University of Strathclyde

Strathclyde Institute of Pharmacy & Biomedical Sciences

Carbapenem and Piperacillin-tazobactam Prescribing in a Hospital Setting in Kingdom of Saudi Arabia: A Mixed Methodology Study

Nada Alsaleh

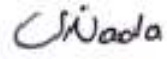
A thesis presented in fulfilment of the requirements for the degree of

Doctor of Philosophy

June 2021

Declaration

This thesis is the result of the author's original research. It has been composed by the author and has not been previously submitted for examination which has led to the award of a degree.

Signed: 

Date: 23/06/2021

Acknowledgements

First, I would like to thank Allah for supporting me with health, knowledge, patience and power to conduct and complete this research.

I would like to express my deep and sincere gratitude to my supervisor, Professor Alexander B Mullen, for giving me invaluable guidance throughout this journey. It was a great honour and privilege to conduct this research under his guidance.

I also would like to express my sincere thanks to my internal supervisors, Dr Hussain Al-Omar and Professor Ahmed Mayet, for their consistent encouragement, guidance and support.

Thanks are also due to the Saudi Ministry of Education and Princess Nourah Bint Abdulrahman University for their financial support and for providing me with this opportunity.

My sincere thanks to the Information Technology department at King Saud University Medical City for their support in retrieving the data used in this research and all the physicians who contributed to the interviews. I would also like to thank Ms Jackie A Cooper for her statistical advice.

Finally, I would especially like to thank my parents, husband, sisters, brothers, daughter and friends for their support and encouragement throughout this PhD journey. The completion of this thesis would not have been possible without them.

Abstract

Background: Antimicrobial resistance (AMR) is spreading rapidly and is considered to be one of the greatest public threats worldwide. The inappropriate use of broad-spectrum antimicrobials has contributed to the emergence of AMR. The WHO has developed Access, Watch, Reserve (AWaRe) classification to support hospitals and countries in promoting the appropriate utilisation of antimicrobials. Studying broad-spectrum antimicrobial utilisation and the determinants of broad-spectrum antimicrobial prescribing can assist in developing strategies and policies to improve the local prescribing practice for these agents.

Aim: To evaluate the practices of broad-spectrum antimicrobial prescribing to provide potentially effective and feasible recommendations and interventions that will result in improvements in broad-spectrum antimicrobial prescribing practices in a hospital setting in the Kingdom of Saudi Arabia (KSA).

Methods: An explanatory sequential mixed methods approach was adopted. First, a quantitative, observational, retrospective, cross-sectional, drug utilisation study, which included adult patient data on carbapenems (imipenem/cilastatin or meropenem) and piperacillin/tazobactam use retrieved from a hospital database for the period from 1 January 2016 to 31 December 2017, was conducted followed by a qualitative study of physicians' views and perceptions of broad-spectrum antimicrobial prescribing. The qualitative study employed semi-structured interviews with 16 physicians to identify and explore the determinants of broad-spectrum antimicrobial prescribing practices, recommendations to improve practice and possible barriers. This study was carried out in a single tertiary care institution in the KSA.

Results: A total of 2,871 patients received 5,250 courses of antimicrobial treatment with at least one of the studied broad-spectrum antimicrobials across 3,671 patient admissions over a two-year period. It was shown that 4,106 (82%) of broad-spectrum antimicrobials were prescribed for empiric indications. Of the assessed prescriptions, only 2,787 (56.5%) were prescribed appropriately, with 2,142 (43.5%) deemed inappropriate. The three most common reasons for inappropriate empiric perceptions were: spectrum of activity was too broad 1029 (40%), antimicrobial used without a culture request 929 (36.2%), and failure of suitable antimicrobial de-escalation 570 (22.2%). Interview findings identified key determinants of broad-spectrum antimicrobial prescribing practices, including patient co-morbidities and clinical presentations, the unavailability of local guidelines, physicians' perceptions and attitudes toward broad-spectrum antimicrobials prescribing and several institutional constraints. Suggestions prioritised by physicians for improvements to the practice of prescribing broad-spectrum antimicrobials included education and training, monitoring and feedback, improved logistics of care and antimicrobial stewardship.

Conclusion: This research adds to our knowledge on broad-spectrum antimicrobial prescribing practices and recommended intervention and strategies for improving the appropriateness of broad-spectrum antimicrobials prescribing in a hospital setting in the KSA. Implementing a multifaceted intervention can possibly improve antimicrobials prescribing practices. Educating physicians about the importance of antimicrobial stewardship practices could be considered. Moreover, introducing antimicrobial prescribing guidelines should be significant part of the intervention to improve the appropriate prescribing of broad-spectrum antimicrobials. Both

education and guidelines should consider the factors that influence physicians prescribing and involve physicians to impact effectively and positively on their inappropriate prescribing practices and reduce the risk of AMR.

Table of contents

Table of figures

Table of tables

List of abbreviations

Abbreviation	Meaning
A. baumannii	*Acinetobacter baumannii*
AMR	Antimicrobial resistance
ASPs	Antimicrobial stewardship programmes
AUV	Antimicrobial Utilisation and Vaccine Advisory
BCIs	Behaviour change interventions
BCW	Behaviour Change Wheel
β-lactam	Beta-lactam
CAP	Community-acquired pneumonia
CDC	Centres for Disease Control and Prevention
C. difficile	*Clostridioides difficile*
COM-B	Capability, opportunity, motivation to perform a behaviour
COVID-19	Coronavirus disease of 2019
CI	Confidence interval
CNS	Central nervous system
COREQ	Consolidated Criteria for Reporting Qualitative Research
DDD	Defined daily dose
DOT	Days of therapy
DUR	Drug utilisation research
E. coli	*Escherichia coli*
ED	Emergency department
ESBL	Extended spectrum beta-lactamase
GAP	Global Action Plan

GASTAT	General Authority for Statistics
GCC	Gulf Cooperation Council
GPs	General medical practitioners
HAP	Hospital-acquired pneumonia
HDU	High-dependency unit
ICU	Intensive care unit
ID	Infectious diseases
IDSA	Infectious Diseases Society of America
IQR	Interquartile range
IV	Intravenous
K. pneumoniae	*Klebsiella pneumoniae*
KSA	Kingdom of Saudi Arabia
KSUMC	King Saud University Medical City
KKUH	King Khalid University Hospital
LOT	Length of therapy
LOS	Length of stay
MDR	Multidrug-resistant
MIC	Minimum inhibitory concentration
MOH	Ministry of Health
MRN	Medical record number
MRSA	Methicillin-resistant *Staphylococcus aureus*
OBG	Obstetrics and gynaecology
P. aeruginosa	*Pseudomonas aeruginosa*
PDD	Prescribed daily dose

PTC	Pharmacy and Therapeutic Committee
RCT	Randomised controlled trial
S. aureus	*Staphylococcus aureus*
SD	standard deviations
SE	Standard error
SHEA	Society for Healthcare Epidemiology of America
SSTI	Skin and soft tissue infection
SPSS	Statistical package for the social sciences
UK	United Kingdom
UNDP	United Nations Development Programme
USA	United States of America
UTI	Urinary tract infection
WHO	World Health Organization

Glossary

Term	Definition
Acinetobacter baumannii	An aerobic gram-negative bacterium that is resistant to most antimicrobials (Mack *et al.,* 2011).
Anaerobe	A microorganism that can live despite a lack of oxygen (Baron, 1996).
Antibiogram	The result of antimicrobial susceptibility testing of an isolated bacterium to different antimicrobials (Mack *et al.,* 2011).
Antimicrobials	"Chemical substances which have the capacity to inhibit the growth and even to destroy pathogenic organisms" (Waksman, 1953, p.259).
Antimicrobial resistance	The potential of a microbial organism to resist the effect of medicine previously used to fight it (CDC, 2013).
Antimicrobial stewardship	''Coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal [antibiotic] drug regimen, including dosing, duration of therapy and route of administration" (Fishman, 2012).
Bactericidal	An antimicrobial that kills bacteria (Nemeth *et al.,* 2015).
Bacteriostatic	An antimicrobial that inhibits bacterial growth (Nemeth *et al.,* 2015).

Broad-spectrum antimicrobials	Antimicrobials that work against a broad range of bacteria (Pagel and Gautier, 2012).
Beta-lactam antimicrobials	A class of antimicrobials that are considered to be critically significant to modern treatment. They act by killing the bacteria where they bind to proteins and stopping the bacteria from appropriately forming a cell wall (Pandey and Cascella, 2020).
Carbapenems	A group of beta-lactam that is effective against many gram-positive and gram-negative bacteria and anaerobes. They are usually reserved for serious resistant bacterial infections (Codjoe and Donkor, 2017).
Co-morbidity	Any additional disorder beyond an index condition (Valderas *et al.,* 2009).
Confirmability	Neutrality or objectivity concerned with ensuring that findings and interpretations clearly originate from the data (Tobin and Begley, 2004).
Credibility	The confidence that the research findings are true, believable and credible (Lincoln and Guba, 1986).
Defined daily dose	The assumed average maintenance dose per day for a drug used for its main indication in adults (WHO Collaborating Centre, 2018).
Dependability	The stability of findings over time and study conditions (Lincoln and Guba, 1985, Connelly, 2016).

Extended-spectrum beta-lactamases	Enzymes that are produced by some *Klebsiella* spp., *E. coli* and other *Enterobacteriaceae* that inactivate certain antimicrobials such as penicillins and cephalosporins (Holmes *et al.,* 2016)
Enterobacteriaceae	A large family of gram-negative bacteria that include *Escherichia coli, Salmonella, Klebsiella, Yersinia pestis and Shigella* (de W Blackburn, 2006).
Escherichia coli	A gram-negative bacterium that belongs to *Enterobacteriaceae* (de W Blackburn, 2006).
Febrile neutropenia	The condition of having fever with an abnormally low count of neutrophils (Mack *et al.,* 2011).
Gram-negative bacteria	Bacteria whose cell wall contains a thin peptidoglycan layer which can make them unable to retain the crystal violet stain used for bacterial differentiation (Mack *et al.,* 2011).
Gram-positive bacteria	Bacteria whose cell wall contains a thick peptidoglycan layer which makes them able to retain the crystal violet stain used for bacterial differentiation (Mack *et al.,* 2011).
Meticillin-resistant *Staphylococcus aureus*	Strains of *Staphylococcus aureus* that are resistant to antimicrobials called β-lactams which include methicillin, and other β-lactam antimicrobials (Mack *et al.,* 2011).

Methodological approach	The plan for research that brings wide assumptions and hypotheses to comprehensive methods of data collection, analysis and explanation (Creswell and Creswell, 2017).
Mixed methods	"The class of research where the researcher mixes or combines quantitative and qualitative research techniques, methods, approaches, concepts or language into a single study" (Johnson and Onwuegbuzie 2004, pp. 17-18).
Multidrug-resistant bacterium	A bacterium that is resistant to more than one antimicrobial (Holmes *et al.,* 2016).
Narrow-spectrum antimicrobials	Antimicrobials that work against a limited range of bacteria (Mack *et al.,* 2011).
Nosocomial infection	An infection that is acquired in hospital (WHO, 2011).
Prescribed daily dose	The average dose prescribed according to a representative sample of prescriptions (WHO Collaborating Centre, 2018).
Pseudomonas aeruginosa	A gram-negative bacterium that causes severe acute infections (Mack *et al.,* 2011).
Recruitment	The process of identifying and inviting participants to take part in research (Given, 2008).
Social desirability	The tendency of participants to provide a response that they believe and expect to be more socially acceptable (Collins *et al.,* 2005).

Spectrum of activity	The range of antimicrobial effectiveness (Holmes *et al.,* 2016).
Thematic analysis	A type of analysis that assists a researcher to find themes within a dataset to a specific research question (Braun and Clarke, 2006).
Transferability	The extent to which findings can be generalised (Lincoln and Guba, 1986).
Triangulation	The use of different sources of data or multiple methodological approaches to enhance the validity of a piece of research (Salkind, 2010).

Scientific contributions

Poster presentation

Alsaleh N, Mullen A, Mayet A, Alomar H. (2020) Carbapenem and Piperacillin-tazobactam Prescribing in Saudi Arabia - A need For Improvement. Dubai International Pharmaceutical & Technology Conference & Exhibition. Dubai, United Arab Emirates. 25-27 February 2020.

Alsaleh N, Mullen A, Mayet A, Alomar H. (2021) Exploring physicians' views, perceptions and experiences about broad-spectrum antimicrobial prescribing in a tertiary care hospital: A qualitative approach. First Pharmacy Research Day at King Saud Bin Abdulaziz University for Health Sciences. Riyadh, Saudi Arabia. 06-07 January 2021 (3rd place winner).

Publications arising from this thesis

Alsaleh, N.A., Al-Omar, H.A., Mayet, A.Y. and Mullen, A.B., 2020. Evaluating the appropriateness of carbapenem and piperacillin-tazobactam prescribing in a tertiary care hospital in Saudi Arabia. *Saudi Pharmaceutical Journal*, 28(11), pp.1492-1498. (Impact factor 2.879)

Alsaleh, N.A., Al-Omar, H.A., Mayet, A.Y. and Mullen, A.B., 2021. Exploring Physicians' Views, Perceptions and Experiences about Broad-Spectrum Antimicrobial Prescribing in a Tertiary Care Hospital Riyadh, Saudi Arabia: A Qualitative Approach. *Antibiotics*, 10(4), 366. (Impact factor 3.893)

Thesis structure

This thesis has a total of four chapters. Chapter 1 provides a general introduction, context and research rationale. Topics outlined in this chapter include antimicrobials, antimicrobial use, AMR, strategies to improve antimicrobial prescribing, ASPs as one of the strategies to prevent AMR and an overview of the background and healthcare system status where the research was conducted. Also, it outlines an overview of the general research methodological approach and rationalises the methodology adopted.

Chapter 2 reports on the quantitative, retrospective, observational, cross-sectional, drug utilisation study of adult hospitalised patients prescribed broad-spectrum antimicrobials, namely, imipenem/cilastatin, meropenem, or piperacillin/tazobactam. It provides the utilisation and details of the studied antimicrobials. It assessed the appropriateness of the therapy and identifies the reasons for giving inappropriate assessments. Finally, it identifies the demographics of the patients and the prescription characteristics associated with inappropriate prescriptions.

Chapter 3 describes the qualitative study of physicians prescribing of broad-spectrum antimicrobials, including their views on these, factors that influence their prescribing, the practices and barriers in antimicrobial stewardship, and their recommendations to improve appropriate broad-spectrum antimicrobial prescribing practices.

Finally, Chapter 4 includes a summary of the main findings from the quantitative and qualitative studies, an overall discussion, and recommendations to improve broad-spectrum antimicrobial prescribing to reduce AMR. Figure 0.1 illustrates the timeline

for quantitiaive and qualtiative studies, implemntation of electronic system and establishment of antimicorbial stewardship commiittee.

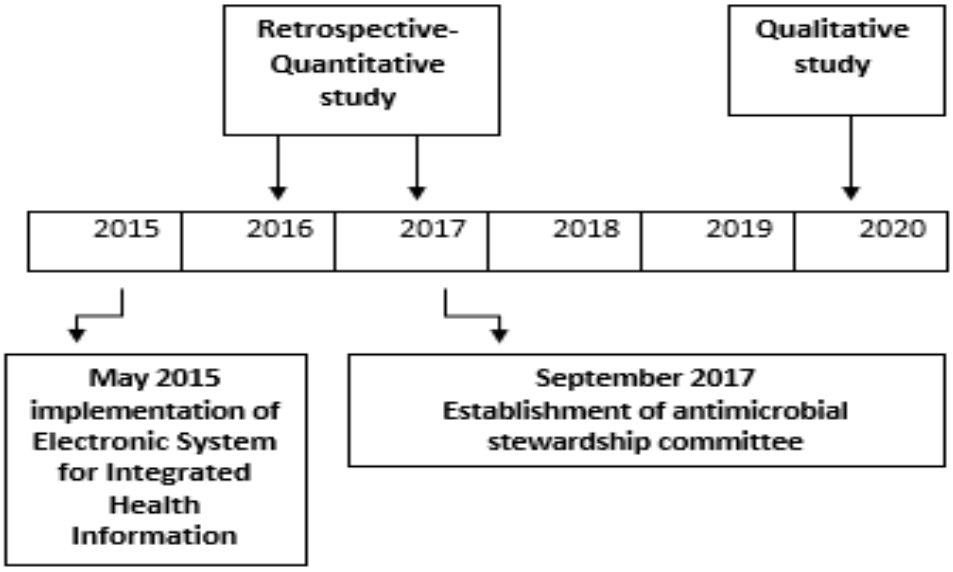


Figure 1.1: Timeline of studies, implemntation of electronic system and establishment of antimicorbial stewardship commiittee

1. Chapter 1 General introduction

Overview:

This chapter comprises six sections that together provide an overview of the research topic, context and methodological approach. The first section provides an overview of antimicrobials, antimicrobial use and AMR; the second outlines the strategies to improve antimicrobial prescribing, including antimicrobial stewardship programmes (ASPs) as one of these strategies; the third gives an overview of the background and healthcare system status where the research was conducted; the fourth illustrates the rationale for the research; the fifth provides an overview of the general research methodological approach and rationalises the methodology adopted in this thesis, and the final section outlines the research questions, and overall thesis aim and objectives.

1.1 Antimicrobials

Antimicrobials are medicines used to destroy or inhibit the growth of microorganisms. These include antibiotics, antifungals, antivirals and antiparasitics. Several terms have been used to illustrate antibiotics in the literature. These terms include antibiotics, antibacterials and anti-infectives. The term antibiotics was initially used in literature by Selman Waksman in 1942 to describe actinomycin, a substance produced by *Actinomyces antibioticus*, a microorganism that had both bactericidal and bacteriostatic properties (Waksman and Tishler, 1942). Since then, the word antibiotics has been commonly used in the literature. Selman defined antibiotics as:

> *"Chemical substances which have the capacity to inhibit the growth and even to destroy pathogenic organisms."* (Waksman, 1953, p.259)

In this thesis, the term antimicrobials will be used to illustrate all of the above terms except in direct quotation text.

1.1.1 Antimicrobials, past and present

The development of antimicrobials in 1941 changed the practice of medicine; it has been one of the most significant public health interventions (Lee *et al.,* 2013). Before the introduction of antimicrobials into clinical practice, infectious diseases (ID) made up a very large percentage of diseases as a whole (Saga and Yamaguchi, 2009). Up to 30% of overall human deaths have been attributed to ID (Centres for disease control and prevention [CDC], 1999).

Paul Ehrlich, a German bacteriologist, proposed the idea of the "magic bullet". This scientific idea describes the ability of a substance to selectively destroy a microorganism with little or no harm to the human organism. In 1909, after a series of preparations, Paul Ehrlich and his colleagues were able to develop a gold-coloured powder; this was preparation number 606 of the tested preparations and was named salvarsan. Salvarsan (arsphenamine or compound 606) was the first effective antimicrobial drug against *Treponema pallidum*, the causative organism of the sexually transmitted disease syphilis (Winau *et al.,* 2004; Gensini *et al.,* 2007).

