic airway- trachea, bronchi, bronchioles, alveolar duct, and alveoli (Patwa and Shah, 2015). Respiratory system invasion by pathogens can lead to illnesses termed Respiratory Tract Infections (RTIs). Upper respiratory tract infections (URTIs) are defined as self-limited irritation and swelling of the upper airways associated with coughing and the absence of pneumonia, in a patient with no other condition that would account for their symptoms, or with no history of restrictive respiratory diseases such as chronic obstructive pulmonary disease, emphysema, or chronic bronchitis (Thomas and Bomar, 2022).While inflammation of the trachea, bronchi, bronchioles, and lung tissue define lower respiratory tract infections (LRTIs) (Liu *et al.*, 2019).

2.2 Symptoms and aetiology of respiratory tract infections

Upper and lower respiratory illnesses are distinguishable by their clinical manifestation, symptoms, and anatomical involvement (Manikandan, 2013). Although, defining most patient respiratory diseases is difficult as the clinical manifestations of RTIs commonly overlap, as presented in Figure 2.1, and the causes might be similar (Thomas and Bomar, 2022). Several publications, report on the most common infections affecting the upper part of the tract, which include the common cold, tonsillitis, pharyngitis, and sinusitis (Pavia, 2011; Jama-Kmiecik *et al.*, 2016; McKay *et al.*, 2016; Liu *et al.*, 2019; Thomas and Bomar, 2022). These upper respiratory tract infections are characterised by coughing, hoarseness, runny nose, nasal congestion, headache, pyrexia (fever), and sore throat. The leading infections of the lower respiratory tract are bronchitis and pneumonia, characterised by high fever, chills, breathing problems, productive or dry cough, wheezing, dyspnoea (difficulty breathing), sore throat, fever, migraine, production of mucus, and chest pain (Torres *et al.*, 2013; Jin *et al.*, 2021).

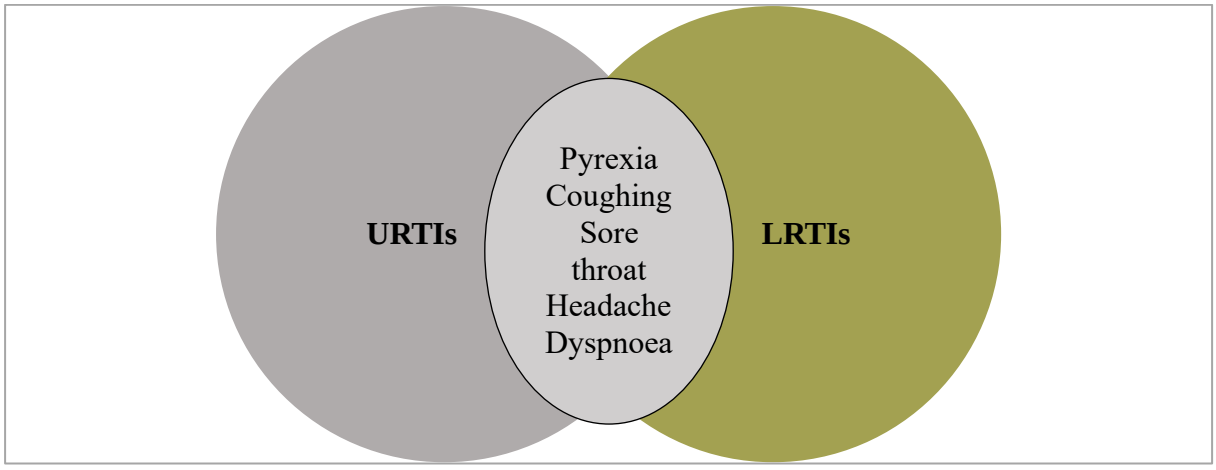

Figure 2.1 Overlapping clinical manifestations of RTIs

Invasion of the respiratory tract by viral and bacterial pathogens lead to respiratory tract infections, which are the second most common cause of morbidity and mortality globally (Zumla *et al.*, 2014). Viruses account for 58% of these respiratory infections (Morpeth *et al.*, 2018), therefore, inferring that respiratory tract infections of viral origin are more frequent than respiratory tract infections of bacterial origin. This section of the review provides insight into various etiologies of RTIs (Table 2.1).

Table 2.1. Summary of clinical presentations and pathogens associated with various URT and LRT infections in adults.

Respiratory tract infections		Clinical manifestation	Common pathogens associated with infection		References
			Bacterial	**Viral**	
URTIs	**Common cold**	Coughing, malaise, myalgia, nasal congestion, post-nasal drip, pyrexia, rhinorrhoea, and sore throat.	*Streptococcus pyogenes, Haemophilus influenzae*	*Rhinovirus*	(Drysdale, Mejias and Ramilo, 2017; Leigh-de Rapper and Vuuren, 2020)
	Influenza/Flu	Coughing, headache, malaise, myalgia, nasal congestion, post-nasal drip, pyrexia, rhinorrhoea, and sore throat.	N.A.	*Influenza virus*	(Moghadami, 2017)
	Pharyngitis	Coughing, conjunctivitis, ear pain, headache, painful cervical adenopathy, pharyngeal erythema, pruritus, pyrexia, rhinorrhoea, sore throat, and tonsillar exudate.	*Streptococcus pyogenes*	*Rhinovirus*	(Leigh-de Rapper and Vuuren, 2020; Kanwal and Vaitla, 2023)
	Rhinosinusitis	Bad breath, coughing, facial pain and/or pressure, headache, nasal congestion, post-nasal drip, pyrexia, rhinorrhoea, and sore throat	*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*	*Rhinovirus, Adenovirus, Influenza virus, parainfluenza virus*	(Rosenfeld, 2016; Leigh-de Rapper and Vuuren, 2020; DeBoer and Kwon, 2024)
	Tonsillitis	Changes in voice/loss of voice, ear pain, odynophagia, painful cervical adenopathy, pyrexia, red spots on the roof of the mouth, pruritis, sore throat, swollen/ inflamed tonsils, and tonsillar exudates (pus/ white patches)	*Streptococcus pyogenes*	N.A.	(Sidell and L. Shapiro, 2012)

URTIs, upper respiratory tract infections; N.A., not applicable.

Table 2.1. continued. Summary of clinical presentations and pathogens associated with various URT and LRT infections in adults.

Respiratory tract infections		**Clinical manifestations**	**Common pathogen associated with infections**		**References**
			Bacterial	**Viral**	
LRTIs	**Bronchitis**	Chest pain, coughing, dyspnoea, headache, production of mucus, pyrexia, sore throat, and wheezing	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*,	*Rhinovirus*, *Parainfluenza virus*, *Influenza virus*	(Kwon *et al.*, 2014; Park *et al.*, 2016)
	Pneumonia	Chest pain, dyspnoea, fatigue, feeling confused, loss of appetite, myalgia, malaise, productive cough, pyrexia, and wheezing	*Streptococcus pneumoniae*, *Mycoplasma pneumoniae*	Adenovirus and Influenza	(Wang *et al.*, 2012; de Groot *et al.*, 2013; Pavia, 2013; Chiu *et al.*, 2015)
	Tuberculosis	Cold sweat, chest pain, cough, dyspnoea, loss of appetite, malaise, purulent sputum, pyrexia, and sudden weight loss	*Mycobacterium tuberculosis*	N.A.	(Sakamoto, 2012; Koch and Mizrahi, 2018; Leigh-de Rapper and Vuuren, 2020; Natarajan *et al.*, 2020)

LRTIs, lower respiratory tract infections; N.A., not applicable.

Zumla *et al* (2014) found that bacterial pathogens often associated with URTIs include *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* (Zumla *et al.*, 2014). Research by Leung (2021) was congruent with that of Zumla *et al* (2014) as it similarly observed the higher prevalence of *S. pneumoniae* and *H. influenzae* associated in respiratory related illness, more specifically sinusitis. Furthermore, Hsieh *et al* (2011) agreed with the findings of Zumla *et al* (2014) and Leung (2021), emphasising the association of *Streptococcus, Staphylococcus aureus* and *Haemophilus* spp. and tonsilitis (Hsieh *et al.*, 2011). Moreover, Barnett, Bowen and Carapetis (2019) reported that Streptococcus was linked to bacterial pharyngitis, resulting in 5% to 36% of infection cases (Barnett, Bowen and Carapetis, 2019). Therefore, augmenting the previous findings by Zumla *et al* (2014), Leung (2021) and Hsieh *et al* (2011) of bacterial pathogens commonly associated with URTIs. Additionally, common bacterial causative pathogens of LRTIs reported by Zubairi *et al*. (2012) included *M. pneumoniae* and *Chlamydia pneumoniae* (Zubairi *et al.*, 2012). Singh, Sharma, and Nag (2020) similarly reported *Pseudomonas* spp. (35%), *K. pneumoniae* (21.3%), *Acinetobacter* spp. (17.5%), *E. coli* (15.4%) and *S. aureus* (Singh, Sharma and Nag, 2020). Khan, Priti, and Ankit (2015) reported similar results to Zubairi *et al* (2012) and Singh, Sharma, and Nag (2020). Conversely, another study observed lower prevalence of *S.pneumoniae* and *H. influenzae* in LRTIs (Ieven *et al.*, 2018). In general, "ESKAPE" pathogens have been prominently associated with both URTIs and LRTIs (Khan, Priti and Ankit, 2015; Ieven *et al.*, 2018; Singh, Sharma and Nag, 2020; Venkateswaran *et al.*, 2023).

The viral spectrum of respiratory tract infections are represented by the influenza virus, adenovirus, respiratory syncytial virus (RSV) and parainfluenza viruses (Jama-Kmiecik *et al.*, 2016). Tsagarakis et al (2018) investigated the prevalence of common URT viral pathogens, assessing 656 samples. Of the 656 samples assessed, 356 (54.3%) ascertained a positive result and 300 (45.7%) assessed negative. From these samples, 420 pathogens were detected, the most common noted as, human rhinovirus (HRV) (n = 130 (31%)), adenovirus (n = 83 (19.8%)), influenza virus (n = 52 (12.5%)), parainfluenza virus (n = 27 (6.4%)) and respiratory syncytial virus (RSV) (n = 36 (8.6%)) (Tsagarakis *et al.*, 2018). A study by Umuhoza et al (2021) also investigated the prevalence of respiratory virus in three African countries, finding adenovirus (13%) respiratory syncytial virus (11%) and parainfluenza (9%) prevalence (Umuhoza *et al.*, 2021). Similarly, another study reported the rhinovirus and influenza virus to be most prevalent among viral pathogens resulting in LRTIs (Ieven *et al.*, 2018). Overall,

several studies augment the correlation between viruses and LRTI (Pavia, 2011; Kwon *et al.*, 2014; Havers and Campbell, 2020; Umuhoza *et al.*, 2021).

Moreover, studies exploring bacterial and viral etiologies of RTIs rely on detection tools, placing emphasis on the complexity of reaching a definitive diagnosis. Definitive diagnosis can become complex due to the overlapping clinical presentations of viral and bacterial infections, the variable sensitivity, and perpetual turn-around time of viral cultures (Zumla *et al.*, 2014). This raises the need for improved rapid detection technology of pathogens in individual cases to propel the best clinical management, public health surveillance, and control outcome (Zumla *et al.*, 2014).

2.3 Antibiotics in the clinical management of respiratory tract infections

The previous section of the review highlighted viral predominance in many upper and lower RTIs and emphasised the difficulty in differentiating between viral and bacterial etiologies without the use of diagnostic tests (Pavia, 2013). Furthermore, despite the greater prevalence of viral pathogen related RTIs, patients are frequently prescribed antibiotics (Table 2.2.) (Harris, Hicks and Qaseem, 2016). This may be explained by the complexities of diagnosis and overlapping RTI symptoms discussed in the previous section (Zumla *et al.*, 2014; Jin *et al.*, 2021; Thomas and Bomar, 2022).

Table 2.2. Overview of antibiotics used in common RTI

Respiratory tract infection		**Line of therapy**	**Antibacterial therapy**	**Reference**
RTIs	Common cold	N.A.	Not indicated	(Kenealy and Arroll, 2013)
	Influenza/ Flu		Not indicated	(Uyeki *et al.*, 2022)
	Pharyngitis	First	*Amoxicillin; Phenoxymethylpenicillin.	(WHO, 2022)
		Second	Cefalexin; Clarithromycin	
	Sinusitis	First	*Amoxicillin; Amoxicillin and Clavulanic Acid.	
	Tonsillitis	First	Amoxicillin; Amoxicillin and Clavulanic Acid.	

Table 2.2. continued. Overview of antibiotics used in common RTIs

Respiratory tract infection		Line of therapy	Antibacterial therapy	Reference
LRTIs	**Bronchitis**	First	Antibiotics are not usually indicated, but confirmation of bacterial infection or development of pneumonia can encourage the use of antibacterial therapy.	(WHO, 2022)
	Pneumonia	First	*Moderate:* amoxicillin, phenoxymethylpenicillin, amoxicillin and clavulanic acid *Severe:* cefotaxime, ceftriaxone (used in both CAP and HAP); piperacillin/tazobactam (HAP)	(WHO, 2022) (Boyles *et al.*, 2018)
		Second	*Moderate:* doxycycline *Severe:* amoxicillin and clavulanic acid; clarithromycin	

CAP, community acquired pneumonia; HAP, hospital acquired pneumonia; LRTIs, lower respiratory tract infections; N.A., not applicable; URTIs, upper respiratory tract infections.* Antibiotics are not usually indicated as these infections are viral (see Table 2.1), but confirmation of bacterial infection or development of pneumonia can encourage the use of antibacterial therapy.

Moreover, the use of antibiotics in virulence is only advised in incidence of viral-bacterial co-infections. However, several studies reported a low prevalence of bacterial co-infection therefore inferring that antibiotic use may be irrational and unnecessary (Melvin and Bomberger, 2016; Bakaletz, 2017a; Kiedrowski and Bomberger, 2018). Co-infection is defined as simultaneous infection of a host by multiple pathogen species, for instance an initial viral infection with a secondary bacterial infection (Bakaletz, 2017b). Furthermore, it is recognised that viral infections may predispose patients to such bacterial co-infections (Feldman and Anderson, 2021). Previous research shows that respiratory viruses are strongly associated with certain bacterial infections including pneumonia and bronchitis (Pavia, 2011, 2013).

A study by Bakaletz (2017) regarding the relationship between viral and bacterial co-infections indicated that respiratory viral infections may facilitate secondary bacterial infections and increase patient immunopathology through the overproduction of inflammatory cytokines (Bakaletz, 2017b). This relationship commences when bacterial infiltration is elevated during acute viral infection. The nature of immune responding cells are altered in the course of concomitant infections. Although immune cells such as natural killer cells and macrophages are the predominant cell respondents to bacterial infections in an ingenuous host, there is also a large T-cell following that is activated upon viral infection. Inflammatory cytokines released by these cells contribute to lethal immunopathology (Bakaletz, 2017b). In addition, viral infection can induce destruction of the airway both histologically and functionally. Depending on the virus, histological induction may be mild or severe and include evidence of cell loss, goblet cell hyperplasia, altered mucus secretion and/or biochemistry, disruption of surfactant, reduced ciliary beat frequency, dis-coordinated mucociliary clearance function and reduced oxygen exchange.

This highlights the need for development of therapeutic strategies to target the initial causative microorganism and the subsequent inflammatory responses. Furthermore, understanding the correlation between viral etiological agents and bacterial co-infections can potentially decrease the inappropriate use of antibiotics. Viral-bacterial co-infection is of importance as these species can interact within the host patient. Subsequently, resulting in unfavourable interactions that can exacerbate the negative health effects of the infection. Therefore, it is critical to further explore the positive or negative effects of the co-infecting micro-organisms on the health outcomes of the host to ascertain a better perspective of factors facilitating the extent of infection (Singer, 2016).

2.4 Past pandemics of viral origin affecting the respiratory system

Globalisation has driven social and economic changes that have blurred the definition of antibiotics, enhanced the threat of disease emergence, and accelerated the spread of diseases. Therefore, facilitating a shift in the role and prescribing of antibacterial agents (Saunders-Hastings and Krewski, 2016). Previous literature acknowledges the evolving role of antibiotics in the treatment of infectious diseases but the area of antibacterial agents in the management of viral infections is yet to be explored. The delineation of antibacterial agents from their natural indication and their role in viral pandemics are essential to not only gauge antibiotics

on the viral treatment spectrum, but to also understand the relationship between viral pandemics and antibiotic utilisation. Therefore, this section will review the causes, symptoms, transmission, impact, and extent of antibacterial agent involvement in the treatment of respiratory pandemics of viral origin. These viral respiratory pandemics include the *Orthomyxoviruses* (Influenza A viruses) and Middle East Respiratory Coronavirus (MERS-CoV) pandemics; occurring during the commencement of the current decade but predating the emergence of *Orthicoronavirinae* (Coronavirus disease-COVID-19) (Levitt *et al.*, 2020).

2.4.1 The Influenza pandemic

Influenza viral infections cause respiratory illnesses that are responsible for significant morbidity and mortality. Influenza A viruses have great pandemic potential, which can happen upon the emergence of a novel influenza A virus and when person to person transmission occurs effectively (Saunders-Hastings and Krewski, 2016).

2.4.1.1 Aetiology of the Influenza virus

Influenza viruses are large, single-stranded Ribonucleic acid (RNA) viruses deriving from the family Orthomyxoviridae, which includes three types: A, B, and C (Havers and Campbell, 2020). Of these types, only influenza A viruses circulate in multiple animal and human reservoirs causing illness (Saunders-Hastings and Krewski, 2016). Influenza A viruses circulating among humans have been limited to Influenza A subtype H1N1, Influenza A subtype H2N2, and Influenza A subtype H3N2. Influenza A (H1N1), also termed swine flu, was responsible for many infection cases during the period of 2009 to 2010 (Levitt *et al.*, 2020). The pandemic spanned over 19 months and was concluded in August the following year. Globally, more than 214 countries were affected by this pandemic. A total ranging from about 700 million to 1.4 billion cases were reported (Bhadoria, Gupta and Agarwal, 2021). The pandemic resulted in more than 18 000 deaths as reported by the WHO (Dawood *et al.*, 2012).

Influenza A viruses can result in many infection cases because it is the only strain with reservoir variability. More specifically aquatic birds and swine are important reservoirs for influenza A (Saunders-Hastings and Krewski, 2016). Levitt *et al* (2020) emphasises that swine have a much greater ability to be infected with either bird or human influenza A viruses due to the presence of a more diverse set of receptors in the swine respiratory tract that increases the binding affinity of viral molecules, in comparison to that of birds and humans. Furthermore, this also means that swine can become co-infected with bird and human influenza type A, facilitating

virus-gene exchange forming a new influenza virus referred to as "reassortants". This important adaptive change in influenza A viruses is referred to as an antigenic shift when humans are infected and represents a strength advantage that may enable the virus to spread efficiently in humans, potentially emerging to cause a global pandemic (Levitt *et al.*, 2020).

2.4.1.2 Transmission of influenza virus

During the 2009 influenza A (H1N1) pandemic, efforts to control outbreaks had to initially rely on non-pharmaceutical interventions (NPIs), such as quarantines, school closure, banning public gatherings, and infection prevention practices like cough and sneeze etiquette and use of facemasks (Saunders-Hastings and Krewski, 2016). This is because of the high viral load in the respiratory secretions of patients infected with influenza, which makes transmission of the virus via coughing and sneezing likely (Moghadami, 2017).

It has been proposed that the disease is transmitted primarily by large particle droplets greater than 5 micrometres. Due to the large size of infectious droplets, close contact is needed for the spread of the disease (Bhat *et al.*, 2005). These large particles usually do not have a lengthy air suspension time and travel short distances. Therefore, airborne transmission is not often considered for disease transmission. A study by Cowling *et al* (2013) suggests that the implementation of NPIs aimed to reduce transmission by contact may not be enough to control the transmission of the influenza A virus in households or communities (Cowling *et al.*, 2013). Moreover, contact with contaminated surfaces containing respiratory droplets is another potential source of disease transmission. In adults without any comorbidities, the onset of transmission commences 24 to 48 hours before disease manifestation and terminates after six or seven days according and after 10 days according to some other investigations (Moghadami, 2017). Therefore, it is necessary to regularly re-evaluate infection control policies and implementation of such policies.

2.4.1.3 Symptoms of influenza virus

Influenza often begins with the rapid onset of symptoms following an incubation period of one to two days (Moghadami, 2017). Studies reported that patients infected with influenza A (H1N1) generally present with a cough, fever, body aches, throat pain, headaches, and weakness (Minodier *et al.*, 2015; Moghadami, 2017; Havers and Campbell, 2020; Uyeki *et al.*, 2022). Similarly, Patel *et al. (2013)* found that uncomplicated influenza presented with systemic symptoms (fever, chills, headache, severe myalgia, malaise, and anorexia) of which

headaches, myalgia, and fever predominantly determined the severity of the disease (Patel *et al.*, 2013). The study concluded that most clinical patients were presented with similar symptoms. Influenza is usually self-limiting, but these symptoms previously referred to can persist, therefore, resulting in progression of illness towards influenza complications (Patel *et al.*, 2013). Additionally, Patel *et al.* (2013) explored the complications and indicated that upon presentation chest x-rays were normal in 31.74% (n = 20) patients, while pulmonary opacities were seen in 68.26% (n = 43) patients. Similarly, studies by Chu *et al.* (2017) and Moghadami (2017) confirmed the commonality of pneumonia as a complication of influenza infection.

Complications as a result of infection with the H1N1 influenza virus can cause acute respiratory disease, which is a consequence of an overactive inflammatory response and virus-induced cytokine dysregulation. Viral invasion results in excessive production of numerous pro-inflammatory cytokines, which leads to the development of clinical conditions such as pneumonia (Roychoudhury *et al.*, 2020). Furthermore, pneumonia may happen as a continuum of the initial uncomplicated influenza when caused by the influenza virus (primary pneumonia) or as secondary infection (Moghadami, 2017).

Primary viral pneumonia occurs after the course of influenza with an abrupt progression of fever, dyspnoea, cough, cyanosis, and difficult breathing. It happens predominantly among individuals with cardiovascular or pulmonary (such as asthma) comorbidities (Moghadami, 2017). Secondary pneumonia may clinically manifest with similar symptoms when compared to primary viral pneumonia. In contrast, secondary pneumonia is caused by bacterial pathogens such as *Streptococcus aureus* and *Streptococcus pneumonia*. Secondary bacterial pneumonia is characterised by recurrent symptoms, therefore, Moghadami (2017) proposes that a biphasic pattern of signs and symptoms in influenza-labelled patients should be considered as secondary *Superimposed bacterial pneumonia* (Moghadami, 2017). Consideration of clinical symptoms alone may be adequate in making a clinical diagnosis. The studies reviewed have reported that the use of clinical decision-making tools such as CURB65 or the Pneumonia Severity Index, but such tools are not formerly validated in influenza pandemics. Therefore, more research efforts need to be directed towards building diagnostic indices and the value of such for future similar pandemics.

2.4.1.4 Treatment of influenza: antibacterial perspective

Details on treatment and disease progression of a total of 910 patients that were infected with influenza as reported in eight case studies have been summarised (Perez-Padilla *et al.*, 2009; Chitnis *et al.*, 2010; Lee *et al.*, 2010; Shieh *et al.*, 2010; Nakajima *et al.*, 2012; Kusznierz *et al.*, 2013; Crotty *et al.*, 2015; Abelenda-Alonso, Rombauts, *et al.*, 2020). Five studies accounted the use of preventive antibiotic therapy in 718 of 743 patients (96.6%) (Perez-Padilla *et al.*, 2009; Chitnis *et al.*, 2010; Nakajima *et al.*, 2012; Kusznierz *et al.*, 2013; Crotty *et al.*, 2015) The frequently used antibiotics were vancomycin (n = 317, 46.2%) and imipenem/meropenem (n = 243, 54.7%). Other antibiotics used in the case studies were azithromycin, ceftriaxone, cephalosporin, piperacillin/tazobactam, linezolid, vancomycin plus cefepime, vancomycin plus meropenem, clarithromycin, levofloxacin and dicloxacillin. In total, 223 patients of 910 (24.5%) developed secondary bacterial infections. The bacterial pathogens treated were *S. pneumoniae*, MRSA, *P. aeruginosa*, *Streptococcus viridians, Staphylococcus hominis, E. faecium, H. influenzae, S. pyogenes, Streptococcus mitis, Streptococcus agalactiae, A.baumannii*, *E. coli, Chlamydophila pneumoniae,* and *Moraxella catarrhalis*. Conversely, A study by Taymaz *et al* (2018) reported antibiotic prescriptions in 40% of the study cohort, with a low prevalence of laboratory confirmed bacterial infection (less than 5%). Antibiotic prescriptions by class includes, fluoroquinolones (12%), macrolides (10%), amoxicillin–clavulanate (10%), cefuroxime (7%), and third generation cephalosporins (3%) (Taymaz *et al.*, 2018).

In another study, Ambrozaitis *et al* (2016) investigated 69 patients during the peak of the pandemic (Ambrozaitis *et al.*, 2016). More than half of the subjects in the group (25; 59.5%) were treated empirically with antibiotics, with only influenza symptoms and clinical manifestation of bacterial infection. The antibiotics used were penicillin G (n = 23; 54.8%), followed by ampicillin (n = 8; 19%), ceftriaxone (n = 7; 10.1%), amoxicillin in combination with clavulanic acid (n = 3; 7.1%), vancomycin (n = 2; 4.8%), and imipenem in combination with cilastatin (n = 1; 2.4%). The study outcome outlines that the rate of antibiotic misuse for influenza subjects was quite high, as 59.5% of subjects with no signs of bacterial infection were given antibiotics. Furthermore, Ambrozaitis *et al* (2016) suggested that antibiotic use could have been delayed as a slightly elevated C-reactive protein (CRP) (less than 30 milligram per liter), without leukocytosis and an increase of erythrocyte sedimentation rate may not be an impending indication of bacterial complications (Ambrozaitis *et al.*, 2016).

Overall, the congruency among these previous studies highlighted two sides to antibiotic use in the influenza pandemic: antibiotic utilisation in secondary bacterial infections and antibiotic utilisation in the absence of confirmed bacterial infections. Both sides place selective pressure on antibiotics. The use of antibiotics in bacterial infections is warranted but the use of antibiotics in the absence of bacterial infections is unnecessary and irrational (Klein *et al.*, 2020). Furthermore, in the absence of bacterial infections, influenza A is susceptible to neuraminidases such as oseltamivir and zanamivir (Moghadami, 2017). Moreover, many studies alongside Moghadami (2017) suggest the use of antivirals (oseltamivir and zanamivir) for the reduction of mild symptoms of the virus as this will reduce the intention and burden of unnecessary antibiotic prescribing (Moghadami, 2017).

Another driver of antibiotic prescribing is vaccination evasion that results in an increase in influenza infections and other secondary complications (Klein *et al.*, 2020). Klein *et al* (2020) investigated the impact of vaccination on antibiotic prescribing and results indicated that a 10% increase in the influenza vaccination rate was associated with a 6.5% decrease in antibiotic use, equivalent to 14.2 ($p = .001$) fewer antibiotic prescriptions per 1000 individuals. Therefore, it is necessary to promote vaccination, definitive treatment, and continual professional development in the management of influenza and flu-like illness to augment and strengthen AMS as well as prevent premature antibiotic prescribing and use.

2.4.2 Middle East respiratory syndrome coronavirus

Middle East respiratory syndrome coronavirus (MERS-CoV) is an extremely transmissible and pathogenic virus that emerged in human-beings in the year 2012 (Cui, Li and Shi, 2019). This virus that causes RTIs first emerged in Saudi Arabia. MERS-CoV has now been reported in more than 27 countries across the Middle East, Europe, North Africa, and Asia. From April 2012 to August 2022, a total of 2591 laboratory-confirmed cases of Middle East respiratory syndrome (MERS) were reported globally, with 894 associated deaths at a case-fatality ratio (CFR) of 34.5%. Most of these cases were reported from Saudi Arabia, with 2184 cases and 813 related deaths (CFR: 37.2%) (El, El and Str, 2022).

2.4.2.1 Aetiology of Middle East respiratory syndrome coronavirus

The commencement of the Middle East respiratory syndrome first manifested in a hospital in Jeddah, located in Saudi Arabia. Therefore, the virus was then designated Middle East respiratory syndrome coronavirus (MERS-CoV). The etiological agent was detected and

identified as a coronavirus (de Groot *et al.*, 2013; Chafekar and Fielding, 2018). Thus, confirming the origin of the MERS-CoV as a member of the Coronaviridae family (de Groot *et al.*, 2013). The MERS-CoV is a single-stranded RNA virus with the largest genome among RNA viruses (Gerber and Watson, 2020). Viruses belonging to the Coronaviridae family, like MERS-CoV, were named coronaviruses because of the club-shaped surface projections that give the viruses a crown-like appearance visible by electron microscopy (Gerber and Watson, 2020)

2.4.2.2 Transmission of Middle East respiratory syndrome coronavirus

The MERS-CoV is a zoonotic coronavirus transferred to humans from infected dromedary camels, although Kusuma *et al* (2021) expresses that the virus was thought to have originated in bats and then been transmitted to camels in the distant past (Kusuma, Paul and Viswanath, 2021). The virus is reportedly widespread in dromedary (single-humped) camels, an animal reservoir, in the Middle East and northern Africa (Killerby *et al.*, 2020; NICD, 2021).

The disease in camels is mild and self-limiting with animals requiring an isolation period to overcome the infectious phase of disease. Transmission to humans occurs through direct interaction with camels or through ingestion of raw or unpasteurised milk or urine, or uncooked meat. Conzade *et al*. (2018) reported that, among cases classified as primary transmission by the WHO, only 54.9% (n = 191) persons reported contact with dromedaries (Conzade *et al.*, 2018). It was then proposed that transmission of MERS between humans was likely through respiratory secretions (NICD, 2021). Another study investigated MERS-CoV transmission chains and observed laboratory-confirmed MERS-CoV cases. Transmission of the virus from animal-to-human was less common (21.4%) than human-to-human transmission (78.6%) (Alhumaid *et al.*, 2018). Camel to human MERS-CoV transmission is well documented but more data on bat reservoirs and transmission to camels is required. Moreover, case-control studies of animal-to-human transmissions and inter-human transmissions with periodical MERS-CoV infections are necessary to identify predisposing risk factors and exposures, highlighting the transmission relationship within human species and between humans and camels (Omrani, Al-Tawfiq and Memish, 2015).

2.4.2.3 Symptoms of Middle East respiratory syndrome coronavirus

Middle East respiratory syndrome coronavirus infection generally results in acute respiratory disease (Killerby *et al.*, 2020). The median incubation period is seven days, with a range of

two to 17 days. Although MERS-CoV affects various ages' groups, studies reported that the older individuals and those with comorbidities are more severely affected and hospitalised (McIntosh & Perlman, 2021).