In 1928, Alexander Fleming, a Scottish bacteriologist, found that his culture plates of *Staphylococci* were contaminated with *Penicillium notatum* mould, which appeared as a zone surrounding the contaminated cultures. A substance produced by this mould seemed to inhibit the *Staphylococci* growth. He isolated the substance and called it penicillin. It was later introduced into clinical use in 1940. Penicillin, which is a remarkable drug in terms of efficacy and safety, established the era of antimicrobials by saving lives during World War II (Moellering, 1995; Saga and Yamaguchi, 2009).

In 1935, Gerhard Domagk, a German pathologist, tested several dyes for the treatment of bacterial infection. He worked on a brilliant red dye for staining leather, which was called prontosil red, and discovered that this dye cured infections caused by *Streptococci* in mice. Domagk's daughter contracted a serious Streptococcal infection from an unsterilised needle and she was given a dose of prontosil. She is considered to be the first person to have received prontosil and to have made a recovery. Later, Therese Trefouel, a French scientist, determined that the prontosil compound could be metabolised into an active drug known as sulfanilamide. Between 1935 and 1948, thousands of sulfanilamide derivatives were produced and assessed for antimicrobial activity (Dubey and Maheshwari, 1999; Iyer, 2008).

In 1940, Selman Waksman, an American microbiologist, discovered streptomycin. Initially, Waksman was interested in establishing soil microbiology which led him, with the aid of one of his students, to the discovery of the soil bacteria named *actinomycetes*. These *actinomycetes* produced a substance that killed the bacteria. Later, he gathered together a group of researchers to work on antimicrobial studies which led them to the discovery of actinomycin, clavacin, fumigacin and streptothricin. Unfortunately, all four drugs were toxic to animals. In further investigations, he isolated a *Streptomyces griseus* strain from the farm soil and found that it produced a substance that killed bacteria. Waksman named it streptomycin. Consequent clinical trials showed that streptomycin was safe and effective in the treatment of tuberculosis caused by *Mycobacterium tuberculosis* (Daniel, 2005; Woodruff, 2014). Figure 1.1 illustrates the trend of antimicrobial discovery and resistance development.

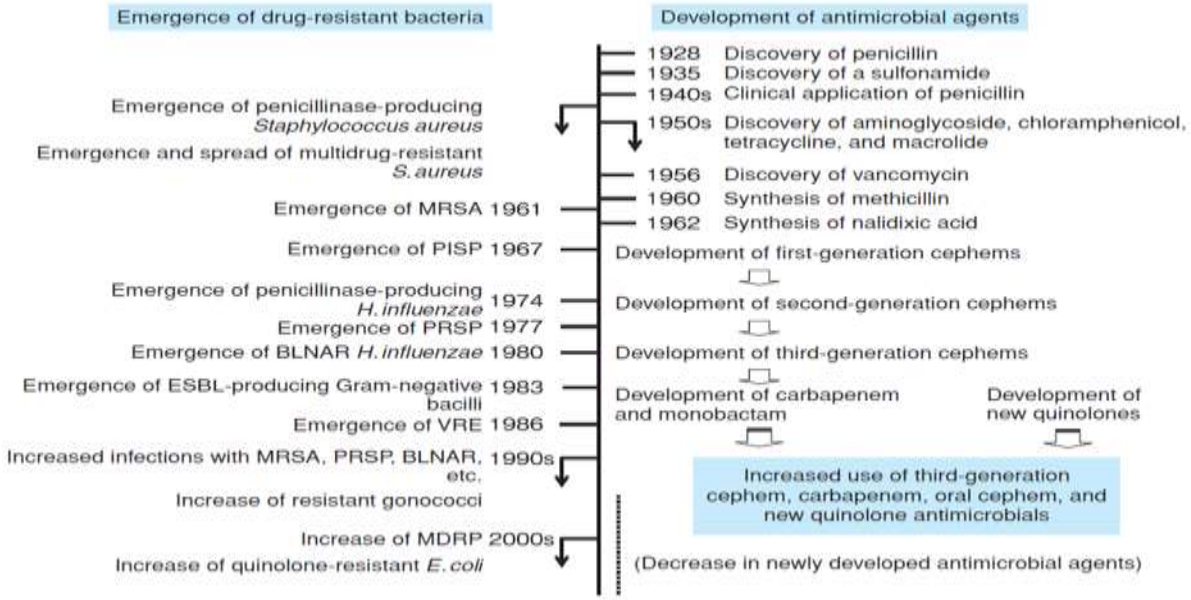


Figure 1.1: Trends of antimicrobials discovery and development of resistance.
Reproduced with permission from (Saga and Yamaguchi, 2009); Copyright 2009 Japan Medical Association

Key: BLNAR: beta-lactamase-negative ampicillin-resistant; MRSA: methicillin-resistant *S. aureus*; MDRP: multidrug resistant *P.aeruginosa*; PISP: penicillin-intermediate *Streptococcus pneumoniae*; PRSP: penicillin-resistant *Streptococcus pneumoniae*; VRE: vancomycin-resistant *enterococci*.

The discovery of the above-mentioned antimicrobials established the paradigms for future antimicrobial discovery research. The period from 1940 to 1960 was the golden era of novel antimicrobial discovery (Chopra *et al.,* 2002). In parallel to antimicrobial discovery, microorganisms that resisted the effect of antimicrobials that were originally effective were also emerging; therefore, modifications to the existing antimicrobials were made (i.e combination with enzyme inhibitors; Lewis, 2013). These modifications have helped combat ID, leading to the improved killing of pathogens, enhanced spectrum of activity and reduced toxicity (Lewis, 2013). The current assessment of the antimicrobial pipeline shows that there are 43 antimicrobials in a clinical development phase (Figure 1.2). However, since 2019, only four antimicrobials have been approved and one is an antimicrobial with a novel mechanism of action (Theuretzbacher *et al.,* 2020; The Pew Charitable Trusts, 2021). Table 1.1 provides a summary of antimicrobial approvals for 2019.

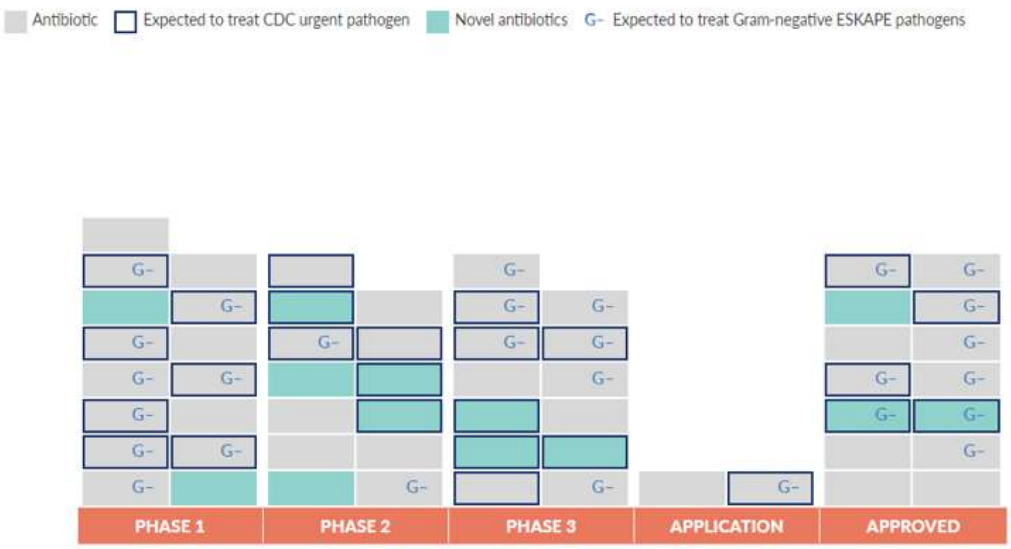


Figure 1.2: Antimicrobials in development from 2014-2020 (The Pew Charitable Trusts, 2021)

Table 1.1: Antimicrobial approvals for 2019 (Pharmaceuticals and Medical Devices Agency, 2019; The Pew Charitable Trusts, 2021; U.S. Food and Drug Administration, 2019)

Antibiotic name	Active ingredient	Approved date	Approved use
Recarbrio	imipenem, cilastatin and relebactam	07/16/2019	To treat complicated urinary tract and complicated intra-abdominal infections
Xenleta (Noval antimicrobial)	lefamulin	08/19/2019	To treat adults with community-acquired bacterial pneumonia
Lasvic	Lascufloxacin	09/20/2019	To treat respiratory and ear, nose and throat infections
Fetroja	cefiderocol	11/14/2019	To treat patients with complicated urinary tract infections who have limited or no alternative treatment options

1.1.2 Antimicrobial classification

More than 5000 antimicrobials have been identified and approximately 100 of these are used clinically to treat bacterial infections (Khardori, 2006). They differ in chemical, physical and pharmacological properties. To make it easier to understand, antimicrobials are classified mainly according to five categories: spectrum of activity,

chemical structure, route of administration, type of activity, or mechanism of action (Adzitey, 2015; Hamid-Ullah and Ali, 2017). Table 1.2 presents an overview of the antimicrobial classification systems.

Table 1.2: Antimicrobial classification systems (Adzitey, 2015; Hamid-Ullah and Ali, 2017)

Classification system	Category	
Mechanism of action	Inhibition of nucleic acid synthesis Inhibition of cell wall synthesis Inhibition of protein synthesis Antimetabolite	
Chemical structure	Aminoglycosides Beta-lactam (β-lactam) Fluoroquinolones Lincosamides Macrolides Polypeptides Sulphonamides Tetracyclines Miscellaneous	
Route of administration	Oral Parenteral	
Type of activity	Bactericidal Bacteriostatic	Bactericidal is an antimicrobial that kills bacteria (Nemeth *et al.,* 2015). Bacteriostatic is an antimicrobial that inhibits bacterial growth (Nemeth *et al.,* 2015).
Spectrum of activity	Broad Narrow	Broad-spectrum antimicrobials are effective against a wide range of microorganisms in contrast to narrow-spectrum antimicrobials, which are effective against a specific group of microorganisms (Adzitey, 2015).

1.1.2.1 Beta-lactam antimicrobials

β-lactam antimicrobials are one of the most commonly prescribed group of antimicrobials (Pandey and Cascella, 2020). This group of antimicrobials are characterised by the presence of a β-lactam ring, which is the 1-nitrogen and 3-carbon ring (Pandey and Cascella, 2020). This group includes penicillins, cephalosporins, carbapenems and monobactams. Table 1.3 illustrates examples of the β-lactam antimicrobials group.

Carbapenems are a group of β-lactam antimicrobials that are structurally related to penicillins (Codjoe and Donkor, 2017). They possess a broad spectrum of antimicrobial activity and are effective against gram-positive/gram-negative bacteria and anaerobes (Codjoe and Donkor, 2017). Meropenem, imipenem, ertapenem and doripenem are all clinically-used carbapenems and are generally considered to be a last line group of antimicrobials for treatment of patients with confirmed or suspected infections involving a multidrug-resistant (MDR) bacterium (Baldwin *et al.,* 2008).

Beta-lactamase inhibitors are a group of agents that primarily work by inhibiting beta-lactamases enzymes, enzymes that cleave the β-lactam ring and deactivate its antimicrobial activity (Pandey and Cascella, 2020). Their clinical impact is realised when they are combined with a β-lactam (Bush and Bradford, 2016). This group of beta-lactamase inhibitors includes clavulanic acid, tazobactam, sulbactam, vaborbactam and avibactam (Pandey and Cascella, 2020).

A combination of tazobactam and piperacillin provides a broad spectrum of antimicrobial activity in a convenient single formulation (Perry and Markham, 1999). Piperacillin/tazobactam has a broad spectrum of antimicrobial activity against most gram-positive and gram-negative organisms and anaerobes. It is effective in patients with febrile neutropenia, intra-abdominal infections, lower respiratory tract infections and skin and soft tissue infections (SSTIs; Young and Plosker, 2001).

Table 1.3: Examples of β-lactam antimicrobials (Pandey and Cascella, 2020)

β-lactam antimicrobials	Examples	
Penicillins	Ampicillin, piperacillin	
Cephalosporins	1st generation 2nd generation 3rd generation 4th generation 5th generation	cefazolin, cephalexin cefuroxime, cefoxitin cefotaxime, ceftriaxone, ceftazidime cefpirome, cefepime ceftaroline, ceftobiprole
Carbapenems	Imipenem/cilastatin, meropenem, doripenem, ertapenem	
Monobactams	Aztreonam	

1.1.2.2 WHO (AWaRe) classification

To support the development of tools for antimicrobial stewardship and to reduce AMR, WHO has developed Access, Watch, Reserve (AWaRe) classification of antibiotiocs where 180 antibiotics are classified into three groups to highlight the importance of their appropriate utilisation. The access group include 48 antibiotics that are recommended as first or second choice in empiric therapy for a number of common infections. They considered essential antibiotics that should be widely available and affordable. The Watch group includes 110 antibiotics that have higher resistance potential and that are recommended as first or second choice for a limited number of infections. These antibiotics should be observed and prioritised as main targets for stewardship programmes. carbapenem and piperacillin/tazobactam are under this group. The Reserve group includes 22 last-resort antibiotics that should be reserved for management of infections due to multi-drug-resistant organisms. This group should be intensively observed and their use should be for certain conditions when all alternatives are not suitable or have failed.

WHO recommends the use of AWaRe classification as a tool inform antimicrobial stewardship programmes (ASPs; WHO, 2019). A national-level targe of at least 60% of antibiotic consumption should be from the antibiotics in the access group

(Sharland et *al.,* 2019). Translating antibiotic utilisation data into AWaRe classification may provide valuable insights into international utilisation patterns and may help to investigate the potential of this classification as a stewardship tool (Pauwels et al., 2021a).

1.1.3 Antimicrobial use and resistance

1.1.3.1 Antimicrobial consumption

Antimicrobial consumption refers to the number of antimicrobials used in a defined setting during a specific period of time (World Health Organization [WHO], 2108c). The identification of volumes and patterns in antimicrobial consumption is essential to understand the epidemiology of AMR (Van Boeckel *et al.,* 2014). The identification of regions with a high rate of antimicrobial consumption can anticipate where the threat of a new AMR infection will be most likely (The Center for Disease Dynamics Economics and Policy, 2020b) and help to introduce initiatives to preserve antimicrobial efficacy (Okeke *et al.,* 2005a; Okeke *et al.,* 2005b). Furthermore, mapping the distribution of antimicrobial consumption provides a baseline for the evaluation of efforts to reduce inappropriate antimicrobial use in the future (Van Boeckel *et al.,* 2014).

Consumption measures are metrics that reflect an average or cumulative amount of antimicrobials being used at the level of the patient, institutionally, nationally or globally (Morris, 2014). The most commonly accepted measure for antimicrobial consumption is the defined daily dose (DDD), a metric that was established in the 1970s and has been refined and promoted by the WHO (WHO Collaborating Centre, 2018). Table 1.4 summarises the commonly used metrics to report antimicrobial consumption.

Table 1.4: Summary of the commonly used metrics to report antimicrobial consumption (Morris, 2014; WHO Collaborating Centre, 2018)

Metric	Advantage	Disadvantage
DDD *"The assumed average maintenance dose per day for a drug used for its main indication in adults"*	• Ease of reporting. • A method of measure to benchmark between institutions.	• Doses recommended by WHO may not reflect the current recommended dose as the doses may have changed; therefore, there is possible confusion with historic data results. • Based on adult dosing, it is not suitable in paediatrics. • Can over or underestimate antimicrobial use in certain patient populations (e.g. obesity, renal impairment).
Days of therapy (DOT) *"The number of days that a patient receives an antimicrobial agent (regardless of dose)"*	• Applicable to paediatrics and neonates. • Offers more clinical relevance than DDD. • Not influenced by changes in the DDD standards.	• Does not reflect the actual given dose.
Prescribed daily dose (PDD) *"The average dose prescribed according to a representative sample of prescriptions"*	• Adjusted to the real situation of the setting or type of patient.	• Does not allow for benchmarking between institutions.
Length of therapy (LOT) *"The number of days in which the selected antimicrobial was received"*	• Applicable to paediatrics and neonates. • An accurate estimate of the duration of therapy.	• Does not reflect multiple therapies and the actual dosage given. • Cannot be used to compare the use of individual drugs.

Key: DDD: defined daily dose; WHO: World Health Organization.

1.1.3.2 Antimicrobial resistance

AMR is the potential of a microbial organism to resist the effect of a medicine previously used to fight it (CDC, 2013). AMR is spreading rapidly and is considered one of the greatest public threats worldwide (CDC, 2013). It is estimated that AMR leads to a 1.3 to 2-fold increase in mortality compared to susceptible infections (Cosgrove and Carmeli, 2003; Hoffmann *et al.,* 2011).

In 1945, Alexander Fleming during his Nobel Prize speech warned that:

> *''The public will demand penicillin …Then will begin an era …Of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicaemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil will be averted."* (Fleming, 1945, p. 21)

Unfortunately, the evil that was foreseen by Fleming has not been averted and the discovery of each new antimicrobial has been followed by the detection of resistance to it (Bartlett *et al.,* 2013).

AMR poses an increasing risk to public health and has had serious clinical and economic influences across all parts of the world (Vanderkooi *et al.,* 2005; Evans *et al.,* 2007; Lee *et al.,* 2007; Carlet *et al.,* 2011; Neidell *et al.,* 2012; CDC, 2013; Smith and Coast, 2013; O'Neil, 2014; Friedman *et al.,* 2016; O'Neill, 2016). It is estimated that around 700,000 people die globally per year from drug-resistant bacterial infections, malaria, tuberculosis and human immunodeficiency viruses. However, this number is probably an underestimation due to poor reporting (O'Neill, 2014).

Moreover, several studies have shown an association between AMR and prolonged hospital stay (Evans *et al.,* 2007; Lee *et al.,* 2007). Evans *et al.* (2007) conducted a retrospective cohort study to determine the association between infections caused by resistant gram-negative bacteria and patient outcomes. The study found that patients with infection caused by resistant gram-negative bacteria had a longer median of hospital stay than patients with infection caused by sensitive strains (29 days versus 13 days, $P < 0.0001$). Similar findings were reported by Lee *et al.* (2007)

who found that patients with infections caused by MDR *Acinetobacter baumannii (A. baumannii)* strains stayed longer in hospital than patients with infections caused by non-MDR *A. baumannii* strains (54 and 34 days, respectively; P= 0.006. (Lee *et al.,* 2007)). This could be explained by the fact that when infections can no longer be treated by first-line antimicrobials, there is a risk of severe illness for which a longer duration of treatment may be needed.

Furthermore, the use of more expensive antimicrobials, increased hospital stay and the severity of illness all contributed to increased health care costs (WHO, 2018a). A study conducted by Neidell *et al.* (2012) showed that the cost of hospitalised patients with community and healthcare-associated infections due to AMR organisms were projected to be $25,573, which was higher than the $15,625 for patients with infection caused by antimicrobially-sensitive strains. The differences were more apparent when compared with costs associated with treating patients without infections (Cosgrove, 2006). In the United States of America (USA), more than two million infections annually are caused by bacteria resistant at least to first-line antimicrobials (CDC, 2013). It is estimated that this costs the USA health care system about $20 billion dollars (Smith and Coast, 2013).

Based on the ongoing escalation in AMR, it is projected to result in up to 10 million deaths annually by 2050, and to account for $100 trillion of lost total production of goods and services worldwide, unless action is taken (O'Neill, 2016). This number is higher than other common causes of death, as shown in Figure 1.3.

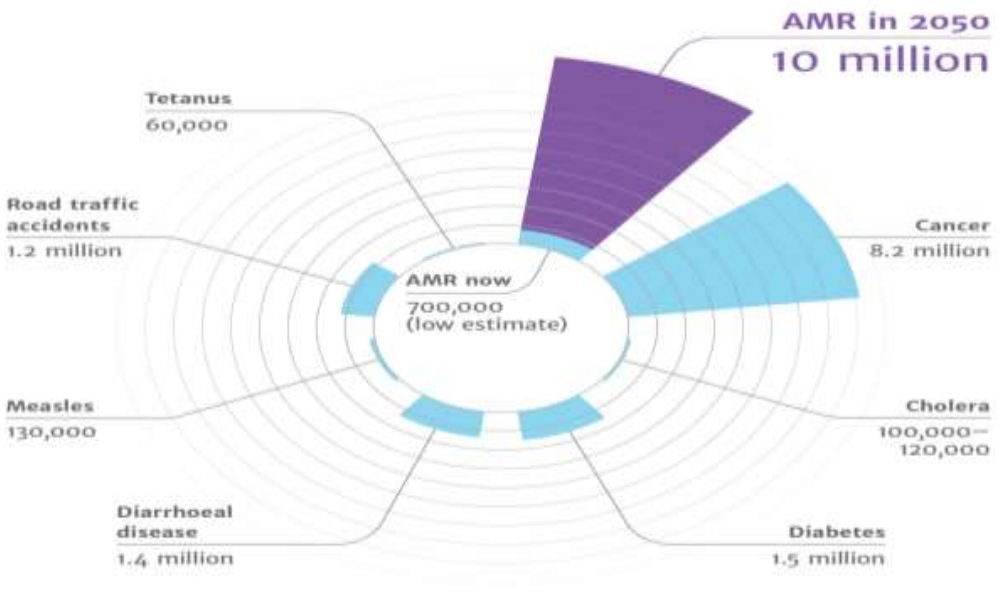


Figure 1.3: Prediction of AMR related deaths compared to other major causes in 2050 (O'Neill, 2016)

In 2017, the WHO, for the first time, identified a list of antimicrobial-resistant "priority pathogens". This included 12 families of bacteria that they identified as causing the greatest public threat. This list was produced by the WHO to address growing global resistance to antimicrobials and to act as a catalyst to encourage research and development into new antimicrobials. The list was sub-divided into critical, high and medium needs for new antimicrobials. The critical group includes MDR bacteria that has created a threat in nursing homes, hospitals, and among patients who need devices such as blood catheters and ventilators. This group of bacteria includes *A. baumannii, Pseudomonas aeruginosa (P. aeruginosa),* and *Enterobacteriaceae* (WHO, 2017b). Table 1.5 illustrates the WHO priority list of AMR organisms for which new antimicrobials are needed.

Table 1.5: WHO priority list of AMR organisms for which new antimicrobials are needed (WHO, 2017b)

Priority 1: CRITICAL
A. baumannii, carbapenem-resistant
P. aeruginosa, carbapenem-resistant
Enterobacteriaceae, carbapenem-resistant, ESBL-producing
Priority 2: HIGH
Enterococcus faecium, vancomycin-resistant
S. aureus, methicillin-resistant, vancomycin-intermediate and resistant
Helicobacter pylori, clarithromycin-resistant
Campylobacter species, fluoroquinolone-resistant
Salmonellae, fluoroquinolone-resistant
Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant
Priority 3: MEDIUM
Streptococcus pneumoniae, penicillin-non-susceptible
Haemophilus influenzae, ampicillin-resistant
Shigella species, fluoroquinolone-resistant

Key: *A. baumannii*: *Acinetobacter baumannii*; ESBL: Extended spectrum beta-lactamase; *P. aeruginosa: Pseudomonas aeruginosa*; *S. aureus*: *Staphylococcus aureus*.

1.1.3.3 Mechanism of antimicrobial resistance

AMR, promoted by the overuse of antimicrobials, may arise from different mechanisms of resistance. The resistance can occur in two ways: intrinsic or acquired. Intrinsic or passive resistance occurs naturally in pathogens who either do not have target sites for the antimicrobials, therefore, they resist their effects, or they have natural barriers that minimise exposure to the agents (Blair *et al.,* 2015). An example of intrinsic resistance is seen with *P. aeruginosa*, where its low membrane permeability to many antimicrobials is a major mechanism for its resistance (Toma and Deyno, 2015; Munita and Arias, 2016). Other examples include the existence of genes providing resistance to self-produced antimicrobials, the outer membrane of gram-negative bacteria reducing permeability to antimicrobials, and the lack of uptake transport systems for antimicrobials and availability of export transport systems to keep antimicrobial levels low (Toma and Deyno, 2015).

Acquired or active resistance, the main mechanisms of AMR, are the result of a specific evolutionary pressure to develop a counter-offensive mechanism against a single antimicrobial or class of antimicrobials so that bacteria formerly sensitive to antimicrobials become resistant. This type of resistance in bacteria may be obtained by mutation in the bacterial genome or by the horizontal transport of resistance genes between species and strains (Toma and Deyno, 2015). An exchange of genes is likely to occur by conjugation, transduction or transformation (Figure 1.4). This type of resistance can occur in different ways (Langton *et al.,* 2005; Toma and Deyno, 2015):

- Through an enzyme that inhibits the antimicrobial
- The presence of a salvage pathway (alternative enzyme(s)) for an essential enzyme that is directly inactivated by the antimicrobial)
- A mutation in the antimicrobial's target that decreases the binding of the antimicrobial
- Decreased uptake/increased efflux of the antimicrobial

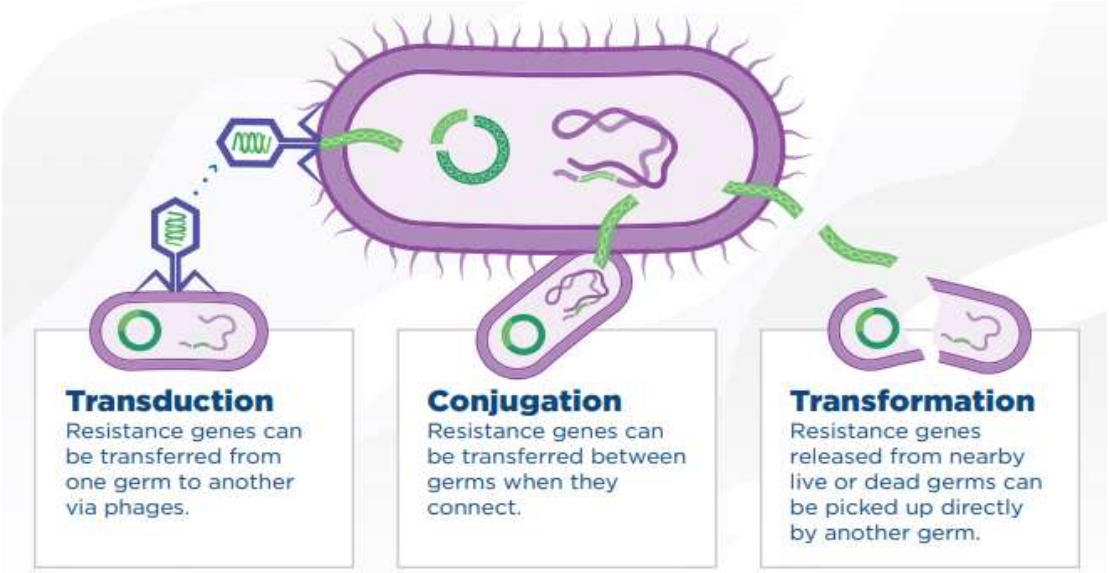


Figure 1.4: Bacterial gene exchange (CDC, 2019)

1.1.3.4 Causes of antimicrobial resistance

Several factors may contribute to the emergence of AMR, with previous antimicrobial use playing a major role in this process. Evidence of this association has been examined in several studies (Muller *et al.,* 2004; Polk *et al.,* 2004; Goossens *et al.,* 2005; Aldeyab *et al.,* 2012; Marchaim *et al.,* 2012; McKinnell *et al.,* 2012; Livermore *et al.,* 2013). For example, studies have found that the prevalence of *P. aeruginosa* and *Enterobacter* species, that were resistant to antimicrobials, increased with the increasing use of them (Muller *et al.,* 2004; Polk *et al.,* 2004). Recent exposure to antimicrobials was identified as the only predictor that was associated with vancomycin-resistant *Enterococci* and carbapenem-resistant *Enterobacteriaceae* (Marchaim *et al.,* 2012; McKinnell *et al.,* 2012). On a wider scale, it is evident that AMR is associated with antimicrobial consumption as high rates of AMR are usually associated with countries that have high antimicrobial consumption (van de Sande-Bruinsma *et al.,* 2008; O'Neill, 2014).

1.1.3.5 Other issues associated with antimicrobial use

In addition to AMR, other drawbacks have been associated with antimicrobial use. It is evident that antimicrobial exposure frequently precedes *Clostridioides* (formerly *Clostridium*) *difficile (C. difficile)* infection, particularly antimicrobials known as the 4Cs (cephalosporins, co-amoxiclav, ciprofloxacin/fluoroquinolones and clindamycin) and broad-spectrum β-lactams, have been implicated (Rupnik *et al.,* 2009; Hensgens *et al.,* 2012; Lawes *et al.,* 2017). *C. difficile* is known as the leading cause of infective nosocomial diarrhoea worldwide and is associated with significant morbidity and mortality (Peery *et al.,* 2012; Wiegand *et al.,* 2012; Chitnis *et al.,* 2013). In addition, *C. difficile* infection can increase the length of hospital stay which, in turn, leads to increased healthcare costs (Kyne *et al.,* 2002). Moreover, *C. difficile* is a spore-forming organism that has the ability

to survive for a long period of time on inanimate surfaces where it can be easily spread amongst immunocompromised patients, leading to additional morbidity, mortality and healthcare expenses (Claro *et al.,* 2014; Vindigni and Surawicz, 2015).

1.1.4 Inappropriate antimicrobial prescribing in hospital settings

It is estimated that between 25% to 50% of hospitalised patients receive antimicrobials, with between 30% to 50% of this antimicrobial use being inappropriate (Dellit *et al.,* 2007; Tamma *et al.,* 2014). The WHO defined appropriate antimicrobial use as:

> *"The cost-effective use of antimicrobials which maximises their clinical therapeutic effect, while minimising both drug-related toxicity and the development of antimicrobial resistance."* (Stamm *et al*., 2001, p.15)

In the literature, inappropriate antimicrobial prescribing has been described as being associated with the following: unnecessarily long treatment duration (Vaughn *et al.,* 2019; Krockow *et al.,* 2020) and antimicrobials that have no medical indications, such as for viral infections (Landstedt *et al.,* 2017). It can also manifest itself as the unnecessary prescribing of broad-spectrum antimicrobials where infections can be treated with narrow-spectrum antimicrobials (Spivak *et al.,* 2016).

1.1.5 Drivers for inappropriate antimicrobial prescribing in hospital settings

Physicians often have a mindset that their primary and only responsibility is to the individual patient they are interacting with, rather than to an abstract anonymous system that is there to globally help all patients. Therefore, it is commonplace for physicians to prescribe antimicrobials for emotional rather than clinical reasons, despite realising that the antimicrobial is likely to be ineffective and with no regard for the potential harm inflicted on the wider population (McDonnell Norms Group, 2008). Furthermore, physicians are challenged by antimicrobial prescribing when it

comes to considering effective management practices. The decision-making process becomes even more complicated when trying to decide the most suitable antimicrobial that is likely to work against a given infection in a specific patient (Niederman, 2003). Other factors, such as patient status, satisfaction, expectations, physicians' attitudes and diagnostic challenges, have been associated with inappropriate antimicrobial prescribing (Teixeira Rodrigues *et al.,* 2013; Gonzalez-Gonzalez *et al.,* 2015; Pinder *et al.,* 2015; Teixeira Rodrigues *et al.,* 2015; Teixeira Rodrigues *et al.,* 2016). Understanding factors that affect physicians' antimicrobial prescribing have been effective at changing inappropriate antimicrobial prescribing (Tonkin-Crine *et al.,* 2015). An in-depth understanding of these factors is vital when it comes to implementing effective intervention and improving such prescribing. Qualitative research has been used to explore factors that influence physicians' antimicrobial prescribing in hospital settings (Teixeira Rodrigues *et al.,* 2013; Skodvin *et al.,* 2015). A systematic review by Teixeira Rodrigues *et al.* (2013) showed that factors that influenced antimicrobial prescribing were grouped into intrinsic (physicians' attitudes and socio-demographics factors) and extrinsic (health care systems, patients, the pharmaceutical companies, financial incentives and cost-saving). However, in this systematic review, most of the studies were conducted in primary care settings, and only a minority were conducted in hospital settings. Factors that influence physicians' antimicrobial prescribing in hospital settings may differ from those in primary care settings. Moreover, these factors may also differ between countries and different healthcare systems (Skodvin *et al.,* 2015; Tarrant *et al.,* 2021).

1.2 Strategies to improve antimicrobial prescribing

1.2.1 Overview of antimicrobial stewardship programmes

1.2.1.1 History of antimicrobial stewardship programmes

Initially, "antimicrobial stewardship" was commonly used in the narrow context of programmes in individual hospitals (Kazanjian, 2016). The first prospective audit and feedback program was in the late 1970s and 1980s, at Hartford Hospital, Hartford, USA. This programme was formed by ID physicians and clinical pharmacists and included transitional therapy and streamlining (de-escalation; Briceland *et al.,* 1988). Later, in the late 1990s, Fraser *et al.* (1997) conducted a randomised controlled trial (RCT) to evaluate a prospective audit and feedback programme. They found that this programme could reduce antimicrobial use without negatively impacting clinical outcomes (Fraser *et al.,* 1997). The success of this programme resulted in later adoption by other hospitals, showing that this strategy was viable (LaRocco, 2003).

In 2007, the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) published guidelines for implementing an institutional programme to improve antimicrobial stewardship (Dellit *et al.,* 2007). According to both societies, effective ASPs are evidence-based, can enhance patient care and can be economically self-supporting (Dellit *et al.,* 2007).

1.2.1.2 Definition of antimicrobial stewardship

Antimicrobial stewardship has been defined by the SHEA, IDSA and the Paediatric Infectious Diseases Society as:

> *"Coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal [antibiotic] drug regimen, including dosing, duration of therapy, and route of administration."* (Fishman, 2012, p.323)

ASPs have many terms, including antimicrobial policies, antimicrobial control programmes, and other terms that refer to any programmes that inform antimicrobial use at a health care institute (MacDougall and Polk, 2005).

They were established to improve antimicrobial prescribing practices. The primary goal was to enhance clinical outcomes while eliminating or reducing the unintended consequences of antimicrobial use (e.g., toxicity, the emergence of AMR; Dellit *et al.,* 2007; Malani *et al.,* 2013; Davey *et al.,* 2017). Reducing health care expenditure without negatively affecting the quality of care was a secondary goal of ASPs (Dellit *et al.,* 2007).

1.2.2 Core elements of hospital ASPs

According to the CDC there are 7 elements of hospital ASPs. These are hospital leadership commitment, accountability, pharmacy expertise, action, tracking, reporting, education (Figure 1.5).

Support from the hospital leadership is essential to the success of ASPs. Priority hospital Leadership Commitment included giving the leaders time to manage and operate the programme, providing resources to run the program successfully, conducting regular meetings with ASPs leaders to evaluate the needed resources to achieve the goals for improving appropriate antimicrobial use, Assigning a senior leader to as a point of contact or for the ASP to ensure that the program has the needed support and resources, reporting ASP activities and outcomes in a regular basis to the hospital board (CDC, 2019b).

The ASP must assign a leader who is accountable for management of the programme and outcomes. Effective management, communication and leadership skills are important for the leader of a hospital ASP (CDC, 2019b).

Engagement of pharmacist as a leader of the program is a key for an effective ASPs. ID pharmacists are effective in improving appropriate antimicrobial use and usually help lead ASPs in hospitals (Yu *et al.,*2014; Bessesen *et al.,* 2015).

Action includes several interventions to improve antimicrobial use. These interventions divided into priority and other. Priority interventions include preauthorisation, prospective audit and feedback and facility-specific treatment guidelines. Other interventions are categorised as pharmacy-based interventions, infection-based interventions, provider-based interventions, microbiology-based interventions and nursing-based interventions (CDC, 2019b). These interventions are reported in details in section 1.2.3.

Tracking is key to identify opportunities for improvement and to assess the impact of interventions. Tacking include monitoring antimicrobial use, impact of stewardship interventions, and other outcomes such as AMR, *C. difficile* infection and financial impact (CDC, 2019b).

ASPs should offer regular reports to leadership, physicians, pharmacists and nurses on antimicrobial use and resistance together with ASP work. Information from antimicrobial use evaluations is a tool to encourage improved appropriate prescribing (CDC, 2019b).

Education is a vital element of any programme aimed at improving antimicrobial prescribing behaviours (Dellit *et al.,* 2007). Education could be delivered in different ways, including formal teaching, conference presentation, provision of written guidelines, email alerts and online learning (Girotti *et al.,* 1990; Bantar *et al.,* 2003; Belongia *et al.,* 2005). The literature has shown that education without the integration of active intervention is only marginally effective in changing prescribing patterns for antimicrobials (Girotti *et al.,* 1990; Bantar *et al.,* 2003; Belongia *et al.,*

2005; Dellit *et al.,* 2007). Cisneros *et al.* (2014) showed that the implementation of education-based ASPs led to a significant improvement in antimicrobial prescribing practice and a reduction in inappropriate antimicrobial use despite no implementation of restrictive antimicrobial measures. However, this could be largely due to the high level of acceptance of the programme by the physicians (Cisneros *et al.,* 2014).