The MERS-CoV viral respiratory infection commonly results in mild illness consistent with the common cold and pneumonia (Gerber and Watson, 2020). Gerber and Watson (2020) further reported common symptoms that included rhinorrhoea, nasal congestion, sore throat, cough, fever, headache, and malaise. Another study by Assiri *et al*. (2013) investigated 47 subjects with laboratory confirmed MERS-CoV. Common symptoms among the study cohort included fever (98%; n = 46), fever with chills or rigors (87%; n = 41), cough (83%; n = 39), shortness of breath (72%; n = 34), and myalgia (32%; n = 15). Gastrointestinal symptoms were also frequent, including diarrhoea (26%; n = 12), vomiting (21%; n = 10), and abdominal pain (17%; n = 8) (Assiri *et al.*, 2013). Several other studies report similar symptoms (Alhumaid *et al.*, 2018; Chafekar and Fielding, 2018; Conzade *et al.*, 2018; Krishnamoorthy *et al.*, 2020).

In addition, symptoms along with other clinical characteristics can indicate the progression of the illness (McIntosh and Perlman, 2021). Ko *et al*. (2016) investigated and analysed the predictive factors associated with the development and progression of pneumonia to respiratory failure during the 2015 MERS-CoV outbreak. The study evaluated clinical variables measured within three days from symptom onset of 45 patients. The results indicated 13 patients (28.9%) did not develop pneumonia, 19 developed pneumonias without respiratory failure (42.2%), and 13 progressed to respiratory failures (28.9%). The identified predictive factors for pneumonia development included age ≥45 years, fever ≥37.5 °C, thrombocytopenia, lymphopenia, CRP ≥ 2 mg/dL, and a threshold cycle value of PCR (Polymerase chain reaction) less than 28.5. For respiratory failure, the predictive indicators included gender, comorbid hypertension, low albumin concentration, thrombocytopenia, lymphopenia, and CRP ≥ 4 mg/dL (all $p < 0.05$). With two or more predictive factors for pneumonia development, 100% of patients developed pneumonia. The study concluded that patients that did not present with any of the predictive indicators did not lead to respiratory failure. Furthermore, this study is significant as it advocates for improved management of disease and highlights variables that facilitate the progression of secondary complications such as pneumonia (Ko *et al.*, 2016).

2.4.2.4 Treatment of Middle East respiratory syndrome coronavirus: antibacterial perspective

The WHO provides recommendations on the treatment of MERS-CoV, but no standard treatment guidelines and antiviral agents are specifically recommended for the treatment of MERS-CoV infection (Arabi *et al.*, 2017). Although a single study accounted the use of antibiotics in the MERS-CoV pandemic.

A study investigated the clinical management of patients hospitalised and suspected of MERS-CoV infection in Paris from 2013 to 2016 (Bleibtreu *et al.*, 2018). The conjecture of MERS-CoV can potentially lead to medical confusion and inappropriate management of acute respiratory syndrome due to causes other than MERS-CoV infection and this notion is conveyed in a study by Bleibtreu *et al* (2018). Bleibtreu *et al* (2018) investigated 93 adult patients hospitalised. 82 (88.2%) patients had returned from Saudi Arabia, and 74 (79.6%) patients were pilgrims. Chest X-ray findings were abnormal in 72 (77%) patients. In this cohort, 93 patients tested negative for MERS-CoV RT-PCR. However, 70 (77.7%) of 93 patients had documented infections. These infections included 47 (52%) viral, 22 (24.4%) bacterial and 1 (0.01%) Plasmodium falciparum malaria. Microbiological analysis revealed Rhinovirus (27.9%), Influenza virus (26.8%), Legionella pneumophila (7.5%), Streptococcus pneumoniae (7.5%), and non-MERS-coronavirus (6.4%). Antibiotics were initiated in 81 (87%) cases. The number of laboratory-confirmed bacterial infections in patients (n = 22; 23.6%]) were considerably less than those receiving antibiotic therapy (n = 81; 87%). This indicates that 63.44 % patients received unnecessary (inappropriate empiric antibiotic use without clinical and laboratory consideration) antibiotic therapy. Furthermore, Among the 93 patients, 87.1% initially received antibiotic therapy: 69.3% antibiotic combinations, and 19.4% received a single antibiotic. Antibiotic combinations were third-generation cephalosporin and macrolides, aminopenicillin and macrolides and third-generation cephalosporin and fluoroquinolone. Monotherapy, amoxicillin, doxycycline and piperacillin/tazobactam (Bleibtreu *et al.*, 2018).

There are no other reports of antibiotic utilisation in relation to the MERS-CoV pandemic, therefore Bleibtreu *et al* (2018) is an important account, evidently exploring the involvement of antibiotic use in a viral respiratory pandemic. This study emphasised the critical need for specialised medical personnel and rapid detection tests to reduce poor prescribing of antibiotics. Moreover, a few studies accounted for the potential use of antivirals and antibiotics,

including ribavirin, interferon, and fluoroquinolones, for the treatment of MER-CoV (Al Ghamdi *et al.*, 2016; Momattin, Al-Ali and Al-Tawfiq, 2019; Scroggs *et al.*, 2020). Randomised trials to recommend MERS-CoV therapy and efficacy of regimens are necessary. Therapeutic agents for the management and treatment for MERS-CoV, therefore allowing the conservative use of antibiotics in microbiologically confirmed bacterial secondary infections.

Table 2.3. Comparison of the characteristics and management of past respiratory viral pandemics

Comparison category	PANDEMICS		References
	Influenza (H1N1)	**Middle East respiratory syndrome coronavirus(MERS-CoV)**	
Pandemic period	2009	2012	(Moghadami, 2017); (Chafekar and Fielding, 2018))
Location of first reported cases	North America	Saudi Arabia	
Outbreak countries	Africa, Europe, North America, South America, South-East Asia	More than 27 countries, prominently Jordan, Saudi Arabia, South Korea, and Qatar	
Natural reservoir	Avian, human, swine	Bat, camel	(Moghadami, 2017; Conzade *et al.*, 2018; Krishnamoorthy *et al.*, 2020)
Viral family	Orthomyxoviridae	Coronaviridae	
Transmission	Droplet spread, close contact with infected humans and animals	Droplet spread, close contact with infected humans and animals	(Dawood *et al.*, 2012; Cowling *et al.*, 2013; Saunders-Hastings and Krewski, 2016; Alhumaid *et al.*, 2018; Conzade *et al.*, 2018)
Clinical symptoms	Chills, cough, diarrhoea, fatigue, headache, pyrexia, nasal congestion, myalgia, nausea, red eyes, rhinorrhoea, sore throat, and vomiting	Cough, diarrhoea, dyspnoea, fatigue, headache, haemoptysis pyrexia, myalgia, nasal congestion, nausea, odynophagia, red eyes, rhinorrhoea, sore throat, sputum production and vomiting	(Kusznierz *et al.*, 2013; Yang *et al.*, 2015)
Clinical management	Oseltamivir, peramivir and zanamivir	No antiviral therapy has been indicated as per the WHO. Studies indicate that drugs (chloroquine, chlorpromazine, lopinavir, etc.) have shown an inhibitory effect on MERS-CoV replication in vitro. Though, in the absence of clinical data, these drugs are not recommended for clinical use outside clinical trials.	(Fiore *et al.*, 2011; Alhumaid *et al.*, 2018; Klein *et al.*, 2020; Roychoudhury *et al.*, 2020)
Median incubation period	1-7 days	5-14 days	(Roychoudhury *et al.*, 2020)

2.5 Present viral respiratory pandemic: Coronavirus Disease 2019

Coronavirus Disease 2019 first emerged and was identified amidst a series of respiratory illness cases in Hubei Province in China. The primary cluster of patients was linked to the Huanan South China Seafood Market in the Wuhan region of Hubei Province. COVID-19 spread rapidly throughout China and, subsequently, to the rest of the globe. The severity of the outbreak and potential of viral transmission on an international scale prompted global efforts. The WHO received an account of the outbreak on December 31, 2019, and by January 2020, the COVID-19 outbreak was declared a "Global Health Emergency" (F. Wu *et al.*, 2020). Therefore, this section of the literature review will explore the aetiology, transmission, symptoms, and management of COVID-19 with emphasis on antibacterial involvement and impact in a viral pandemic.

2.5.1 Aetiology of coronavirus disease 2019

Over the past two decades, coronaviruses (CoVs) have been associated with sizable disease outbreaks in East Asia and the Middle East. The first two CoVs to cause a pandemic and spread among populations included the emergence of severe acute respiratory syndrome (SARS) and MERS-CoV in 2002 and 2012, respectively. In late 2019, a novel coronavirus, termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), emerged causing a perpetual global pandemic (Dhama *et al.*, 2020; Wang *et al.*, 2020). COVID-19 originates from the family *Coronaviridae (*subfamily *Orthocoronavirinae)* and is reported to belong to the group of 2β – coronavirus (Wang *et al.*, 2020; de Groot *et al.*, 2022). COVID-19 has a shape resembling a crown with projected spikes made of protein; comprising of a capsid with single-stranded ribonucleic acid (ssRNA), which is associated with a nucleoprotein in matrix protein (Kumar *et al.*, 2020). The spike S protein contains a receptor binding domain (RBD) that binds to the human angiotensin-converting enzyme 2 (ACE2), promoting membrane fusion and the uptake of the virus into the human cells (dos Santos, 2020).

GISAID, an older influenza genomic database, was utilised in the pandemic reporting more than 42000 SARS-CoV-2 genomes (dos Santos, 2020). Studies indicate that SARS, MERS-CoV and SARS-CoV-2 share a lineage; however, this novel virus is genetically distinct. Comparing the genome of SARS-CoV-2 with that of the closely related SARS/SARS like CoV revealed that the sequence coding for the spike protein, with a total length of 1,273 amino acids,

showed 27 amino acid substitutions. Six of these substitutions are in the region of the RBD, and another six substitutions are in the underpinning subdomain (A. Wu *et al.*, 2020; Krishnamoorthy *et al.*, 2020). Furthermore, SARS-CoV-2 is genetically distinct from SARS-CoV (79% similarity) and MERS-CoV (nearly 50%) (Lu *et al.*, 2020).

COVID-19 demonstrated the complex and rapid evolution potential of CoVs, as multiple variants came into play within just the first year of the pandemic. The rapid evolving nature of COVID-19 and resulting variants might be due to the presence of three-O-linked glycan, a polybasic cleavage site located at the intersection of the S1 and S2 subdomains (Krishnamoorthy *et al.*, 2020). It is therefore inferred that the variation in the S1 and S2 spike proteins appear as a major site of mutation facilitating the occurrence of new viral variants of COVID-19 (Krishnamoorthy *et al.*, 2020). Furthermore, high genetic diversity and the ability to infect multiple host species are a result of high-frequency mutations in CoVs. A study by Vasireddy *et al* (2021), highlighted the variants of concern and that have become rapidly dominant. Variants of concern were characterised by high disease transmissibility, increased disease variability with reference to mortality and hospitalisation, reduced antibody neutralisation and diagnostic detection failure, origin, transmissibility, and development of new drug targets (Vasireddy *et al.*, 2021). These variants include B.1.1.7, B.1.351 and P1. In addition, the occurrence of multiple variants across the globe, emphasises the evolutionary scale of viral pandemics. These notions highlight the critical importance of continuous disease surveillance with regards to pathogen evolution. Table 2.4 provides an overview of COVID-19 variants and mutations.

Studies have reported on COVID-19 wave forecasting and surveillance. A study proposed that time-dependent models be parametrised on initial transmission rates and the intensity of infection preventative measures to efficiently determine wave saturation, wave projection and forecasting the epidemic spread of the virus (Cherednik, 2022). In addition, another study introduced a generalised logistic model with a time-dependent parameter to analyse case fatality curves in various countries (Vasconcelos *et al.*, 2021, 2023). The development and integration of COVID-19 predictive models and subsequent estimates are vital to strengthen the implementation of strategies to increase the health system capacity and enactment of protective measures. Therefore, potentially limiting the progression of novel variant emergence. However, further exploration pertaining to this is required.

Table 2.4. Overview of COVID-19 variants and mutations

Variants	Country of first observation	Mutation	Mutation location	Function of mutation	Reference
B.1.1.7 OR 20I/501Y.V1 (UK)	United Kingdom	S: N501	RBD	Suspected increase in ACE2 binding	(McLean *et al.*, 2022)
B.1.351 OR 20H/501Y.V2 (SA)	South Africa				
20J/501Y.V3 (BR)	Brazil				
B.1.351 OR 20H/501Y.V2 (SA)	South Africa	S: E484	RBD	Suspected increase in ACE2 binding	(Slavov *et al.*, 2022)
20J/501Y.V3 (BR) *20B/S.484K (BR)*	Brazil				
B.1.1.7 OR 20I/501Y.V1 (UK)	United Kingdom	S: H69-	Spike N-terminal domain	Suspected alteration of recognition by antibodies	(Kostaki *et al.*, 2021)
C0H.20G/501Y	United States of America	S: Q677	Outside the furin building pocket	Hypothesised to influence S1/S2 cleavage	(Vasireddy *et al.*, 2021)
Cluster 5 "mink" variant	Netherlands	S: Y453F	RBD	Suspected to increase ACE2 binding	(Changrob *et al.*, 2021; Vasireddy *et al.*, 2021; Slavov *et al.*, 2022)
	Netherlands	S: S477	RBD	Suspected to increase ACE2 binding	
20H/501Y.V2 (SA)	South Africa	S: L18F	Spike N-terminal domain	Reduction in binding for monoclonal antibody	
20J/501Y.V3 (BR)	Brazil				
20I/501Y.V1, 20A/S: 484K (UK)	United Kingdom	S: Y144	Spike N-terminal domain	Associated with antibody binding escape	
20J/501Y.V3 (BR)	Brazil				
20I/501Y.V1 (UK)	United Kingdom	S: P681	Furin cleavage	Antibody recognition reduction	(McLean *et al.*, 2022)
20H/501Y.V2 (SA)	South Africa	S: K417	RBD	Antibody binding escape and ACE2 receptor binding reduction	

ACE2, angiotensin-converting enzyme 2; BR, Brazil; SA, South Africa; RBD, Receptor-binding Domain; UK, United Kingdom.

2.5.2 Transmission of coronavirus disease 2019

Until 2020, six CoVs were known to infect humans, including human CoV 229E (HCoV-229E), HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV (Dhama *et al.*, 2020). Based on virus genome sequencing results, evolutionary analysis and phylogenetic analysis SARS-CoV-2 has been linked to SAR-like CoVs derived from bats. Furthermore, a suspected bat origin was suggested after 96% genome sequence identity was demonstrated between SARS-CoV-2 and another CoV, termed Bat-CoV-RaTGB, isolated from bat species that colonised a province situated nearly 2000 kilometres away from Wuhan (Poulter, 2020; Singhal, 2020). Several other research outputs discuss and support the transmission of SARS-CoV-2 from bats through unknown intermediate hosts to infect humans (Dhama *et al.*, 2020; Guo *et al.*, 2020; Zhou *et al.*, 2020). However, bats have not been established as the only potential reservoir of SARS-CoV-2, Wagner dos Santo (2020) also highlighted pangolins as another possible natural host. The emergence of novel CoV, SARS-CoV-2, may have become possible because of multiple CoVs being maintained in their natural host. Table 2.5 provides an overview of coronavirus. More research is required to isolate the intermediate host of SARS-CoV-2 to better understand the zoonotic pathway therefore possibly identifying other ways to limit the transmission of the virus from animals to humans (dos Santos, 2020).

Table 2.5. Zoonotic coronavirus resulting in respiratory illness in humans in the last decade

Coronavirus	Affected host	Intermediate host	Reservoir host	Disease	Cell receptor	Reference
MERS-CoV (2012)	Human	Dromedary camels	Bat	MERS	DPP4	(Yu *et al.*, 2017)
SARS-COV-2 (2019-)	Human	NR	NR	COVID-19	ACE2	(Lu *et al.*, 2020; Zhou *et al.*, 2020; Trougakos *et al.*, 2021)

ACE2, angiotensin-converting enzyme 2; COVID-19, Coronavirus disease 2019; DPP4, dipeptidyl peptidase 4, MERS-CoV; Middle East respiratory syndrome-coronavirus; NR, no report; SARS-CoV-2; severe acute respiratory syndrome-coronavirus-2

Lotfi, Hamblin and Rezaei (2020) explores the spread of COVID-19 through both direct and indirect means. Direct means refer to droplet and inter-human transmission. Indirect contact refers to transmission through contaminated objects and airborne contagion, although human-human spread is much more common (Lotfi, Hamblin and Rezaei, 2020). It is proposed that viral droplet size is about five micrometres and can travel up to two meters. Infected people spread viral particles through conversing, breathing, coughing, or sneezing, as previously seen with influenza and MERS-CoV (Jayaweera *et al.*, 2020). Many countries responded to the outbreak and transmission mechanisms through the implementation of non-pharmaceutical measures such as face masks, face shields, gloves, hygiene protocols, social distancing, and quarantining (Guo *et al.*, 2020). This approach, as adopted in the H1N1 pandemic (2009 to 2010) and MERS-CoV pandemic (2012), is considered standard procedure in infection prevention and control. However, COVID-19 appeared abruptly years after influenza and MERS-CoV, thus infection control and prevention procedures advanced since the early days of this decade. Moreover, previous CoV respiratory pandemics such as SARS and MERS-CoV have resulted in major outbreaks with high mortality, although SARS-CoV-2 demonstrated a greater transmissibility among humans accounting for 4, 249, 929 infection cases and 1, 813, 188 COVID deaths globally in the first year of the pandemic (Agarwal *et al.*, 2020; World Health Organization, 2020). High transmissibility and infection rates facilitated the development of more advanced viral detection methods during the COVID-19 pandemic. Kollu *et al* (2022) reports on artificial intelligence advancements for COVID-19; including illness monitoring, risk forecasting, monitoring of surgical examination, healing studies, studies and simulations of the virus and site recognition (Kollu *et al.*, 2022).

2.5.3 Symptoms of coronavirus disease 2019

Studies accounted infected patient symptoms which included fever, cough, tiredness, loss of taste or smell, sore throat, headache, aches and pains, diarrhoea, a rash on skin, or discoloration of fingers or toes, red or irritated eyes, difficulty breathing or shortness of breath, loss of speech or mobility, or confusion and chest pain (World Health Organization, 2020). The most common symptoms associated with COVID-19 are fever, cough, dyspnoea, expectoration, headache, and myalgia or fatigue. In contrast, less common signs at the time of hospital admission include diarrhoea, haemoptysis, and shortness of breath. Individuals with asymptomatic infections were also suspected of transmitting infections, which further adds to the complexity of disease transmission dynamics in COVID-19 infections (Dhama *et al.*, 2020). Alimohammadi *et al.*

(2020) investigated the common symptoms associated with COVID-19 infection and results indicated fever 81.2% (95% CI: 77.9-84.4); cough: 58.5% (95% CI: 54.2-62.8); fatigue 38.5% (95% CI: 30.6-45.3); dyspnoea: 26.1% (95% CI: 20.4-31.8); and the sputum: 25.8% (95% CI: 21.1-30.4). The study concluded fever, cough, fatigue, and dyspnoea can have a key role in early detection of this disease and prevent the transmission of the disease to other people (Alimohammadi et al., 2020). Overall, COVID-19 symptoms across studies reviewed reconciled and were congruent with some clinical manifestations in influenza and MERS-CoV patients. Figure 2.2 depicts the overlapping symptom of COVID-19, influenza and MERS-CoV.

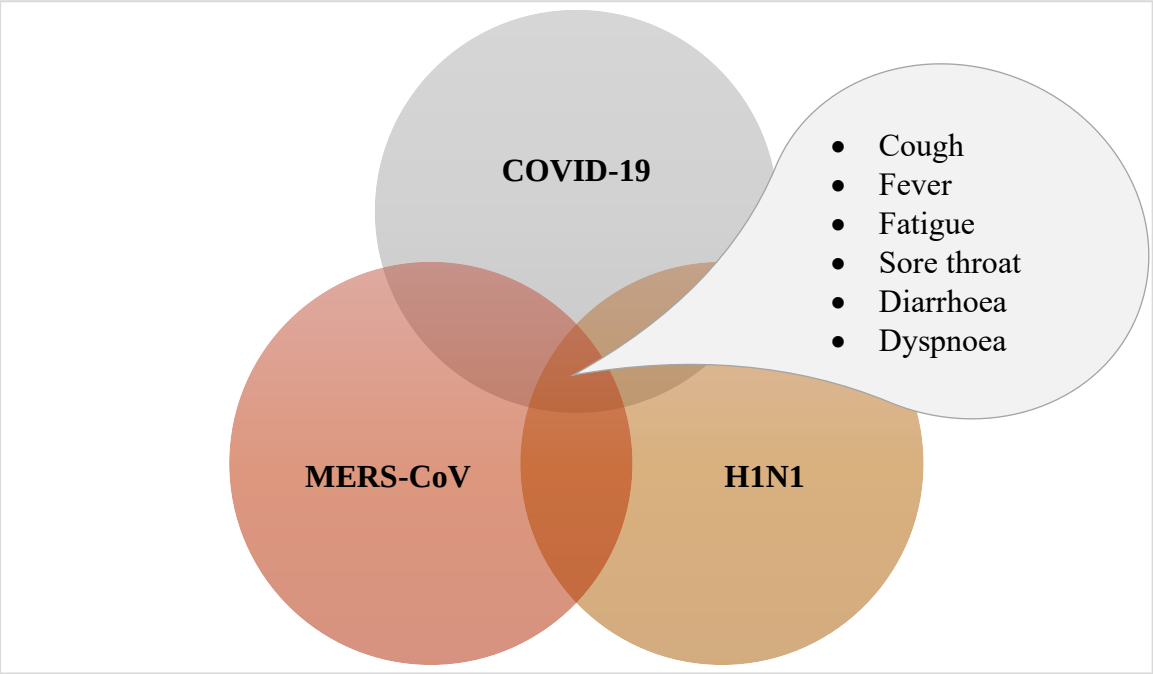

Figure 2.2 Common symptoms associated with COVID-19, influenza and MERS-CoV. Abbreviations: COVID-19, coronavirus disease 2019; H1N1, Influenza A; MERS-CoV, Middle East respiratory syndrome coronavirus.

Previously, rapid detection of viral infection in the context of influenza and MERS-CoV was lacking. Furthermore, the commonality among symptoms of RTIs made diagnosis difficult. At the start of the COVID-19 pandemic, commonly used diagnostic tools included detection by real-time-Polymerase Chain Reaction using quantitative reverse transcription-PCR (rt-PCR/qPCR), a variety of isothermal amplification and screened via Computer tomography scans for lungs (Yang *et al.*, 2020). However, Abdul *et al* (2020) described the global COVID-

19 outbreak and the high transmissibility of the virus that presented the urgent need for fast and accurate diagnostic tools to screen patients and confirm the positive or negative cases. Moreover, the global merging of resources and worldwide joint efforts, propelled the development of virus-specific rapid diagnostic tools that previously were unavailable in the influenza pandemic and MERS-CoV pandemic. Despite, the advantage of rapid detection which meant the identification of the viral causative agent (SARC-CoV-2) cases (Abdul *et al.*, 2020), the conjecture of COVID-19 led to medical confusion with regards to COVID-19 therapeutics (Singh and Ravinetto, 2020).

2.5.4 Treatment of coronavirus disease: antibacterial perspective

The WHO COVID-19 treatment recommendations are evidence based and are evolving with several randomised controlled trials (Agarwal *et al.*, 2020). At the commencement of the COVID-19, there was no approved treatment for the virus. Pandemic reprofiling/ and the repurposing of medicines became a prominent approach to treating and preventing illness (Khataniar *et al.*, 2022). Repurposing of medicines is defined as a process to identify new roles for existing drugs (Khataniar *et al.*, 2022). This process has been successfully used in the past and brought back several drugs to the pharmaceutical market. Zidovudine for instance, an established antiviral drug active against human immunodeficiency virus (HIV) has been shown to exhibit in-vitro activity against colistin-resistant and Carbapenem-resistant isolates (Peyclit *et al.*, 2018). Various pharmacological agents are being investigated for potential use in the clinical management of coronavirus diseases (Gautret *et al.*, 2020; Grein *et al.*, 2020). The inclusion of antibiotics in the clinical management of COVID-19 is aimed at achieving the resolution of any bacterial infections co-existing with the COVID-19 infections (Yacouba, Olowo-okere and Yunusa, 2021b). Bacterial co-infections would then encourage the use of antibacterial therapy for the resolution of the infection.

The WHO recommended that antibiotic therapy or prophylaxis should not be used in patients with mild/moderate COVID-19 unless it is well founded (Agarwal *et al.*, 2020). Adler *et al* (2020) acknowledge that several countries employ clinical treatment guidelines that employ the use of empiric antibiotics, thusly collected data to inform and update hospital antimicrobial policy. A study by Adler *et al* (2020) evaluated all microbiology results for patients admitted to Whiston hospital (Prescot, UK) with PCR-confirmed COVID-19 infection between March 6, 2020, and April 7, 2020. The hospital policy advocates and recommends blood cultures and pneumococcal and Legionella urinary antigen tests based on clinical severity, in line with

national guidelines, for patients admitted with community-acquired pneumonia, including suspected COVID-19 cases. The investigation observed 195 patients, 5 (3% or 4% of 137 patients specifically tested) patients presented with pneumococcal co-infection. One of 31 patients tested positive for the Legionella antigen without lower respiratory tract samples to confirm legionellosis. Bacteria grew from four of 26 sputum samples. All bacteria were Gram-negative bacilli more typically associated with oropharyngeal colonisation than community-acquired pneumonia (Adler *et al.*, 2020). The study concluded that bacterial co-infection is uncommon in patients with COVID-19 who are newly admitted to hospital. The co-prevalence of pneumococcus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was low, and *Staphylococcus aureus* was not detected (Adler *et al.*, 2020). Wang *et al* (2021) assessed the prevalence of bacterial co-infections in COVID-19 and the appropriateness of empirical antibiotic treatment received. The study investigated 1396 adult non-pregnant COVID-19 patients. The study included 37 patients (2.7%) with clinically important bacterial co-infection within 48 hours of admission. Most patients (36/37 in those with co-infection and 98/100 in selected patients without co-infection) received empirical antibiotic treatment. There was no significant difference in age, gender, pre-existing illnesses, ICU admission or 30-day all-cause mortality in those with and without bacterial co-infection. The study noted that patients with bacterial co-infections had significantly high white cell count, neutrophil count, and CRP on admission. L. Wang *et al* (2021) study deduce the same as Adler *et al* (2020), that bacterial co-infection is infrequent in hospitalised COVID-19 patients (Adler *et al.*, 2020; L. Wang *et al.*, 2022). Furthermore, these results also suggest that empirical antimicrobial treatment may not be necessary in all patients presenting with COVID-19 infection, although the decision could be directed by high inflammatory markers (Wang *et al.*, 2021).

Many other studies concluded that the prevalence of bacterial co-infections in COVID-19 cases are low resulting in overstimulation of antibiotic utilisation (Mahmoudi, 2020; Garcia-Vidal *et al.*, 2021a; Langford *et al.*, 2021). Contrarily, Yang *et al* (2021) investigated the frequency and characteristics of respiratory co-infections in COVID-19 patients in the (ICU and concluded that there was a high frequency of respiratory bacterial and fungal co-infections in critically ill COVID-19 patients admitted to the ICU. Bacterial culture identified 56 (58.3%) positive samples for respiratory pathogens. RT-PCR detected 38 (76.0%) and 58 (87.9%) positive results in the severe and critical groups, respectively. The study advocates for careful examinations and necessary tests should be performed to exclude co-infections to appropriately treat critically ill ICU COVID-19 patients (Yang *et al.*, 2021).

Another study on antibiotic utilisation in African countries (Ghana, Kenya, Uganda, Nigeria, South Africa, Zimbabwe, Botswana, Liberia, Ethiopia, and Rwanda) summarised common antibiotics used in COVID-19 (Adebisi *et al.*, 2021a). Adebisi *et al* (2021) found that antibiotics in use included, azithromycin, doxycycline, clarithromycin, ceftriaxone, amoxicillin, amoxicillin-clavulanic acid, ampicillin, gentamicin, erythromycin, benzylpenicillin, piperacillin/tazobactam, ciprofloxacin, ceftazidime, cefepime, vancomycin, meropenem, and cefuroxime. The antibiotics were recommended for use in COVID-19 cases that were presented at various levels of severity (asymptomatic, mild, moderate, and severe COVID-19 with/without complications) (Adebisi *et al.*, 2021a). The study also considered the circumstances that brought about antibiotic use and cross referenced the treatment with the WHO guidelines, the outcome drawn indicated that there was no alignment between the use of antibiotics and the WHO guidelines (Agarwal *et al.*, 2020; Adebisi *et al.*, 2021a).

Chedid *et al* (2021) evaluated nineteen clinical studies using COVID database and Google search, reporting data from 2834 patients were included. Mean rate of antibiotic use was 74% of cases. Half the studies reported occurrence of bacterial co-infection or complication (10 studies). Amongst the latter, at least 17.6% of patients who received antibiotics had secondary infections. Pooled data of four studies show that half of patients receiving antibiotics were not severe nor critical. Detailed data on antibiotic use is lacking in most articles. The study highlights the need for further research to determine relevant indications for antibiotic use in COVID-19 patients is critical in view of the significant mortality associated with secondary infections in these patients and the emerging antibiotic resistance (Chedid *et al.*, 2021; Livermore, 2021; Martinez-Guerra *et al.*, 2021). Furthermore, apart from spreading resistance, antibiotic overprescribing in COVID-19 may also be associated with other problems. Thus, further examination and investigation is essential in determining possible associated variables which may include increasing severity of diseases, length of disease, risk of complications, mortality rate, healthcare costs, risk of adverse effects, re-attendance due to infectious diseases and medicalisation of self-limiting infectious conditions.

2.6 The long-term impact of using antibiotics in viral infections

One of prominent contributors to the emergence of antibiotic resistance is the unnecessary and excessive use of antibiotics (Livermore, 2021). It is likely that the COVID-19 pandemic has fuelled the emergence of antibiotic resistance due to high rates of inappropriate antibiotic

prescribing and the interruption of treatment for other conditions (Rusic *et al.*, 2021). The WHO acknowledges the importance of integrating AMS measures into the COVID-19 response of the healthcare system(Getahun *et al.*, 2020). Furthermore, the WHO encourages the use of antibiotics in severe COVID-19 infections and suspicion of a bacterial co-infection. However, despite low evidence to support such practice, azithromycin, at one point, became a common treatment for COVID-19 (Getahun *et al.*, 2020). In addition, according to Adebisi *et al* (2021) most antibiotics recommended across the African countries were from the "watch" (antibiotics that have higher resistance potential) and "reserve" (antibiotics and antibiotic classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms) categories of WHO "AWaRe" classification (Adebisi *et al.*, 2021a). The use of high potential resistance classified antibiotics along with the initial healthcare disruption caused by COVID-19, could have aggravated and fuelled antibiotic resistance (Adebisi *et al.*, 2021a; Rusic *et al.*, 2021). Moreover, the shift of AMS personnel focus to deal with the COVID-19 pandemic can lead to a loss of developed frameworks.

Rusic *et al* (2021) conducted a meta-analysis on 30,623 patients that estimated the prevalence of antibiotic prescribing in patients with COVID-19 at 74.6%. Fluoroquinolones were prescribed in most cases (20.0%), followed by macrolides (18.9%), β-lactam with β-lactam inhibitors (15.0%) and cephalosporins (15.0%). The prevalence of concomitant bacterial infections with COVID-19 was 8.6%. Antibiotic stewardship was reported only in 1.9% of the studies included. Antibiotic prescribing was highly prevalent in ICU at 86.4%, followed with inpatient hospital settings (74.8%) and lowest in mixed inpatient/outpatient settings (59.3%). The prevalence of antibiotic prescribing escalated with patients requiring mechanical ventilation (Langford *et al.*, 2021). Another study by Martin *et al* (2021) evaluated antibiotic utilisation rates and identified risk factors for antibiotic prescribing in hospitalised patients. The study investigated 208 patients admitted from March 1, 2020, to May 31, 2020, and treated for COVID-19. Of 208 encounters, 198 patients were included in the final analysis. In this cohort, 83% of patients received at least one course of antibiotics, despite low rates of microbiologically confirmed infection (12%). Almost one-third of patients (30%) received more than one course of antibiotics. The study also identified risk factors for the prescribing of antibiotics. These included increased hospital length of stay (median 12 days), ICU admission, and the necessity for mechanical ventilation (Martin *et al.*, 2021). Martin *et al* (2021) also provides more insight to this notion through a study on antimicrobial prevalence and prescribing in a tertiary hospital in Singapore. The study deployed one of five AMS

pharmacists. Antimicrobial stewardship rounds with infectious disease physicians were reduced from five to two times a week. A survey in acute inpatients was conducted using the Global Point Prevalence Survey methodology in July 2020 and compared with those in 2015 and 2017 to 2019. The prevalence of antibacterial prescribing (54% in 2015 to 45% in 2019 and 42% in 2020, $p < 0.01$) have been reducing despite the pandemic prescribing and use. The study concluded that there was no increase in antibacterial prescribing (slight declination was observed though due to improved or compact stewardship) and no significant differences in antibiotic prescribing quality indicators (Ng *et al.*, 2021). Ng *et al* (2021) contrasts the study outcomes of Martin *et al* (2021) but highlights that the COVID-19 pandemic and the response to the pandemic may have both positive and negative impacts on antibiotic resistance. COVID-19, alongside previous viral respiratory pandemics in the last decade, has propelled and fuelled the progression of resistance. It is of great importance that past and current viral pandemic knowledge converge to bring about a reduction in the impact of antibiotic use on antibiotic resistance.

2.7 Strategies to reduce the impact

At the commencement of the COVID-19 pandemic, personal protective equipment, quarantining practices, and social distancing was a prominent approach to reducing the impact of the viral pandemic (Wang *et al.*, 2020). Furthermore, integration of restrictions can also reduce antibiotic prescribing. Gillies *et al* (2022) investigated the impact of COVID-19 restrictions on antibiotic dispensing in Australia. Over the study period (November 2015 to October 2020), an estimated 19 921 370 people had 125 495 137 antibiotic dispensing, 71% prescribed by general practitioners. Following COVID-19 restrictions, a sustained 36% reduction in antibiotic dispensing was observed from April 2020. Antibiotics recommended for managing respiratory tract infections showed large reductions (range 51% to 69%), contrastingly, antibiotics recommended for non-respiratory infections were unchanged/constant. Dispensing prescribed by general practitioners decreased from 63.5 per 1000 population for the periods of April to October 2019 to 37.0 per 1000 for April to October 2020. The study concluded that in a setting with a low COVID-19 incidence, restrictions were associated with a substantial reduction in community dispensing of antibiotics primarily used to treat respiratory infections. The study findings are informative for post-pandemic AMS and highlight the potential to reduce inappropriate prescribing by general practitioners and specialists for respiratory viral infections (Gillies *et al.*, 2022).

The antibiotic resistance repercussions of the current pandemic have the potential to stretch well into the post-COVID-19 era. With increased global sensitisation towards emerging threats from infectious diseases and the concepts of transmission and acquisition of disease, this may subsequently drive greater activation of antimicrobial resistance (Rawson *et al.*, 2020). Crucial support structures are necessary for the strengthening and intensification of antibiotic monitoring and AMS (Rusic *et al.*, 2021). Rodríguez-Baño *et al* (2021) highlights key recommendations for continued support for antimicrobial resistance research. These recommendations include the development of context-specific interventions, generation of national and international network for data sharing, enforcement of science and policy collaborations and improved communication with decision and policy makers (Rodríguez-Baño *et al.*, 2021). Furthermore, there is an equally greater need for stricter yet adaptable antibiotic prescribing policies that can encompass transitionary contingencies like the pre-COVID-19 to COVID-19 bridging. Charani *et al* (2021) elaborates on medication systems and prescribing, the importance of timely access to antimicrobials is recognised internationally through their inclusion in country specific EMLs. However, maintaining a current EML remains a challenge due in part to the number of medicines that though withdrawn from the market remain on EMLs (Charani *et al.*, 2021). Further research is required to address this gap. How countries and different setting use and adapt the WHO "AWaRe" system is necessary in optimising antibiotic utilisation (Charani *et al.*, 2021). There is a great need for studies correlating antibiotic use, resistance, antibiotic WHO "AWaRe" classification and assessing AMS compliance in COVID-19.

Therefore, the present study research aims to determine antibiotic consumption during the pandemic era and pre-pandemic era in ICU patients, while investigating the pre-pandemic and pandemic era antibiotics considerations when prescribing in the government healthcare settings. Furthermore, the study will place emphasis on shifts in antibiotic prescribing across the two eras and with intent to monitor resistance patterns. Additionally, the study will provide future insight to potential development of resistance through the surveillance of current commonly used antibiotics; therefore, allowing the development of improved future treatment policies, step-by-step procedures to be followed for diagnosis through to treatment and finally the functioning and value of an antibiogram in the pandemic era.

CHAPTER 3

METHODOLOGY

Chapter Overview

This chapter details the methods that were undertaken to conduct the study. The methodology chapter has been structured, foremost with an overview of common methodological characteristics. Thereafter, the organisation of methodological characteristics in accordance and order of the study objectives.

3.1 Ethical considerations

The University of the Witwatersrand Health Research Ethics Committee (HREC) granted the approval (HREC approval reference number: M220928) to conduct the study after protocol review by the research review committee of the University of the Witwatersrand. Permissions necessary to support and implement this study at the selected study sited was obtained from the Hospital Chief Executive Officer (CEO) and the Head of Department (HOD) of Internal Medicine of Tembisa Provincial Tertiary Hospital. Informed patient consent was not necessary as practice with retrospective record review, HOD and CEO permission from study site is accepted as consent on behalf of the patient because the CEO is considered the legal custodian of the institution. Ethics certificates and site permission documentation can be found in appendix E.

3.2 Common methodological characteristics

3.2.1 Study design

A retrospective and cross-sectional study was conducted by analysis of ICU charts and corresponding National Health Laboratory Service (NHLS) microbiology lab reports of patients admitted in the ICU at a select Gauteng Provincial Tertiary Hospital (GPTH) for the selection and use of antibiotics among this cohort.

3.2.2 Study setting

The study was conducted in the ICU of a GPTH, namely Tembisa Provincial Tertiary Hospital (TPTH), located in a township situated on the East Rand in the city of Ekurhuleni in South Africa. The study site selected is a South African Department of Health-designated COVID-19 hospital site. This designation was employed to facilitate and aid in standardising care, optimise resource utilisation, and protect non-COVID-19 patients and healthcare workers. Thus, TPTH was an ideal study site to assess pre-to-COVID-19 antibiotic utilisation. The designated study hospital had a single Main ICU (MICU) until the year 2021, in which a COVID-19 ICU (C-19-ICU) was established. Therefore, both ICUs were considered.

3.2.3 Study period

Medical files of patients admitted to the ICU between the period of January 2017 and December 2021 were reviewed. Periods before January 2020 were considered pre-pandemic and the period during and following January 2020 was considered the COVID-19 pandemic period (Figure 3.1)

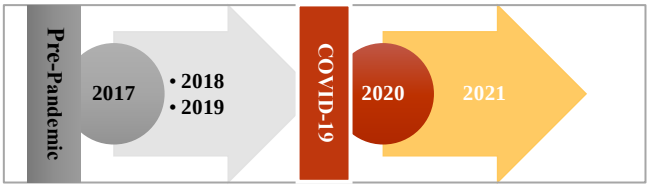

Figure 3.1 Overview of study period

3.2.4 Study population

The study population comprised of patients admitted in the C-19-ICU and MICU at TPTH. The study constituted and reviewed medical charts for older adolescent and adult patients, aged 18 years and older, who received antibiotic treatment within the ICU.

3.2.5 Sample size

The selected government hospital, TPTH, had received approximately 2 552 ICU COVID-19 cases since the start of the pandemic in March 2020, that resulted in the hospitalisation of patients in the pandemic era. Therefore, the sample size formulated by the Raosoft® software

is based on a population size of 2 552, margin of error of 5 % and a confidence interval (CI) of 95% (Rasoft, 2004). The Raosoft® software's sample size calculation capability is based on the formula conveyed in Equation 3.1. Where, N is the population size, r is the fraction of favoured responses, and $Z(c/100)$ is the critical value ($Z_c = 1.96$ *for 95% CI*) for the confidence interval c. The recommended sample size, based on the above-mentioned variables, was 335 across all years within the defined study period. The sample size was partitioned according to strata for both periods (the pre-pandemic and during the COVID-19). Each prescription was randomly selected until a saturation of 335 prescriptions were obtained and reviewed.

$$x = Z(^{c}/_{100})^{2}r(100\text{-}r)$$
$$n = {}^{N\,x}/_{((N\text{-}1)E^{2} + x)}$$
$$E = \mathrm{Sqrt}[{}^{(N\,-\,n)x}/_{n(N\text{-}1)}]$$

Equation 3.1 Sample size formula

3.2.6 Sampling technique

All 335 patient medical files that had antibiotics prescribed were retrieved and assessed for completeness. All files that were used in the study were then selected using stratified random sampling (StRS). The StRS method stratified samples into strata defined by the year of patient admittance/study (2017 to 2021). Therefore, the StRS method ensured that the sample size per stratum was proportionate to the number of patients admitted per year of study. StRS divides the desired sample size into strata.This maximises variation among strata but minimises variation within a stratum. The year of ICU admission was considered as the strata. The study duration encompasses five years of study (2017, 2018, 2019, 2020, 2021), thus there were five strata. Equation 3.2 displays the formula used to determine the proportion of patients per year of study that constituted the sample size.

$$\frac{\text{Number of patients per stratum x 335}}{\text{Total sum of patients across all years of study}}$$

Equation 3.2 Sample size StRS proportion calculation

A detailed StRS spreadsheet is presented in appendix C, representing the determination of the proportion of patients from each year of study that form part of the sample size. Hospital charts/files of patients prescribed antibiotics were selected for review until the required sample size was reached for each stratum as indicated in Table 3.1. The total ICU admissions (population) were disproportionate, therefore StRS was used to ensure relevant distribution within the required sample size.

Table 3.1. Overview of patient sample size proportions by study year

Steps	**StRS Procedure**
One	Patient numbers for each stratum were determined (Stratum-patients admitted per year of study)
Two	The quotients of each stratum to the total population admitted across all years of study were determined (as represented in *equation 3.2*)
Three	Sample size based on the estimated sample size (n=335) was determined for each stratum (as represented in *equation 3.2):* 2017: 44 2018: 59 2019: 56 2020: 61 2021: 115 **Total estimated sample size: 335**

StRS, stratified random sampling.

Random sampling was used to select patient charts/files within each stratum (2017; 2018; 2019; 2020; 2021) using random sampling generator functions in Microsoft Excel. The functions used to randomly select patient files based on patient hospital file numbers are summarised in Figure 3.2. This sampling method ensures charts from the chosen population are selected at random and are unduplicated, ensuring a fair opportunity for analysis. Random selection aids in generalising the results of the population in a rational and reliable manner while eliminating sampling biases such as expediency sample selection based on date, alphabetical or numerical positioning.

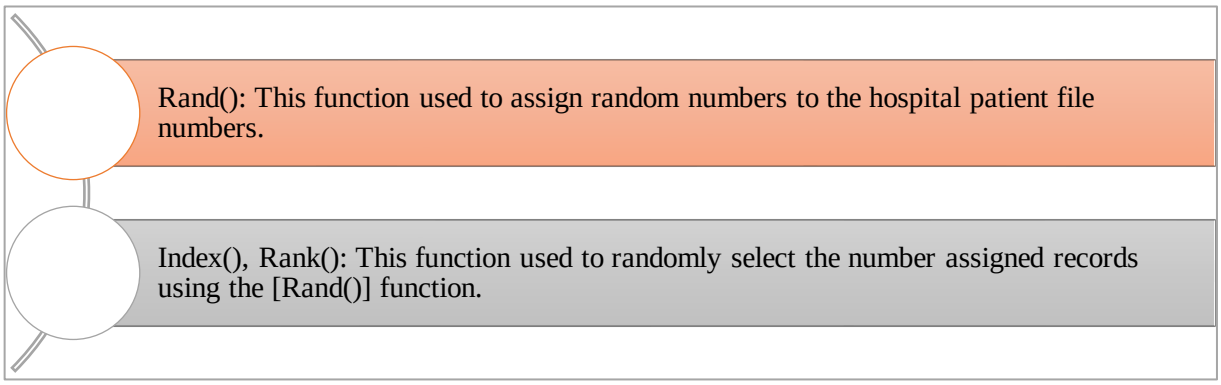

Figure 3.2 Random sampling functions used during patient file selection

3.2.7 Eligibility for study intensive care unit patient medical files

The following inclusion and exclusion criteria were applied:

3.2.7.1 Inclusion criteria

This study included adult patients from age 18 years old and older. Moreover, patients admitted to TPTH ICU and that received antibiotic treatment were included. The patient data between the periods of January 1, 2017, and December 31, 2021, which can be considered as two years preceding (pre-pandemic era), and two years into the pandemic era were considered. Patient charts included various age group ranges relating to adults (18 years of age and older) through to geriatrics, who were prescribed an antibiotic(s). These patient charts are included and justifiable as it provides a broad scope of ages, genders, treatment history and comorbidities that idiosyncratically present with unique challenges for prescribing antibiotics agents against the backdrop of the COVID-19 pandemic and pre-pandemic times, respectively. Furthermore, these patients being institutionalised inferred that healthcare workers upheld their antibiotics consumption and compliance therefore facilitating the reliability of data in conjunction with AMS, patient charts, etc.

3.2.7.2 Exclusion criteria

Patients' charts were excluded due to irretrievable records, incompleteness, and illegibility. The exclusion criteria was also applied to hospital readmissions of the same patient. Patients that received antibacterial pharmacotherapy before being admitted to the Hospital was

excluded (for example, instances of Tuberculosis diagnosis during scheduled regular checkups and resulting regimen therapy prescription).

Table 3.2. Criteria for the selection of study the population

Criteria	Inclusion criteria	Exclusion criteria
Period	1 January 2017 to 31 December 2021	Preceding 2017
Study population	18 years of age and older	Neonates (birth-1 month), infants (1 month-1 year), children (1-12 years of age) and adolescents (13-17 years of age)
Setting	Tembisa Provincial Tertiary Hospital Intensive Care Unit and COVID-19 Intensive Care Unit	Designated wards, general wards, High Care Unit, Neonatal and Pediatric Intensive Care Unit
Prescription/chart items	All antibiotics prescribed in the hospital Intensive Care unit	Antibacterial therapy received prior to hospital admission
Prescription/chart integrity	Indicates medication prescribed, dosing, frequency, and duration of therapy	Incomplete and illegible
Sampling	Patient specific hospital number	Record number duplication and patient re-admittance

The sampling technique specified in *section 3.2.6* was applied in combination with the eligibility criteria in *section 3.2.7.* Figure 3.3 illustrates an overview of the distribution of ICU patients throughout the patient selection process.

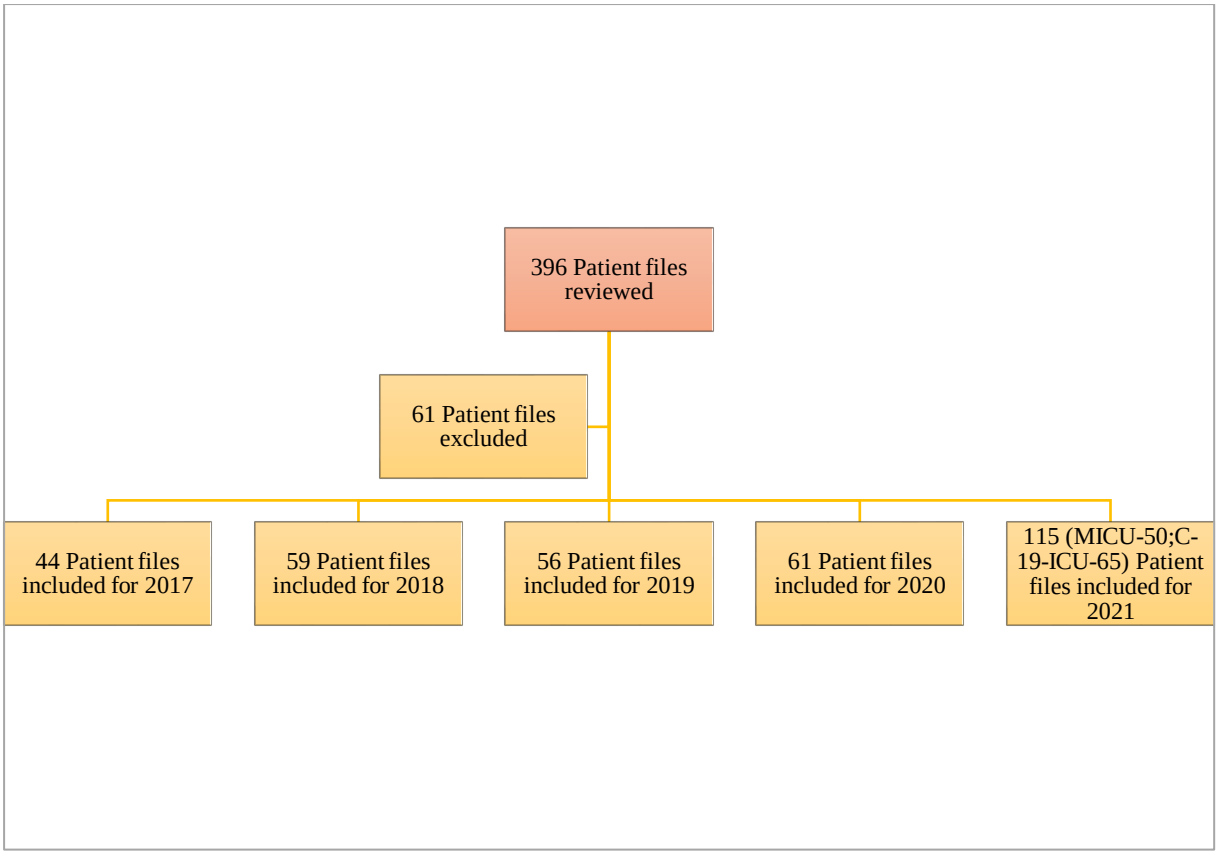

Figure 3. 3 Overview of patient selection and review

3.3 Methodological characteristics by objectives

3.3.1 Objective one and two methodology

Objectives one and two have common methodological characteristics as both pertain to antibiotic utilisation, thus these objectives are represented together.

3.3.1.1 Data collection tool

Patient chart/file data was manually inscribed into a DUR form designed and coded using the Research Electronic Data Capture (REDCap) tools hosted at the University of Witwatersrand (Harris *et al.*, 2009, 2019). The REDCap DUR form and the corresponding codes are depicted in appendix D_1 and D_2. Table 3.3 provides an overview of the information captured in the DUR form, which included: study identification number (ID), hospital case number, ICU type, period of admittance, duration of stay, medical diagnosis, COVID-19 status, comorbidities, allergies, adverse drug reactions (ADR) and antibacterial prescribing details.

Table 3. 3. Summary of patient chart/file information captured in the DUR form

DUR variables	Study Context
Study ID	ID code assigned to each form collected by researcher
Hospital case number	Patient number assigned by TPTH; necessary for Orbit® search. Orbit® is a data repository used to archive patient data at TPTH.
ICU Type	MICU; C-19-ICU
Period of admittance	Instance of admittance to the ICU through to ward transfer/discharge occurring within the study period of 1 January 2017 to 31 December 2021
Duration of stay	Time spent in the ICU (measurable in days, weeks, and months)
Medical diagnosis	Diagnosis made and recorded by attending physician
COVID-19 status	Positive or negative testing. It is important to note that patients admitted to the ICU prior to the COVID-19 period would not have been assessed, thus take on a negative COVID-19 status.
Comorbidities	Presence of two or more diseases/medical conditions in a patient
Allergies	Allergies induced by antibacterial or other medication prescribed in conjunction to antibacterial therapy
Adverse drug reaction	Harmful or unpleasant reaction resulting from an intervention related to the use of antibiotics or other medication prescribed in conjunction to antibacterial therapy
Antibiotic prescription	Name of antibiotic for the indication, dosage, duration, frequency, and route of administration.
Antibiotic appropriateness	This refers to the correct antibiotic for the indication, dosage, duration, frequency, and route of administration established with reference guides such as standard treatment guidelines.

COVID-19, coronavirus disease 2019; C-19-ICU., coronavirus disease 2019 intensive care unit; MICU, main intensive care unit.

3.3.1.2 Primary data source

Hospital patient files and charts are completed manually in the ICU by all clinical staff assigned to the department which include nurses, doctors, pharmacists, and medical interns.

Subsequently, files and charts are scanned and uploaded onto the Orbit ® hospital record repository system in the hospital records archive department (Figure 3.4). Therefore, retrospective review of identified ICU study cohort was conducted in the hospital record archive unit by ICU patient number search. Records were screened on Orbit ® for age, sex, diagnosis of specific infections, antibiotics prescribed (dose, route, frequency, duration), any chronic medications used, any comorbid conditions, medication allergies and adverse reactions. The procedure of data collection is further discussed in the *study procedure, section 3.3.1.3.*

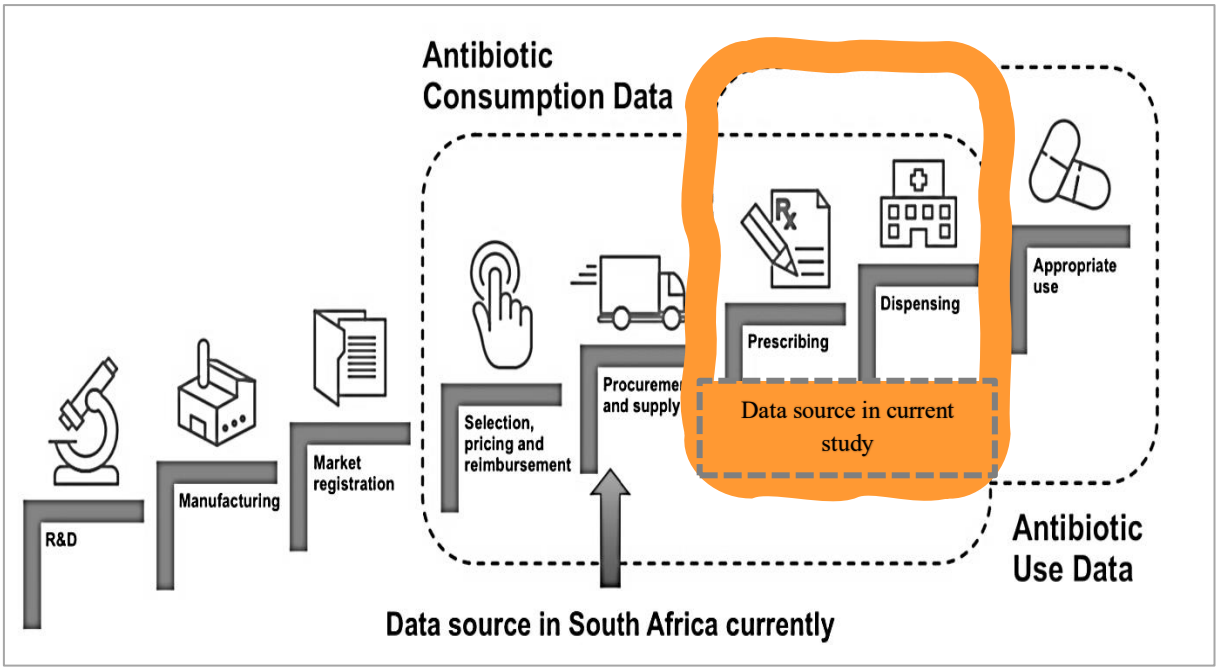

Figure 3. 4 Data source of current study within the drug cycle, adapted from figure 1.5 (South African National Department of Health, 2021)

3.3.1.3 Study data collection procedure

A minimum of 335 patient files were reviewed across all years within the designated study period, of 1 January 2017 to 31 December 2021, from ICU patients admitted at TPTH. The researcher accessed, screened, selected, and reviewed eligible patient case file that met inclusion criteria, during the stated study period. Data was collected using the validated tool created on REDCap Software®, discussed in *section 3.3.1.1*. Data extracted from selected patient files included: age, sex, diagnosis of specific infections, antibiotics prescribed (dose,

route, frequency, duration), any concurrent medications used and any comorbid conditions. In addition, data collected from reviewed files was compared to the South African Standard treatment guideline. The decision of adherence to guidelines and appropriateness was based on the most recent guidelines and resources available and accessible. Classification of antibiotics into the AWaRe groups was done based on the WHO AWaRe tool (WHO, 2022).

Furthermore, as this was a retrospective study, it was not necessary for the researcher to obtain patient permission to access patient files. The patients' information extracted was kept confidential. Confidentiality was maintained by de-identifying patient case numbers linked to TPTH records through de-coding. De-coding/de-identifying patient identifiers (hospital case number) included assigning letters denoting the hospital of record retrieval, followed by randomly assigning study ID numbers. For instance, the random number generator tool was allocated a random study ID number/code (e.g., 123) and the researcher assigned the letters to the reviewed file based of the hospital of retrieval (e.g., a script from the Tembisa Hospital will be allocated "T") thus the new patient case identifier was "T-123". This not only ensured discretion but also enabled traceability and organisation of patient case files reviewed and collected. Other identifiable information of participants was not recorded during any stage of research and patient case number not used in the study was securely discarded.

3.3.1.4 Data analysis

a) Derived and calculated variables

The data collected using REDCap, was exported into Microsoft® Excel® 365 MSO (Version 2310 Build 16.0.16924.20054) where the data was cleaned. Furthermore, certain variables were used to derive variables before being imported to the statistical software. Derived variables included, PDD and the PDD- DDD ratio. The PDD for each antibiotic that was calculated from the quotient of the total dose and duration of antibiotic therapy to determine dose utilisation (Equation 3.3) (Venkateshwarlu *et al.*, 2018).

$$\text{PDD} = \frac{\text{Total dosage prescribed (grams)}}{\text{Number of days of antibiotic therapy}}$$

Equation 3.3 Prescribed daily dose formula

The PDD and the corresponding WHO assigned DDD was used to calculate the quotient of the PDD and DDD to determine the PDD-DDD ratio (Equation 3.4). In relation to the PDD-DDD ratio, the study considered suboptimal use, optimal or overuse as variables according to the difference from the unit: when the quotient of the PDD and DDD is less than 1.0, then it was considered suboptimal use or overuse if a value is greater than 1.0. Optimal use was considered at a prescribed dose equal to 1.0 (Sánchez-Huesca *et al.*, 2020).

$$\text{PDD-DDD Ratio} = \frac{\text{PDD for each antibiotic}}{\text{WHO assigned DDD}}$$

Equation 3.4 Prescribed daily dose and defined daily dose quotient formula

b) Statistical analysis

Statistical analysis was conducted using Statistical and Data Science® Special Edition (STATA/SE; version 17.0). Descriptive statistics was used to summarise nominal, binary, and continuous data. Nominal and binary variables (COVID period, ICU type, gender, age range, length of stay range, primary and secondary diagnosis, comorbidities, concurrent pharmacotherapy, antibiotic prescribed, dose utilisation classification, WHO AwaRe classification and appropriateness) were represented as frequencies and proportions. Continuous variables (PDD, DDD and PDD-DDD ratio) were represented as measures of central tendency, means (PDD) and medians (PDD-DDD ratio). All statistical tests considered significance at a P-value of 0.05. The PDD and DDD for most antibiotics used were normally distributed as determined by Kolmogorov-Smirnov (KS) test, which revealed a non-significant probability value (P-value>0.05) failing to reject the null hypothesis that the data was normally distributed. Chi-squared test was performed to determine whether there was an association between primary diagnosis, secondary diagnosis, comorbidities, concurrent pharmacotherapy, and antibiotics used was compared to the COVID-19 status. In the comparative analyses, the null hypothesis for the chi-squared test was that there were no associations between the

explanatory variables and the outcome variables Conversely, the alternative hypothesis was that there was an association between explanatory variables and outcome variables.

Table 3.4 Variables compared using Chi-square test

Chi-square test		Explanatory variable
Outcome variable	COVID status	Primary diagnosis
		Secondary diagnosis
		Concurrent pharmacotherapy
		Antibiotic(s) prescribed

COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Parametric assumptions about distribution (normal distribution by KS test and equal variance determination by Levene test) were met, thus the parametric independent t-test was conducted for the comparison of the mean PDD pre-pandemic and the mean PDD during COVID-19. This test was applied to determine whether there was a difference in dose utilisation before and during COVID-19. The null hypothesis of the t-test was that there was no significant difference between the pre-pandemic PDD and the COVID-19 PDD. The alternative hypothesis assumed that there was a difference between the dose utilisation before and during the COVID-19 pandemic.