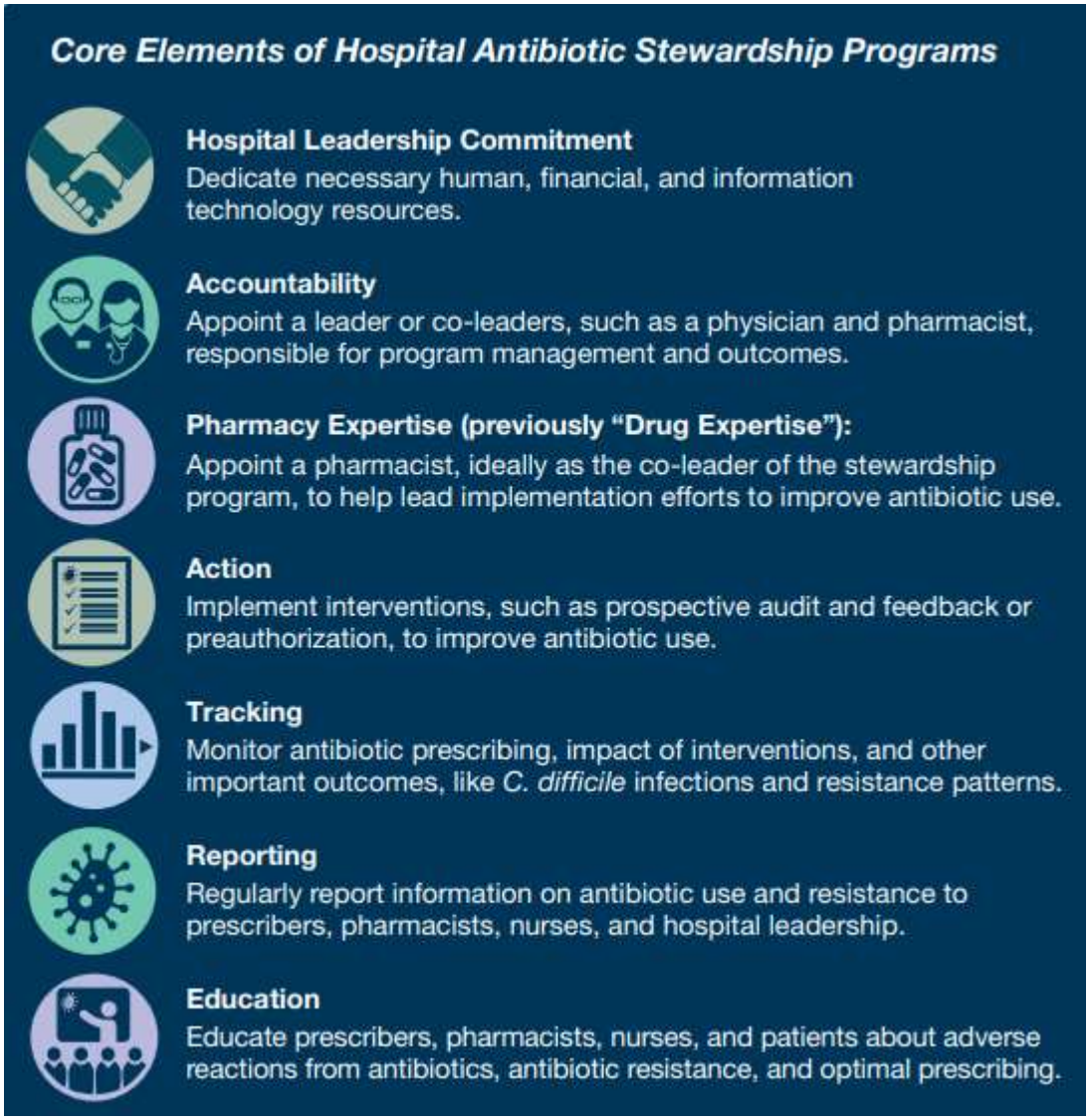


Figure 1.5: CDC core elements of hospital ASPs (CDC, 2019b).

1.2.3 Hospital inpatient stewardship interventions

A wide range of interventions to improve antimicrobial prescribing in hospital inpatients have been attempted worldwide (Davey *et al.,* 2017; Bertollo *et al.,* 2018). Stewardship interventions are commonly classified according to the strategy with which they aim to affect antimicrobial use (Dellit *et al.,* 2007). As identified by IDSA and SHEA guidelines, proactive programmes to promote antimicrobial stewardship include formulary restriction and preauthorisation, and prospective audit with intervention and feedback (Dellit *et al.,* 2007). Other supplemental programmes involve education, guidelines and clinical pathways, antimicrobial order forms, de-escalation of therapy, intravenous (IV) to oral switch therapy, and dose optimisation (Dellit *et al.,* 2007). Many ASPs adopt mixed strategies. Thus, strict classification is not always possible (Fishman, 2006; Dellit *et al.,* 2007). Previous reviews from the literature have used different classification categories (Owens *et al.,* 2004; Paskovaty *et al.,* 2005; Akpan *et al.,* 2016; Davey *et al.,* 2017). When choosing a programme or set of programmes to implement, it is important to consider the available resources, local culture and attitudes (Dellit *et al.,* 2007). According to the CDC antimicrobial stewardship interventions are classified to priority interventions, pharmacy-based interventions, infection-based interventions, provider-based interventions, microbiology-based interventions and nursing-based interventions (CDC, 2019b). These interventions are discussed in details below.

1.3.2.1 Priority interventions

1.3.2.1.1 Preauthorisation

Formulary restriction include limiting the use of certain antimicrobials to specific indications, length of therapy, or prescribers or patient population. This method

often includes preauthorisation for dispensing of restricted antimicrobial agent through assessment by an ID physician or clinical pharmacist (MacDougall and Polk, 2005; Drew, 2009). From the literature, restricting antimicrobial use either through formulary restriction or preauthorisation have been widely implemented (Davey *et al.,* 2017; Bertollo *et al.,* 2018). This approach is considered to be the most effective method of achieving the aim of controlling antimicrobial use (Dellit *et al.,* 2007; Altunsoy *et al.,* 2011). Longitudinal studies implementing antimicrobial restrictions have shown significant reductions in antimicrobial use (Dellit *et al.,* 2007).

Moreover, formulary restriction and preauthorisation requirements have resulted in reductions in AMR (Quale *et al.,* 1996; White *et al.,* 1997; Bantar *et al.,* 2003; Martin *et al.,* 2005; Pakyz *et al.,* 2009; Lewis *et al.,* 2012; Abdallah *et al.,* 2017). Pakyz *et al.* (2009) conducted a retrospective, multicentre study to evaluate the impact of carbapenem restriction on the use of carbapenems and the proportion of carbapenem-resistant *P. aeruginosa* from 2002 to 2006. In this study, hospitals that restricted the prescribing of carbapenems used significantly smaller volumes of them than those that did not (p=0.04). In addition, they reported lower incidence rates of carbapenem-resistant *P*. *aeruginosa* (p = 0.01) over the study period. Similarly, a retrospective study to compare carbapenem-resistant *P. aeruginosa* before and after three months of carbapenem restriction showed that the resistance of *P. aeruginosa* to meropenem and imipenem decreased significantly from 74.1% to 30% (P = 0.012) and from 76% to 38.5% (P = 0.019), respectively (Abdallah *et al.,* 2017).

The effectiveness of a preauthorisation programme depends on the education and skills of the authorised person who makes the recommendations (Dellit *et al.,* 2007; Barlam *et al.,* 2016). It has been found that the restriction of antimicrobial use through a preauthorisation requirement from an attending physician or chief resident had no

impact on its use (DeVito and John, 1985). In another study, recommendations from an antimicrobial team involving a pharmacist and an ID specialist led to an increase in antimicrobial appropriateness and improved economic outcome, compared to recommendations from ID colleagues (Gross *et al.,* 2001).

Interventions that restrict antimicrobial choice by requiring preauthorisation can have unintended consequences. Generally, there is some evidence that prescribers may view restrictions as a loss of autonomy, i.e., the capability for self-determination, which may create controversy and conflict between ID specialists and other clinical specialities (Garau, 2006; Drew *et al.,* 2009). In a large academic medical centre, 50% of the staff felt that being forced to request approval was frustrating and limited their autonomy. Furthermore, approval by the antimicrobial team may create tensions where they are anxious to keep good relationships with other colleagues, which may in turn affect their approval practices (Seemungal and Bruno, 2012).

Restricting the use of some antimicrobial agents may simply shift issues on to an alternative agent, a phenomenon known as “squeezing of the balloon” (MacDougall and Polk, 2005, Dellit *et al.,* 2007). This phenomenon is exemplified in a study by Rahal *et al.* (1998) in which a preauthorisation policy for cephalosporin resulted in a decrease in cephalosporin use and a significant decrease in the incidence of the resistant *Klebsiella* infection. Concomitantly, imipenem use increased and there was an increase in the incidence of imipenem resistant *P. aeruginosa*. This untoward phenomenon may counteract the benefits of such a programme approach (Burke, 1998). Accordingly, in institutions that use restriction to limit the use of some antimicrobials, it is important to monitor the overall trends in antimicrobial use to evaluate and respond to such shifts in it.

In addition to “squeezing the balloon” and staffing challenges, additional potential limitations surrounding prior authorisation and formulary restriction include delays in starting the antimicrobial therapy. Research has shown that such a strategy could delay the time of the first antimicrobial dose (LaRosa *et al.,* 2007; Winters *et al.,* 2010). This drawback can be avoided by the allowance of a first dose during 24 to 72 hours of therapy before any restriction is then applied. However, this may still result in unnecessary initiation and/or hinder considering de-escalation sooner.

A concern with the preauthorisation approach is that it is considered to be labour intensive. This process requires skilled personnel to be available to provide immediate approval of the desired antimicrobials. However, integration of this practice into routine workflow can be challenging. Researchers have shown that prescribers tended to exaggerate the severity of patients’ illnesses to gain approval for the use of a restricted antimicrobial (Calfee *et al.,* 2003; Linkin *et al.,* 2006). In addition, in settings where after-hours availability of antimicrobials without preauthorisation is implemented, they avoid the restriction control by waiting until after hours to order these restricted antimicrobials (LaRosa *et al.,* 2007). However, these limitations can be corrected by implementing programmes or interventions that consider these issues.

1.2.2.1.2 Prospective audit with feedback

Prospective audit with feedback involves the assessment of the appropriateness of antimicrobial therapy and making recommendations to the prescriber if the prescribed therapy is suboptimal (Dellit *et al.,* 2007; Drew, 2009). This type of intervention is mainly a team-based approach to optimise patient therapy with a focus on both patient and hospital outcomes (Griffith *et al.,* 2012). This usually occurs within 48-72 hours after the initiation of antimicrobial therapy, allowing for more

clinical and microbiological data to become available before revaluating the empiric therapy (Fraser *et al.,* 1997; Chan *et al.,* 2011; Yeo *et al.,* 2012). It can also be initiated earlier, within 24 hours, to ensure the appropriate prescribing of empiric therapy (Tamma and Cosgrove, 2011).

A number of studies reporting the impact of this strategy have been published and most of them measured the outcome using before and after study design (Hamilton *et al.,* 2000; Carling *et al.,* 2003; Feucht and Rice, 2003; Elligsen *et al.,* 2015; Morrill *et al.,* 2016). However, some RCTs have been reported (Fraser *et al.,* 1997; Gums *et al.,* 1999; Solomon *et al.,* 2001).

Studies have consistently reported decreased antimicrobial use, antimicrobial costs and /or duration of hospital stay (Fraser *et al.,* 1997; Gums *et al.,* 1999; Solomon *et al.,* 2001; Elligsen *et al.,* 2015; Morrill *et al.,* 2016). Solomon *et al.* (2001) conducted an RCT in a large teaching hospital involving the implementation of an antimicrobial prescribing review and feedback to improve the appropriateness of broad-spectrum antimicrobial prescribing. In this study, the intervention group had prescribing reviewed by an antimicrobial stewardship team, which included either an ID physician or a pharmacist. A reduction of 37% in the duration of inappropriate antimicrobials compared with the control group was recorded (Solomon *et al.,* 2001). Another study conducted in a teaching hospital to evaluate the impact of prospective audit and feedback showed that there was a trend towards decreased antimicrobial costs, length of stay (LOS) and adverse events (Morrill *et al.,* 2016). In the study, the difference in overall antimicrobial use between the pre- and post-period was not significant; however, there was a significant decrease in the use of broad-spectrum antimicrobials, including carbapenems and piperacillin-tazobactam, during the post-period.

A Study with longer evaluation period has reported an impact on AMR. Carling *et al.* (2003) performed a time series methodology comparing a three-year pre-implementation period versus a seven-year post-implementation period. The programme involved a multidisciplinary team, including a clinical pharmacist and an ID physician, to review and provide feedback on broad-spectrum antimicrobial prescribing to physicians. This type of intervention led to a decrease in the use of third-generation cephalosporins and aztreonam, while the rate of fluroquinolones and imipenem use were stable over the study period. Rates of nosocomial infection caused by drug-resistant *Enterobacteriaceae* and *C. difficile* infections decreased compared with the pre-implementation period (Carling *et al.,* 2003).

Ohashi *et al.* (2019) evaluated the clinical outcome of prospective audit and feedback programme over a two-year period. Their programme was expanded from patients prescribed specific antimicrobials to those prescribed all IV antimicrobials.They found that the average days of therapy for IV antimicrobials was significantly shorter during the expansion period than during the pre-expansion period. Moreover, the ratio of Methicillin-resistant *Staphylococcus aureus* (MRSA) to *Staphylococcus aureus* (S. aureus) was significantly lower during the expansion period compared with the pre-expansion period.

A recent review that evaluated the evidence on the impact of prospective audit with feedback intervention on AMR stated that the evidence that this type of intervention may play a beneficial role in controlling AMR is lacking and there is a need to conduct a well-designed study to fill this gap in the literature (Chatzopoulou *et al.,* 2020).

From the literature, it is evident that post-prescription review improves antimicrobial use in specific settings, such as intensive care units (ICU; Elligsen *et al.,* 2015), long-

term facilities (Jump *et al.,* 2012; Pate *et al.,* 2012) and community hospitals with limited resources (Carling *et al.,* 2003; LaRocco, 2003; Curcio, 2010; Yam *et al.,* 2012). Prospective audit and feedback programmes have the advantage that prescribers do not perceive loss of autonomy as accepting recommendations from a stewardship team is optional (Heineman and Watt, 1986, Seto *et al.,* 1996; Dellit *et al.,* 2007). In addition, the feedback component of these programmes provides educational opportunities to prescribers, which may improve future prescribing. Figure 1.6 illustrates the general workflow schematic for a prospective audit and feedback programme as well as a formulary restriction and preauthorisation programme for antimicrobial stewardship.

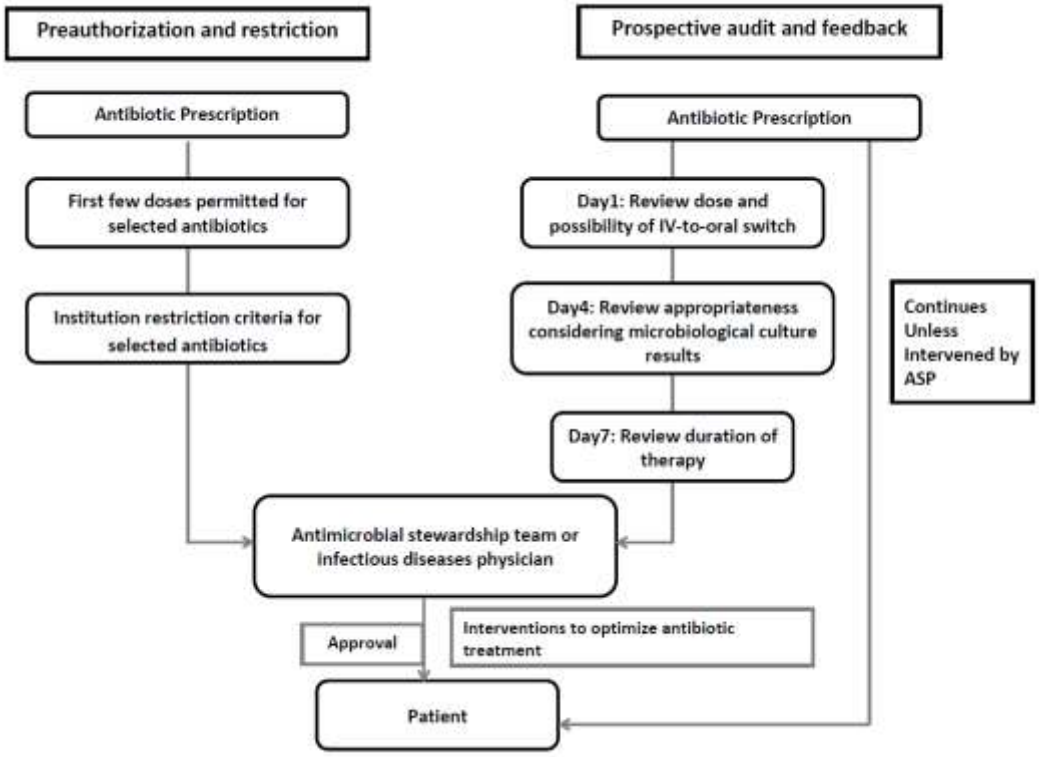


Figure 1.6: General workflow schematic for a prospective audit and feedback programme as well as a formulary restriction and preauthorisation programme for antimicrobial stewardship (Chung *et al.,* 2013).

3.2.1.3 Facility-specific treatment guidelines

Guidelines are *"statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"* (Institute of Medicine, 2011).

Clinical pathways are tools that are developed and used to guide healthcare decisions (Kinsman *et al*., 2010). Adherence to national guidelines is often poor because of their lack of local applicability (MacDougall and Polk, 2005). However, guideline implementation has been shown to improve antimicrobial prescribing use if the institutional formulary and local AMR pattern are taken into consideration (Dellit *et al.,* 2007). These guidelines and clinical pathways should be implemented with multidisciplinary input from ID physicians, clinical pharmacists with ID backgrounds and clinical microbiologists. Guideline implementation has been shown to increase the likelihood of adequate initial antimicrobial therapy (Ibrahim *et al.,* 2001; Hauck *et al.,* 2004), enhance the use of narrow-spectrum antimicrobials (Marrie *et al.,* 2000; Jenkins *et al.,* 2011; Newman *et al.,* 2012), and lead to shorter duration of therapy (Marrie *et al.,* 2000; Ibrahim *et al.,* 2001; Dellit *et al.,* 2008; Jenkins *et al.,* 2011; Carratalà *et al.,* 2012) all without adversely affecting other clinical outcomes.

1.3.2.2 Pharmacy-based Interventions

Pharmacy-based interventions include documentation of antimicrobials indications, IV to oral switch therapy, dose adjustments and optimisation, duplicative therapy alerts, time-sensitive automatic stop orders and prevention and detection antimicrobial-related drug-drug interactions. Table 1.6 provides a summary of pharmacy-based interventions.

Table 1.6: Summary of pharmacy-based antimicrobial stewardship interventions.
(Kollef, 2000, MacDougall and Polk, 2005; Dellit *et al.,* 2007; Drew, 2009; Drew *et al.,* 2009; Gilchrist and Geoghegan, 2018**;** CDC, 2019b)

Strategy
Documentation of antimicrobials indications • Can facilitate other interventions such as prospective audit and feedback
IV to oral switch *The switch from intravenous to oral therapy* • May decrease hospital LOS and costs. • May reduce risk of complications associated with IV access. • May face difficulty in identifying patients in whom switching therapy is appropriate.
Dose adjustment and optimisation *The consideration of patients' characteristics, the site of infection, the causative organism and the pharmacodynamic and pharmacokinetic characteristics* • Can reduce costs. • Decrease adverse effects. • Dosing in special populations may not always be available.
Duplicative therapy alerts *Alerts in situations where therapy might be unnecessarily duplicative including simultaneous use of multiple agents with overlapping spectra*
Time-sensitive automatic stop orders *Stop orders useful for specified antibiotic prescriptions and indications, especially antibiotics administered for surgical prophylaxis*
Prevention and detection antimicrobial-related drug-drug interactions

Key: AMR: antimicrobial resistance; IV: intravenous; LOS: length of stay

1.3.2.3 Infection-based interventions

Infection-based interventions include interventions to improve appropriate use in common infections such as lower respiratory tract infection, urinary tract infections (UTI) and SSTIs. Interventions focused on improving diagnostic accuracy, tailoring therapy to culture and sensitivity results, optimising duration of therapy and avoiding unnecessary broad-spectrum antimicrobials (CDC, 2019b).