3.3.2 Objective three methodology

3.3.2.1 Secondary data source and collection

The study data was retrieved from two institutions, TPTH and the NHLS. Patient demographic information, medical history and prescription data was available in-patient ICU charts and files, however, these files and charts lacked microbiological laboratory outcomes. Due to the absence of essential microbiology lab report data in patient files reviewed, such data was requested through the NHLS. The NHLS is the lab service provider for the selected hospital and therefore was the secondary data source for the lab data retrieval. The NHLS is a national public entity established according to of the National Health Laboratory Service Act, No. 37 of 2000, governed by a board and objectifies the provision of quality, affordable, and sustainable health laboratory services, training, and research. The Data was applied for and requested through the NHLS Academic Affairs and Research Management System (AARMS) according to the data

request guidelines set out by the NHLS. The guidelines had no restrictions concerning the data requested, however, approved study documentation (study protocol, ethics certificate, study site approval) was necessary. Selected patient files numbers, in accordance with *section 3.2.6 and 3.2.*7, were shared with the NHLS. Data requested included, any microbiology test data requested by the primary medical practitioner at the initial point of lab data request (corresponding to the patient numbers from the primary data source) and testing, specimens taken, organisms detected and antibacterial susceptibly data (Table 3.5). Data was received as a Microsoft® Excel® spreadsheet.

Table 3.5 Description of data retrieved from the NHLS of eligible TPTH ICU patients

NHLS variables	Description
Patient information	Patient case number corresponding the TPTH assigned patient identifier, age, and corresponding diagnosis
Specimen details	Type of specimen (urine, blood,etc.) and collection date
Isolates	Pathogenic microorganisms detected from collected specimens
Susceptibility results	Sensitivity of isolate to antibacterial agents

3.2.2.2 Data analysis

Data was cleaned and merged with data described in *section 3.3.1.4* in Microsoft® Excel® 365 MSO (Version 2310 Build 16.0.16924.20054) before being exported to the statistical software. Statistical analysis was conducted using Statistical and Data Science® Special Edition (STATA/SE; version 17.0). Descriptive statistics was used to summarise categorical variables. Categorical variables (specimen type, organism(s) detected and antibiotic susceptibility) were represented as frequencies and proportions.

3.2.2.3 Overview of study methodology and objectives

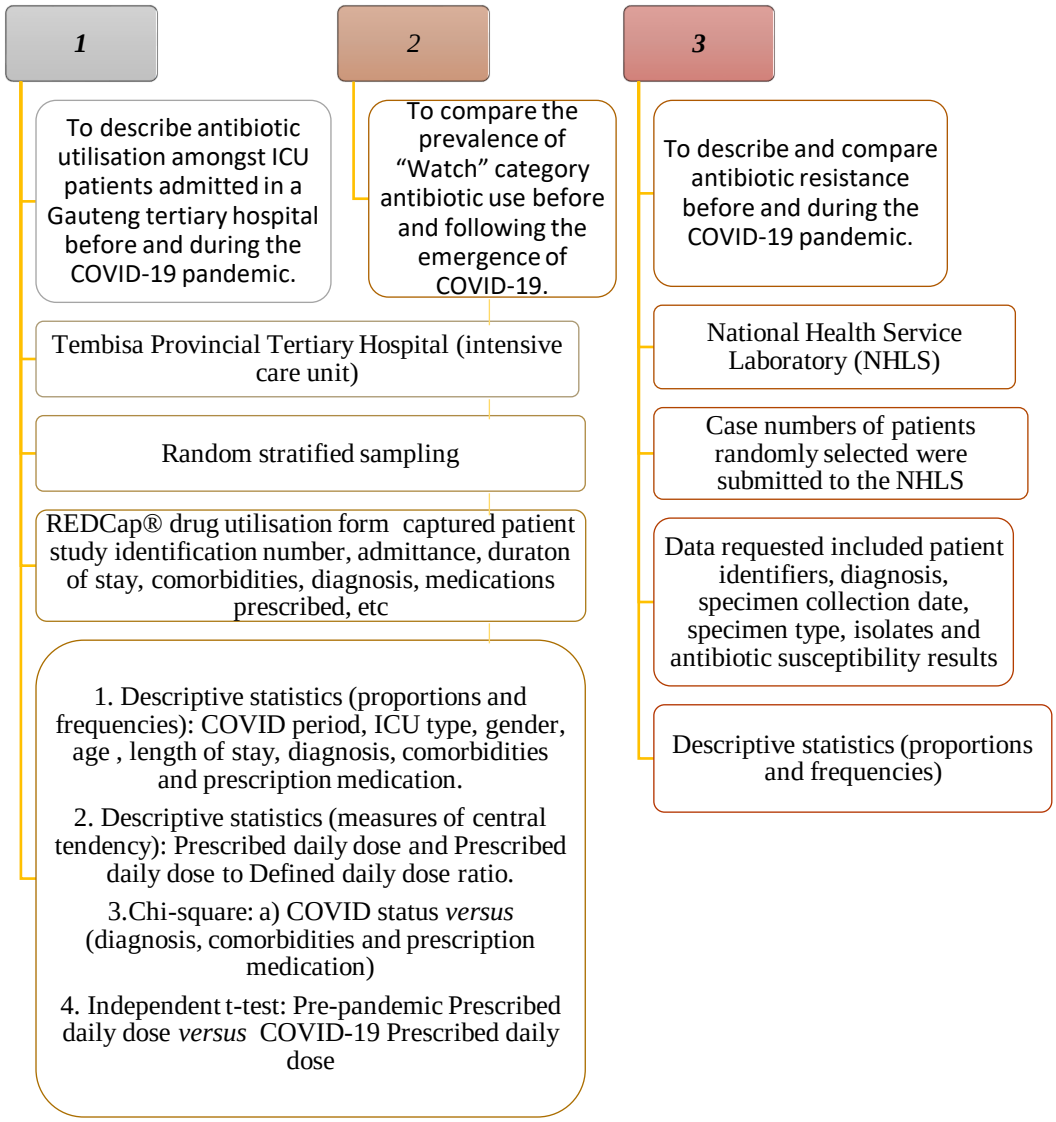

Figure 3.5 Overview of study methodology by objectives

CHAPTER 4

RESULTS AND DISCUSSION

Chapter Overview

This chapter will elucidate results in accordance with the study objectives. Furthermore, findings in the current study will be critiqued and compared to previous studies in antibiotic utilisation locally and internationally.

4.1 Patient demographics

4.1.1. Pre-pandemic patient demographics

Table 4.1. Patient demographic variables for patients admitted in the ICU at TPTH between January 2017 and December 2021

Variables	Study Period					
	Pre-COVID-19		COVID-19		Total	
	n	%	n	%	n	%
Sex						
Female	84	48.8	103	63.2	187	55.8
Male	88	51.2	60	36.8	148	44.2
Total	172	100	163	100	335	100
Age group (years)						
18-25	27	15.7	17	10.4	44	13.13
26-40	54	31.4	73	44.8	127	37.9
41-60	61	35.5	52	31.9	113	33.7
61	30	17.4	21	12.9	51	15.22
Total	172	100	163	100	335	100

COVID-19, Coronavirus Disease 2019; n. frequency

The pre-pandemic period accounted for 51.3% (n = 172) of the study population. During this period male predominance was observed, with these files accounting for 51.2% (n = 88). The majority across both genders, 35.5% (n = 61), were between the ages of 41 and 61 years of age. The age range, 26 to 40 years of age, was the second most prevalent age category (Table 4.1).

Contrarily to the present study, another study on in-patient antibiotic use and the prevalence of associated adverse antibiotic events during the pre-pandemic period, observed female predominance (57%) (Tamma *et al.*, 2017). Another study by Thomas *et al* (2015), evaluated the prolonged use of antibiotics and agreed with the current study's pre-pandemic gender findings, as the males constituted 58% of the study (Thomas *et al.*, 2015). Similarly, a multicentre ICU study noted pre-pandemic male prevalence of 66.1% (Singh *et al.*, 2016). This agreed with the current study's pre-pandemic gender findings. Furthermore, Singh *et al* (2016) showed a mean age of 54.1 ± 17.1 years of age in alignment with the present study's pre-pandemic dominant age prevalence (Singh *et al.*, 2016). Additionally, Tamma *et al* (2017) found a median age, across all in-patients, of 59 (IQR, 49-69) years of age which was within the age range of the current study. The median age and corresponding interquartile range of ages observed by Thomas *et al* (2015) were 60 (IQR, 49-71) years of age, and agreed of the current study's age range (Tamma *et al.*, 2017).

4.1.2 COVID-19 pandemic patient demographics

During the COVID-19 period, the current study showed female predominance. Female patients within the pandemic period (n=163) accounted for 63.2% (n=103) (Table 4.1). Similarly, Dong *et al* (2020) reported 54.5% of the study cohort to be females that were prescribed antibiotics in the COVID-19 period. Another study by Trujilluo *et al* (2020) reported females, 70% were more prevalent within the study. Contrarily, Chen *et al* (2020) reported 55.6% male predominance, therefore opposing the pandemic gender finding of the current study. A review by Al-Hadidi (2021) reviewing the spectrum of antibiotic prescribing during COVID-19 indicated that several studies reported that females were predominantly prescribed antibiotics as with the current study. Additionally, the present study reported that 44.8% (n=73) of patients across both genders were between the ages of 26 and 40 years of age (Table 4.1). The age range, 41 to 60 years, was the second most prevalent age category in the COVID-19 period. Likewise, another study observed a median age of 36.6 (IQR, 2-69) years of age congruent with that of the current study (Dong *et al.*, 2020). In addition, a study observed a mean age of 54 ±10 years, forming part of the secondary predominant age category of the current study (Trujillo *et al.*, 2020). Additionally, another study reported a study sample aged 42 (IQR, 14-56) years corresponding to the second most prevalent age category in the present study (Chen *et al.*, 2020).

4.1.3 Overview of baseline study demographics across the study period

In the present study, 335 medical files of ICU patients on antibiotic pharmacotherapy were included (Table 4.1). In general, the COVID-19 period observed a downward shift in age with majority of the study population clustered into a younger age category (pre-pandemic: 41 to 60 years of age *versus* COVID-19: 26 to 40 years of age). In addition, the study further highlighted a shift from male predominance in the pre-pandemic period to female predominance during the COVID-19 period. The demographic shift towards younger patients (26 to 40 years of age) and more female patients in the COVID-19 period was congruent with reports of changing demographics in other countries (Goldstein and Lipsitch, 2020; Taylor, 2021; Amin *et al.*, 2022; Bird *et al.*, 2022).

Guimaraes *et al* (2021) and Amin *et al* (2022) proposed that the initial vaccination prioritisation of the elderly might partially explain why younger individuals were at risk of serve illness and hospitalisation. Furthermore, social distancing and demobilisation may have provided protection from COVID-19 and other diseases for the elderly. However, this may not have been the case for younger frontline workers that were exposed to many illnesses and contagions (Guimarães *et al.*, 2021; Amin *et al.*, 2022). Another study by Ricoca Peixoto *et al* (2023) also emphasised that age is a relevant risk factor for ICU admission with a decreased risk of admission associated with increasing age (Ricoca Peixoto *et al.*, 2023a). Clinical manifestations in older groups versus younger groups are different, therefore more studies prioritising the identification of factors predicting risks of clinical deterioration is required. This is essential as it will inform escalation of care for patients at risk (Kämpe *et al.*, 2023). However, research is necessary to determine the reasoning behind female prevalence during the pandemic era. Studies have investigated ICU admission but further gender-based analysis is critical (Grasselli *et al.*, 2020; Giacomelli *et al.*, 2021; Izadi *et al.*, 2023). This will be significant in the South African context as coexistence, outcomes and interactions between COVID-19 and the vast burden of disease is unclear (Jassat *et al.*, 2021).

Overall, previous studies were mostly congruent with the gender and age findings in both study periods. Although, the present study's demography is similar to other demographic representations in prior studies, heterogeneities do exist. These differences may be due to the difference in study design and study location that would then inform variation in the study population. Furthermore, precedent studies on demographic and critical care disparities emphasise that these differences are multifactorial, performing on an individual, community,

and hospital level. Additionally, notable factors within this complex multifactorial network include illness severity, ventilatory support, venous catheter use and antibiotic resistance. These factors effect variation of antibiotic prescribing and use informing variation in the patients who receive antibacterial pharmacotherapy(Gahbauer, Gonzales and Guglielmo, 2014; Lee *et al.*, 2020; Yin, Tambyah and Perencevich, 2020).

4.2. Patient characteristics and concurrent pharmacotherapy

Table 4.2. Patient characteristics

Variables	Study Period					
	Pre-COVID-19		COVID-19		Total	
	n	%	n	%	n	%
ICU Type						
MICU	172	100	98	60.1	270	80.6
C-19-ICU	0	0	65	39.9	65	19.4
Total	172	100	163	100	335	100
COVID-19 Status						
Negative	172	100	87	53.4	259	77.3
Positive	0	0	76	46.6	76	22.7
Total	172	100	163	100	335	100
Length of Stay (days)						
0-6	119	69.2	127	77.9	246	73.4
7-14	39	22.7	33	20.2	72	21.5
14-21	3	1.7	3	1.8	6	1.8
>21	11	6.4	0	0	11	3.3
Total	172	100	163	100	335	100
Diagnosis						
Cardiovascular	5	2.91	9	5.52	14	4.18
Dermatological	14	8.14	15	9.20	29	8.66
Endocrine	8	4.65	12	7.36	20	5.97
Gastrointestinal	14	8.14	10	6.13	24	7.16
Neurological	36	20.9	16	9.82	52	15.5
Gynaecology	8	4.65	10	6.13	18	5.37
Respiratory	38	22.1	55	33.74	93	57.1
Sepsis	16	9.30	9	5.52	25	15.3
Trauma and injuries	17	9.88	11	6.75	28	17.2
other	16	9.30	16	9.82	32	19.6
Total	172	100	163	100	335	100
One Comorbidity						
No	100	58.1	101	62	201	60
Yes	72	41.9	62	38	134	40
Total	172	100	163	100	335	100

COVID-19, Coronavirus Disease 2019; MICU, main intensive care unit; n, frequency; C-19-ICU, COVID-19 intensive care unit.

Table 4.2. continued. Patient characteristics

Variables	Study Period					
	Pre-COVID-19		COVID-19		Total	
	n	%	n	%	n	%
Two Comorbidities						
No	145	84.3	137	84	282	84.2
Yes	27	15.7	26	16	53	15.8
Total	172	100	163	100	335	100
Three or More Comorbidities						
No	169	98.3	151	92.6	320	95.5
Yes	3	1.7	12	7.4	15	4.5
Total	172	100	163	100	335	100

COVID-19, Coronavirus Disease 2019; MICU, main intensive care unit; n, frequency; C-19-ICU, COVID-19 intensive care unit.

4.2.1. Pre-pandemic patient characteristics

The select study hospital had two ICUs (MICU, and C-19-ICU) during the study periods of interest. The C-19-ICU was established in 2021, hence no patients were reported to be admitted in the C-19-ICU and all patients (n=172) were admitted to the MICU during the pre-pandemic period. The pre-pandemic study cohort's COVID-19 status was reported as negative as the corresponding study period pre-dated the emergence of COVID-19. Furthermore, in the current study most of the pre-pandemic patients, 69.2% (n = 119), remained in the ICU for up to six days.

A study by Valade *et al* (2018) reported a median ICU length of stay of 16.5 (IQR, 9.5-30.5) days in critically ill respiratory infection patients, synonymous with the pre-pandemic period of the current study (Valade *et al.*, 2018). This study contrasted the current studies pre-pandemic findings. Since the focal point of Valade *et al* (2018) research was respiratory conditions, whereas the current study investigated a broader array of medical diagnoses in relation to antibiotic usage and prescribing. Other studies also reported higher mean length of stays in the ICU, contradicting the present study (Carson *et al.*, 2016; Curtis *et al.*, 2016; White *et al.*, 2018). Differences in length of stay can be diversity in diagnoses, disease severity and the prevalence of comorbidities (Grasselli *et al.*, 2020). Furthermore, the present study also reported common diagnoses, respiratory (22.1%; n = 38) and neurological conditions (20.9%; n = 36) during the pre-pandemic period. Other studies on respiratory illness in the ICU and

neuro-ICU incidence are congruent with the current studies finding (Abulhasan *et al.*, 2018; Ieven *et al.*, 2018; Busl, 2019; Wang *et al.*, 2019).

The current study also reported on the prevalence of comorbidities with 72 patients presenting with at least one comorbidity, 27 patients with two comorbidities and three patients with three or more comorbidities. Larsson *et al* (2021) noted that 59.2% (n=154) of the study population admitted in the ICU had at least one comorbidity (Larsson *et al.*, 2021). Another study by Dal Negro *et al* (2015) during the pre-pandemic period found at least one comorbidity of clinical relevance in 78.6 % of patients, but at least two in 68.8 %, and three or more were found in 47.9 % of subjects. Overall, most studies agreed with present findings regarding greater prevalence of patients with at least one comorbidity. The prevalence of comorbidities, the number of coexisting comorbid conditions in patient and diagnosis remains an important risk for ICU admission. Table 4.2 reports patient characteristics of patients admitted in the ICU at TPTH between January 2017 and December 2021.

4.2.2 COVID-19 pandemic patient characteristics

During the COVID-19 period, 60.1% (n=98) were admitted to the MICU and 39.9% (n=65) were admitted to the C-19-ICU. During the COVID-19 period, 46.6% (n=76) of the ICU patients tested positively and 53.4% (n=87) tested negatively for COVID-19 (Table 4.2). A study by Sadeghi *et al* (2020) reported 27.5% (n=55) ICU admission of COVID-19 patients during the Pandemic period (Sadeghi *et al.*, 2020). This was congruent with current study's findings. Conversely, another study reported 10.22% (n=1851) COVID-19 ICU admissions which was lower than the current studies COVID-19 positive admissions (Ricoca Peixoto *et al.*, 2023b).

Studies have also indicated that ICU admissions between countries varies by 5% to 32% (Sadeghi *et al.*, 2020). A study by Larsson *et al* (2021) reported a median ICU length of stay of 12 (IQR, 6-18) days during the COVID-19 period(Larsson *et al.*, 2021). As with the present study's predominant ICU duration category (0-6 days) fell within the lower 25% quartile of the ICU duration reported by Larsson *et al* (2021). Another study by Roedl *et al* (2021) observed a median length of stay of 13 (IQR, 5-24) days during the COVID-19 period (Roedl *et al.*, 2021). This partially agreed with the ICU length of stay as the lower quartile reported by Roedl *et al* (2021) aligned with the most prevalent ICU duration category reported in the present study. Patients presenting with comorbidities in COVID-19 were similar to the pre-pandemic

population. However, patient with three or more comorbidities observed an increase in the pandemic period. This may be due to the complex coexistence and probable interaction of COVID-19 infection and patient comorbidities that can lead to complication and subsequent ICU admission (Baradaran *et al.*, 2020; Grasselli *et al.*, 2020). Though more insight is necessary, especially in the South African context, to determine the relationship between comorbidities, COVID-19, disease severity and ICU admission.

4.2.3 Patient comorbidities: a study period comparison

In the current study 1.7% (n=3) of the pre-pandemic cohort and 7.4% (n=12) of the COVID-19 cohort had three or more comorbidities reported. The presence of three or more comorbidities was associated with both the pre-pandemic period and COVID-19 period. The prevalence of most comorbidities in the COVID-19 pandemic period appeared similarly to that in the general study population before the emergence of COVID-19. Figures 4.1 depicts comorbidities reported in the current study during the pre-pandemic and COVID-19 periods, respectively.

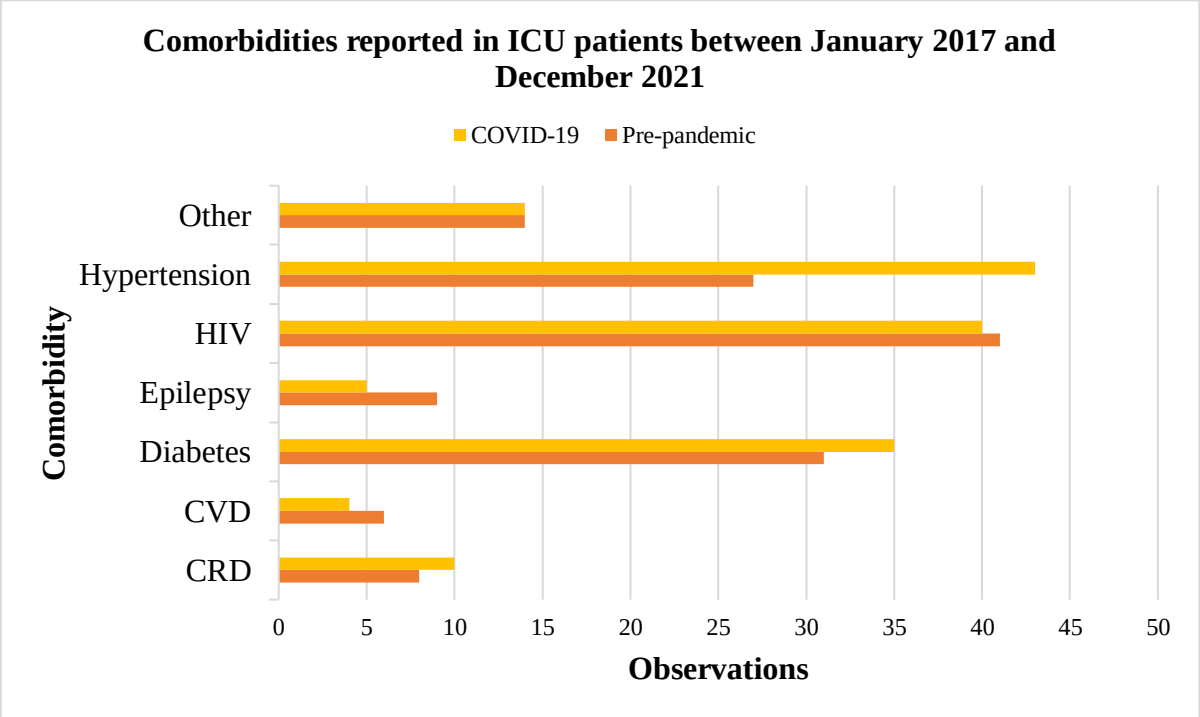

Figure 4.1 Distribution of patient comorbidities. Abbreviations: HIV, Human Immunodeficiency Virus; CRD, chronic respiratory diseases; CVD, cardiovascular diseases.

Another study on patients presenting with comorbidities by Abdelhafiz *et al* (2021), reported significantly worse laboratory parameters in comparison to patients without comorbidities (Abdelhafiz, Emmerton and Sinclair, 2021). Furthermore, ICU admission of these patients were higher in patients with comorbidities (35.8%) (Abdelhafiz, Emmerton and Sinclair, 2021). The current study reported diabetes in 18% (n=31) and 21.5% (n=35) of patients in the pre-pandemic and COVID-19 periods, respectively. Several studies have reported on COVID-19 and diabetes concluding that diabetes in coexistence with other chronic comorbidities such as hypertension, obesity and cardiovascular disease may complicate COVID-19 diagnosis and worsen prognosis (Baradaran *et al.*, 2020; Abdelhafiz, Emmerton and Sinclair, 2021; Khedr *et al.*, 2022). Perhaps in the current study diabetes indicated a decline moving into the pandemic period due to better management of the disease but other studies have reported a disruption in management thus influencing hospital admission of diabetic patients in the COVID-19 period (Anjorin *et al.*, 2021). Furthermore, the current study found a slight increase in the prevalence of chronic respiratory conditions moving into the COVID-19 period. The prevalence of hypertension in the present study observed a surge moving from the pre-pandemic period (15.7%; n=27) into the COVID-19 period (26.4%; n=43). A study by Shah *et al* (2021) agreed with the hypertension findings in the current study (Shah *et al.*, 2022). Another study on the prevalence of hypertension pre-to-COVID-19 reported a median increase of 0.1% (IQR, -1.3-1.5), further augmenting the current study's findings (Lee *et al.*, 2022). The changes in the prevalence of various comorbidities moving into the COVID-19 era, necessitates further analysis to explore the influence on patient outcomes.

4.2.4 COVID-19 status and associated diagnoses

In the present study, the Chi-square test was used to compare primary diagnoses and patient COVID-19 status. COVID-19 status was associated with the primary diagnosis of ICU patients ($P<0.01$). Overall, the larger proportion of the diagnoses were respiratory related, which accounted for 26.76% (n=93) of all diagnoses (Table 4.3). Subsequently, the larger proportion of ICU patients that tested positively for COVID-19 were attributed to respiratory diagnoses, 54% (n=41). This is justifiable as COVID -19 was marked by a rapid increase of respiratory illness. In addition, previous pandemics (MERS-CoV and influenza A) in the last ten years, also reported surges in respiratory infections amidst the respective pandemics (Joseph, Togawa and Shindo, 2013; Ko *et al.*, 2016; Saunders-Hastings and Krewski, 2016; Moghadami, 2017; Chafekar and Fielding, 2018).

Table 4.3. Patient diagnosis by COVID-19 status

Variables	COVID-19 Status					
	Positive		Negative		Total	
	n	%	n	%	n	%
Diagnosis						***P=0.000**
Cardiovascular	5	6.58	9	3.47	14	4.18
Dermatological	1	1.32	28	10.8	29	8.66
Endocrine	4	5.26	16	6.18	20	5.97
Gastrointestinal	3	3.95	21	8.11	24	7.16
Neurological	6	7.89	46	17.8	18	5.37
Gynaecology	2	2.63	16	6.18	52	15.5
Respiratory	41	54.0	52	20.1	93	26.76
Sepsis	2	2.63	23	8.88	25	7.46
Trauma and injuries	2	2.63	26	10.0	28	8.36
other	10	13.2	22	8.49	32	9.6
Total	76	100	259	100	335	100

COVID-19, Coronavirus Disease 2019; n, frequency; *Significant: *p<0.05 versus COVID-19 status*

4.2.5 COVID-19 status and prevalence of pneumonia

The Chi-square test was used to compare secondary diagnoses and patient COVID-19 status. Secondary diagnoses of pneumonias were significantly associated with ICU patient COVID-19 status (P<0.05). CAP accounted for 31.6% (n=24) positive ICU COVID-19 cases. Of 76 positive COVID-19 cases, 68.4% (n=52) reported no coinfection with pneumonia (Table 4.5).

Table 4.4. ICU patient encounters with secondary diagnosis of pneumonia

Variables	COVID-19 Status					
	Positive		Negative		Total	
	n	%	n	%	n	%
Secondary diagnosis of Pneumonia						***P=0.020**
Aspiration Pneumonia	0	0	9	3.47	9	2.69
Community Acquired Pneumonia	24	31.6	47	18.2	71	21.2
Hospital Acquired Pneumonia	0	0	6	2.32	6	1.79
No Pneumonia reported	52	68.4	197	76.1	249	74.33
Total	76	100	259	100	335	100

COVID-19, Coronavirus Disease 2019; n, frequency; *Significant: *p<0.05 versus COVID-19 status*

A study by Karaba *et al* (2021) similarly reported no evidence of pneumonia in 69% of patients (Karaba *et al.*, 2021). Larrazabal *et al* (2021) observed 30.99 (n=110) severe cases of COVID-19 related CAP, supporting the finding of the current study. Conversely, another study by Garcia-Vidal *et al* (2021) found CAP coinfection with COVID-19 uncommon, 3.1% (n= 31 of 989) (Garcia-Vidal *et al.*, 2021b). A study by Di Mitri *et al* (2021) indicated a higher prevalence on non-COVID pneumonia (24%) in comparison to COVID related pneumonia (17%), therefore opposing the findings of the current study. (Di Mitri *et al.*, 2021). Several studies (Chiu *et al.*, 2015; Abelenda-Alonso, Rombauts, *et al.*, 2020; Adler *et al.*, 2020; Mahmoudi, 2020; Feldman and Anderson, 2021) report on the coinfection however more research is needed to investigate the contextual interactions and determinants of pneumonia coinfection with COVID-19 especially in LMIC countries.

4.2.6 Associated concurrent pharmacotherapy: a study period comparison

The present study observed increases in most concurrent pharmacotherapy prescriptions including, anticoagulants, COVID-19 supplement combinations, minerals and vitamins moving into the COVID-19 period. The COVID-19 supplement combination was previous not prescribed prior to the COVID-19 period. The commencement of the COVID-19 period sought a sudden 22.1% incline of this drug combination. Individual mineral (pre-pandemic = 5.81%, n = 10; COVID-19 = 35%, n = 57) and vitamin (pre-pandemic:6.40%, n = 11; COVID-19: 43.6%, n = 71) substances also showed an increase moving into the COVID-19 period (Table 4.5).

Table 4.5. Prescription concurrent pharmacotherapy in ICU patients

Associated variables	Study Period					
	Pre-pandemic		COVID-19		Total	
	n	%	n	%	n	%
Anticoagulants						
Yes	109	63.7	84	51.5	193	57.6
No	63	36.6	79	48.5	142	42.4
Total	172	100	163	100	335	100
COVID-19 supplement combination**						
Yes	0	0	36	22.1	36	10.8
No	172	100	127	77.9	299	89.3
Total	172	100	163	100	335	100
Minerals						
Yes	10	5.81	57	35.0	67	20.0
No	162	94.2	106	65.0	268	80.0
Total	172	100	163	100	335	100
Vitamin						
Yes	11	6.40	71	43.6	82	24.5
No	161	93.6	92	56.4	253	75.52
Total	172	100	163	100	335	100

COVID-19, Coronavirus Disease 2019; n, frequency; **COVID-19 supplement combination: vitamin c + vitamin D + zinc

Moreover, the following concurrent pharmacotherapies have been significantly associated with ICU patient COVID-19 status in the current study: analgesics and anti-inflammatories ($P<0.01$); bronchodilators ($P<0.05$); corticosteroids ($P<0.05$); COVID-19 supplement combination ($P<0.01$); minerals ($P<0.01$); vitamins ($P<0.05$) and psychotropic agents (Risperidone, Lorazepam, Sodium Valproate, Carbamazepine, Citalopram) ($P<0.01$). The largest proportion of ICU COVID-19 positive cases prescribed concurrent pharmacotherapy was attributed to vitamins (73.7%), followed by minerals (60.5%), corticosteroids (Dexamethasone, Prednisolone, Prednisone) (47.4%), analgesics and anti-inflammatories (46.1%), COVID-19 supplement combination (46.1%), bronchodilators (9.2%) and psychotropic agents (7.89%) (Table 4.6).

Table 4.6. Concurrent pharmacotherapy associated with COVID-19 status

Associated variables	COVID-19 Status					
	Positive		Negative		Total	
	n	%	n	%	n	%
Concurrent Pharmacotherapy						
Analgesics and anti-inflammatories *P<0.01						
Yes	35	46.1	194	74.9	229	68.4
No	41	54.0	65	25.1	106	31.6
Total	76	100	259	100	335	100
Bronchodilators *P<0.05						
Yes	7	9.21	7	2.70	14	4.18
No	69	90.8	252	97.3	321	95.8
Total	76	100	259	100	335	100
Corticosteroids *P<0.05						
Yes	36	47.4	70	27.03	106	31.6
No	40	52.6	189	73.0	229	68.4
Total	76	100	259	100	335	100
COVID-19 supplement combination *P<0.01						
Yes	35	46.1	1	0.39	36	10.8
No	41	54.0	258	99.6	299	89.2
Total	76	100	259	100	335	100
Minerals *P<0.01						
Yes	46	60.5	21	8.11	67	20.0
No	30	39.5	238	91.9	268	80.0
Total	76	100	259	100	335	100
Psychotropic *P<0.01						
Yes	6	7.89	102	39.4	108	32.2
No	70	92.1	157	.60.6	277	67.8
Total	76	100	259	100	335	100
Vitamins *P<0.05						
Yes	56	73.7	26	10.0	82	24.5
No	20	26.3	233	90.0	253	75.5
Total	76	100	259	100	335	100

COVID-19, Coronavirus Disease 2019; n, frequency; * Significant: *p<0.01 and p<0.05 versus COVID-19 status*;

**COVID-19 supplement combination: vitamin c + vitamin D + zinc

The use of anticoagulants (mostly Clexane®, Enoxaparin) in the current study decreased from 63.7% (n = 109) in the pre-pandemic period to 51.5% (n=84) in the COVID-19 period. Additionally, another study also observed Enoxaparin prevalence in COVID-19 patients (Rahman *et al.*, 2023). Moreover, several studies have highlighted the association between coagulation and COVID-19, as well as the potential coagulase parameters (Guan *et al.*, 2020; Yu *et al.*, 2020; Chandra *et al.*, 2022). However, the mechanism of coagulation is unknown and weak treatment modalities exist coupled with approved guidelines for thromboprophylaxis in COVID-19 patients (Chandra *et al.*, 2022).

Ao *et al* (2022) reported a significant association between analgesics and COVID-19 ICU admission in agreement with the findings of the present study (Ao *et al.*, 2022). Rahman *et al* (2023) further reported an increase in various medications within the ICU during the COVID-19 pandemic augmenting the current study's observations (Rahman *et al.*, 2023). Enoxaparin (67.06%) appeared as the most prescribed medicine, followed by montelukast (60.51%), paracetamol (58.41%), and dexamethasone (51.64%) (Rahman *et al.*, 2023). Li *et al* (2020) also observed an association between corticosteroid use and COVID-19. Although the use of this drug did not clear COVID-19 infection, it did reveal improved quality of life (Li *et al.*, 2020). Another study by Ho *et al* (2021) further reported decrease ICU admissions and mortality rates with the use of corticosteroids in patients with COVID-19 and pneumonia (Ho *et al.*, 2021). Despite the benefits of short-term steroid use in COVID-19 positive patients, Paassen *et al* (2020) concluded that these drugs bare long-term effects such as a delay in viral clearance and increase in secondary infections (van Paassen *et al.*, 2020).

Nawaiseh *et al* (2023) also reported an increase in the consumption of vitamin C. Contrary to the current study, Nawaiseh *et al* (2023) further reported that 46% of the study population did not consume vitamin D and there was no change in the consumption of zinc moving into the pandemic period (Nawaiseh *et al.*, 2023). A meta-analysis study by Corrao *et al* (2021) investigated the nutraceutical support offered by supplementation in the COVID-19 period. The study found that the use of supplementation such as zinc and vitamin C was significantly associated with a decreased in the C-reactive protein inflammatory marker. In the absence of antiviral COVID-19 specific treatment, supplementation has nutraceutical benefits in relation to immune and inflammatory state (Corrao *et al.*, 2021). In addition, Asoudeh *et al* (2023) observed a decrease in severity of patients symptoms in COVID-19 positive in association with the use of vitamin C, vitamin D and zinc (Asoudeh *et al.*, 2023a). Overall other studies have

reported the use of supplementation in COVID-19 cases supporting the current studies finding (Corrao *et al.*, 2021; Asoudeh *et al.*, 2023b; Nawaiseh *et al.*, 2023).

Overall, prescription psychotropic agents, corticosteroids, analgesics, and anticoagulants presented in the current study align with the COVID-19 palliative care drug therapy recommendations made by the NdoH (National Department of Health, 2020, 2021). However, the use of vitamins, minerals and supplement combinations are not recommended in the SA COVID-19 guidelines (National Department of Health, 2021). Previous literature reviewed and the present study drew attention to other potential drugs (such as zinc, vitamin C and vitamin D) that could be supportive therapy in COVID-19 infections and other viral respiratory infections where the use of antibiotics are not indicated and in the absence of approved antiviral drugs. Therefore, reducing the intention and burden of unnecessary antimicrobial prescribing (Moghadami, 2017). Furthermore, research related to concurrent pharmacotherapy is sparse to provide a definite outcome and more research efforts are required to explore the mechanisms and physiological interactions of actions of these drugs in viral respiratory infections.

4.3 Antibiotic prescribing

4.3.1 Pre-pandemic antibiotic prescription encounters

The most prescribed antibiotic classes in the pre-pandemic period included penicillins and extended beta-lactamase inhibitors (n = 124), cephalosporins (n = 51), carbapenems (n = 36) and macrolides (n = 21). Figure 4.2 provides the encounters with these pharmacological classes.

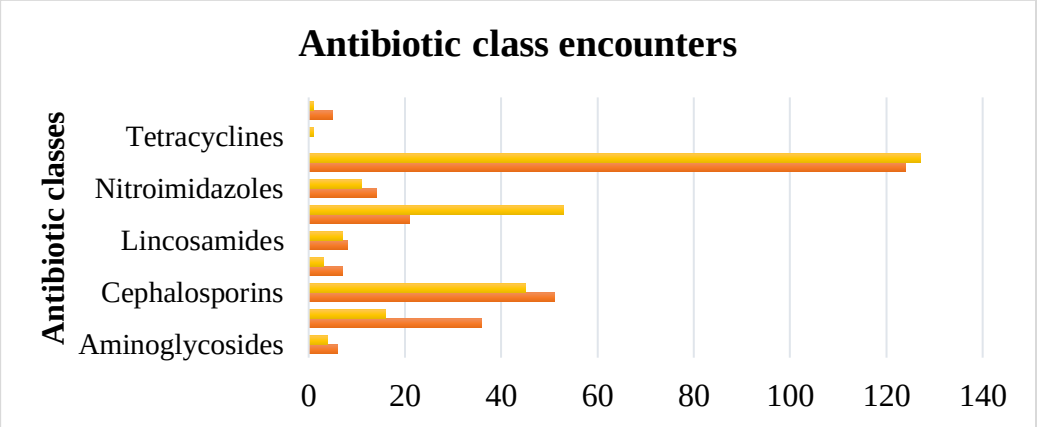

Figure 4.2 Antibiotic prescription by antibiotic class before and during the COVID-19 pandemic

Antibiotic prescriptions in the TPTH ICU patients included the prescription of 21 antibiotics derived from ten pharmacological classes. The most prescribed antibiotics within these classes were amoxicillin/clavulanate (31.99%), followed by ceftriaxone (15.44%), piperacillin/tazobactam (11.40%) and azithromycin (7.72%) (Table 4.7).

Several studies singularly evaluated and analysed antibiotic prescription data before the COVID-19 pandemic in South Africa and internationally. Johnston et al (2018) conducted a review in the ICU of a tertiary-level hospital in South Africa, reporting that the most frequently prescribed antibiotics in the ICU were amoxicillin/clavulanate, piperacillin/tazobactam, and cefazolin (Johnston *et al.*, 2018). Similarly, the current study also observed high frequencies of amoxicillin/clavulanate and piperacillin/tazobactam in the pre-pandemic period. Contrarily, the present study was inconsistent with the prescribing frequency of cefazolin reported by Johnston *et al* (2018). Furthermore, the current study observed additional high prescribing frequencies in antibiotics such as ceftriaxone and azithromycin. Another study by Dlamini *et al* (2019) assessed antibiotic utilisation in 39 wards in a South African hospital, the overall prevalence of antibiotics was higher in the ICU. Moreover, the study reported that beta-lactamase inhibitors were more prevalent within the ICU, corroborating the high usage of beta-lactamase inhibitors such as piperacillin/tazobactam and amoxicillin/clavulanate in the current study (Dlamini *et al.*, 2019). Balkhy *et al* (2018) investigated antibiotic usage across five adult ICUs, reporting that the most frequently prescribed antibiotics were meropenem, piperacillin/tazobactam, vancomycin, and colistin across all ICUs (Balkhy *et al.*, 2018). The study partially supported the findings of the current study, conversely, the current study found a relatively low frequency in meropenem and vancomycin. Furthermore, no patients in the current study were prescribed colistin.

Diversity within the present study in conjunction to previous studies examining antibiotic prescribing, may be due to differences in patient characteristics, settings, disease severity, EMLs and STGs (Gahbauer, Gonzales and Guglielmo, 2014; Lee *et al.*, 2020). Despite, variations in antibiotic use among the studies, previous studies as well as the current study highlight and provide pre-pandemic baseline levels of antibiotic prescribing and utilisation providing perspective on the extent of antibiotic engagement before the COVID-19 pandemic. This is crucial as these studies overall indicate that antibiotic usage was already relatively high before the commencement of the COVID-19 pandemic.

Table 4.7. Comparison of antibiotics prescribed prior to and amid COVID-19

Variables	Study Period					
	Pre-pandemic		COVID-19		Total	
	n	%	n	%	n	%
Amikacin						
Yes	4	2.3	3	1.8	7	2.1
No	168	97.7	160	98.2	328	97.9
Total	172	100	163	100	335	100
Amoxicillin						
Yes	3	1.7	1	0.6	4	1.2
No	169	98.3	162	99.4	331	98.8
Total	172	100	163	100	335	100
Azithromycin						
Yes	21	12.2	53	32.5	74	22.1
No	151	87.8	110	67.5	261	77.9
Total	172	100	163	100	335	100
Cefepime						
Yes	5	2.9	2	1.2	7	2.1
No	167	97.1	161	98.8	328	97.9
Total	172	100	163	100	335	100
Ceftriaxone						
Yes	42	24.4	39	23.9	81	24.2
No	130	75.6	124	76.1	254	75.8
Total	172	100	163	100	335	100
Cefotaxime						
Yes	2	1.16	0	0	2	0.60
No	170	98.8	163	100	33	99.4
Total	172	100	163	100	335	100
Ciprofloxacin						
Yes	4	2.3	1	0.6	5	1.5
No	168	97.7	162	99.4	330	98.5
Total	172	100	163	100	335	100
Clindamycin						
Yes	8	4.65	7	4.29	15	4.48
No	164	95.4	156	95.7	320	95.5
Total	172	100	163	100	335	100
Amoxicillin/Clavulanate						
Yes	87	50.6	103	63.2	190	56.7
No	85	49.4	60	31.8	145	43.3
Total	172	100	163	100	335	100
Doxycycline						
Yes	0	0	1	0.61	1	0.30
No	172	100	162	99.4	334	99.7
Total	172	100	163	100	335	100
Ertapenem						
Yes	11	6.4	0	0	11	3.3
No	161	93.6	163	100	324	96.7
Total	172	100	163	100	335	100

Table 4.7. continued. Comparison of antibiotics prescribed prior to and amid COVID-19

Variables	Study Period					
	Pre-pandemic		Pre-pandemic		Pre-pandemic	
	n	%	n	%	n	%
Imipenem						
Yes	10	5.8	9	5.5	19	5.7
No	162	94.2	154	94.5	316	94.3
Total	172	100	163	100	335	100
Meropenem						
Yes	15	8.7	7	4.3	22	6.6
No	157	91.3	156	95.7	313	93.4
Total	172	100	163	100	335	100
Metronidazole						
Yes	14	8.1	11	6.7	25	7.5
No	158	91.9	152	93.3	310	92.5
Total	172	100	163	100	335	100
Piperacillin/Tazobactam						
Yes	31	18	23	14.1	54	16.1
No	141	82	140	85.9	281	83.9
Total	172	100	163	100	335	100
Moxifloxacin						
Yes	1	0.58	0	0	1	0.30
No	171	99.4	163	100	334	99.7
Total	172	100	163	100	335	100
Cloxacillin						
Yes	1	0.58	0	0	1	0.030
No	171	99.4	163	100	334	99.7
Total	172	100	163	100	335	100
Ampicillin						
Yes	2	1.16	0	0	2	0.60
No	170	98.8	163	100	33	99.4
Total	172	100	163	100	335	100
Gentamycin						
Yes	2	1.16	1	0.61	3	0.90
No	170	98.8	162	99.4	332	99.1
Total	172	100	163	100	335	100
Cefazolin						
Yes	2	1.2	4	2.5	6	1.8
No	170	98.8	159	97.5	329	98.2
Total	172	100	163	100	335	100
Vancomycin						
Yes	7	4.1	3	1.8	10	3
No	165	95.9	160	98.2	325	97
Total	172	100	163	100	335	100

COVID-19, Coronavirus Disease 2019; n, frequency

4.3.2 COVID-19 period antibiotic prescription encounters

The most prescribed antibiotic classes during the COVID-19 period included penicillins and extended beta-lactamase inhibitors (n = 127) and macrolides (n = 53) (Figure 4.2). The most prescribed antibiotics within these classes were amoxicillin/clavulanate (38.43%) and azithromycin (19.78%) (Table 4.7).

The high transmissibility and critical severity associated with COVID-19 have since changed most attributes of healthcare globally related to diagnosis, clinical management, repurposing of antibiotics, and administration of AMS (Monnet and Harbarth, 2020; Yacouba, Olowo-okere and Yunusa, 2021b). A few studies have since quantified, assessed, and compared antibiotic utilisation and prescribing during the COVID-19 pandemic. A study on antibiotic utilisation in African countries (Ghana, Kenya, Uganda, Nigeria, South Africa, Zimbabwe, Botswana, Liberia, Ethiopia, and Rwanda) summarised common antibiotics used in COVID-19 (Adebisi *et al.*, 2021a). Adebisi *et al* (2021) found that antibiotics used included, azithromycin, doxycycline, clarithromycin, ceftriaxone, amoxicillin, amoxicillin-clavulanic acid, ampicillin, gentamicin, erythromycin, benzylpenicillin, piperacillin/tazobactam, ciprofloxacin, ceftazidime, cefepime, vancomycin, meropenem, and cefuroxime. The current study's findings are partially congruent with findings of Adebisi *et al* (2021), the variation in predominant antibiotics use could be due to varying access to EML items and the vast study population and patient characteristics. Additionally, a study reported third generation cephalosporin (36.8%) and azithromycin (34.2%) antibiotics were the most prevalent antibiotics reported during the management of COVID-19 in patients admitted to ICUs (Abu-Rub *et al.*, 2021). Overall, most studies highlighted increased use of amoxicillin/ clavulanate and azithromycin which is consistent with the current study's findings.

4.3.3 Overview of antibiotic prescriptions encounters across the study period

The overall trend observed was a decrease in antibiotic prescription transitioning into the COVID-19 period. This was noted within antibiotic classes (Figure 4.2) as well as by individual antibacterial agents. Particularly, amoxicillin/clavulanate (access category antibiotic, penicillins, and extended beta-lactamase inhibitor class) demonstrated an 18.39% (n = 16) increase in prescribing and was significantly ($P<0.05$) associated with both study periods. Among the macrolides class observed, azithromycin prescribing increased by 152.38% across the pre-pandemic period (7.72%; n = 21) to the COVID-19 pandemic period (19.78%; n = 53)

and was also significantly (P<0.01) associated with both study periods (Table 4.7). Although studies related to South African antibiotic consumption context comparing the pre-pandemic and COVID-19 pandemic use of these drugs could not be found at the time of review. A study by Bednarčuk *et al* (2023) compared the period of interest (2018 to 2022) observing an increase in the use of amoxicillin/clavulanate and azithromycin (Bednarčuk *et al.*, 2023). These findings augmented the results of the current study that demonstrated an increase in the consumption of amoxicillin/clavulanate and azithromycin across both periods of the study.

Another study by Gonzalez-Zorn (2021) investigated antibiotic use between the periods of January 2017 to February 2020. The use of azithromycin in March 2020 was 400% the use of the same drug in February 2020 and greater than 320% the use of azithromycin in January 2019 (Gonzalez-Zorn, 2021). The current study observed an increase in azithromycin by approximately 152% between the periods of January 2017 and December 2021, which is comparatively lower than the cumulative increase in azithromycin reported by Gonzalez-Zorn *et al* (2021) (Gonzalez-Zorn, 2021). Despite the inconsistencies in findings, both studies reported an increase in azithromycin use.

Additionally, Andrews *et al* (2021), compared antibiotic utilisation pre-COVID-19 and during COVID-19 in communities and hospitals, concluding an overall decrease in antibiotic consumption from pre-to-COVID-19. Furthermore, the study also noted that more antibiotics were prescribed in a hospital setting over community prescriptions. Similarly, the current study observed an overall decrease in antibiotic use across most antibiotic classes. Contrary, amoxicillin/clavulanate and azithromycin sustained utilisation, and a further increase in prescribing and use was observed moving into the COVID-19 pandemic. The study further reported a respiratory infection-related increase in the "watch" category antibiotics, such as azithromycin, in April 2020 in alignment with the COVID-19 wave emergence period (Andrews *et al.*, 2021). The current study correlated the increase in respiratory illness observed by Andrews *et al* (2021), having observed a 45% incline in respiratory diagnoses since the commencement of COVID-19.

Malcolm *et al* (2020) compared weekly antibiotic prescriptions between the years 2019 and 2020. A steep increase in the number of prescription antibiotics related to respiratory infections was observed in March 2020, 44% higher than the corresponding week in March 2019 (Malcolm *et al.*, 2020). This study further emphasises the increased use of antibiotics attributed to respiratory infections reported by the current study. The increase in respiratory conditions

alongside the overall increase in amoxicillin/clavulanate and azithromycin could be related to the broad-spectrum activity of these two drugs indicated for various conditions including respiratory infections as per EML and STGs (Goyal *et al.*, 2018). Furthermore, a systematic review revealed that azithromycin intended for the management of COVID-19 during the pandemic period was initially used as an adjuvant anti-inflammatory and antiviral therapy rather than for antibacterial properties (Abu-Rub *et al.*, 2021). Thus, highlighting the delineation of common drugs used in the treatment of bacterial respiratory infections. It is therefore crucial to drive more drug profiling and randomised control trial studies determine COVID-19 specific therapy alongside thorough examination of patients to avoid unnecessary use and prescribing of antibiotics.

4.3.4 Antibiotic prescriptions and COVID-19 status

The following antibiotics were prescribed to COVID-19 positive ICU patients and were found to be significantly associated with their COVID-19 status: Amoxicillin in combination with clavulanate (76.3%; $P<0.01$), azithromycin (57.9%; $P<0.01$), and piperacillin in combination with tazobactam (2.6%; $P<0.01$) (Table 4.8). Imipenem ($P<0.05$) and meropenem ($P<0.01$) were also significantly associated with COVID-19 status, however, only of the COVID-19 negative patients were prescribed these drugs. Of the antibiotics associated with COVID-19 status, only azithromycin (for severe bacterial pneumonia) and amoxicillin/clavulanate (for bacterial pneumonia without signs of severe pneumonia) are recommended in the South African COVID-19 guidelines for the management of adult inpatients (National Department of Health, 2020). This may explain the frequent use of these antibiotics for COVID-19 positive cases.

Table 4. 8. Prescription antibiotics associated with COVID-19 status

Associated variables	COVID-19 Status					
	Positive		Negative		Total	
	n	%	n	%	n	%
Amoxicillin/clavulanate						**P<0.01**
Yes	58	76.3	132	51.0	190	56.7
No	18	23.7	127	49.0	145	43.3
Total	76	100	259	100	335	100
Azithromycin						**P<0.01**
Yes	44	57.9	30	11.6	74	22.1
No	32	42.1	229	88.4	261	77.9
Total	76	100	259	100	335	100
Imipenem						**P<0.05**
Yes	0	0	19	7.34	19	5.67
No	76	100	240	92.7	316	94.3
Total	76	100	259	100	335	100
Meropenem						**P<0.01**
Yes	0	0	22	8.49	22	6.57
No	76	100	237	91.5	313	93.4
Total	76	100	259	100	335	100
Piperacillin/tazobactam						**P<0.01**
Yes	2	2.63	52	20.1	54	16.12
No	74	97.4	207	79.9	281	83.9
Total	76	100	259	100	335	100

COVID-19, Coronavirus Disease 2019; n, frequency; ***** Significant: *p<0.05 versus COVID-19 status*

Mustafa *et al* (2021) in partial agreement with the current study reported that the most prescribed antibiotics in ICU COVID-19 patients were ceftriaxone/cefotaxime plus a macrolide in 17 case (32.7%), ceftriaxone/cefotaxime in 15 cases (28.8%), ampicillin/amoxicillin plus clavulanic acid or sulbactam five cases (9.6%), and quinolones five cases (9.6%). Imipenem was the most frequently used antibiotic in the ICU 30 case (57.7%), followed by ceftriaxone 28 cases (53.8%), and piperacillin/tazobactam and fluoroquinolone 17 cases (32.7%) (Mustafa *et al.*, 2021). In contrast to the current study, Karami *et al* (2021) reported the predominate prescription of amoxicillin, cefuroxime, and ciprofloxacin. Furthermore, Lian *et al* (2020) found that cephalosporins, quinolones, carbapenem, tigecycline, and linezolid was more prevalent in COVID-19 patients (Karami *et al.*, 2021). Another study by Rothe *et al* (2021) conversely reported on the prescription of ampicillin/sulbactam, moxifloxacin, cephalosporins and similarly to the current study, azithromycin, meropenem and piperacillin tazobactam in COVID-19 patients (Rothe *et al.*, 2021). Differences in COVID-19 antibiotic prescription may be a result of antibiotic availability at facilities. Furthermore, during the COVID-19 pandemic,

the sudden emergence of an uncharted threat disrupted practices and prescribing guidelines lacked COVID-19 prescribing parameters. Thus, a vast array of antibiotics was prescribed and used globally (Adebisi *et al.*, 2021b; Wang *et al.*, 2021; Mohamad *et al.*, 2022). Therefore, the study highlights the need for further research to determine relevant indications for antibiotic use in COVID-19 patients is critical in view of the significant mortality associated with secondary infections in these patients and the emerging antibiotic resistance (Chedid *et al.*, 2021; Livermore, 2021; Martinez-Guerra *et al.*, 2021).

4.3.5 Antibiotic encounters by WHO AwaRe classification

The access group of antibiotics showed an increase in utilisation patterns of approximately 7% following the commencement of COVID-19. Watch antibiotics decreased in use by 8% from the pre-pandemic period (52.10%; n= 149) to the COVID-19 period (47.90%; n=137) (Table 4.9). Reserve antibiotics were not prescribed among the study cohort in both pre-pandemic and COVID-19 periods. The overall observation between both periods is a decline of 8.1% in the use and prescribing of watch-category antibiotics. Antibiotics that were most prevalent within the watch category, represented as (pre-pandemic percentage; COVID-19 percentage) included, piperacillin/tazobactam (20.81%; 16.79%), ceftriaxone (28.19%; 28.48%) and azithromycin (14.09%; 38.69%). However, azithromycin deviated from the general usage reduction trend as the use and prescribing of this drug increased from the pre-pandemic (14.09%; n=21) to the COVID-19 pandemic period (38.69%; n=53) (Table 4.10).

Table 4. 9. Antibiotic encounters by WHO AWaRe classifications

WHO AWaRe Category	**Pre-Pandemic**	**COVID-19**	**Relative change**
	n (%)	**n (%)**	**%**
Access antibiotics	123 (45.2)	131 (48.9)	6.5
Watch antibiotics	149 (54.8)	137 (51.1)	-8.1
Reserve antibiotics	0 (0)	0 (0)	0.0
Total	272 (100)	268 (100)	-1.5

WHO, World Health Organization., Green= "Access" category; Yellow = "Watch" category and Red= "Reserve" category

The "AwaRe" classification is intended to promote the importance of optimal watch and reserve category antibiotics use in consideration of the potential for antibiotic resistance

advancement and advocating the availability and use of access category antibiotics for global health coverage(WHO, 2022). At the time of review only one study was conducted in South Africa according to the WHO AWaRe antibiotic classification methodology (Mthombeni *et al.*, 2014).

A study by Mthombeni *et al* (2022) described and tracked antibiotic consumption between 2014 and 2018, comparable to the pre-pandemic period, in the public sector of the Limpopo province in South Africa. The study reported a consumption of 19,7% relative to the "watch" category antibiotics (Mthombeni *et al.*, 2014). Contrary to this study, the present study observed a high frequency and proportion of "watch" category antibiotics (52.10%) during the pre-pandemic period. Another study by Nguyen *et al* (2020) assessed antibiotic consumption from September 2017 to July 2018, reporting 792 (59%) "access" category encounters, 527 (39.30%) "watch" category antibiotics, and no reports of "reserve" category antibiotics (Nguyen *et al.*, 2020). Conversely, the current study observed high proportions of "watch" category antibiotics to "access" category antibiotics, this inconsistency may be due to the difference in antibiotics stipulated on the essential medicines list across different countries and facilities, as well as the variation in clinical severity and indications.

Al-Azzam *et al* (2021) investigated antibiotic consumption from 2019 to 2020, synonymous with the pre-to-COVID-19 transition period. An increase in third generation cephalosporins, carbapenems, macrolides, and lincosamides in the period of 2019 to 2020. Similarly, the study observed an increase in azithromycin and a decrease in amoxicillin/clavulanate (Al-Azzam *et al.*, 2021). Al-Azzam *et al* (2021) further concluded an overall decrease in "access" category antibiotics (18%) and an increase in "watch" category antibiotics (24%). On the other hand, the current study indicated an increase in antibiotic consumption in penicillins (amoxicillin/clavulanate) and macrolides (azithromycin) classes of antibiotics, with an overall increase in access antibiotics and a decline in the consumption of "watch" category antibiotics. Wang *et al* (2022) evaluated antibiotic use before and after the emergence of COVID-19 using an interrupted time series. Contrary to the current study, the study reported a long-term slight increase in both "access" and "watch" categories between January 2019 and December 2021 (Wang et al., 2022).

Table 4.10. Prevalence of "Watch" category antibiotics, represented as n (%), before and during COVID-19

ATC	WHO Watch Category Antibiotics	Pre-Pandemic n=149	COVID-19 n=137
J01DH03	Ertapenem	11 (7.38)	0 (0)
J01DH51	Imipenem	10 (6.71)	9 (6.57)
J01DH02	Meropenem	15 (10.06)	7 (5.11)
Total prescriptions of carbapenems		**36 (24.15)**	**16 (11.68)**
J01DE01	Cefepime	5 (3.36)	2 (1.46)
J01DD01	Cefotaxime	2 (1.34)	0 (0)
J01DD04	Ceftriaxone	42 (28.19)	39 (28.48)
Total prescriptions of cephalosporins		**47 (31.54)**	**41 (29.93)**
J01XA01	Vancomycin	7 (4.70)	3 (2.19)
Total prescriptions of glycopeptides		7 (4.70)	3 (2.19)
J01FA10	Azithromycin	21 (14.09)	53 (38.69)
Total prescriptions of macrolides		**21 (14.09)**	**53 (38.69)**
J01CR05	Piperacillin/tazobactam	31 (20.81)	23 (16.79)
Total prescriptions of penicillins and beta-lactamase inhibitors		**31 (20.81)**	**23 (16.79)**
J01MA02	Ciprofloxacin	4 (2.68)	1 (0.73)
J01MA14	Moxifloxacin	1 (0.67)	0 (0)
Total prescriptions of quinolones		**5 (3.36)**	**1 (0.73)**

ATC- anatomical, therapeutic, and chemical; n, frequency; WHO, World Health Organization.

In comparison to the current study, variability in results across all studies considering the AwaRe classification of antibiotics emphasises the diversity in antibiotic utilisation patterns across institutions and countries. Furthermore, there are not many studies that adopt the rationale of the WHO AwaRe methodology especially in LIMCs like South Africa (Nguyen *et al.*, 2020). A study by Abu-Ajaleh *et al* (2023), demonstrated that healthcare worker educational intervention on AWaRe classification of antibiotics and the related risk of antibiotic resistance is effective. The study concluded that hospital antibiotic use of “access” antibiotics increased by 6.6% from pre-to-post intervention. While the use of “watch” and “reserve” group antibiotics decreased by 1.7%, and 43.1%, respectively (Abu-Ajaleh *et al.*, 2023). Therefore, more efforts and public strategies need to be implemented in educating prescribers and dispensers about the WHO AWaRe classification of antibiotics as well as system integration.

4.4. Dose utilisation

4.4.1 Prescribed daily dose: a study period comparison

The change in mean PDD of most antibiotics before and during COVID-19 were not determined to be statistical different (Table 4.11). However, the mean PDD of azithromycin ($P<0.01$), amoxicillin in combination with clavulanate ($P<0.05$), and ertapenem ($P<0.01$) were significantly different between the pre-pandemic period and COVID-19 period.

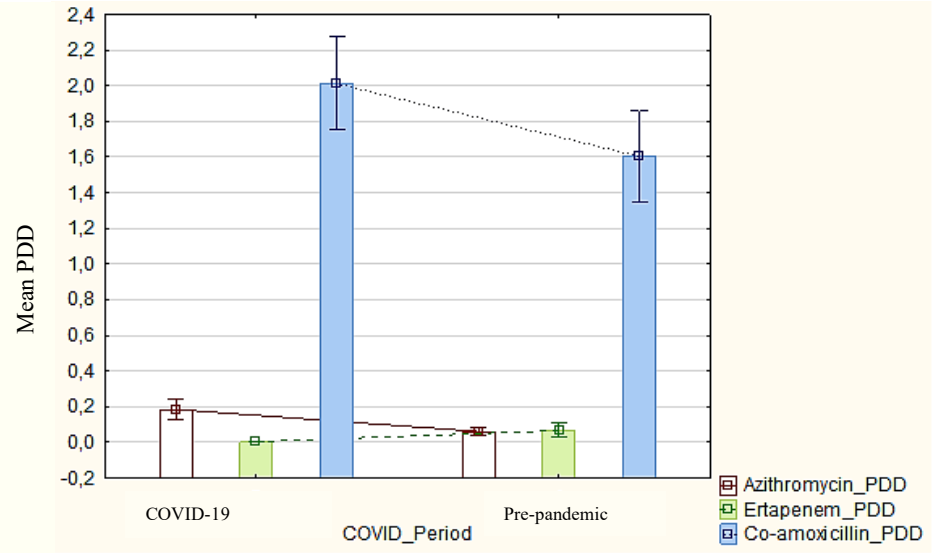

Figure 4.3 Prescribed daily dose mean plot. Abbreviations: COVID-19, coronavirus disease 2019; PDD, prescribed daily dose.