1.3.2.4 Provider-based interventions

Provider-based interventions include antibiotic timeout and assessing penicillin allergy. Antibiotic timeout is a physician re-evaluation of the need of the continuation and choice of antimicrobials when more diagnostic data such as culture and sensitivity results is available. Assessing penicillin allergy and ensure the proper

assessment of the allergy should be considered as a part of the stewardship intervention (CDC, 2019b).

1.3.2.5 Microbiology-based interventions

Microbiology-based interventions include selective reporting of antimicrobial susceptibility testing results is tailoring susceptibility reports to provide only few antimicrobials, first-line and narrow-spectrum agents, that are recommended by the ASP or according to the hospital guidelines. Another intervention is providing comments in the microbiology reports that could help the physicians (i.e pathogens that might represent contamination or colonisation (CDC, 2019b).

1.3.2.6 Nursing-based interventions

Nursing- based interventions include optimising microbiology cultures through the use of proper techniques to obtain cultures, initiating discussion on IV to oral switch and promoting antibiotic timeouts (CDC, 2019b).

Antimicrobial stewardship interventions are effective in improving appropriate antimicrobial prescribing. A systematic review of 221 studies to evaluate the safety and effectiveness of interventions to improve antimicrobial prescribing to hospital inpatients, found that antimicrobial stewardship interventions are effective in improving compliance with antimicrobial policies, reducing duration of antimicrobial therapy and it may reduce length of hospital stay without increasing mortality. Moreover, interventions were effective in safely reducing excessive antimicrobial use (Davey *et al.,* 2017).

Moreover, Antimicrobial stewardship interventions are effective in reducing the incidence of infections and colonisation with multidrug-resistant bacteria. In a systematic review of 32 studies to evaluate the impact of antimicrobial stewardship

on the incidence of infections and colonisation with antimicrobial-resistant bacteria in hospital inpatients indicated that ASPs decrease the incidence of C.difficile infections and infections and colonisation with antimicrobial-resistant bacteria, particularly carbapenem-resistant and ESBL-producing Gram-negative bacteria (Baur et al., 2017).

1.3 Research context

1.3.1 Overview of Kingdom of Saudi Arabia

The Kingdom of Saudi Arabia (KSA), the largest country in the Middle East, is spread over two million square kilometres (Figure 1.7). It is considered to be one of the wealthiest and fastest-growing countries in the Middle East (Almalki *et al.,* 2011). According to the United Nations Development Programme (UNDP), the Human Development Index, which assesses progress in life expectancy, education and standard of living, ranks the KSA very highly (0.854), placing it at 38 out of 189 countries (UNDP, 2020).

The last official census in 2019 measured the population of the KSA to be 34.2 million, compared with 33.4 million in 2018 and registering a population growth rate of 2.4%. Saudi nationals comprise around 62.2 % of the total population, while 37.8% are non-Saudi; 57.7% are males and 42.3% are females. Approximately 48.6% of the population is under the age of 30 years and 3.2% are over the age of 65 years (General Authority for Statistics [GASTAT], 2019). It is estimated that the population of the KSA will reach 39.8 million by 2025 and 54.7 million by 2050, which will increase the demand for essential services and facilities, including healthcare, while, at the same time, create economic opportunities (United Nations, 2003).

Figure 1.7: The map of the KSA (Country Reports, 2018)

1.3.2 Saudi healthcare system background

The healthcare system was established in the first quarter of the 20th century and it was called the Directorate of General Health and Ambulance (Mufti, 2000). Later, after the discovery of oil, significant changes in the health system occurred which led to the establishment of the Ministry of Health (MOH) in 1950 (Mufti, 2000). This is considered to be the real beginning of healthcare provision in the KSA. In the 1970s, a 5-year national development plan was implemented by the government to improve the healthcare system (Mufti, 2000; Almalki *et al.,* 2011). Great expansion and the development of health facilities were evident during that period, including the initiation of primary healthcare, hospitals, research centres and the entire infrastructure (Mufti, 2000). Both the development of the healthcare system and the human resources led to promoting scholarships in the medical sciences and establishing medical science colleges (Albejaidi, 2010; Yusuf, 2014). Accordingly, the KSA is ranked 26th in the WHO's measurement of overall healthcare system performance (Tandon *et al.,* 2000).

1.3.3 Structure analysis of the current health care system

The health care system in the KSA is based on the principle of providing free healthcare services to all its citizens (Walston *et al.,* 2008). The MOH is the major healthcare provider through hospitals and a network of primary healthcare centres that are distributed throughout the country. In addition, other governmental bodies provide healthcare services. These bodies are organised and are independent of the MOH in that they have their own budgetary allocations and supervise the administration of their facilities (Walston *et al.,* 2008; Almalki *et al.,* 2011). The private sector also provides healthcare services, predominantly in cities and large towns. All sectors should achieve the government's health objectives. An overview of the structure of the health care system is provided in Figure 1.8.

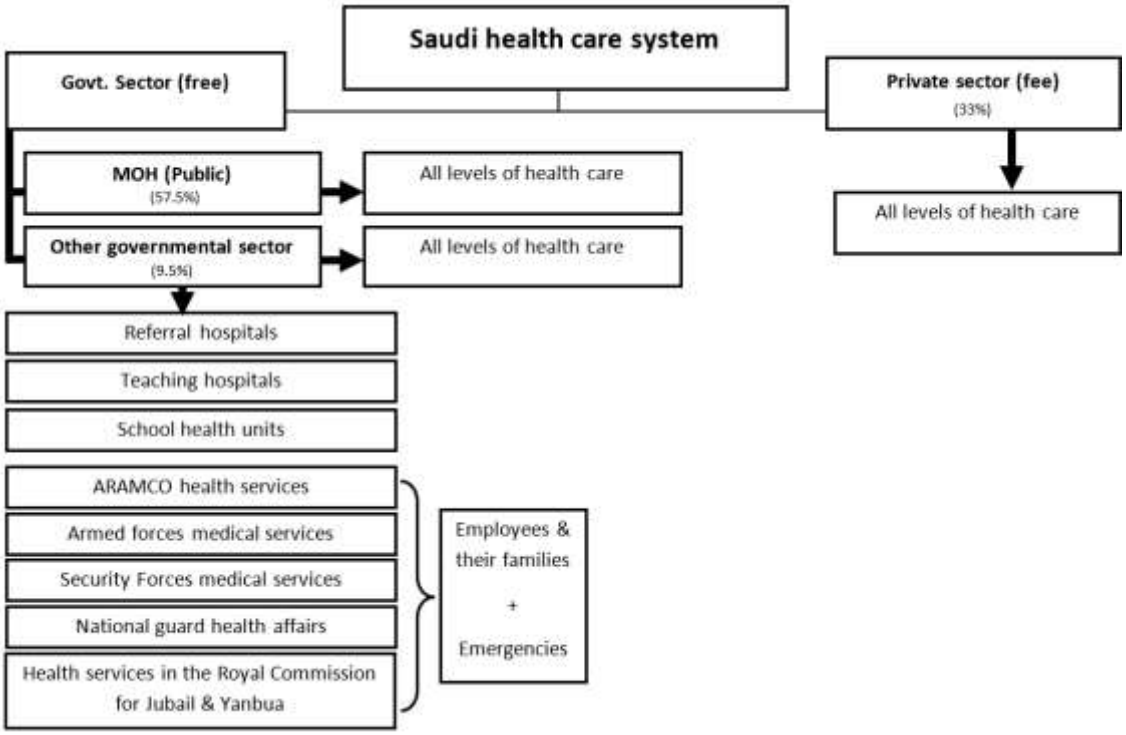


Figure 1.8: Structure of the health care system in the KSA (Almalki *et al.,* 2011; MOH, 2018).

1.3.4 King Saud University Medical City

King Saud University Medical City (KSUMC) is a 1,800-bed tertiary care academic and referral medical city with long experience in multidisciplinary and multi-facility administration. There are eight centres and hospitals under KSUMC. These include a Cardiac Centre, Diabetes Centre, Oncology Centre, Ear Specialist Centre, the Family Medicine Centre, King Khalid University Hospital (KKUH), King Abdul-Aziz University Hospital and the Dental Hospital. KSUMC employs more than 1,300 physicians, 853 fellows and residents and around 2,072 other health personnel who provide care for more than 1,229,628 outpatients, 45,966 inpatients and carry out around 14,231 procedures annually (KSU, 2018).

KKUH is a tertiary care facility that provides medical, surgical, intensive care, emergency, family medicine, dental, occupational health and home healthcare services. KKUH has an approximately 1,100-bed capacity spread across inpatients (939*),* ICU (104), the emergency room (64) and operation room (32) (KSUMC, 2018). KKUH serves all eligible paediatric (0-17 years) and adult (above 17) patients from the local population, providing them with inpatient and outpatient services. In addition, referrals from other KSUMC hospitals and centres and other KSA hospitals are received. In 2016 and 2017, KKUH served a total of around 47,000 inpatients and 940,000 outpatients (KSUMC, 2018).

The department of pharmacy at KKUH is responsible for providing and ensuring optimal pharmaceutical care to ambulatory care patients and inpatients. The pharmacy department includes ambulatory care, inpatient and emergency care services, an inventory management unit and a pharmacy support department (KSUMC, 2018). It also serves in an educational, evaluation and advisory capacity through the Pharmacy and Therapeutic Committee (PTC) to ensure the coordination,

development and review of all professional standards, policies and procedures related to all aspects of medication use.

1.3.5 Antimicrobial resistance rates and surveillance in the Kingdom of Saudi Arabia

The Intercontinental Marketing Service Health MIDAS® is a database that estimates global antimicrobial consumption from the volume of antimicrobials sold in retail and hospital pharmacies. Antimicrobial consumption is collected directly from manufacturers and indirectly from wholesalers, with the volume of consumption estimated in standard units; these are the number of doses sold by formulation presentation. Between 2000 and 2010, the antimicrobial consumption in 71 countries, including the KSA, increased by 35% overall (from 52,057,163,835 standard units to 70,440,786,553 standard units; Van Boeckel *et al.,* 2014). It was found that the consumption of carbapenems increased by 45% (Van Boeckel *et al.,* 2014). A more recent study that analysed the trends of antimicrobial consumptions in 76 countries from 2000 through to 2015 reported that antimicrobial consumption, expressed in DDD, increased by 65% (from 21.1 to 34.8 billion DDDs; Klein *et al.,* 2018). The findings from this study cannot be compared with the previously reported study (Van Boeckel *et al.,* 2014) because the consumption data were not reported as DDD. However, in both studies, there was an underestimation of antimicrobial consumption by several countries as the audit did not cover the whole market. This is important from a KSA perspective, where only retail sales (50%) were included (Van Boeckel *et al.,* 2014; Klein *et al.,* 2018). Figure 1.9 illustrates consumption data of some antimicrobials from retail sales in the KSA.

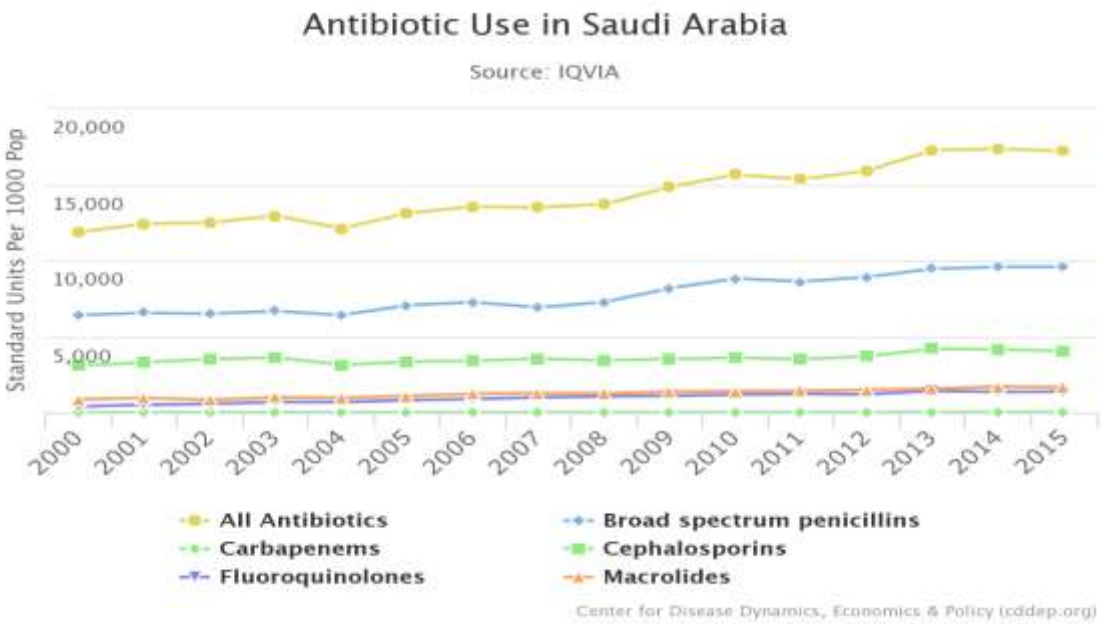


Figure 1.9: Antimicrobial consumption data from retail sales in the KSA (The Center for Disease Dynamics Economics and Policy, 2020a).

The KSA has several challenges that can promote the emergence and spread of MDR bacteria (Zowawi, 2016). For example, travel is a known risk factor for acquiring and transmitting AMR bacteria (Rogers *et al.,* 2011; Ostholm-Balkhed *et al.,* 2013) and the KSA experiences heavy international travel due to the large population of expatriate workers and the hosting of over nine million pilgrims and visitors throughout the year to the holy city of Mecca for Umrah and Hajj (Kapiszewski, 2006; Ostholm-Balkhed *et al.,* 2013; Azeem *et al.,* 2014; GASTAT, 2019). The adherence of healthcare providers to infection control practices and the lack of legislation covering the prudent and responsible use of antimicrobials are further challenges (Balkhy *et al.,* 2016). Most hospitals have no established stewardship programmes, and community pharmacies frequently dispense antimicrobial agents with no prescription (Aly and Balkhy, 2012). AMR among Gram-negative bacteria is a global problem, including in the KSA, with major concerns regarding *A. baumannii, P. aeruginosa,* and *Enterobacteriaceae*. In the KSA, there has been an increase in the prevalence of extended-spectrum beta-lactamase (ESBL)-producing isolates, where some institutions reported 53.8% ESBL

rates among *Klebsiella pneumonia*e (*K. pneumoniae*; Rahim and Mohamed, 2014), 16.6%-23.1% ESBL rates among *Escherichia coli* (*E. coli*; Al Johani *et al.,* 2010; Mashwal *et al.,* 2017) and 16% ESBL rates among *P. aeruginosa* (Tawfik *et al.,* 2012). A systematic review of MDR in gram-negative bacilli showed a significant increase in the rate of carbapenem-resistant gram-negative bacteria in the KSA over recent years in comparison to the rates of the 1990s (Zowawi *et al.,* 2013). The first reported outbreak of carbapenem-resistant *K. pneumonia*e in the KSA was from 2009 to 2010 (Balkhy *et al.,* 2012). A multicentre study on gram-negative bacteria isolated from 24 hospitals showed that 15.9% of *P. aeruginosa* isolates were resistant to imipenem (Memish *et al.,* 2012). In a tertiary hospital in Riyadh, the rate of carbapenem susceptible *P. aeruginosa isolates* in the ICU declined from 66% in 2004 to 26% in 2009 (Al Johani *et al.,* 2010). A study conducted in KSUMC found that among 33 *P. aeruginosa isolates*, there was a high level of resistance to imipenem (90.9%) and meropenem (81.8%), with 39.4% being resistant to doripenem (Somily *et al.,* 2012). Carbapenem-resistant *A. baumannii* has increased dramatically in the KSA over the years (Zowawi *et al.,* 2013). A study conducted in Riyadh between 2004 and 2009 showed that the susceptibilities of *A. baumannii* to imipenem decreased from 55% to 10% and the susceptibilities of *A. baumannii* to meropenem decreased from 33% to 10% (Al Johani *et al.,* 2010). Similarly, a study conducted in Riyadh found that the susceptibilities of *A. baumannii* to meropenem and imipenem in 2006 were between 64-81.2%; in 2009, they were between 34.5–45.3%, and in 2012 between 8.3-11% (Al-Obeid *et al.,* 2015). A study conducted in KSUMC reported that most *A. baumannii* strains were resistant to meropenem (90.5%), imipenem (90.5%) and doripenem (77.4%; Somily *et al.,* 2012).

Studies in the KSA have shown that gram-negative bacteria resistance to piperacillin/tazobactam is increasing (Ahmed, 2016; Youssif *et al.,* 2018). Youssif *et al.* (2018) showed that from 2014 to 2015, *P. aeruginosa* sensitivity was reduced from 71% to 67%, *E. coli* sensitivity from 69% to 66% and *K. pneumoniae* sensitivity from 61% to 55%.

The AMR in the KSA is not only limited to gram-negative bacteria, with AMR in gram-positive bacteria also increasing. A Saudi national survey of AMR on gram-positive bacteria showed that 32% of *S. aureus* are meticillin-resistant and 33% of *Streptococcus pneumoniae* are resistant to penicillin G (Shibl *et al.,* 2014). In a study conducted among 200 health care workers in KSUMC, *S. aureus* was colonised in the nasal cavity of 80 (40%), and 36 (18%) were MRSA (Al-Humaidan *et al.,* 2015).

1.3.6 Antimicrobial stewardship programmes in the Kingdom of Saudi Arabia

In 2015, the World Health Assembly endorsed the Global Action Plan (GAP), which provides the structure for national action plans to tackle AMR. It described the key actions that the involved stakeholders should take, using an accumulative approach, over the next ten years (WHO, 2015). The plan aims to assure the continuation of successful therapy and prevention of ID with safe and effective drugs that are quality assured (WHO, 2015). To achieve this aim, the GAP determined five strategic objectives, as illustrated in Figure 1.10.