Figure 4.3 depicts the mean difference in the PDD of each of these antibiotics during the relevant study period. An incline in the mean PDD is observed in azithromycin and amoxicillin/clavulanate moving from the pre-pandemic period into the COVID-19 pandemic. Conversely, ertapenem observed a mean decrease across both periods of interest. Studies of PDDs derived from periods synonymous to the pre-pandemic period juxtaposed against PDDs derived from the COVID-19 pandemic period is uncommon. Though a few studies have compared these periods using other utilisation indicators to report antibiotic utilisation trends. A study by Balapasheva *et al* (2023) conducted a pharmacoepidemiological analysis of antibacterial agents used in COVID-19, similarly, comparing the period prior to and during the COVID-19 pandemic (Balapasheva *et al.*, 2023). Azithromycin and amoxicillin/clavulanate

marked a surge in the DDD metric moving into the COVID-19 pandemic, thus partially augmenting the current study's findings. Conversely, the current study also reported a significant decline in the use of ertapenem. However, ertapenem was not reported amongst the antibiotic array in Balapasheva's study this may be due to hospital EML difference and/or availability. In addition, Balapasheva *et al* (2023) also reported an increase in utilisation metric of metronidazole, levofloxacin, ciprofloxacin, and gentamicin. These finding contradicted the present study's observations on a decline in consumption metric of these antibiotics, although other cephalosporin classed antibiotics (cefotaxime and cefazolin) also indicated a decline in use (Balapasheva *et al.*, 2023).

Another study by Foxlee *et al* (2022), conversely reported on the decline of azithromycin transitioning into the COVID-19 period (Foxlee *et al.,* 2022). Moreover, Foxlee *et al* (2022) further observed an increase in the COVID-19 pandemic of amoxicillin/clavulanate augmenting the increase in the same drug observed in the current study. Contrary to the present study, Foxlee *et al* (2022) additionally reported an incline in metronidazole, doxycycline, cloxacillin, ciprofloxacin and amoxicillin (Foxlee *et al.,* 2022). Similarly, to the current study, other studies demonstrated an overall antibiotic prescription during the COVID-19 pandemic in countries such as Jordan, England, and Spain observed a decline in utilisation metric (Mustafa *et al.,* 2021; Daria and Islam, 2022; Balapasheva *et al.,* 2023). Despite the overall decrease observed in this study and other studies, it is still critical to further evaluate the upsurge in select antibiotics to determine systematic factors associated with prescription of such medication caused by the COVID-19 pandemic to curb usage and guide future pandemic prescribing.

Table 4.11. Prescribed daily dose (PDD) of antibiotics prescribed before and during COVID-19 in ICU patients. PDD is represented as the mean.

Antibiotic class	WHO AWaRe	ATC Code	Antibiotic	Pre-Pandemic Mean PDD (g)	COVID-19 Mean PDD (g)	P-Value
Aminoglycosides	*Access*	J01GB03	Gentamicin	0,003	0,003	0,910
		J01GB06	Amikacin	0,020	0,017	0,808
Carbapenems	*Watch*	J01DH03	Ertapenem	0,067	0,000	0,002*
		J01DH51	Imipenem	0,106	0,135	0,625
		J01DH02	Meropenem	0,285	0,132	0,133
Cephalosporins	*Access*	J01DB04	Cefazolin	0,081	0,074	0,911
	Watch	J01DE01	Cefepime	0,105	0,049	0,358
		J01DD01	Cefotaxime	0,058	0,000	0,177
		J01DD04	Ceftriaxone	0,886	1,090	0,443
Glycopeptides	*Watch*	J01XA01	Vancomycin	0,084	0,025	0,146
Lincosamides	*Access*	J01FF01	Clindamycin	0,080	0,072	0,833
Macrolides	*Watch*	J01FA10	Azithromycin	0,061	0,185	0,000*
Nitroimidazoles	*Access*	J01XD01	Metronidazole	0,126	0,099	0,533
Penicillins and beta-lactamase inhibitors	*Access*	J01CA04	Amoxicillin	0,047	0,012	0,271
		J01CA01	Ampicillin	0,076	0,000	0,199
		J01CF02	Cloxacillin	0,047	0,000	0,331
		J01CR02	Amoxicillin/ Clavulanate	1,606	2,015	0,027*
	Watch	J01CR05	Piperacillin/Tazobactam	2,058	1,850	0,706
Tetracyclines	*Access*	J01AA02	Doxycycline	0,006	0,001	0,452
Quinolones	*Watch*	J01MA02	Ciprofloxacin	0,017	0,005	0,248
		J01MA14	Moxifloxacin	0,002	0,000	0,331

ATC, anatomical, therapeutic, and chemical; COVID-19, Coronavirus Disease 2019; g, grams; PDD, Prescribed Daily Dose, * Significant: *$p<0.05$ versus study period*

4.4.2 Discrepancy in dose utilisation

The PDD and DDD quotients for each antibiotic was calculated to determine the discrepancy in dose utilisation. During the pre-pandemic period, overuse occurred in 17 out of the 21 antibiotics assessed, with nine of these antibiotics prescribed more than once. The drug that showed the greatest extent of overuse in the period was amoxicillin/clavulanate. The suboptimal use category reported 14 of the 21 antibiotics in the sample, which indicated that nine of 21 antibiotics were prescribed more than once during the pre-pandemic period. Amoxicillin/clavulanate represented the higher proportion of suboptimal use. Optimal use was reported in 14 of the 21 antibiotics assessed, and eight of 21 antibiotics were prescribed more than once during the pre-pandemic period. Ceftriaxone, azithromycin, and metronidazole constituted the higher proportions of optimal use across both periods of the study. During the COVID-19 pandemic, overuse occurred in 11 of the 21 antibiotics assessed, with six of 21 antibiotics being prescribed more than once. Amoxicillin/clavulanate showed the greatest extent of use in the COVID-19 period. Optimal use was observed in 11 of 21 antibiotics assessed, eight were prescribed more than once. Azithromycin, ceftriaxone, and metronidazole also demonstrated optimal use during the COVID-19 period. Suboptimal use occurred in eight of the 21 antibiotics assessed, seven were prescribed more than once. Amoxicillin/clavulanate alongside ceftriaxone showed considerable suboptimal use during COVID-19 (Table 4.12).

The current study also evaluated dosage utilisation through the comparison of the PDD and DDD (as determined by the WHO), reporting overuse in amoxicillin/clavulanate across the pre-pandemic and COVID-19 pandemic periods. This is consistent with prescribing patterns across both periods in the study. Azithromycin, however, optimal use across both periods of interest despite the consumption increase from pre-to-COVID-19. Therefore, demonstrating that there was a low discrepancy between the PDD and DDD of azithromycin. The study further indicated variability in usage categories for piperacillin/tazobactam and ceftriaxone, since dose utilisation is an estimation and does not always correspond to each dosage regimen, clinical indication, and pharmacokinetic properties. Therefore, dosage utilisation will differ based on patient groups and age (Grimmsmann and Himmel, 2011; World Health Organization, 2023). A study by Johnston *et al* (2018) in the ICU of a South African tertiary hospital reported that the PDD exceeded the DDD in most of the antibiotics prescribed. However, to our knowledge, there are no other studies in South Africa that have compared the PDD to the DDD to evaluate dosage utilisation before and amidst the COVID-19 pandemic (Johnston *et al.*, 2018). Moreover, very

few international; studies have compared PDD and DDD for patients. A study by Sánchez-Huesca *et al* (2020) estimated the PDD and compared it against DDD in outpatients in Mexico City. The study reported a high prevalence of either suboptimal use or overuse. A significant difference was reported in PDD from DDD in 14 antibiotic classes assessed accounting for overuse that occurred in 15 out of the 27 antibiotics prescribed. The antibiotics that showed the greatest extent of overuse included amoxicillin either alone or in combination with clavulanic acid, azithromycin, levofloxacin, and clarithromycin (Sánchez-Huesca *et al.*, 2020). Similarly, our study showed overuse in 17 and 11 of 21 antibiotics in the pre-pandemic and COVID-19 periods, respectively. The greatest extent of overuse was demonstrated by amoxicillin in combination with clavulanate, however, azithromycin was mostly optimally used, and no patients were prescribed levofloxacin and clarithromycin in the current study. Furthermore, Sánchez-Huesca *et al* (2021) reported suboptimal use in 63% of antibiotics assessed, while the current study reported higher suboptimal use pre-pandemic (66.7%) and comparatively lower suboptimal use in the COVID-19 period (38.1%) (Sánchez-Huesca *et al.*, 2020). Despite the variation in results between the studies, the overuse of amoxicillin/clavulanate is consistent, due to the broad-spectrum activity and micro-organism coverage of this drug.

Compared to the scarcity of studies using PDD, several studies have quantified and evaluated antibiotic dosage utilisation using calculated DDDs (based on medication package quantity, size, and strength), DDD per 1000 inhabitants per day (DID), and days of therapy (DOTs) (Luyt *et al.*, 2014; Mthombeni *et al.*, 2014; Patel *et al.*, 2016; Moolchandani *et al.*, 2017; Hussein *et al.*, 2022). The WHO recommends the use of the DDD utilisation indicator (World Health Organization, 2023). However, very few studies have quantified and evaluated the discrepancies and differences between PDD, calculated DDD, and recommended daily dose (RDD) (de With *et al.*, 2009; Grimmsmann and Himmel, 2011; Först *et al.*, 2017). Studies have considered and proposed that the DDD fails to address the discrepancies that exist between the actual prescribed daily dose (PDD) (Först *et al.*, 2017). Furthermore, overestimation in consumption is often reported using DDD measurements in antibiotic classes such as penicillins and macrolides (de With *et al.*, 2009; Först *et al.*, 2017). Först *et al* (2017) recommended the use of a validated RDD as a supplementary measure to measure the DDD for a detailed analysis and to avoid misclassification in benchmark analysis. Thus, using actual dose measures enables more precision in estimating dose utilisation and is an alternative to overcoming the paucity of variables (strength, quantity, and pack size) required to calculate the DDD, which is often the case in the South African healthcare setting context.

Table 4.12. Association PDD/DDD, suboptimal use (PDD/DDD<1.0), optimal (PDD/DDD=1.0), and overuse (PDD/DDD>1.0) for antibiotics prescribed. PDD/DDD ratio is described as median (25th percentile- 75th percentile). Suboptimal use, overuse, and overuse are represented a proportion

Antibiotic class	Antibiotic	n	DDD (g)	Pre-Pandemic				COVID-19			
				PDD/DDD	Suboptimal use	Optimal	Overuse	PDD/DDD	Suboptimal use	Optimal	Overuse
Aminoglycosides	Gentamicin	3	0.2	0.9(0.8-1.0)	1 (1.33)	1(1.05)	0	2.0(2.0-2.0)	0	0	1(0.87)
	Amikacin	7	0.6	1.7(1.3-1.7)	1(1.33)	0	3(2.91)	1.7(1.3-1.7)	0	0	3(2.61)
Carbapenems	Ertapenem	11	1.0	1.0(1.0-1.0)	1(1.33)	8(8.42)	2(1.94)	1.0(1.0-1.0)	0	0	0
	Imipenem	19	2.0	0.8(0.5-1.5)	6(8.00)	0	4(3.88)	1.5(1.1-1.5)	2(3.45)	0	9(7.83)
	Meropenem	22	3.0	1.0(1.0-1.0)	3(4.00)	9(9.47)	3(2.91)	0.7(0.5-1)	4(6.90)	2(2.06)	1(0.87)
Quinolones	Ciprofloxacin	5	0.8	1.1(0.6-1.3)	1(1.33)	1(1.05)	2(1.94)	1.0(1.0-1.0)	0	1(1.03)	0
	Moxifloxacin	1	0.4	1.0(1.0-1.0)	0	1 (1.05)	0	0	0	0	0
Cephalosporins	Cefazolin	6	3.0	2.3(2.0-2.7)	0	0	1(0.97)	1.0(1.0-1.0)	0	4(4.12)	0
	Cefepime	7	4.0	0.8(0.8-0.8)	4(5.33)	0	1(0.97)	0.1(0.1-0.1)	0	2(2.06)	0
	Cefotaxime	2	4.0	1.3(1.0-1.5)	0	1(1.05)	1(0.97)	0	0	0	0
	Ceftriaxone	81	4.0	1.0(0.5-1.0)	14(18.67)	27(28.42)	1(0.97)	1.0(0.5-1.0)	15(25.86)	18(18.56)	6(5.22)

ATC, anatomical, therapeutic, and chemical; COVID-19, Coronavirus Disease 2019; DDD, Defined Daily Dose; g, grams; n, frequency; PDD, Prescribed Daily Dose.

Table 4.12. continued. Association PDD/DDD, suboptimal use (PDD/DDD<1.0), optimal (PDD/DDD=1.0), and overuse (PDD/DDD>1.0) for antibiotics prescribed. PDD/DDD ratio is described as median (25th percentile- 75th percentile). Suboptimal use, overuse, and overuse are represented a proportion

Antibiotic class	Antibiotic	n	DDD (g)	Pre-Pandemic				COVID-19			
				PDD/DDD	Suboptimal use	Optimal	Overuse	PDD/DDD	Suboptimal use	Optimal	Overuse
Glycopeptides	Vancomycin	10	2.0	1.0(0.5-1.0)	2(2.67)	4(4.21)	1(0.97)	0.5(0.5-1.0)	2(3.45)	1(1.03)	0
Lincosamides	Clindamycin	15	1.8	1.0(0.7-1.2)	3(4.00)	3(3.16)	2(1.94)	1.0(0.7-1.0)	2(3.45)	4(4.12)	1(0.87)
Macrolides	Azithromycin	74	0.5	1.0(1.0-1.0)	0	21(22.11)	0	1.0(1.0-1.0)	0	51(52.58)	2(1.74)
Tetracyclines	Doxycycline	2	0.1	10(10-10)	0	0	1(0.97)	2.0(2.0-2.0)	0	0	1(0.87)
Nitroimidazoles	Metronidazole	26	1.5	1.0(1.0-1.0)	2(2.67)	13(13.68)	0	1.0(1.0-1.0)	1(1.72)	10(10.30)	0
Penicillins	Amoxicillin	4	1.5	2.0(1.0-2.4)	0	1(1.05)	2(1.94)	1.3(1.3-1.3)	0	0	1(0.87)
	Ampicillin	2	6.0	1.1(0.7-1.5)	1(1.33)	0	1(0.97)	0	0	0	0
	Cloxacillin	1	2.0	4.0(4.0-4.0)	0	0	1(0.97)	0	0	0	0
	Amoxicillin/ clavulanate	190	3.0	1.2(1.2-1.2)	20(26.67)	1(1.05)	66(64.08)	1.2(1.0-1.2)	23(39.66)	3(3.09)	77(66.96)
	Piperacillin/ tazobactam	54	14	0.6(0.4-1.3)	16(21.33)	4(4.21)	11(10.68)	1.3(0.5-1.3)	9(15.52)	1(1.03)	13(11.30)

4.4.3 Measures of antibiotic use appropriateness: a study period comparison

Using the South African STG and COVID-19 guidelines for managing adults in an inpatient setting, adherence and antibiotic appropriateness were determined with focus on indication, frequency, and duration. Prior to the COVID-19 pandemic, these measures were 92.4%, 97.7% and 82% respectively. During the COVID-19 period, adherence by indication, frequency and duration were 85%, 98.7% and 79.1% (Table 4.13). An overall decrease in STG and COVID-19 guidelines adherence were observed moving into the COVID-19 period.

Table 4.13. Comparison of antibiotic appropriateness before and during COVID-19

Variables	Study Period					
	Pre-pandemic		COVID-19		Total	
	n	%	n	%	n	%
Indication diagnosis						
Yes	159	92.4	139	85.3	298	89
No	13	7.6	24	14.7	37	11
Total	172	100	163	100	335	100
Frequency of dose						
Yes	168	97.7	160	98.2	328	97.9
No	4	2.3	3	1.8	7	2.1
Total	172	100	163	100	335	100
Duration						
Yes	141	82	129	79.1	270	80.6
No	31	18	34	20.9	65	19.4
Total	172	100	163	100	335	100
Antibiotic prescription type						
Empirically directed						
Yes	109	63.4	117	71.8	226	67.5
No	63	36.6	46	28.2	109	32.5
Total	172	100	163	100	335	100
Definitively directed						
Yes	61	35.5	40	24.5	101	30.1
No	111	64.5	123	75.5	234	69.9
Total	172	100	163	100	335	100
Prophylaxis						
Yes	9	5.2	17	10.4	26	7.8
No	163	94.8	146	89.6	309	92.2
Total	172	100	163	100	335	100

COVID-19, Coronavirus Disease 2019

Additionally, a study investigated antibiotic appropriateness indicators during the pandemic period and the observations (98.6% = indication, 99.7% = frequency and 96.9% = duration) were similar to the current study (Mudenda *et al.*, 2023). Additionally. these finding were congruent with finding from other studies (Alehegn *et al.*, 2021) (Zhao *et al.*, 2022). The current study's pre-pandemic findings is supported by previous literature, as indicators/measurements presented high adherence. This can be due to consistent AMS practices. Pandemic appropriateness outcomes of this study were unexpected since the emergence of COVID-19 disrupted prescribing practices and ASPs therefore deviation from existing prescribing guidelines would be expected (Getahun *et al.*, 2020). However, pandemic STG adherence is relatively high.

Reasons for this could be the fact that the current study observed a high prevalence of empiric prescription of 67% that would then mean that antibiotics prescribed were within normal empiric directed prescribing parameters. In, addition there was a low co-prevalence of secondary pneumonia and COVID-19 positive cases that do not support the elevated empiric prescription prevalence. Furthermore, a study suggested that empirical antimicrobial treatment may not be necessary in all patients presenting with COVID-19 infection, although the decision could be directed by high inflammatory markers (Wang *et al.*, 2021). Thus, this notion can be considered as another reason behind elevated empiric prescription prevalence. Though the present study did not consider patient inflammatory markers, with this inherent limitation making it difficult to deduce the correlation between inflammatory markers and empiric prescription volumes.

Conversely, Murillo-Zamora *et al* (2022) reported lower levels of empiric prescribing to the present study of 25%. Similarly, another study reported a low prevalence of empiric prescription in the ICU during the COVID-19 pandemic. Moreover, the present study observed a low prevalence of definitive prescribing at 30%. This may be due to the release of COVID-19 specific guidelines for the management of adult inpatients that dictated approved treatments and scenarios for antibiotic use for patients infected with COVID-19, curbing initial pandemic drug repurposing (National Department of Health, 2020). Coenen *et al* (2021) further reported that among 281 included COVID-19 patients, bacterial co-infection was classified as improbable in 233 of these patients (82.9%), possible in 35 patients (12.4%) and probable in 3 patients (1.1%). Ten patients (3.6%) could not be classified due to inconclusive data. Within three days of hospital admission, 81% of the total study cohort and 78% of patients classified as improbable bacterial co-infection received antibiotic therapy (Coenen *et al.*, 2021). This augmented the findings of other studies (Mahmoudi, 2020; Langford *et al.*, 2021; Yacouba,

Olowo-okere and Yunusa, 2021b; Bednarčuk *et al.*, 2023). Therefore, emphasising the negative impact COVID-19 had of prescribing attitudes and practices.Overall, the lack of definitive testing and high prevalence of empiric antibiotic-initiated therapy highlighted the pressure and panic caused by the COVID-19 pandemic (Balapasheva *et al.*, 2023). In addition, it is likely that the COVID-19 pandemic has fuelled the emergence of antibiotic resistance due to high rates of inappropriate antibiotic prescribing and the interruption of treatment for other conditions (Rusic *et al.*, 2021). The sudden emergence of COVID-19 coupled with the clogged healthcare institution and high turnover of public sector patients in the context of this study and in general, precipitated further weakened AMS programs. Perhaps STG revisions, pandemic prescribing protocols and guidelines are just a foundational phase to improved prescribing practices in an evolving burden of disease.

4.5 Antibiotic resistance

This section of chapter 4 will review and discuss the microbiological data obtained from the NHLS (specimens, bacterial microorganisms, and antibiotic resistance patterns) of ICU patients admitted at TPTH before and during the COVID-19 pandemic.

4.5.1 Specimens volumes: study period comparison

During the pre-pandemic period, the greater proportion of specimen collections from ICU patients admitted at TPTH were aspirate specimens (22.4%), blood cultures (20.6%), unknown specimens (13.1%), swabs (12.1%) and catheter tip specimens (11.2%) (Figure 4.4).

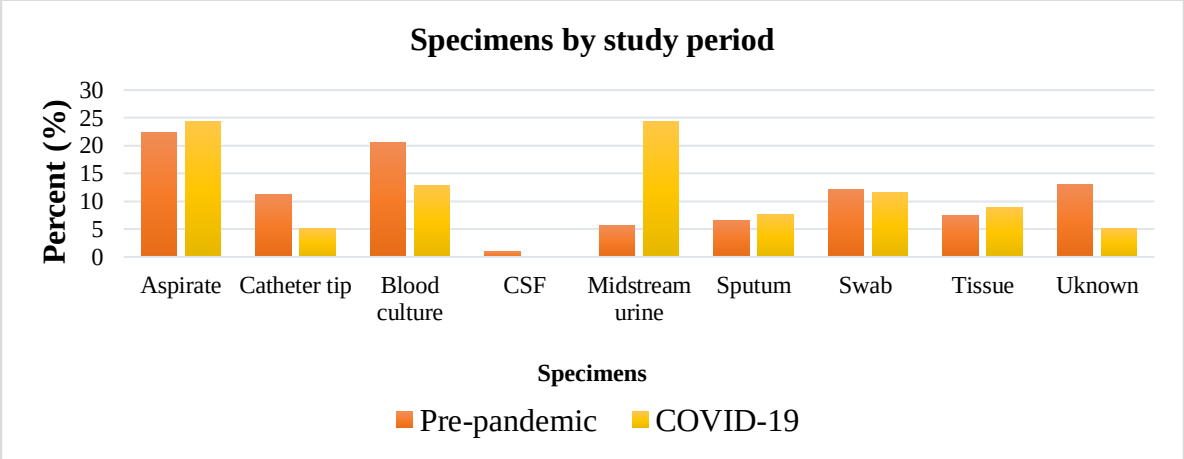

Figure 4.4 Specimens collected from ICU patient admitted between January 2017 and December 2021. Abbreviations: COVID-19, Coronavirus Disease 2019; CSF, cerebrospinal fluid.

Amidst the COVID-19 pandemic, aspirate specimens (24.4%) sustained an increase. In addition, midstream urine (24.4%), tissue (9.0%) and sputum (7.5%) specimens, were linked to an incline in collection volumes during COVID-19. Conversely, moving into the COVID-19 period, blood cultures (12.8%), swabs (11.5%) and unknow specimens and catheter tip specimens (5.1%) decreased. These specimens are associated with definitive antibiotic prescriptions described in Table 4.13 of *section 4.4.3*. Therefore, definitive antibiotic prescriptions accounted for 30.1% (n = 101/335) of the study cohort of which 35.5% (n = 61/172) were from the pre-pandemic cohort and 24.5% (n = 40/163) were from the COVID-19 cohort. Overall, five of the nine specimen volumes assessed, observed an increase moving into the COVID-19 pandemic. Despite this incline in general specimen volumes across the periods of study, antibiotic prescription volumes are unmatched in this regard. Thus, emphasising the urgent need for more pathogen directed therapy especially amidst viral pandemics. Moreover, a study highlighted the worldwide dissemination of this virus and the implications for cytology laboratories (Pambuccian, 2020; Xie *et al.*, 2020; Shinoda, 2021). These studies collectively underscore the initial reduction of specimen volumes due to the sudden emergence of COVID-19 and advocated the need for increased laboratory testing for diagnoses.

4.5.2 Bacterial isolates detected in ICU patients

In this study, several Gram-positive and Gram-negative bacteria were detected from specimens retrieved from ICU patients. Table 4.14 summarises the prevalence of bacteria detected in the study cohort.

Table 4.14. Bacterial microorganisms isolated in ICU patients before and during COVID-19

Bacterial Isolates	Pre-Pandemic		COVID-19		Directionality
	n	%	n	%	
Gram-positive					
Enterobacter aerogenes	4	20.0	2	15.4	↓
Enterococcus faecalis	8	40.0	4	30.8	↓
Enterococcus faecium	3	15.0	3	23.1	–
Staphylococcus aureus	2	10.0	4	30.8	↑
Streptococcus pneumoniae	3	15.0	0	0	↓
Total	20	100	13	100	↓
Gram-negative					
Acinetobacter baumannii complex	14	29.2	9	20.9	↓
Enterobacter cloacae complex	5	10.4	6	14.0	↑

Table 4.1.4 continued. Bacterial microorganisms isolated in ICU patients before and during COVID-19

Bacterial Isolates	Pre-Pandemic		COVID-19		Directionality
	n	%	n	%	
Gram-negative					
Escherichia coli	11	22.9	11	25.6	−
Klebsiella pneumoniae	12	25.0	8	18.6	↓
Proteus mirabilis	3	6.25	2	4.65	↓
Pseudomonas aeruginosa	3	6.25	7	16.3	↑
Total	48	100	43	100	↓

COVID-19, Coronavirus Disease 2019; n, frequency; Subsp., sub-species, ↑, increase; ↓, decrease; −, constant.

4.5.2.1 Pre-pandemic bacterial prevalence

Gram-positive bacteria detected in the pre-pandemic cohort included *E. aerogenes* (20%), *E. faecalis* (40%), *E. faecium* (15%), *S. aureus* (10%) and *S. pneumoniae* (15%). While Gram-negative bacteria detected in the pre-pandemic cohort included *A. baumannii* (29.2%), *E. cloacae* (10.4%), *E. coli* (22.9%), *K. pneumoniae* (25%), *P. mirabilis* (6.25%) and *P. aeruginosa* (6.25%). A study by Savanur and Gururaj (2019), during the pre-pandemic, reported mostly Gram-negative bacilli, of which *E. coli* was (18.6%), *A. baumannii* (14.5%), *K. pneumoniae* (11.6%), *P. aeruginosa* (9.8%), and *P. mirabilis* (1.74%) (Savanur and Gururaj, 2019). Conversely the current study reported higher prevalence of these gram-negative bacterial isolates. Furthermore, Savanur and Gururaj (2019) also observed gram-positive organisms, of which *coagulase negative Staphylococcus* (15.6%) was mostly isolated followed by *Streptococcus* (2.32%). This contradicted the findings of the current study. Another study by found *A.baumannii* (26%), *K. pneumoniae* (26%), followed by *E. coli* (15%), *S. aureus* (6%) and *Citrobacter spp*. (1.5%) were the common pathogens isolated from the medical and surgical ICUs in the study (Ahmed, Hussain and Biswal, 2015). This study yielded comparable results to that of the current study however, the prevalence of *S. aureus* and *E. coli* was greater in the present study. Furthermore, *Citrobacter spp.* was not reported in the study.

4.5.2.2 COVID-19 bacterial prevalence

In the COVID-19 cohort, most of Gram-positive bacteria were less frequently detected in comparison to the pre-pandemic period, except for *S. aureus* (30.8%) that observed an increase and constituted the larger proportion (alongside *E. faecalis*) of isolates detected during COVID-19 (Table 4.14). *A. baumannii* (20.9%), *K. pneumoniae* (18.6%) and *P. mirabilis* (4.65%) observed a decrease during COVID-19. Contrarily, *E. cloacae* (14%) and *P. aeruginosa* (16.3%) observed increases, while *E. coli* remained constant during COVID-19. A study during

the COVID-19 period by Kaur *et al* (2023), found *Klebsiella spp*.(24.4%), followed by *A. baumannii* (22.9%) and *Pseudomonas spp*.(19.1%), congruent with the current findings (Kaur et al., 2023). Additionally, a study found that *E. coli* and *A. baumannii* was significantly lower during the COVID-19 period as with the present study (Hamidi and Yilmaz, 2021). Another study reported similar Gram-negative finding to the current study; *A. baumannii* (28.9%), *P. aeruginosa* (22.7%) and *K. pneumoniae* (14.4%) (Costa *et al.*, 2022).

4.5.2.3 Overview of bacterial isolated across study period

Overall, a decrease trend was observed transitioning from the pre-pandemic period into the COVID-19 pandemic for both Gram-positive and Gram-negative bacteria isolated. However, *S, aureus* (pre-pandemic = 2 to COVID-19 = 4), *E. cloacae* (pre-pandemic = 5 to COVID-19 = 6), and *P. aeruginosa* (pre-pandemic = 3 to COVID-19 = 7), indicated an increase in frequency of detection moving into the COVID-19 pandemic. Though, larger proportions of Gram-negative bacterial isolates detected across both periods of study remained *A. baumannii, K. pneumoniae* and *E. coli.* Furthermore, even though most studies present with similar margins in prevalence, variations might be due to disparities in health status and pathogen variations across countries (Shah *et al.*, 2016). Despite the decrease in prevalence of most "ESKAPE" pathogens detected from ICU patient specimens transitioning into the COVID-19 pandemic, it still necessitates the application of consistent infection control measures.

4.5.3 Antibiotic resistance before and during COVID-19

4.5.3.1 Antibiotic resistance prior to COVID-19

In the present study, pre-pandemic antibiotic resistance was commonly found in gentamicin (10.9%), imipenem (7.3%), meropenem (7.7%), cefepime (12.7%), cefotaxime (13.2%), amoxicillin/clavulanate (9.6%) and ciprofloxacin (11.4%) (Table 4.15). Resistance to *A. baumannii* was observed for gentamicin, amikacin, imipenem, meropenem, cefepime, cefotaxime, piperacillin/tazobactam and ciprofloxacin (Table 4.16). *E. cloacae* resistance was mostly seen against cefepime, cefotaxime, amoxicillin/clavulanate and piperacillin/tazobactam. *E.faecalis and E.faecium* showed resistance to doxycycline, ciprofloxacin, and azithromycin. *E. coli* showed resistance against meropenem, imipenem, cefepime, cefotaxime, amoxicillin/clavulanate, piperacillin/tazobactam, doxycycline and ciprofloxacin. *K.pneumoniae* observed resistance against gentamicin, meropenem, imipenem, cefepime, cefotaxime, amoxicillin/clavulanate and piperacillin/tazobactam. Similarly to the current study,

Saxena *et al* (2019) found that most of the *Klebsiella* spp. and *Acinetobacter* spp. were resistant to beta-lactam group of antibiotics such as cephalosporins and piperacillin-tazobactam. Conversely, 60% of isolates of *S. aureus* were found to be MRSA (Saxena *et al.*, 2019). Bhatia *et al* (2018) reported that *Coagulase negative Staphylococci* was the predominant single blood culture isolate (35.58%), this was not the case in the current study. As in the present study, *K.pneumoniae* (13.46%), *E. coli* (12.50%), *A.baumannii complex* (7.69%) were commonly isolated gram-negative organisms. Gram-positive isolates were resistant to beta-lactams in most patients.