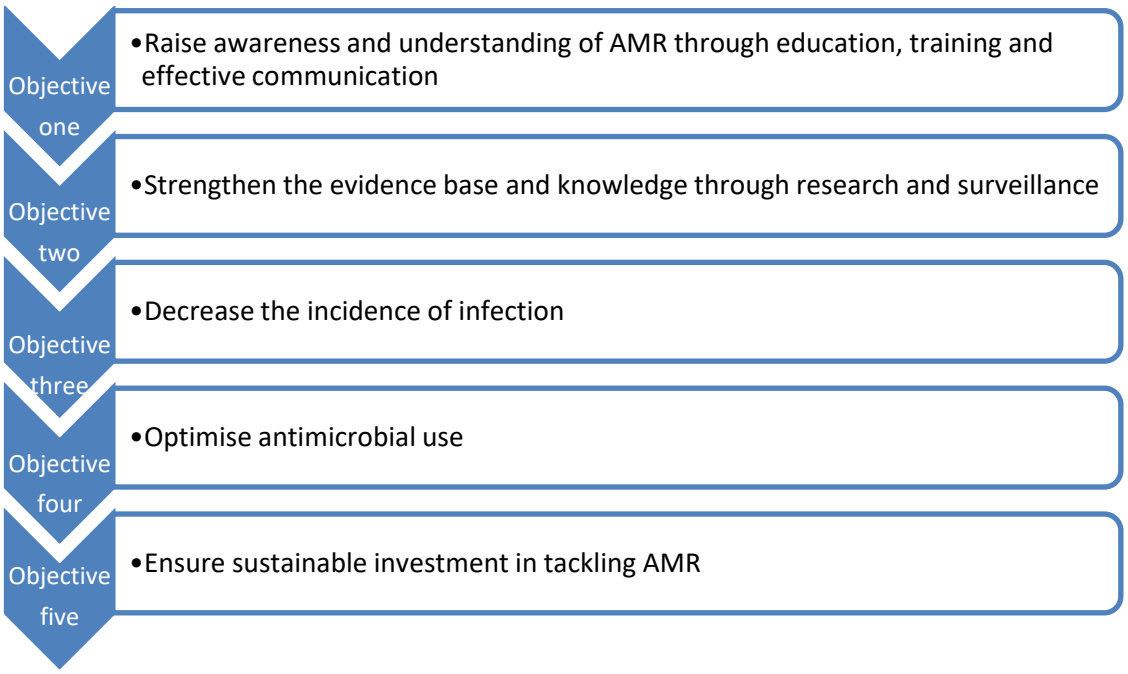


Figure 1.10: The GAP five objectives (WHO, 2015)

As a response to the GAP, many countries, including Australia (Australian Department of Health and Department of Agriculture, 2015), Canada (Public Health Agency of Canada, 2015), the United Kingdom (UK) (Department of Health, 2013) and the USA (The White House, 2015) initiated their own national action plans to combat AMR. In 2017, the WHO published the KSA national action plan developed by the MOH to combat AMR (MOH, 2017b). This action plan was created in the line with the GAP's five objectives (MOH, 2017a). It highlights the need for an effective "one health" approach involving human and veterinary medicine. To achieve the five objectives, a set of strategic activities were initiated, including improving the awareness of AMR and behavioural change, implementing antimicrobial stewardship and infection control programmes and studying both the pattern and the economic burden of AMR (MOH, 2017a). Since then, the national committee for the national action plan has been initiated involving all health sectors, including government agencies and private sectors (MOH, 2017b). In addition, sub-committees have been created, including the AMR awareness committee, antimicrobial use optimisation committee, laboratory

surveillance committee, infection control committee and the AMR pharmacoeconomic studies and research committee (MOH, 2017b). There is no published national surveillance data on antimicrobial use.

Initially, there was no structured national plan on laboratory surveillance of AMR in the KSA (MOH, 2017a). In 2015, a survey of MOH laboratories showed that 18 out of 20 hospital laboratories reported antibiograms with the current Clinical and Laboratory Standards Institute reference (MOH, 2017a). Although reporting on an institutional level, there was no coordination between the institutions (MOH, 2017a). In 2017, the KSA was enrolled in the global AMR surveillance system (WHO, 2018b).

Enani, (2016) conducted a study to describe the prevalence and characteristics of ASPs in Gulf Cooperation Council (GCC) countries, namely the KSA, Kuwait, the UAE, Qatar, Bahrain and Oman. A web-based survey was sent to these countries in 2015 and there was a total of 44 responses from four countries as the following: the KSA (38/47, 81%), the UAE, Bahrain and Oman (6/47, 19%). Of the participating hospitals, the majority were tertiary care teaching hospitals and 29 (62 %) had an ASP. The top three objectives for the ASP were to decrease resistance (72.3%), enhance clinical outcomes (70.2%) and decrease costs (44.7%). Restriction and preauthorisation seem to be the core APS strategies practised in GCC countries. A noticeable finding from this study was the reported positive impact on both patients and hospitals after the initiation of their ASP. The impacts involved the reduction of inappropriate antimicrobial prescribing (68%), reduction of broad-spectrum antimicrobial use (63.8%), reduction of healthcare-associated infections (61.7%), reduction of length of hospital stay or mortality (59.6%), reduction in direct antimicrobial costs (57.4%) and reduction of reported AMR (55.3%). These results, however, may be an overestimation as 30-40% of the participants did not know the impact of their ASP.

Overall, these findings suggest a great opportunity for the implementation of a new ASP and the improvement of the existing ASPs through the sharing of best practices and assistance in the development of local guidelines across the GCC countries.

Alghamdi *et al.* (2019) conducted a qualitative study to explore barriers to implementing antimicrobial stewardship programs in Saudi hospitals. They found that the implementation of these programmes is low due to several reasons including, lack of enforcement of guidelines and policies and guidelines from the hospital administration and MOH, poor communication, lack of health information technology, disintegration of teams, lack of training and education and shortage of antimicrobial stewardship team members.

1.3.7 Situation of APS in King Saud University Medical City

In September 2017, an antimicrobial utilisation and vaccine advisory (AUV) subcommittee was established under the PTC with the aim of supervising the antimicrobial utilisation delivered within KSUMC and supporting the PTC in the management of antimicrobials. The AUV committee members included an ID consultant, the chairman of the committee, a clinical pharmacist, the deputy chairman, an adult ID consultant, a paediatric ID consultant, a consultant from the infection control department, a microbiologist and an additional two clinical pharmacists. One of the objectives of the AUV committee was to initiate and improve antimicrobial stewardship. Table 1.7 illustrates the objectives of this committee.

Initially, before the initiation of the AUV committee, there was no antimicrobial stewardship programme at KSUMC. In September 2017, after the initiation of the committee, the existing antimicrobial stewardship programme consisted of formulary restriction, dose optimisation and surgical prophylaxis guidelines. Plans to collate and

utilise antimicrobial use data have not progressed due to the Coronavirus disease of 2019 (COVID-19) pandemic.

Table 1.7: Objectives of the AUV committee at KSUMC

1	To promote optimal antimicrobial therapy, prevent antimicrobial-related complications, evaluate the effectiveness of antimicrobial therapy, improve patient care and establish interdisciplinary consensus on antimicrobial use processes.
2	To monitor antimicrobial drug therapy for appropriate indication, dosage form, regimen, route and drug-drug interactions.
3	To organise educational activities for healthcare providers to improve antimicrobial utilisation.
4	To collaborate with the microbiology laboratory to provide antimicrobial susceptibility data reports according to the clinical services and patient care units.
5	To collaborate with other hospital clinical services and infection control to improve antimicrobial therapy practice.
6	To evaluate new antimicrobials for formulary addition/deletion, and to recommend changing prescribing privileges and dosage forms based on an objective and evidence-based evaluation of their respective metrics, safety and cost.
7	To monitor antimicrobial use restriction whenever deemed necessary to improve antimicrobial utilisation.
8	To exercise certain measures to minimise the costs of antimicrobial therapy whenever possible.
9	To initiate and continuously improve the antimicrobial stewardship programme.
10	To review all antimicrobial formulary guidelines, order set, and clinical pathways as developed by the antimicrobial stewardship programme (members of the AUV subcommittee).
11	The subcommittee shall review all clinical pathways or practice guidelines that include antimicrobial prescribing.
12	To perform an annual review of the formulary of antimicrobials.
13	The AUV subcommittee chair shall submit an annual written report to the chair of the PTC detailing the AUV subcommittee activities, policy and procedures on antimicrobial use and AMR.
14	All actions or recommendations shall be submitted to the PTC for approval.
15	Participate in prescribing a quality assurance programme and drug use evaluations to ensure the use of effective antimicrobials of adequate quality only when clinically indicated, in the correct dose and for the appropriate length of time.

1.4 Research rationale

In the last decade, there has been a dramatic increase in the proportion of bacterial organisms resistant to several antimicrobial drugs. AMR is currently considered to be an emergent global disease and a major public health problem (WHO, 2017a). From the literature, the KSA shows a high prevalence of resistant and MDR bacteria, such as *A. baumannii* (Al Johani *et al.,* 2010; Somily *et al.,* 2012; Zowawi *et al.,* 2013; Abdalhamid *et al.,* 2014; Lakshmana Gowda *et al.,* 2014; Al-Obeid *et al.,* 2015; Elabd *et al.,* 2015), ESBL-producing *K. pneumoniae* (Rahim and Mohamed, 2014), ESBL-producing *E. coli* (Al Johani *et al.,* 2010; Mashwal *et al.,* 2017), ESBL-producing *P. aeruginosa* (Tawfik *et al.,* 2012) and MRSA (Shibl *et al.,* 2014).

Pharmaceutical companies, meanwhile, find it difficult to keep up with the rising resistance for many reasons. Antimicrobials are normally administered for a limited duration, making them less profitable than drugs used to treat long-term conditions. In addition, newly approved drugs are immediately prescribed, while new antimicrobials are reserved and only prescribed for infections that are resistant to the established antimicrobials (Fair and Tor, 2014).

Antimicrobial use is the most significant driver behind the development of AMR (Ventola, 2015). A study conducted in the KSA showed that antimicrobials are the second most commonly used agents (AlKhamees *et al.,* 2018). Several studies have demonstrated a correlation between antimicrobial use and the emergence of antimicrobial-resistant organisms at the community and hospital levels (Fishman, 2006; Bell *et al.,* 2014). Infections caused by resistant bacteria may be difficult to treat or untreatable (Frieri *et al.,* 2017). These infections can prolong patient hospitalisations, increase morbidity and mortality, and increase the healthcare cost (Cosgrove, 2006). Antimicrobial use has been

associated with other problems such as *C. difficile* infection, which increases mortality among hospitalised patients (Dial *et al.,* 2008; Hensgens *et al.,* 2012; Wenisch *et al.,* 2012). Increases in the prevalence of antimicrobial-resistant organisms in hospitals may be justified by the high selective pressure of unnecessary broad-spectrum antimicrobials in hospitalised patients (Zaha *et al.,* 2020). One of the remaining strategies to combat AMR is the preservation of existing antimicrobials; specifically, measures that can prevent inappropriate antimicrobial prescribing (WHO, 2015). Thus, in hospital settings, it is important to identify surveillance data on antimicrobial utilisation (Zaha *et al.,* 2020).

Limited information is currently available in the literature about carbapenem and piperacillin/tazobactam prescribing in the KSA. Previous studies either included hospitalised patients in specific departments (Balkhy *et al.,* 2018; Youssif *et al.,* 2018; Alharthi *et al.,* 2019; Huwait *et al.,* 2019) or focused on narrow patient populations (Balkhy *et al.,* 2019).

On a local level, there is no published paper that quantifies antimicrobial use or describes the patterns of antimicrobial prescribing in KSUMC. To address this gap, there is a need to conduct an antimicrobial utilisation review.

From the literature, qualitative studies have been conducted to identify the contextual factors that influence physicians' antimicrobial prescribing in hospital settings. This method of study has been shown to be useful for understanding the subjective perceptions of physicians (Teixeira Rodrigues *et al.,* 2013). In the KSA, no qualitative work has been reported to identify factors that influence physicians' broad-spectrum antimicrobial prescribing in hospital settings. As mentioned in section 1.1.5, the factors influencing prescribers in the KSA may be different from those reported from other countries. This demonstrates the need to conduct a qualitative study to

understand factors that determine inappropriate prescribing which may be used to guide the implementation of successful interventions aimed at rationalising broad-spectrum antimicrobial prescribing in the hospital setting.

Linking this knowledge gap in broad-spectrum antimicrobial utilisation and factors influencing prescribing might assist in developing strategies to improve the local prescribing practice for broad-spectrum antimicrobials which may be directly applicable to supporting a deepened understanding of antimicrobial use, tailor evidence-based strategies and inform policies in antimicrobial prescribing and controlling AMR.

1.5 Research methodological approach

A research methodological approach is a plan for research that brings wide assumptions and hypotheses to comprehensive methods of data collection, analysis, and explanation (Creswell and Creswell, 2017). Research methodological approaches can be quantitative, qualitative or mixed methods. These approaches will be discussed in the following sections.

1.5.1 Quantitative research

Quantitative research is a method for examining objective hypotheses by testing the relationship between attributes. These attributes can be measured and quantified so that numerical data can be analysed by statistical measures (Creswell and Creswell, 2017). In quantitative research, researchers seek to define and characterise current issues or situations and determine and explain relationships between variables (Creswell and Creswell, 2017).

Drug utilisation research (DUR) can be defined as:

> *"An eclectic collection of descriptive and analytic methods for the quantification, understanding and evaluation of the processes of*

prescribing, dispensing, and consumption of medicines and for the testing of interventions to enhance the quality of these processes."
(Wettermark *et al.,* 2016)

Research into drug utilisation is considered a potential tool that can be used in assessing and evaluating a healthcare system (Meena and Jayanthi, 2019). The research can be conducted using either quantitative or qualitative study designs (LeLorier *et al.,* 2003). Quantitative DUR can be descriptive or analytical. Descriptive DUR involves studies that are designed to quantify trends and the frequency of drug use. It includes collecting, organising and presenting the measurements or estimates of such use (Meena and Jayanthi, 2019). Analytical DUR includes studies that are designed to identify underlying implications about hypothesised relationships. These types of studies aim to achieve a greater in-depth understanding of the issues behind drug consumptions or prescribing patterns (Elseviers *et al.,* 2016).

Continuous data collection on antimicrobial use is not feasible due to the workload and resources needed. An alternative method is to collect antimicrobial use data at a single point in time using the point prevalence survey (PPS; WHO, 2018f).

PSS has many advantages including the ease of performance, the need for less resources and time and the possibility of quick data analysis. PPS on antimicrobial use have been widely used in hospital settings around the world and have been shown to be useful in informing and assessing stewardship activities (Pauwels *et al.,*2021b). This method reflects the level of resources in low- and middle-income countries where surveillance cannot be obtained, while maintaining comparison with consumption data from high-income countries (WHO, 2018f).

PSSs look at a specific point in time therefore the results can be influenced by day-to-day and seasonal variation in antimicrobial use. Moreover, the PPS does not collect

detailed information such as information about the duration of antimicrobial treatment and whether appropriate culture was obtained, where other study designs would be desired to obtain such information (WHO, 2013).

The global PPS is an international collaboration which began in 2015, to provide key information about antimicrobial use and resistance in hospitals worldwide. This method provides standardised tool that it is can be applied to all types of hospitals and allow comparison of data at different levels; locally, nationally and internationally (Versporten *et al.,* 2018).

1.5.2 Qualitative research

Qualitative research is a form of social investigation that focuses on how people view their experiences (Holloway, 1997). It has been defined in the following way:

> *"Qualitative research begins with assumptions and the use of interpretive/theoretical frameworks that inform the study of research problems addressing the meaning an individual or groups ascribe to a social or human problem. To study this problem, qualitative researchers use an emerging qualitative approach to inquiry, the collection of data in a natural setting sensitive to the people and places under study, and data analysis that is both inductive and deductive and establishes patterns or themes. The final written report or presentation includes the voices of participants, the reflexivity of the researcher, a complex description and interpretation of the problem, and its contribution to the literature or a call for change."* (Creswell and Poth, 2016, p. 44)

Qualitative research has many advantages. It generates detailed and in-depth explanations of participants' experiences, opinions and feelings and allows the interpretation of the meanings of their own actions (Denzin, 2001). Moreover, it provides the ability to deal with sensitive or complex matters to formulate an

explorative or inductive hypothesis, rather than applying the results to a wider population (Bowling, 2014). Generally, qualitative research is considered ideally suitable for identifying the individual's opinions and behaviour as it helps to recognise and answer the questions of "why" and "how" (Smith, 2002).

1.5.2.1 Data collection in qualitative research

In qualitative research, data can be obtained through interviews, focus group discussions and observations (Barbour, 2007). These approaches generate data actively from interactions with the study participants. Nevertheless, other techniques can include the investigation of documents such as video material or diaries (Barbour, 2008).

Interviews can be structured, semi-structured or unstructured. Structured interviews aim to gain answers to particular questions where all the participants are asked the same questions in the same way and there is no space for veering off the subject in question (Ryan *et al.,* 2009). Semi- structured interviews provide a more flexible technique for the interviews. The use of open-ended questions allows for unanticipated responses and spontaneous issues to be raised and explored (Ryan *et al.,* 2009). Unstructured interviews do not involve a specific question framework. During the unstructured interview, the researcher and participant have a conversation about a particular topic, the conversation being mainly led by the participant, where the direction of the interview follows the participant's responses (Ryan *et al.,* 2009).

Interviews can be conducted face-to-face or by telephone. Face-to-face interviews are commonly used for data collection in qualitative research (Ryan *et al.,* 2009). The advantage of face-to-face interviews is that the researcher can capture the participant's non-verbal cues, which may lead to the achievement of a deeper

understanding of the data. Nonetheless, this approach may be considered to be time-consuming and expensive (Opdenakker, 2006). Moreover, the presence of the researcher may have an influence on the participant's responses (Opdenakker, 2006). Telephone interviews are less common in qualitative data collection. A low response rate or the absence of non- verbal cues could be of the reasons behind not considering them (Carr and Worth, 2001; Novick, 2008). However, besides being inexpensive and time-efficient, telephone interviews enable access to difficult-to-reach participants such as those living in distant geographic regions or in situations of quarantine, like during the present COVID-19 pandemic. In addition, it may allow participants to disclose sensitive data (Sturges and Hanrahan, 2004; Opdenakker, 2006)

1.5.2.2 Sampling in qualitative research

There are a number of sampling approaches in qualitative research, including convenience, theoretical, purposive, and snowball sampling. Convenience sampling is an approach where candidate selection is dependent on the basis of who is accessible and near at hand (Ritchie *et al.,* 2014). Theoretical sampling is an approach in which sampling is guided by the theories that have emerged during the research process (Farrugia, 2019). Purposive sampling is where candidates are selected based on particular characteristics. Snowball sampling is a form of purposive sampling, where initial participants are asked to recommend other potential candidates (Farrugia, 2019).

1.5.2.3 Qualitative data analysis

Broadly, qualitative data can be analysed either deductively or inductively. Deductive analysis is an approach that analyses data using a predetermined structure or framework. This approach is suitable when researchers are aware of possible

participant responses (Burnard *et al.,* 2008). Inductive analysis is an approach that analyses data with no or little predetermined framework, structure or theory and utilises the actual data to develop the framework of analysis. This approach is suitable when little is known about the research phenomenon (Burnard *et al.,* 2008). There are many different approaches for qualitative data analysis. A brief explanation of some of the key qualitative analysis approaches is given below:

- Narrative analysis is an analytical approach that aims to recognised and understand how individuals make sense of themselves through story telling (Sullivan and Forrester, 2019).
- Grounded theory is a type of analysis that aims at building theory from the data of the participants (Sullivan and Forrester, 2019).
- Phenomenographic analysis is an analytical approach where the data analysis and discussion are obtained from a second-order viewpoint that describes how the phenomenon was understood and viewed by the participants instead of how it was understood and viewed by the researcher (Larsson and Holmström, 2007).
- Thematic analysis is a type of analysis that assists a researcher to find themes within a dataset to a specific research question (Braun and Clarke, 2006). Braun and Clarke (2006) identified a six-step guide for thematic analysis. These steps are illustrated in Figure 1.11.