Conversely, the current study has not found a high prevalence of resistance of gram-positive isolates against beta-lactams (Bhatia *et al.*, 2018). Bhatia *et al* (2018) further reported that common gram-negative isolates were resistant to Tigecycline, which was not an antibiotic prescribed to any patient in the current study. Another study found resistance against ceftriaxone (88%), ceftazidime (80%), ciprofloxacin (77%), cefepime (75%), levofloxacin (72%). The current study reported no resistance against ceftriaxone, ceftazidime, and levofloxacin. However, the current study agreed with the resistance against ciprofloxacin. The three commonly isolated microorganisms were *Acinetobacter* (n = 75), *Klebsiella* (n = 39), and *P.aeruginosa* (n = 29). Acinetobacter baumannii were resistant to ceftazidime, ceftriaxone, piperacillin, imipenem, meropenem, ertapenem, ciprofloxacin and levofloxacin. Therefore, augmenting the current study's findings. On the other hand, Tran *et al* (2017) observed high rates (greater than 70%) of ceftriaxone and ceftazidime resistant Klebsiella, that were not seen in the current study were also observed (Tran *et al.*, 2017).

Table 4.15. Prevalence of resistance in antibiotics prescribed before and during COVID-19

Antibiotic Prescribed	WHO AWaRe	Pre-pandemic		COVID-19		Directionality
		n	%	n	%	
Gentamicin	*Access*	24	10,91	18	10,59	↓
Amikacin		4	1,82	0	0,00	↓
Ertapenem	*Watch*	3	1,36	3	1,76	−
Imipenem		16	7,27	14	8,24	↓
Meropenem		17	7,73	14	8,24	↓
Cefepime		28	12,73	19	11,18	↓
Cefazolin	*Access*	0	0	0	0,00	−
Cefotaxime	*Watch*	29	13,18	25	14,71	↓
Ceftriaxone		0	0	0	0,00	−
Vancomycin		0	0	0	0,00	−
Clindamycin	*Access*	2	0,91	1	0,59	↓
Azithromycin	*Watch*	8	3,64	7	4,12	↓
Metronidazole	*Access*	0	0,00	0	0,00	−
Amoxicillin		0	0,00	0	0,00	−
Ampicillin		6	2,73	6	3,53	−
Cloxacillin		0	0,00	0	0,00	−
Amoxicillin/clavulanate		21	9,55	16	9,41	↓
Piperacillin/tazobactam	*Watch*	28	12,73	19	0,11	↓
Doxycycline	*Access*	9	4,09	6	3,53	↓
Ciprofloxacin	*Watch*	25	11,36	22	12,94	↓
Moxifloxacin		0	0	0	0,00	−
Total		220	100	170	100	↓

AwaRe-Access, Watch, Reserve; COVID-19, Coronavirus disease 2019; n, frequency; WHO, World Health Organization; ↑, increase; ↓, decrease; −, constant.

4.5.3.2 Antibiotic resistance in the COVID-19 pandemic

The present study observed an overall decrease in resistance moving into the COVID-19 period, gentamicin (10.6%), imipenem (8.24%), meropenem (8.24%), cefepime (11.2%), cefotaxime (14.7%), amoxicillin/clavulanate (9.6%) and ciprofloxacin (12.9%) (Table 4.15). A decline in *A. baumannii* resistance was predominantly observed to gentamicin, amikacin, imipenem, meropenem, cefepime, cefotaxime, piperacillin/tazobactam and ciprofloxacin (Table 4.17).

Enterobacter aerogenes resistance was previously lower during the pre-pandemic period. Furthermore, during the pandemic period, with at least one resistant strain isolated against ertapenem, meropenem, imipenem, amoxicillin/clavulanate and piperacillin/tazobactam. A reduction in *E. cloacae* resistance was seen against most antibiotics, except for amoxicillin/clavulanate. An overall reduction in *E. faecalis and E. faecium* resistance to doxycycline, ciprofloxacin, and azithromycin was also observed. *E. coli* predominately showed an increase in resistance against cefepime, cefotaxime, amoxicillin/clavulanate,

piperacillin/tazobactam and ciprofloxacin. However, *E. coli* resistance to meropenem, imipenem and doxycycline was observed. *K. pneumoniae* observed a decline in resistance against gentamicin, meropenem, imipenem, cefepime, cefotaxime, amoxicillin/clavulanate and piperacillin/tazobactam. In addition, *P. aeruginosa* showed an increase in resistance against meropenem and imipenem. While *S. aureus* resistance showed no change in both periods of the study.

Despotovic *et al* (2022) reported resistance rates greater than 80% for most tested agents. In COVID-19 patients, *Acinetobacter* spp. was the dominant cause of HAIs and more frequently isolated than in non-COVID-19 patients. (67 vs. 18, P = 0.001). Resistance was higher for imipenem (56.8% vs. 24.5%, P<0.001), meropenem (61.1% vs. 24.3%, P<0.001) and ciprofloxacin (59.5% vs. 36.9%, P = 0.04). In addition, an increased presence of *Acinetobacter* spp. and a positive trend in *Klebsiella* spp. resistance to fluoroquinolones (R2 = 0.980, P = 0.01) and carbapenems (Despotovic *et al.*, 2021). Conversely, *A. baumannii* and *K. pneumoniae* showed a decline in resistance against fluoroquinolones (such as ciprofloxacin and moxifloxacin in the current study) and carbapenems (such as imipenem and meropenem in the current study). Contrary to the current study, Saini *et al* (2021) reported gram negative bacteria, *A. baumannii* was the predominant bacteria isolated during COVID-19 compared to the pre–COVID-19 period with reduced susceptibility to gentamicin, amikacin, and ciprofloxacin. Before the pandemic, *K. pneumoniae*, followed by *Acinetobacter* spp., *E. coli,* and *P. aeruginosa* were the common isolates in blood culture. The COVID-19 period signed a shift towards *A. baumannii* emerging as the most predominant pathogen followed by *E. coli* and *K. pneumoniae* supporting the findings of the current study (Saini *et al.*, 2021).

Table 4.16. Antibiotic resistant isolates detected in TPTH ICU patients prior to COVID-19, represented as number of isolates.

Antibiotic	***Acinetobacter baumannii* complex**	***Enterobacter aerogenes***	***Enterobacter cloacae* complex**	***Enterococcus faecalis***	***Enterococcus faecium***	***Escherichia coli***	***Klebsiella pneumoniae***	***Proteus miribalis***	***Pseudomonas aeruginosa***	***Staphylococcus aureus***
Gentamicin	11			4	1	1	6		1	
Amikacin	1			1			1		1	
Ertapenem							3		0	
Imipenem	12					1	2		1	
Meropenem	13					1	2		1	
Cefepime	13		3			1	10		1	
Cefazolin										
Cefotaxime	13		3			1	10		2	
Ceftriaxone										
Vancomycin										
Clindamycin				1						1
Azithromycin				5	3					
Metronidazole										
Amoxicillin										
Ampicillin				1	2					3
Cloxacillin										
Amoxicillin/clavulanate	2	1	4			3	11			
Piperacillin/tazobactam	13		3			1	10	1		
Doxycycline				5	3	1				
Ciprofloxacin	13			2	3	2	3		1	1
Moxifloxacin										

Green= “Access” category; Yellow = “Watch” category and Red= “Reserve” category

Table 4.17. Antibiotic resistant isolates detected in TPTH ICU patients during COVID-19, represented as number of isolates.

Antibiotic	***Acinetobacter baumannii* Complex**	***Enterobacter aerogenes***	***Enterobacter cloacae* Complex**	***Enterococcus faecalis***	***Enterococcus faecium***	***Escherichia coli***	***Klebsiella pneumoniae***	***Proteus Miribalis***	***Pseudomonas aeruginosa***	***Staphylococcus aureus***
Gentamicin	8			2	1	4	3			
Amikacin										
Ertapenem		1					2			
Imipenem	9	1					2		2	
Meropenem	9	1					2		2	
Cefepime	9	2				4	4			
Cefazolin										
Cefotaxime	9	2	1			4	4		5	
Ceftriaxone										
Vancomycin										
Clindamycin										1
Azithromycin				4	2					1
Metronidazole										
Amoxicillin										
Ampicillin				1	2					3
Cloxacillin										
Amoxicillin/clavulanate		2	5			4	5			
Piperacillin/tazobactam	9	2	1			3	4			
Doxycycline				4	2					
Ciprofloxacin	8	1	1	1	2	5	3		1	
Moxifloxacin										

Green= “Access” category; Yellow = “Watch” category and Red= “Reserve” category

4.5.3.3 Overview of antibiotic resistance across study period

In summary of the current study's resistance findings, there was an overall decline in resistance to antibiotics prescribed across both periods of the study. Figure 4.5 depicts the overview of resistance to "Access" and "Watch" categories. A decrease trend in resistance was observed in the "Access" category (pre-pandemic, 30%; COVID-19, 27.6%), while a slight increase in "Watch" category antibiotics (pre-pandemic, 70%; COVID-19, 72.4%) was observed in the COVID-19 period. Antibiotic prescriptions related to "Access" (pre-pandemic, 45.2%; COVID-19, 48.9%) and "Watch" (pre-pandemic, 54.8%; COVID-19, 51.1%) categories of antibiotics did not overlap with the prevalence of the pathogenic agents they are intended to treat. Furthermore, GPL critical level pathogens such as carbapenem-resistant *A. baumannii* and carbapenem-resistant *Enterobacteriaceae* observed an overall decrease in the COVID-19 period. However, carbapenem-resistant and third generation cephalosporin-resistant (namely, cefotaxime) *P. aeruginosa* sought a slight increase. Despite, this slight increase in *P. aeruginosa*, the overall prevalence of these critical classed bacteria were low in the current study relative to high engagement of antibiotic use and prescribing. Therefore, rigorous, and consistent AMS practices, as well as advanced health practitioner educative measures are needed to improve and subsequently maintain low levels of unnecessary antibiotic use and restrain progressing resistance.

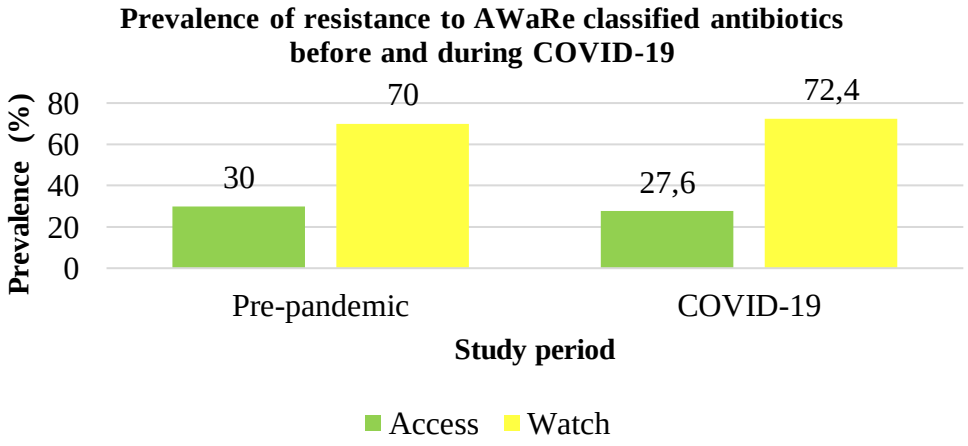

Figure 4.5 Prevalence of resistance amongst WHO AWaRe classified antibiotics before and during COVID-19. Abbreviations: AwaRe-Access, Watch, Reserve; COVID-19, Coronavirus disease 2019; WHO, World Health Organization

CHAPTER 5

CONCLUSION

5.1 Summary of findings

This study aimed to determine whether changes exist in antibiotic utilisation across the pre-COVID-19 era and during the COVID-19 era, in the management of ICU patients in Gauteng.

This aim was met by the following objectives:

The first objective of the study was to determine antibiotic utilisation amongst ICU patients admitted in a GPTH before and during the COVID-19 pandemic. The study observed an overall decrease trend in antibiotic prescription transitioning into the COVID-19 period. This was noted within antibiotic classes as well as within individual antibiotics. Particularly, amoxicillin/clavulanate ($P<0.05$) and azithromycin ($P<0.01$), antibiotics commonly used in RTIs, were associated with the study period. Amoxicillin/clavulanate demonstrated an 18.39% (n=16) increase in prescribing and azithromycin prescribing increased by 152.38% across both study periods. These antibiotics also indicated a mean increase in dose utilisation as per the mean PDD, corresponding to the surge in prescribing of those antibiotics. Furthermore, the mean PDD of azithromycin ($P<0.01$) and amoxicillin/clavulanate ($P<0.05$) were significantly different between the pre-pandemic period and COVID-19 period. Therefore, emphasising the shift in antibiotic prescribing and use moving into the COVID-19 pandemic.

Secondly, the study objectified determining the prevalence of "Watch" list antibiotic use before and following the emergence of COVID-19. These antibiotics decreased in use by 8% from the pre-pandemic period (52.10%; n = 149) to the COVID-19 period (47.90%; n =137). Antibiotics that were most prevalent within the "Watch" category, represented as (pre-pandemic percentage; COVID-19 percentage) included, piperacillin/tazobactam (20.81%; 16.79%), ceftriaxone (28.19%; 28.48%) and azithromycin (14.09%; 38.69%). However, azithromycin deviated from the general prescribing trend as the use and prescribing of this drug increased from the pre-pandemic (14.09%; n =21) to the COVID-19 pandemic period (38.69%; n =53), necessitating stricter control of this antibiotic and the "Watch" category at large as these antibiotics are more prone to resistance.

The final objective of the study was to determine the potential of resistance of WHO "AWaRe" classified antibiotics, that require close utilisation surveillance to curb the progression of antibiotic resistance within the ICU. A decrease trend in resistance was observed in the "Access" category (pre-pandemic, 30%; COVID-19, 27.6%). While a slight increase in "Watch" category antibiotics (pre-pandemic, 70%; COVID-19, 72.4%) was seen moving into the COVID-19 period corresponding the increased usage and prescribing of azithromycin in the "Watch" category. Furthermore, even though the overall prevalence of "ESKAPE" pathogens was low, an increase of resistance among " Watch" category antibiotics advocates for consistent AMS practices and surveillance measures to reduce the intent to prescribe these drugs, reduce use and subsequently reduce selective pressure placed on these drugs.

5.2 Study limitations

This study was conducted in a single hospital and hospital setting (ICU). This restricted the number of potential patients and hospital departments, thus affecting the variability of observations. Patients were not followed up after being transferred out of the ICU to other departments. Furthermore, the inclusion of various designated COVID-19 institutions would have enabled the analysis for regional variability in antibiotic utilisation pre-COVID-19 and during COVID-19. Due to the lack of pharmacy prescription data such as package size and quantity, the DDD could not be calculated. Moreover, the randomisation of patient selection did not allow for the alignment and comparison of the study's results to the epidemiological weeks of the COVID-19 pandemic in South Africa. Therefore, it could not be concurred whether surges in antibiotic prescription and use occurred during the COVID-19 waves.

5.3 Recommendations for future studies

Future studies should focus on factors associated with inappropriate prescribing amidst the COVID-19 pandemic in the public healthcare system to inform timeously, effective, and improved pandemic response strategies and prevent irrational antibiotic use as seen in the COVID-19 pandemic. Furthermore, the exploration of antibiotic utilisation in all hospital wards, across various hospital levels (district, regional, tertiary, and quaternary) and inter-provincially are crucial in establishing a national antibiotic consumption baseline. Moreover, comparative analysis between the pre-pandemic and COVID-19 period with regards to prevalence of COVID-19 infection and subsequent co-infection in vaccinated individuals

should also be a focus. In addition, gender survival analysis studies accounting for confounding factors and adjusting for age, disease severity, obesity, smoking, comorbidities, and antimicrobial therapy is recommended to improve the comprehension of patient demography and correlation and interactions of such information with other patient factors. Furthermore, research on patient characteristics is critical (gender, age, COVID-19 status, length of stay, comorbidity, concurrent pharmacotherapy) with the intent to understand disease trajectories and the interactive network that may exist between these aspects, especially in the context of LMICs characterised by high prevalence of disease.

5.4 Conclusion

The data revealed a rise in the use of macrolides and penicillin classes of antibiotics transitioning from the pre-pandemic period into the COVID-19 pandemic. The most frequently used antibiotics in these classes were azithromycin (pre-pandemic = 7.73%; COVID-19 = 19.78%) and amoxicillin in combination with clavulanate (pre-pandemic = 31.99%; mid-COVID-19 = 38.43%). An overall decline in "Watch" category antibiotics was seen, azithromycin negatively increased by 152.38%, within the category shifting into the COVID-19 pandemic. The bacterial resistance profile regarding the "Access" category antibiotics prescribed observed a decreased (30% to 27.6%) transitioning into the COVID-19 pandemic. While resistance within the " Watch" category antibiotics observed an increase (70% to 72.4%) in the COVID-19 pandemic. Furthermore, the resistance profile in this study is unmatched by the high prevalence of antibiotic prescriptions. These results, therefore, precipitate the need for improved drug surveillance policies and programs within the public health sector that encompass pandemic factors as well as the embedded public sector systematic issues that may be associated with antibiotic prescribing, usage, and resistance.

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APPENDIX A

A_1: Research publication submission:

The pattern of antibiotic utilization among intensive care unit patients hospitalised in a Gauteng (South African) Provincial Tertiary Hospital: Comparing findings before and amidst COVID-19

L Spinickum, [1]BPharm; **Z Booth**, [1]MPharm; **S de Rapper**, [1]PHD

[1] *Department of Pharmacy and Pharmacology, School of Therapeutic Science, Faculty of Health Science, University of the Witwatersrand*

Abstract

Background

Various mechanisms may contribute to and direct the progression of antibiotic resistance. A prominent driver associated with antibiotic resistance is inappropriate use or consumption. The sudden emergence of Coronavirus Disease 2019 (COVID-2019) changed the conventional practices related to antibiotic utilization through repurposing the use of antibiotics. Apart from the implementation of antibiotic stewardship programs, the pressure COVID-19 placed on healthcare systems resulted in poor prescribing and medication review practices potentially exacerbating antibiotic resistance. Furthermore, the public health system has issues that make it difficult to routinely monitor, quantify antibiotic consumption, and offer evaluation, feedback, and intervention; particularly in low- and middle-income countries (LMIC) like South Africa. Therefore, this study aimed to determine antibiotic utilization before and amidst the COVID-19 pandemic in a Gauteng provincial tertiary hospital (GPTH) in South Africa.

Objective

The objectives of the study were to determine, examine, and compare antibiotic consumption amongst intensive care unit (ICU) patients admitted to a GPTH during the pre-COVID-19 period and amidst the COVID-19 pandemic. In addition to determining the prevalence of the

World Health Organisation (WHO) “Watch” category antibiotics before and following the emergence of COVID-19.

Methods

A retrospective cross-sectional data analysis of 335 medical files of ICU patients hospitalised in a GPTH between January 2017 and December 2021. Descriptive statistics were used to examine patient characteristics and antibiotic prescribing variables (antibiotic selection, dosage, route of administration, frequency, duration of course, and indication for which antibiotic was prescribed).

Results

The study found that the most frequently prescribed antibiotics were amoxicillin in combination with clavulanate (pre-pandemic 31.99%; amid-COVID-19 38.43%), followed by ceftriaxone (pre-pandemic=15.44%; amid-COVID-19=14.55%), piperacillin in combination with tazobactam (pre-pandemic=11.40%; amid-COVID-19=8.58%) and azithromycin (pre-pandemic=7.725; amid-COVID-19=19.78%).

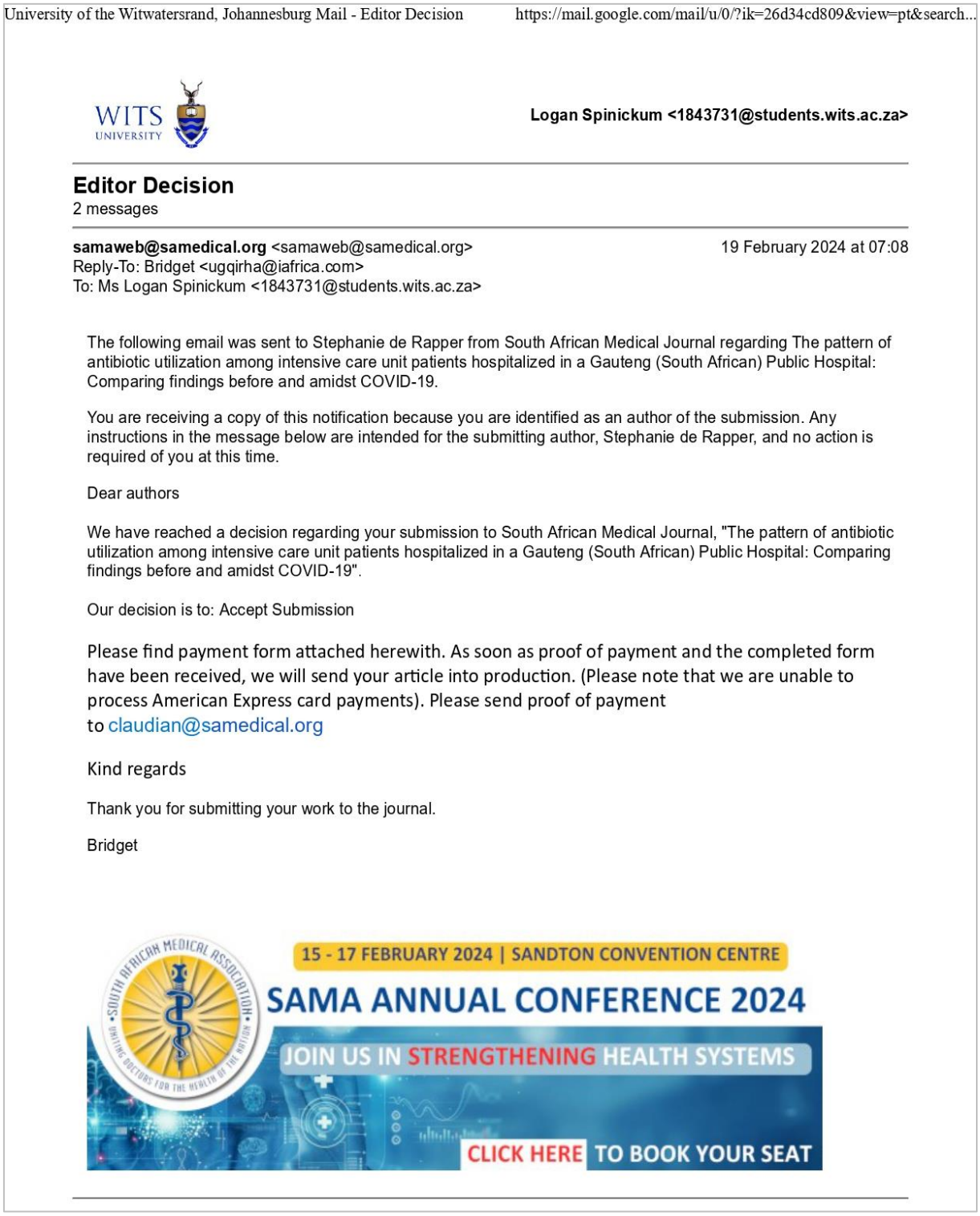
Conclusion

The macrolide and penicillin (in combination with a beta-lactamase inhibitor) classes demonstrated an increase in consumption from the pre-pandemic period moving into the COVID-19 pandemic. This highlights the need for improved antibiotic stewardship programs and policies to combat inappropriate and unnecessary antibiotic usage.

Keywords

Antibiotic use, antibiotic prescribing, AwaRe antibiotics, COVID-19, PDD, DDD, Gauteng, tertiary hospital.

A_2: Research publication submission:



University of the Witwatersrand, Johannesburg Mail - Editor Decision https://mail.google.com/mail/u/0/?ik=26d34cd809&view=pt&search...

WITS UNIVERSITY

Logan Spinickum <1843731@students.wits.ac.za>

Editor Decision

2 messages

samaweb@samedical.org <samaweb@samedical.org> 19 February 2024 at 07:08
Reply-To: Bridget <ugqirha@iafrica.com>
To: Ms Logan Spinickum <1843731@students.wits.ac.za>

The following email was sent to Stephanie de Rapper from South African Medical Journal regarding The pattern of antibiotic utilization among intensive care unit patients hospitalized in a Gauteng (South African) Public Hospital: Comparing findings before and amidst COVID-19.

You are receiving a copy of this notification because you are identified as an author of the submission. Any instructions in the message below are intended for the submitting author, Stephanie de Rapper, and no action is required of you at this time.

Dear authors

We have reached a decision regarding your submission to South African Medical Journal, "The pattern of antibiotic utilization among intensive care unit patients hospitalized in a Gauteng (South African) Public Hospital: Comparing findings before and amidst COVID-19".

Our decision is to: Accept Submission

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

Kind regards

Thank you for submitting your work to the journal.

Bridget

Figure A.1. Research journal article proof of acceptance

APPENDIX B

B_1: WHO AwaRe antibiotic classification

Table B.1. Complete WHO AWaRe classification list

Antibiotic	Class	ATC code	Category
Amikacin	Aminoglycosides	J01GB06	Access
Amoxicillin	Penicillins	J01CA04	Access
Amoxicillin/clavulanic Acid	Extended beta-lactam inhibitor	J01CR02	Access
Ampicillin	Penicillins	J01CA01	Access
Azithromycin	Macrolides	J01FA10	Watch
Benzathine benzylpenicillin	Penicillins	J01CE08	Access
Benzylpenicillin	Penicillins	J01CE01	Access
Cefalexin	cephalosporins	J01DB01	Access
Cefazolin	cephalosporins	J01DB04	Access
Cefixime	cephalosporins	J01DD08	Watch
Cefotaxime	cephalosporins	J01DD01	Watch
Ceftazidime	cephalosporins	J01DD02	Watch
Ceftazidime-avibactam	cephalosporins	J01DD52	Reserve
Ceftriaxone	cephalosporins	J01DD04	Watch
Cefuroxime	cephalosporins	J01DC02	Watch
Chloramphenicol	Amphenicols	J01BA01	Access
Ciprofloxacin	Fluoroquinolones	J01MA02	Watch
Clarithromycin	Macrolides	J01FA09	Watch
Clindamycin	Lincosamides	J01FF01	Access
Cloxacillin	Penicillins	J01CF02	Access
Colistin	Polymyxins	J01XB01	Reserve
Doxycycline	Tetracyclines	J01AA02	Access
Fosfomycin (IV)	Phosphonics	J01XX01	Reserve
Gentamicin	Aminoglycosides	J01GB03	Access
Linezolid	Oxazolidinones	J01XX08	Reserve
Meropenem	Carbapenems	J01DH02	Watch
Meropenem-vaborbactam	Carbapenems	J01DH52	Reserve
Metronidazole (IV)	Imidazole	J01XD01	Access
Metronidazole (oral)	Imidazole	P01AB01	Access
Nitrofurantoin	Nitrofurantoin	J01XE01	Access
Phenoxymethylpenicillin	Penicillins	J01CE02	Access
Piperacillin/tazobactam	Extended beta-lactamase inhibitors	J01CR05	Watch

Table B.1. continued. Complete WHO AWaRe classification list

Antibiotic	Class	ATC code	Category
Plazomicin	Aminoglycosides	to be assigned	Reserve
Polymyxin B	Polymyxins	J01XB02	Reserve
Procaine benzylpenicillin	Penicillins	J01CE09	Access
Spectinomycin	Aminocyclitols	J01XX04	Access
Sulfamethoxazole/trimethoprim	Trimethoprim - sulfonamide combinations	J01EE01	Access
Vancomycin (IV)	Glycopeptides	J01XA01	Watch
Vancomycin (oral)	Glycopeptides	A07AA09	Watch

APPENDIX C

C_1 Stratified random sampling

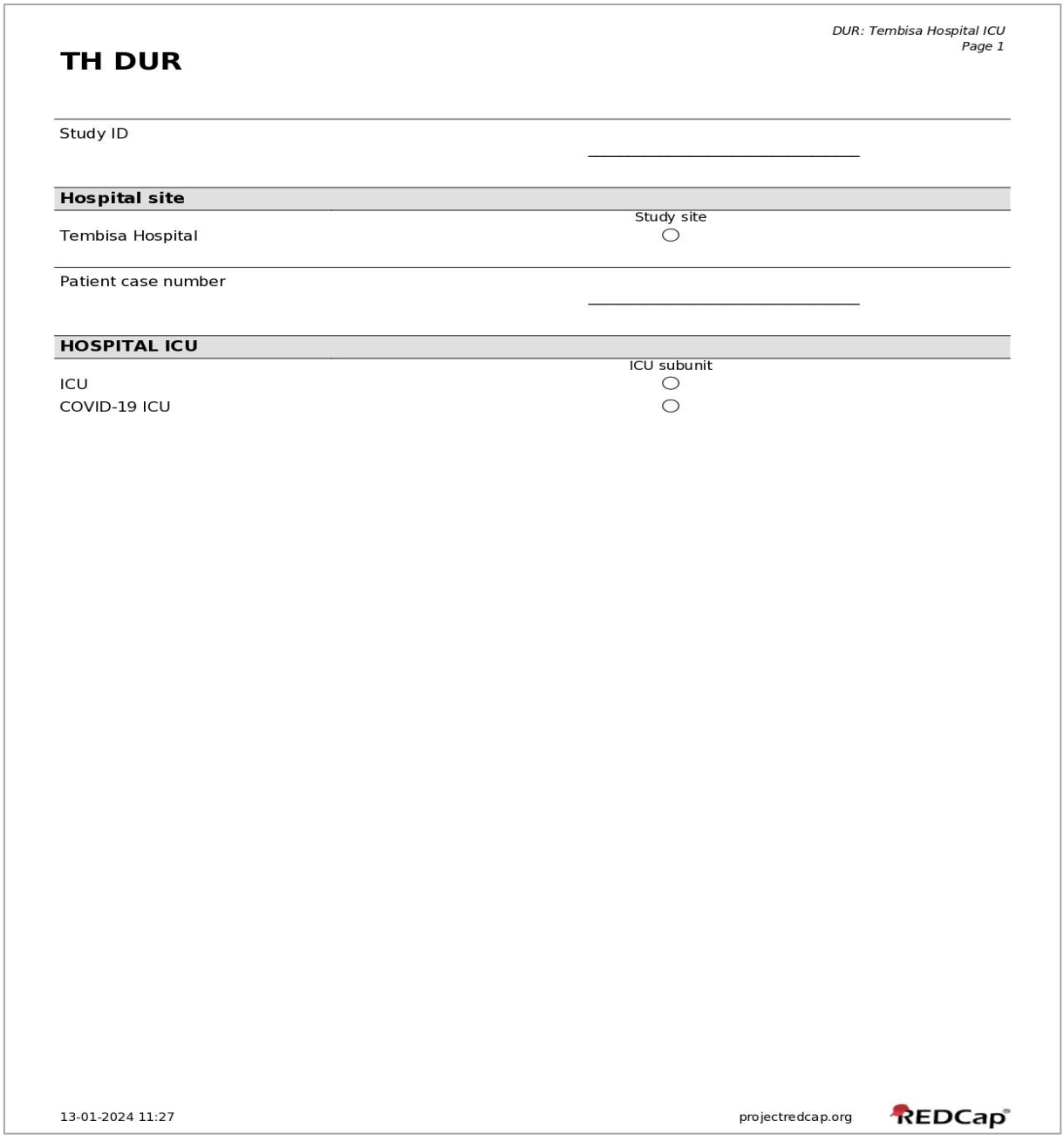
	A	B	C	D	E	F	
1	Year of study & Admission	Count	Count:Total ratio	Patients per strata	Rounded figures to c	KEY	CODE
2	2017	434	0,132600061	44,42102047	44	Total admissions	
3	2018	578	0,176596395	59,15979224	59	Count-Total ratio	
4	2019	549	0,167736022	56,19156737	56	Patients per strata	
5	2020	594	0,181484876	60,79743355	61	Total strata	
6	2021	1118	0,341582646	114,4301864	115	COVID-ICU & ICU general	
7	Total	3273		335	335		
8	Desired sample space			335			
9							
10	YOS (ICU DiV):2021						
11	ICU GEN	Count:total ratio	PPIS	Rounded figures			
12	Count: 484	0,432915921	49,78533095	50			
13							
14	ICU COVID	Column1	PPIS	Rounded figures			
15	Count: 634	0,567084079	65,21466905	65			
16							
17	Total ICU admissions: 1118						
18	Desired sample size: 115		115	115			
19							
20							

COVID-19, Coronavirus Disease 2019; ICU, intensive care unit; YOS, year of study

Figure C.1. Excel spreadsheet of StRS calculations

APPENDIX D

D_1: DUR REDCap® data collection form



DUR: Tembisa Hospital ICU
Page 1

TH DUR

Study ID _____

Hospital site

Study site

Tembisa Hospital ○

Patient case number _____

HOSPITAL ICU

ICU subunit

ICU ○

COVID-19 ICU ○

13-01-2024 11:27 projectredcap.org REDCap

Figure.D.1. REDCap data collection tool

ICU Date of admission	◯ JAN 2017 ◯ FEB 2017 ◯ MAR 2017 ◯ APR 2017 ◯ MAY 2017 ◯ JUN 2017 ◯ JUL 2017 ◯ AUG 2017 ◯ SEP 2017 ◯ OCT 2017 ◯ NOV 2017 ◯ DEC 2017 ◯ JAN 2018 ◯ FEB 2018 ◯ MAR 2018 ◯ APR 2018 ◯ MAY 2018 ◯ JUN 2018 ◯ JUL 2018 ◯ AUG 2018 ◯ SEP 2018 ◯ OCT 2018 ◯ NOV 2018 ◯ DEC 2018 ◯ JAN 2019 ◯ FEB 2019 ◯ MAR 2019 ◯ APR 2019 ◯ MAY 2019 ◯ JUN 2019 ◯ JUL 2019 ◯ AUG 2019 ◯ SEP 2019 ◯ OCT 2019 ◯ NOV 2019 ◯ DEC 2019 ◯ JAN 2020 ◯ FEB 2020 ◯ MAR 2020 ◯ APR 2020 ◯ MAY 2020 ◯ JUN 2020 ◯ JUL 2020 ◯ AUG 2020 ◯ SEP 2020 ◯ OCT 2020 ◯ NOV 2020 ◯ DEC 2020 ◯ JAN 2021 ◯ FEB 2021 ◯ MAR 2021 ◯ APR 2021 ◯ MAY 2021 ◯ JUN 2021 ◯ JUL 2021 ◯ AUG 2021 ◯ SEP 2021 ◯ OCT 2021 ◯ NOV 2021 ◯ DEC 2021

ICU Date of discharge/ward transfer	◯ JAN 2017 ◯ FEB 2017 ◯ MAR 2017 ◯ APR 2017 ◯ MAY 2017 ◯ JUN 2017 ◯ JUL 2017 ◯ AUG 2017 ◯ SEP 2017 ◯ OCT 2017 ◯ NOV 2017 ◯ DEC 2017 ◯ JAN 2018 ◯ FEB 2018 ◯ MAR 2018 ◯ APR 2018 ◯ MAY 2018 ◯ JUN 2018 ◯ JUL 2018 ◯ AUG 2018 ◯ SEP 2018 ◯ OCT 2018 ◯ NOV 2018 ◯ DEC 2018 ◯ JAN 2019 ◯ FEB 2019 ◯ MAR 2019 ◯ APR 2019 ◯ MAY 2019 ◯ JUN 2019 ◯ JUL 2019 ◯ AUG 2019 ◯ SEP 2019 ◯ OCT 2019 ◯ NOV 2019 ◯ DEC 2019 ◯ JAN 2020 ◯ FEB 2020 ◯ MAR 2020 ◯ APR 2020 ◯ MAY 2020 ◯ JUN 2020 ◯ JUL 2020 ◯ AUG 2020 ◯ SEP 2020 ◯ OCT 2020 ◯ NOV 2020 ◯ DEC 2020 ◯ JAN 2021 ◯ FEB 2021 ◯ MAR 2021 ◯ APR 2021 ◯ MAY 2021 ◯ JUN 2021 ◯ JUL 2021 ◯ AUG 2021 ◯ SEP 2021 ◯ OCT 2021 ◯ NOV 2021 ◯ DEC 2021

Case/Prescription Profiling

	Female	Male
Gender	◯	◯

Length of Stay in the ICU

◯ Less than 24 hours
◯ 1 Day
◯ 2 Days
◯ 3 Days
◯ 4 Days
◯ 5 Days
◯ 6 Days
◯ 7 Days
◯ 1-2 weeks
◯ 2-3 weeks
◯ 3-4 weeks
◯ 1-2 months
◯ 2-3 months
◯ 3-4 months
◯ 4-5 months
◯ 5-6 months
◯ 6-7 months
◯ 7-8 months
◯ 8-9 months
◯ 9-10 months
◯ 10-11 months
◯ 11-12 months
◯ Greater than 12 months

Patient Age range

◯ 18-25
◯ 26-40
◯ 41-60
◯ >60
(Patient age must be > 18)

Diagnosis

_____

COVID-19 Status

◯ Positive
◯ Negative
◯ N/A

Comorbidities

☐ AIDS/HIV
☐ Asthma
☐ Cancer
☐ Diabetes
☐ Epilepsy
☐ Hypertension
☐ Heart disease
☐ Kidney disease
☐ Lung disease
☐ Obesity
☐ Stroke

Other Condition and/or comorbidities

_____
(Any chronic or acute conditions)

Medication

_____

Allergies

_____

Adverse reactions

_____
(ADRs - unintended, harmful events attributed to the use of medicines)

ANTIBIOTIC THERAPY

	Antibiotics prescribed
Amikacin	☐
Amoxicillin	☐
Azithromycin	☐
Cefepime	☐
Ceftriaxone	☐
Cefotaxime	☐
Ceftazidime	☐
Ciprofloxacin	☐
Co-amoxicillin (clavulanate and amoxicillin)	☐
Colistin	☐
Doxycycline	☐
Ertapenem	☐
Imipenem	☐
Levofloxacin	☐
Linezolid	☐
Meropenem	☐
Ofloxacin	☐
Piperacillin/Tazobactam	☐
Teicoplanin	☐
Tigecycline	☐
Vancomycin	☐

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Duration of course	______________________________ (Separate different drug course termination with a semi-colon [;](in days))
Route of administration	◯ Oral ◯ Parenteral (intravenous, intramuscular, and subcutaneous) ◯ Nasal ◯ Ocular ◯ Transmucosal (buccal, vaginal, and rectal) ◯ Transdermal
Route of administration	◯ Oral ◯ Parenteral (intravenous, intramuscular, and subcutaneous) ◯ Nasal ◯ Ocular ◯ Transmucosal (buccal, vaginal, and rectal) ◯ Transdermal
Route of administration	◯ Oral ◯ Parenteral (intravenous, intramuscular, and subcutaneous) ◯ Nasal ◯ Ocular ◯ Transmucosal (buccal, vaginal, and rectal) ◯ Transdermal

Duration of course	__________________________________ (Separate different drug course termination with a semi-colon [;](in days))
Duration of course	__________________________________ (Separate different drug course termination with a semi-colon [;](in days))
Duration of course	__________________________________ (Separate different drug course termination with a semi-colon [;](in days))
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Route of administration	◯ Oral ◯ Parenteral (intravenous, intramuscular, and subcutaneous) ◯ Nasal ◯ Ocular ◯ Transmucosal (buccal, vaginal, and rectal) ◯ Transdermal
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Route of administration	◯ Oral ◯ Parenteral (intravenous, intramuscular, and subcutaneous) ◯ Nasal ◯ Ocular ◯ Transmucosal (buccal, vaginal, and rectal) ◯ Transdermal
Reason for Antibiotic Prescribing/use	☐ Empiric ☐ Microbiological ☐ Prophylaxis ☐ Standard treatment guideline ☐ Unconfirmed

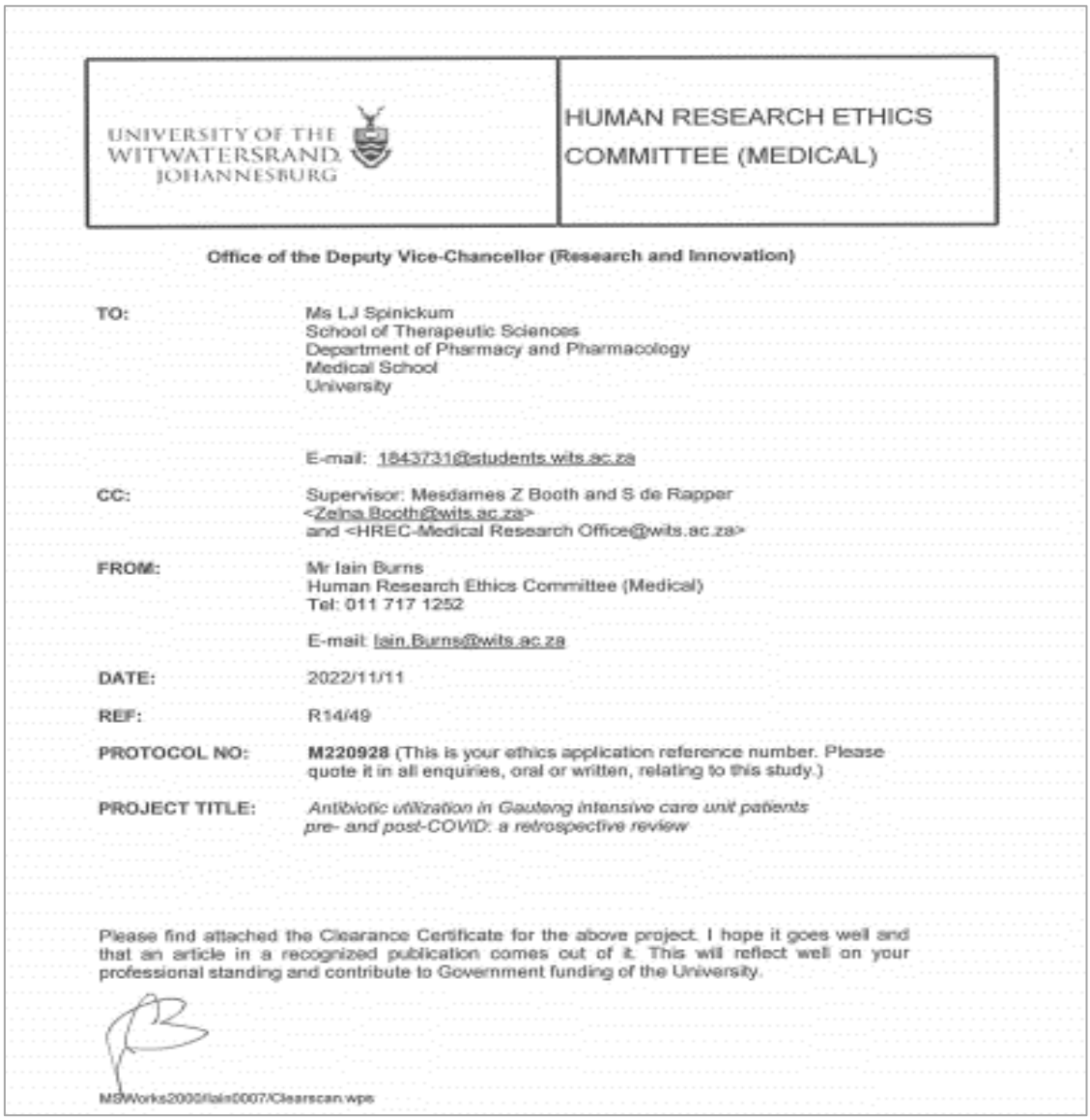
D_2: Summary of codes for binary and nominal variables

Category	Code	Code_Name
Hospital ICU	1	main ICU
	2	C19 ICU
COVID period	1	Pre-pandemic
	2	Pandemic
Gender	1	Female
	2	Male
Age range	1	18 to 25
	2	26 to 40
	3	41 to 60
	4	> 60
Length of stay range (days)	1	< 1
	2	1
	3	2
	4	3
	5	4
	6	5
	7	6
	8	7
	9	7 to 14
	10	14 to 21
	11	21 to 28
	12	28 to 35
COVID19 status	1	Positive
	2	Negative
Secondary diagnosis_Cap	1	Yes
	2	None
Comorbities (AIDS/HIV to peptic ulcer disease)	0	None
	1	Yes
Concurrent Pharmacotherapy (Analgesics to C19 supp	0	None
	1	Yes
Patient allergies	0	None
	1	Aspirin
	2	Enalapril
	3	Penicillin
Prescribed EML antibiotics	0	None
	1	Yes

Figure.D.2 Variable codes used during data collection

APPENDIX E

E_1: Human Research Ethics Committee approval certificate



UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Ms LJ Spinickum
School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

E-mail: 1843731@students.wits.ac.za

CC: Supervisor: Mesdames Z Booth and S de Rapper
<Zelna.Booth@wits.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2022/11/11

REF: R14/49

PROTOCOL NO: **M220928** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Antibiotic utilization in Gauteng intensive care unit patients pre- and post-COVID: a retrospective review*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Figure E.1. Human ethics certificate

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R49 Ms LJ Spinickum

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M220928

NAME: (Principal Investigator)	Ms LJ Spinickum
DEPARTMENT:	School of Therapeutic Sciences Department of Pharmacy and Pharmacology Medical School University
PROJECT TITLE:	*Antibiotic utilization in Gauteng intensive care unit patients pre- and post-COVID: a retrospective review*
DATE CONSIDERED:	2022/09/30
DECISION:	Approved unconditionally
CONDITIONS:	This approval applies only to the study sites listed in Annex 1 attached Further sites may be added on presentation of evidence of management approval to the HREC (Med)
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Mesdames Z Booth and S de Rapper
APPROVED BY:	Dr N Naran, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	2022/11/11

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Philip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **September** and therefore reports and re-certification will be due in the month of **September** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator — Date: 5 October 2022

E_2: Ethics approval of amendments study methodology and secondary data source

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

2023/04/04

Ms LJ Spinickum
School of Therapeutic Sciences
Department of Pharmacy and Pharmacology
Medical School
University

Sent by e-mail to: 1843731@students.wits.ac.za

Dear Ms Spinickum

Re: **Protocol Ref No:** M220928
Protocol Title: *Antibiotic utilization in Gauteng intensive care unit patients pre- and post-COVID: a retrospective review*
Principal Investigators: Ms LJ Spinickum

Thank you for your letter of 2023/03/20

We noted in our letter of 2023/02/07 that you would be collecting NHLS patient microbiological records. We understand these to be retrospective records and would not expect you to try to obtain patient consent.

Thank you for keeping us informed.

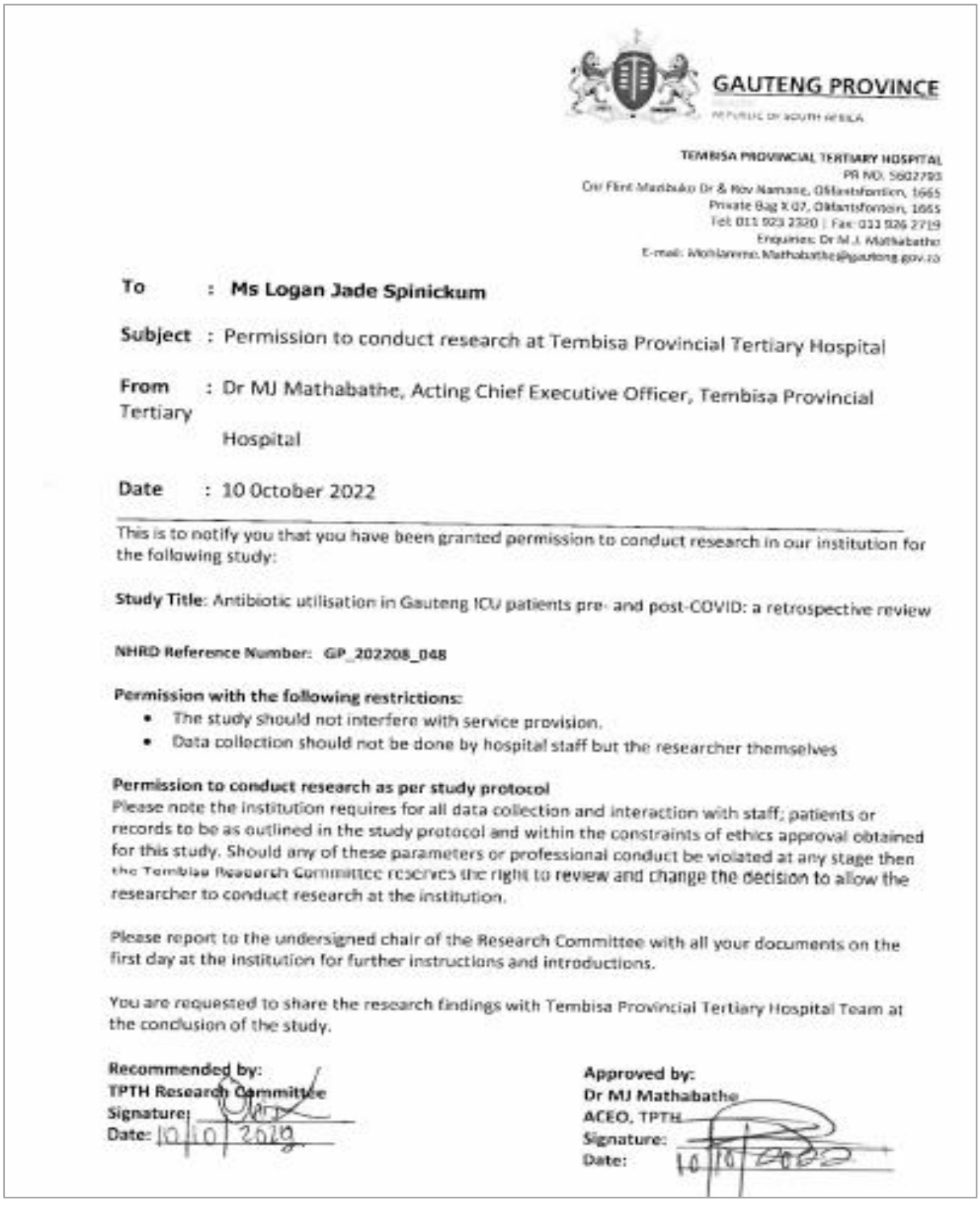
Yours Sincerely

Mr I Burns
For the Human Research Ethics Committee (Medical)

Dr CB Penny, Chairperson, Human Research Ethics Committee (Medical)

Figure E.2. Ethic approval of methodology amendments

E_3: Study site approval



GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

TEMBISA PROVINCIAL TERTIARY HOSPITAL
PR NO: 5902793
Cnr Flint Mashiloane Dr & Rev Namane, Olifantsfontein, 1665
Private Bag X 07, Olifantsfontein, 1665
Tel: 011 923 2320 | Fax: 011 926 2719
Enquiries: Dr M.J. Mathabathe
E-mail: Mohlaleme.Mathabathe@gauteng.gov.za

To : **Ms Logan Jade Spinickum**

Subject : Permission to conduct research at Tembisa Provincial Tertiary Hospital

From : Dr MJ Mathabathe, Acting Chief Executive Officer, Tembisa Provincial Tertiary Hospital

Date : 10 October 2022

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

Study Title: Antibiotic utilisation in Gauteng ICU patients pre- and post-COVID: a retrospective review

NHRD Reference Number: GP_202208_048

Permission with the following restrictions:

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

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

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

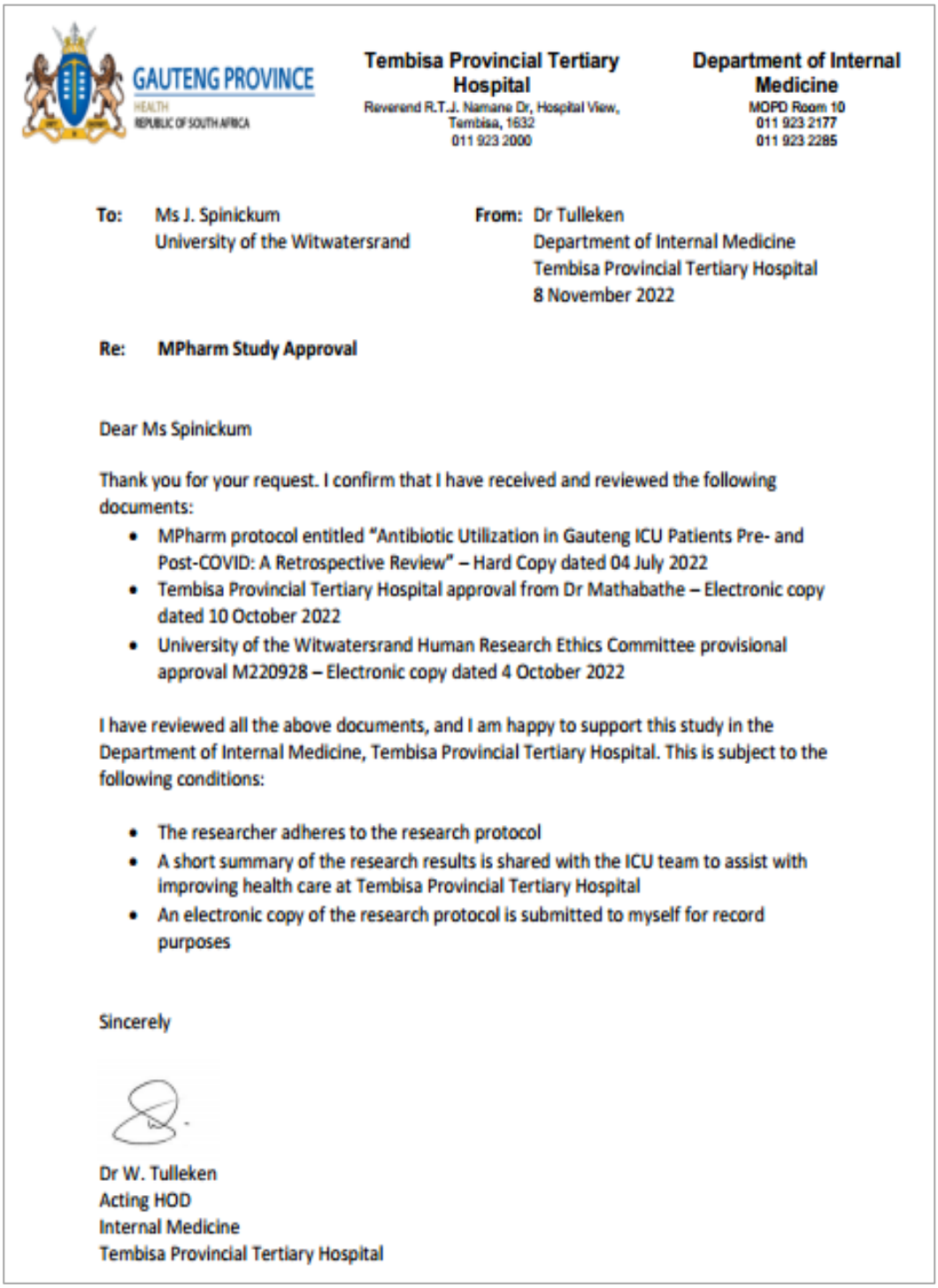
You are requested to share the research findings with Tembisa Provincial Tertiary Hospital Team at the conclusion of the study.

Recommended by:
TPTH Research Committee
Signature:
Date: 10/10/2022

Approved by:
Dr MJ Mathabathe
ACEO, TPTH
Signature:
Date: 10/10/2022

Figure E.3. Study site approval

E_4: TPTH internal medicine H.O.D approval



GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Tembisa Provincial Tertiary Hospital
Reverend R.T.J. Namane Dr, Hospital View, Tembisa, 1632
011 923 2000

Department of Internal Medicine
MOPD Room 10
011 923 2177
011 923 2285

To: Ms J. Spinickum
University of the Witwatersrand

From: Dr Tulleken
Department of Internal Medicine
Tembisa Provincial Tertiary Hospital
8 November 2022

Re: **MPharm Study Approval**

Dear Ms Spinickum

Thank you for your request. I confirm that I have received and reviewed the following documents:

- MPharm protocol entitled "Antibiotic Utilization in Gauteng ICU Patients Pre- and Post-COVID: A Retrospective Review" – Hard Copy dated 04 July 2022
- Tembisa Provincial Tertiary Hospital approval from Dr Mathabathe – Electronic copy dated 10 October 2022
- University of the Witwatersrand Human Research Ethics Committee provisional approval M220928 – Electronic copy dated 4 October 2022

I have reviewed all the above documents, and I am happy to support this study in the Department of Internal Medicine, Tembisa Provincial Tertiary Hospital. This is subject to the following conditions:

- The researcher adheres to the research protocol
- A short summary of the research results is shared with the ICU team to assist with improving health care at Tembisa Provincial Tertiary Hospital
- An electronic copy of the research protocol is submitted to myself for record purposes

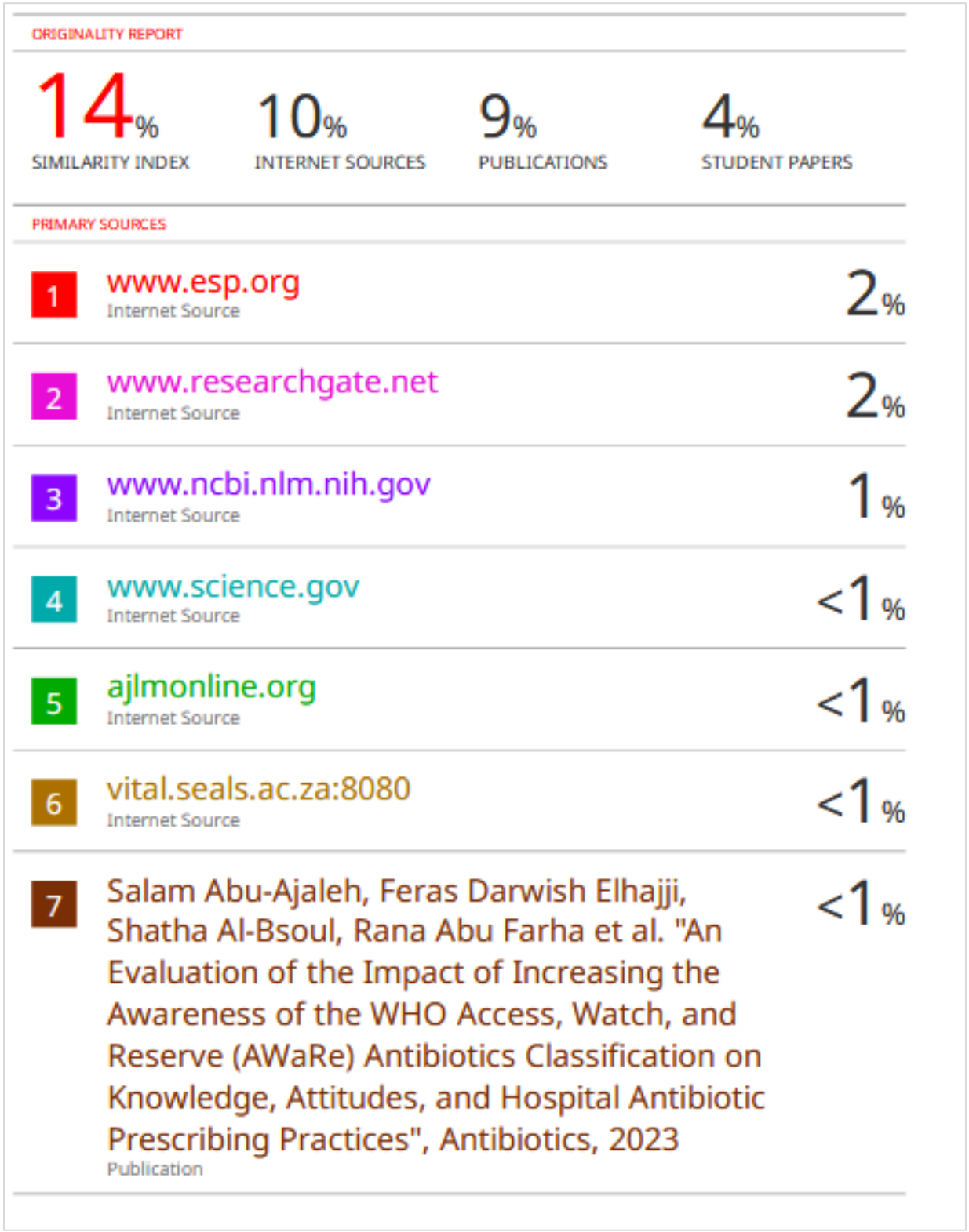
Sincerely

Dr W. Tulleken
Acting HOD
Internal Medicine
Tembisa Provincial Tertiary Hospital

Figure E.4. Internal Medicine H.O.D approval

APPENDIX F

F_1: Turnitin Plagiarism Report[2]



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[2] Full report available on request