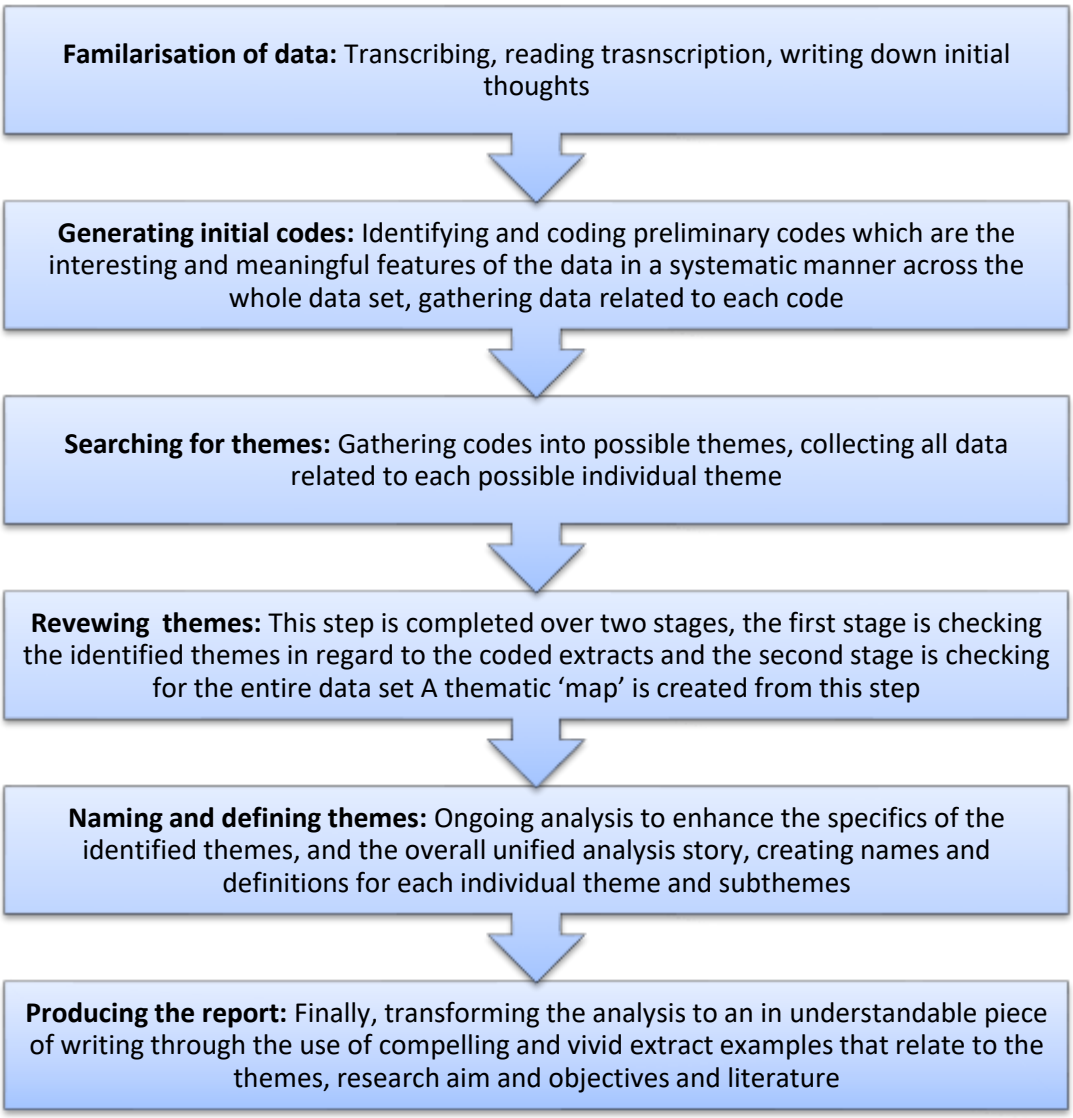


Figure 1.11: Steps in thematic analysis (Braun and Clarke, 2006)

1.5.2.4 Trustworthiness in qualitative research

The trustworthiness or rigour of a piece of research refers to the level of confidence in the methodology, the collected data and its interpretation to ensure the quality of the study (Connelly, 2016). While there is a general agreement that trustworthiness is essential, there have been debates about what frames it (Leung, 2015). Lincoln and Guba (1985) identified four key components of trustworthiness: credibility, transferability, dependability and confirmability. They described these components as follows:

- **Credibility:** Credibility is the confidence that the research findings are true, believable and credible (Lincoln and Guba, 1986). Credibility, similar to internal validity in quantitative research, is considered to be the most important component for trustworthiness (Connelly, 2016). Techniques to address credibility include prolonged engagement with research participants, persistent observation, data collection triangulation, member-checking to test the results and explanations from the research participants and peer debriefing to offer an external assessment on the research procedure, findings and interpretation (Lincoln and Guba, 1985).
- **Transferability:** Transferability refers to the extent to which the findings can be generalised. It is similar to external validity in quantitative research. In qualitative research, it is about case-to-case transfer which includes the use of the study findings with an entirely different population or setting (Tobin and Begley, 2004). The researcher's responsibility is to provide rich descriptions so that the reader can assess and judge if the study findings are transferable to their own situation (Lincoln and Guba, 1985).
- **Dependability:** Dependability refers to the stability of the findings over time and over study conditions (Lincoln and Guba, 1985, Connelly, 2016). It is analogous to reliability in quantitative research. One technique to determine the dependability of a piece of research is to audit the process (Koch, 2006).
- **Confirmability:** Confirmability, similar to neutrality or objectivity, is concerned with ensuring that the findings and interpretations clearly originate from the data, necessitating the researcher to explain how interpretations and conclusions have been achieved (Tobin and Begley, 2004).

1.5.3 Mixed method approach

Mixed methods research can be defined as:

> *"The class of research where the researcher mixes or combines quantitative and qualitative research techniques, methods, approaches, concepts or language into a single study. Mixed methods research also is an attempt to legitimate the use of multiple approaches in answering research questions, rather than restricting or constraining researchers' choices (i.e., it rejects dogmatism). It is an expansive and creative form of research, not a limiting form of research. It is inclusive, pluralistic, and complementary, and it suggests that researchers take an eclectic approach to method selection and the thinking about and conduct of research."* (Johnson and Onwuegbuzie 2004, p. 17-18).

A mixed method approach allows the researcher to view problems from different perspectives, which leads to a better understanding of research problems and delivers more complete evidence (Creswell and Creswell, 2017). Using this type of method is useful in some research areas, such as healthcare research, as the complexity of the phenomena requires data from a large number of perspectives (Sale *et al.,* 2002). A mixed method approach provides strengths that overcome the inherent weaknesses of both quantitative and qualitative research**,** offset method biases that cannot be avoided and give insights not possible when an individual approach is used. Using a mixed methods approach in a single study is a widely used and accepted approach in many areas of health care and prescribing research (Sale *et al.* 2002).

1.6 Research questions

1. What is the utilisation pattern of carbapenem and piperacillin/tazobactam for adult hospitalised patients?
2. Is physicians' carbapenem and piperacillin/tazobactam prescribing practices for adult hospitalised patients appropriate?
3. What is the association between appropriate prescribing and patients' length of hospitalisation?
4. What are the factors that might affect physicians' broad-spectrum antimicrobial prescribing for adult hospitalised patients?
5. What is the impact of the results of this thesis on practice and further research?

1.7 Thesis aim and objectives

1.7.1 Aim

The aim of the thesis is to evaluate the utlisation of carbapenems (imipenem/cilastatin or meropenem) and piperacillin/tazobactam, to investigate physicians' views, perceptions and experiences regarding broad-spectrum antimicrobial prescribing in a hospital setting and to develop recommendations

1.7.2 Objectives

1. To generate data on carbapenem and piperacillin/tazobactam utilisation pattern.
2. To determine the appropriateness of carbapenem and piperacillin/tazobactam prescribing, based on the IDSA guidelines, and to identify reasons for their inappropriate use.
3. To identify patient or prescription characteristics that are associated with inappropriate prescribing.
4. To identify the association between appropriate prescribing and patients' length of hospitalisation.
5. To explore physicians' perceptions and views about broad-spectrum antimicrobials.
6. To identify factors that influence physicians' broad-spectrum antimicrobial prescribing for hospitalised patients.
7. To identify barriers to appropriately prescribing broad-spectrum antimicrobials to hospitalised patients.

8. To obtain physicians' recommendations to improve the appropriateness of broad-spectrum antimicrobial prescribing.
9. To map themes to COM-B framework to support behaviour change to improve the appropriateness of broad-spectrum antimicrobial prescribing.
10. To make recommendations for improved appropriate practices in KKUH and identify areas for further research on improving appropriate broad-spectrum antimicrobial prescribing practices.

To achieve the research aim and objectives, this thesis adopted a mixed method approach. The mixed method approach applied in this thesis is known as the explanatory sequential approach, which implies the analysis of quantitative data followed by qualitative data within a single study (Creswell and Clark, 2017).

2. Chapter 2: Drug utilisation review of broad-spectrum antimicrobials prescribed for adult hospitalised patients in a tertiary care hospital

Overview: This chapter comprises an introduction, the aim, objectives, methodology and results of this study on carbapenem and piperacillin/tazobactam prescribing in adult hospitalised patients, from a quantitative point of view using DUR as the methodological approach.

2.1 Introduction

In the last decade, there has been a substantial increase in bacterial organisms resistant to multiple antimicrobial drugs (WHO, 2017a). At present, the WHO considers AMR as a significant global public health crisis (WHO, 2017a). There is no reliable estimation of AMR cases worldwide, primarily due to inadequate surveillance (Toner *et al.,* 2015). Limitations of any surveillance system or AMR research are those characteristics associated with the assumptions, design, methodology and data used that influence the explanation for and interpretation of the findings (WHO, 2018b). The development and implementation of a standard method for estimating AMR may generate a reliable estimate of AMR globally (Limmathurotsakul *et al.,* 2019). Despite inadequate surveillance, some evidence suggests that the incidence is much higher in developing countries (Ayukekbong *et al.,* 2017). As explained in section 1.1.3, the inappropriate use of broad-spectrum antimicrobials contributes to the emergence of AMR (Ventola, 2015). Several studies have demonstrated a correlation between antimicrobial use and the emergence of antimicrobial-resistant organisms in hospital settings (McKinnell *et al.,* 2012; Livermore *et al.,* 2013). Moreover, excessive antimicrobial use has been associated with superinfection and disease associated

with antimicrobial use, for example, *C. difficile*, both of which increase morbidity and mortality in hospitalised patients (Dial *et al.,* 2008; Wenisch *et al.,* 2012).

Broad-spectrum antimicrobials, such as piperacillin/tazobactam, imipenem/cilastatin, and meropenem, have excellent activity against many gram-positive, anaerobic and gram-negative organisms, including many MDR strains of *P. aeruginosa and Enterobacteriaceae* species (Perry and Markham, 1999; Wilson, 2017). These antimicrobials are often considered the last resort in treating multi-drug-resistant bacterial infections and have been classified by the WHO as critically essential antimicrobials since 2005 (WHO, 2018d). Evidence has shown that the disproportionate use of piperacillin/tazobactam has been associated with the isolation of piperacillin-tazobactam-resistant *P. aeruginosa* (Harris *et al.,* 2002; Patel *et al.,* 2008; Sonmezer *et al.,* 2016). Furthermore, increased use of carbapenems has been linked to carbapenem-resistant *P. aeruginosa, Enterobacteriaceae, and Acinetobacter* species (Mladenovic-Antic *et al.,* 2016; WHO, 2018d; Codjoe and Donkor, 2017). In Saudi Arabian hospital settings, studies have shown that the rates of carbapenem-resistant *P. aeruginosa, A. baumannii,* and ESBL-producing *Enterobacteriaceae* are generally high (Yezli *et al.,* 2014; Zowawi, 2016).

In KSA, data on antimicrobial utilisation patterns in hospital settings have been reported from PPS (Enani *et al*., 2018: Al Matar *et al.,* 2019; Yaser *et al.,* 2020). A point prevalence survey of antimicrobial use in 26 Saudi hospitals found that prevalence of antimicrobial prescribing was 46.9%. A total of 3240 antibiotic doses were administered and 2613 (80.6%) doses were administered parenterally. The most frequent prescribed antimicrobials were ceftriaxone 379 (11.6%), metronidazole 324 (10%), carbapenem 266 (8.2%), cefuroxime 225 (6.9%) and piperacillin tazobactam 210 (6.4%). The most common indication was respiratory tract infections 597

(18.2%). The rate of adherence to antimicrobial guidelines was 1558 (48.1%). The indications for antimicrobials were not recorded in the patients' notes for 1818 (51.1%) of the prescriptions (Al Matar *et al.,* 2019).

Another point prevalence survey was conducted in two hospitals in Madinah, Saudi Arabia in September 2016 and November 2016, during and after pilgrims stay, in Madinah. In this study, a total of 675 patients were included; among them, 332 (49.18%) patients received antimicrobial therapy. In September 2016, 168 patients received antimicrobials, with a prevalence rate of 50.6 %, while, in November 2016, 164 patients received antimicrobials, with a prevalence rate of 49.4 %. In September 2016, the most commonly prescribed antimicrobials were piperacillin-tazobactam 45 (17.6 %) followed by ceftriaxone 28 (10.95%) and in November 2016, the most commonly prescribed antimicrobials were ceftriaxone 39 (14.6%), followed by piperacillin-tazobactam 31 (11.6%) (Yaser *et al.,* 2020). Enani et al. (2018) conducted a PPS in 2015 and 2017, in a tertiary care hospital. They found that the prevalence of antimicrobial prescribing in adults wards in 2015 and 2017 was 24.2% and 32.4%, respectively. The most commonly prescribed antimicrobials across the hospital in 2015 and 2017 were β-lactams (59%) and (51.2%), respectively. In adult ICU, fourth generation cephalosporins was the most commonly prescribed in 2015 (40.9%), while carbapenems was the most commonly prescribed antimicrobials in 2017 (68.8%).

Appropriate antimicrobial prescribing is essential to ensure that patients receive the optimal therapy to treat certain infection and to avoid unintended consequences of inappropriate antimicrobial use including the emergence of AMR, the risk of C. *difficile* infection and other adverse effects (Drew, 2009). Standardised definition of appropriate antimicrobial prescribing is lacking (Daryl *et al.,* 2014). In the literature, studies have used a variety of definitions to evaluate appropriate antimicrobial

prescribing. Appropriate antimicrobial prescribing is defined as selection of an antimicrobial that has susceptibilities against the identified organism (Depestel *et al.,* 2014; Spivak *et al.,* 2016). This definition of appropriate prescribing considered of the least subjective evaluation of appropriate antimicrobial therapy (Spivak *et al.,* 2016). As this definition required obtaining culture, it excludes many infections lacking culture results. Obtaining culture before starting the antimicrobial therapy may be added to the definition of appropriate prescribing (Youssif *et al.,* 2018). However, in some infections not obtaining culture could be for valid reasons such as in intra-abdominal infections and mild pneumonia. Another definition of appropriateness is selection of an antimicrobial that is in agreement with the international or local guidelines (McCabe et al., 2009; Wathne et al., 2019). This definition is widely used to reduce subjectivity and provide a method to evaluate antimicrobial prescribing across hospitals that share similar guidelines (Spivak *et al.,* 2016). Some studies have used the more subjective approach of expert opinion-based definition of appropriate antimicrobial prescribing (Schwartz *et al.*, 2009; Drekonja *et al.,* 2010; Akhloufi *et al.,* 2015). This approach expands from antimicrobial selection and assesses further measures or elements in the antimicrobial prescribing pathways (e.g., duration of antimicrobial therapy, diagnostic work-up). Nevertheless, besides being subjective, definition used usually lack details, leading to lack of reproducibility outside single institutions (Spivak *et al.,* 2016). Assessment of appropriate antimicrobial prescribing in inpatient settings includes several steps or criteria, such as empirical, targeted or prophylactic antimicrobial choice (Goede *et al.,* 2013; Casaroto *et al.,* 2015; Ciccolini *et al.,* 2015), obtaining culture (Youssif *et al*., 2018; Mekdad and AlSayed 2020), duration (Schwartz *et al.*, 2009; James *et al.,* 2015) and de-escalation (Schwartz *et al.*, 2009; James *et al.,* 2015).

Evidence of the association between appropriate prescribing and AMR shows that reducing inappropriate utilisation of broad-spectrum antimicrobials can minimise the emergence of AMR (Drew, 2009). Studying antimicrobial utilisation can assist in developing strategies to improve the local prescribing practice for antimicrobials, help tailor evidence-based antimicrobial prescribing, develop antimicrobial prescribing policies and augment ASP to control AMR and improve patient outcome (Birkett *et al.,* 2003).

A study conducted by Robson *et al.* (2018) to assess the implementation of the Scottish antimicrobial prescribing group guidance and to examine its impact on the use of piperacillin/tazobactam and carbapenems. This guidance was developed to support clinicians in the management of gram-negative infections, decrease emergence of MDR-Gram negative bacilli and promote judicious use of broad-spectrum antimicrobials. In this study, they found good compliance with local guidelines, particularly for carbapenem, lack of confidence in de-escalating treatment and decreased usage of piperacillin/tazobactam and carbapenems during the improvement programme period. The study showed how a multifaceted quality improvement programme can be used to optimise use of broad-spectrum antimicrobials.

Part of this study was published (Appendix 1) and permission to include it in the thesis was obtained from the publisher (Appendix 2).

2.2 Aim and objectives

2.2.1 Aim:

This research aims to evaluate the appropriateness of carbapenems imipenem/cilastatin or meropenem) and piperacillin/tazobactam prescribing in a hospital setting.

2.2.2 Objectives:

1. To generate data on carbapenem and piperacillin/tazobactam utilisation pattern.
2. To determine the appropriateness of carbapenem and piperacillin/tazobactam prescribing, based on the IDSA guidelines, and to identify reasons for their inappropriate use.
3. To identify patient or prescription characteristics that are associated with inappropriate prescribing.
4. To identify the association between appropriate prescribing and patients' length of hospitalisation.

2.3 Methodology

2.3.1 Study design, data source and duration

This study used a quantitative, observational, retrospective, cross-sectional, drug utilisation study that included adult patient data retrieved from a hospital information system called eSiHi (Electronic System for Integrated Health Information) covering a 24-month period, from 1 January 2016 to 31 December 2017. The study was conducted at KKUH, a 1,100-bed, tertiary care hospital.

The rationale for choosing a retrospective drug utilisation study was that it is known for its efficiency in identifying and describing drug prescribing patterns and

appropriateness (Birkett *et al.,* 2003). In addition, it aids in planning for interventions to improve inappropriate prescribing. Furthermore, it is quick, easy to conduct and carries little additional cost. However, the main drawbacks of this design are the limited number of variables and the source of error due to bias and confounding. Adhering to a well-structured design can avoid bias and confounding in this type of study (Shalini *et al.,* 2010).

2.3.2 Ethical consideration

Patients were not identified by their names and all information was kept electronically secure in a password-protected personal computer with encrypted files. Ethical approval was obtained from the Institutional Review Board, King Saud University College of Medicine in February 2018 (Appendix 3).

2.3.3 Study population

The study included all adult hospitalised patients aged 18 years and older who received at least one dose of imipenem/cilastatin, meropenem or piperacillin/tazobactam for the period between 1 January 2016 and 31 December 2017.

2.3.4 Data extraction and cleansing

2.3.4.1 Hospital information system

The Health Information system is from Cerner company. It was implemented in May 2015 and given the name ESiHi (Electronic System for Integrated Health Information). The system contains all solutions (i.e registration, scheduling, emergency, operation room, medical record, laboratory, pharmacy, inpatient, outpatient)

Each patient has a unique medical record number (MRN), where the physician can access each patient electronic health record through this number and proceeds to

document the patient's progress notes, prescribe medicine and review laboratory results. Coding is according to international classification of diseases, 10th revision.

2.3.4.2 Extraction process

A list of patient information extracted from the hospital database can be found in Appendix 4. All data was retrieved by the IT department. Retrieved data were separated into several MS Excel® files: a basic file, a lab test file, a surgery file, a microbiology file, a readmission file, an all-medications file, a diagnosis file and an antimicrobial therapy file. Retrieved data was received in the form of code description. To ensure that the retrieved data captured all the hospitalised patients on antimicrobial therapy, data for this therapy were retrieved for one day, and on the same day, the researcher went to the pharmacy and recorded the medical record numbers (MRN) for all the prepared antimicrobials. The list from the retrieved data was matched with the list from the prepared antimicrobials in the pharmacy. In addition, the retrieved data was assessed to ensure that the appropriate data were retrieved. The results of the pilot assessment allowed the extraction of more patient data where it was expected that surgery would be required with the diagnosis; however, these data were filed under a separate criterion. The retrieved data were reviewed and checked for any missing values or incomplete entries before data processing. No missing values or incomplete entries were identified.

2.3.5 Data linking

Each patient was linked to his/her antimicrobial therapy and microbiology data by matching the patient MRN using the Ultimate Suite for Excel®, a toolset to manage and rearrange data in Excel®. A sample of 100 patients was checked manually to ensure data accuracy. A new Excel® file was created and saved as the main file, which was used for recoding and analysis.

2.3.6 Computing and recoding variables

Variables from the retrieved data were coded into categories (Appendix 5), as follows:

1. Co-morbidities were coded into 15 categories:

    - Diabetes
    - Cardiovascular disease
    - Respiratory disease
    - Dyslipidemia
    - Psychiatric disorders
    - Musculoskeletal disorders
    - Hypertension
    - Haematological disorders
    - Gastrointestinal disease
    - Liver disease
    - Neurological disorders
    - Thyroid disorders
    - Cancer
    - Vitamin D deficiency
    - Kidney disease

2. Patient locations were coded into new 13 location categories

    - Internal medicine
    - Cardiology
    - Surgical wards
    - Orthopaedics
    - Burns unit
    - ICU
    - Oncology/Haematology
    - Day surgery
    - Emergency department (ED)
    - High-dependency unit (HDU)
    - Long-stay unit
    - Neurology
    - Obstetrics and gynaecology (OBG)

Details about the different locations under these categories can be found in Appendix 6.

2.3.7 Type and indication of antimicrobial therapy categories

Carbapenems and piperacillin/tazobactam prescriptions were categorised according to the type of therapy into three main categories: empirical, targeted and

prophylactic. Empirical antimicrobial therapy was defined as an antimicrobial prescribed for a patient suspected to have an infection with unknown pathogen(s) before the availability of culture and susceptibility results. Targeted antimicrobial therapy was defined as antimicrobial therapy prescribed for a patient with an identified infection documented in culture and sensitivity results. Prophylactic antimicrobial therapy was defined as antimicrobial therapy prescribed for a patient to prevent an infection or for a patient undergoing a surgical procedure to avoid surgical site infections (Leekha *et al*., 2011).

Indication for antimicrobial therapy was categorised into:

- Community-acquired pneumonia (CAP)
- Diabetic foot infection
- Febrile neutropenia
- Hospital-acquired pneumonia (HAP)
- Intra-abdominal infection
- Sepsis
- SSTIs
- Urinary tract infection (UTI)
- Ventilator-associated pneumonia
- Surgical prophylaxis
- Prophylaxis
- Spontaneous bacterial peritonitis
- Bone and joint infection
- Genital tract infection
- Ear, nose and throat infection
- Meningitis
- Endocarditis

2.3.8 Appropriateness of carbapenems and piperacillin/tazobactam prescriptions

2.3.8.1 Process of assessing antimicrobial therapy

For each prescription, indication, dose and duration of antimicrobial therapy, culture and susceptibility results and concomitant antimicrobial were reviewed to identify whether antimicrobial therapy was empiric, targeted or prophylactic and to assess its appropriateness. The appropriateness of antimicrobial therapy was evaluated

according to the IDSA guidelines. The IDSA guidelines were chosen through consensus with two local clinical pharmacists since these guidelines are commonly used in clinical practice in KSA. In some indications the guideline indicated several treatment options and suggested to refer to the local antibiogram (Appendix 7). For these indications, a discussion with the clinical pharmacist were made for more clarification. The microbiological findings for each patient were also considered. Several meetings with the clinical pharmacist to resolved unclear issues and there was no involvement of clinical microbiologist.

If the type of antimicrobial use was empiric therapy, all the cases were reviewed to identify if a microbiology culture had been requested. If a microbiology culture had been requested, the case was reviewed for the follow-up of antimicrobial discontinuation if no microorganisms had been isolated, escalation if the microbiology results showed that the organism was not susceptible/resistant, or de-escalation if the microbiology results showed sensitivity to a narrow-spectrum antimicrobial. De-escalation refers to changing an empiric broad-spectrum antimicrobial regimen to a narrower antimicrobial regimen by changing the antimicrobial agent or changing from combination therapy to monotherapy (Dellit *et al.,* 2007).

If the indication for treatment was targeted therapy and the antimicrobial was not used initially as empiric therapy, the culture and susceptibility results were reviewed to check whether the targeted therapy was based on susceptibility data where the organism was not susceptible to a narrow-spectrum antimicrobial (IDSA, 2018).

If the type of antimicrobial use was prophylaxis, the indication was checked if it was according to the guideline.

The process of assessing antimicrobial therapy for each prescription is illustrated in Figure 2.1. Some patients had more than one admission during the study period. In addition, some patients may have been prescribed more than one antimicrobial, or the same antimicrobial but at different times during the same admission period. Each antimicrobial prescription was assessed independently, according to its appropriateness.

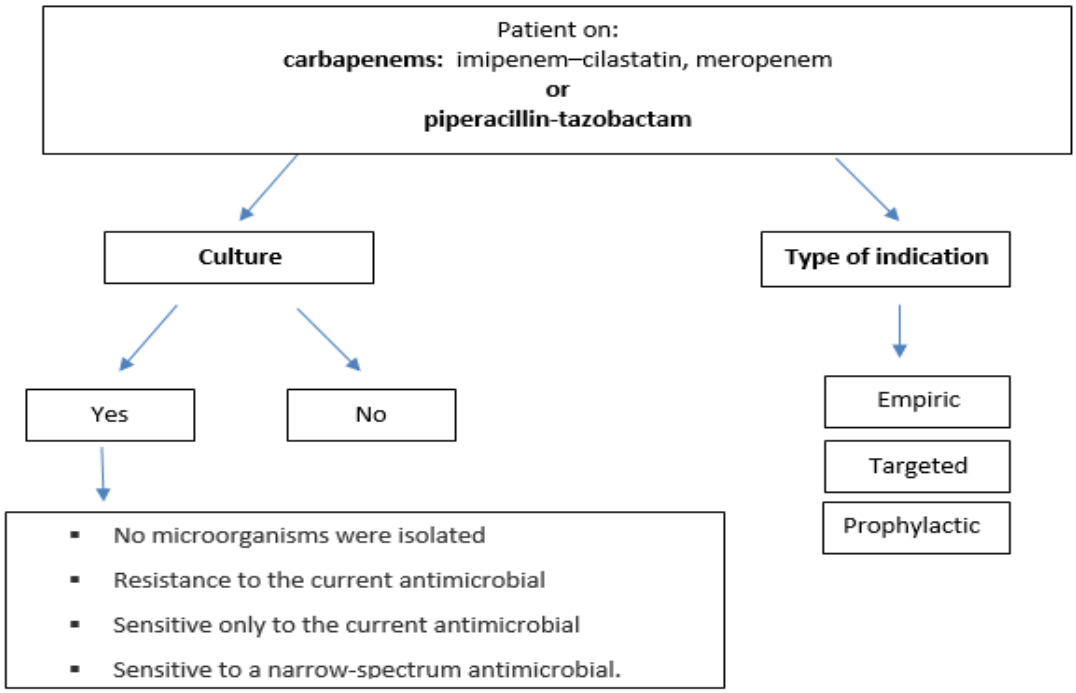


Figure 2.1: Process of assessing antimicrobial therapy for each prescription

2.3.8.1 Criteria to determine the appropriateness of carbapenem and piperacillin-tazobactam

In this study, appropriateness is defined as any prescription that is according to the guideline or culture and sensitivity results. Some criteria were not included such as duration of therapy. It is difficult to assess the appropriateness of duration of therapy, because antimicrobial therapy should be tailored to each patient and the duration is dictated by the clinical course. This could be better assessed during the time of the time of clinical decision-making rather than retrospectively.

The appropriateness of carbapenem and piperacillin/tazobactam therapy was based on the following criteria:

1. Empirical therapy with carbapenem or piperacillin/tazobactam was assessed at two levels:

- Initial choice, according to the IDSA guideline. The indication for empiric therapy according to the IDSA guideline can be found in Appendix 8.
- Re-evaluation of the antimicrobial therapy after culture and sensitivity results.

2. Targeted therapy according to the IDSA guideline and culture and susceptibility results.
3. Prophylactic therapy according to IDSA guideline.

Some patients died or were discharged before the culture results were obtained. In such cases, the result was categorised under patient died before the culture results were obtained and it was excluded from the analysis.

2.3.8.2 Reasons for inappropriateness

Reasons for inappropriateness were defined after determining the appropriateness criteria. Some antimicrobial prescriptions had more than one reason for inappropriateness. Table 2.1 illustrates the definition of each reason for the inappropriateness of antimicrobial therapy.

Table 2.1: Reasons for inappropriateness of antimicrobial therapy

Reason	Definition	Example
Spectrum too broad	The guideline indicated the use of a narrower spectrum antimicrobial	Prescribe piperacillin/tazobactam or carbapenem for uncomplicated CAP Use of
No culture request	Patient was prescribed antimicrobial and there was no microbiology request	Started on piperacillin/tazobactam for UTI and no culture were requested
Failure to de-escalate	The culture and susceptibility results indicated susceptibility to a narrow-spectrum antimicrobial but there was no de-escalation	Continued use of carbapenem started empirically although culture results indicated susceptibility to ceftriaxone
Known allergy to the prescribed antimicrobial	Patient had a known allergy to the prescribed antimicrobial	piperacillin/tazobactam allergy was mentioned however, patient was prescribed piperacillin/tazobactam
Microbiology indicates resistance to the current treatment	Continuation of antimicrobial prescribing despite microbiology results indicating resistance	piperacillin/tazobactam was continued despite the microbiological results showing that the pathogens were resistant to piperacillin/tazobactam

2.3.9 Study outcomes

The primary outcomes were the number of carbapenem and piperacillin/tazobactam prescriptions in hospitalised adult patients, empiric targeted and prophylactic, expressed as the number and percentage prescriptions and DDD per 100 bed-days. Secondary outcomes were the appropriateness of these prescriptions, expressed as the percentage of antimicrobial prescriptions that were prescribed according to the IDSA guideline, the factors that may be associated with inappropriate prescribing and the association between appropriate prescribing and LOS.

2.3.9 Statistical analysis

The Shapiro-Wilk test of normality was carried out on all data to verify the fit to a normal distribution (age, weight, hight, BMI and LOS). Descriptive statistics, including

means, standard deviations (SD), medians, range, frequencies and percentages were performed. Mean and SD were used as parametric data, median and range were used as non-parametric data. Carbapenem and piperacillin/tazobactam consumption was reported as a number and percentage of prescriptions. In addition, the DDD was used to report carbapenem and piperacillin/tazobactam use (WHO, 2020). To define the antimicrobial consumption rate in an inpatient setting, it is suggested that DDD be expressed per 100 bed-days. Therefore, the antimicrobial consumption rate was expressed as DDD per 100 bed-days (Birkett *et al.,* 2003). Bed-days were obtained from the hospital records and the days of admission and of discharge were each counted as one day. The calculations are explained in Appendix 9.

To assess whether there was an association between any independent factors (age, gender, patient location (ICU versus non-ICU), Co-morbidities, Reason for antimicrobial therapy) and inappropriate antimicrobial prescribing, the percentage with inappropriate prescribing in the reference category was subtracted from the percentage in the exposed category to obtain the percentage risk difference.

The odd ratio which is the measure of association between exposure and an outcome (Szumila, 2010) was also calculated. Confidence intervals (CI) were calculated using the normal approximation to the binomial distribution. An explanation of the CI calculation is provided in Appendix 10.

As the distribution for LOS was skewed, data were described using medians and interquartile ranges [IQR]. As some patients had more than one prescription per admission, if any of the prescriptions were inappropriate all prescriptions were considered inappropriate.

The Mann-Whitney U test was used to study the association between appropriate prescribing and LOS. The median differences and CIs were calculated using the

quantile regression model (Koenker, 2005). Quantile regression is a type of regression that estimates the conditional median of the outcome variable and is used when the assumptions of linear regression do not meet. Sex, age, location (ICU or non-ICU), and number of co-morbidities and infection type (respiratory, urinary tract, gastrointestinal, skin and soft tissue, bone and joint and others) were assessed as adjustment variables. As death prevents discharge, so the LOS estimates are interpreted differently for those who died; we looked at appropriateness separately in those who did not die.

Two sensitivity analyses were conducted. The first analysis was to compare the LOS between appropriate and inappropriate prescribing among only those patients who received only one antimicrobial per admission, and the second analysis was to compare the LOS between appropriate and inappropriate prescribing among only those patients who had HAP. Analysis of patients who received only one antimicrobial per admission in following the hypothesis that for patient who had more than one prescription during the same admission, considering the overall prescription inappropriate if any prescription was inappropriate may have an influence on the results. Analysis of HAP cases were conducted in following the hypothesis that patient having HAP maybe more likely to stay longer in hospital. All data were analysed using IBM SPSS Statistics for Windows, version 24.0 (Armonk, NY: IBM Corp, 2016).

2.4 Results

The first part of the results section presents the patients' demographic information. The results regarding antimicrobial therapy include duration, doses and frequencies, indication, type of indication and prescribers' specialities. Overall antimicrobial appropriateness, reasons for inappropriateness, appropriateness according to the indication and to the prescriber speciality are also presented. Finally, the

appropriateness of antimicrobial therapy for pre-defined subgroups of patients and prescriptions and the association between appropriate prescribing and patients' length of hospitalisation are presented.

2.4.1 Patient demographics

A total of 2,871 patients received 5,250 courses of antimicrobial treatment with at least one of the studied broad-spectrum antimicrobials across 3,671 patient admissions over a two-year period. Six hundred and sixty-eight (23.2%) patients were prescribed two courses of antimicrobials, and 1,219 (42.5%) patients were prescribed more than two courses. One hundred and forty patients who received 245 (4.7%) courses of antimicrobials during 167 visits were excluded from the assessment due to a lack of documentation of the diagnosis. The mean age of the patients was 55.5 years (SD= ±20.3, range 18-108 years), and 1,389 (50.9%) were male. During the study period, 377 (13.8%) patients died, and 885 (32.4%) had surgery. The demographic characteristics of the patients are presented in Table 2.2.

Table 2.2: Demographic characteristics of all adult patients prescribed imipenem/cilastatin, meropenem, or piperacillin/tazobactam during the study period

Variables	Characteristics	N (%)
Age (years)	Mean± SD	55.5±20.3
Weight (kg)		81.23±26.8
Height (cm)		163.63±29.9
BMI (kg/m^2)		30.82±10.9
Length of stay	Median (IQR)	14 (7-29)
Sex:	Male Female	1389 (50.9%) 1342 (49.1%)
Allergy status:	Documented drug allergy Documented antimicrobial allergy	91 (3.3%) 48 (1.8%)
Co-morbidities:	Diabetes mellitus Hypertension Cardiovascular disease Dyslipidaemia Cancer Kidney disease Haematological disorder Respiratory disease Neurological disorders Gastrointestinal disease Psychiatric disorder Musculoskeletal disorder Vitamin D deficiency Thyroid disorder Liver disease	1079 (39.5%) 767 (28.1%) 702 (25.7%) 526 (19.3%) 510 (18.7%) 365 (13.4%) 359 (13.1%) 355 (13%) 303 (11.1%) 232 (8.5%) 226 (8.3%) 220 (8.1%) 215 (7.9%) 178 (6.5%) 154 (5.6%)
Surgery		885 (32.4%)
In-hospital mortality		377 (13.8%)

2.4.2 Antimicrobial use

A total of 5,005 of the studied antimicrobials were prescribed. Piperacillin/tazobactam was the most frequently prescribed antimicrobial compared to imipenem/cilastatin and meropenem. The most prescribed piperacillin/tazobactam regimens were 4.5 g every 6 hours, 4.5 g every 8 hours and 2.25 g every 6 hours. Table 2.3 illustrates the duration, dose, frequency and median duration of treatment for imipenem/cilastatin, meropenem and piperacillin/tazobactam.

Overall, on 4,106 (82%) occasions, antimicrobials were prescribed as empiric therapy, 757 (15.2%) as targeted therapy after a pathogen had been identified in a clinical specimen, and 142 (2.8%) as prophylactic therapy. Table 2.4 shows the types of prescriptions for imipenem/cilastatin, meropenem and piperacillin/tazobactam.

Table 2.3: Duration, dose, frequency and median duration of treatment for Imipenem/cilastatin, meropenem and piperacillin/tazobactam

Antimicrobial therapy	Median duration of treatment (range)	Dose and frequency	N
Imipenem/cilastatin (n=776) 15.5%	7 (1-53)	1000 mg Q6	9
		1000 mg Q8	18
		1000 mg Q12	2
		500 mg Q4	1
		500 mg Q6	381
		500 mg Q8	133
		500 mg Q12	40
		500 mg Q24	1
		250 mg Q6	38
		250 mg Q8	77
		250 mg Q12	76
Meropenem (n=1021) 20.4%	7 (1-64)	2000mg Q6	4
		2000mg Q8	45
		2000mg Q12	3
		1000 mg Q6	27
		1000 mg Q8	475
		1000 mg Q12	261
		1000 mg Q24	7
		500 mg Q6	10
		500 mg Q8	37
		500 mg Q12	89
		500 mg Q24	58
		250 mg Q12	1
		250 mg Q12	3
		250 mg Q24	1
Piperacillin/tazobactam (n =3208) 64.1%	7 (1-48)	4.5 g Q6	1366
		4.5 g Q8	653
		4.5 g Q12	1
		3.375 g Q6	266
		3.375 g Q8	68
		3.375 g Q24	1
		2.25 g Q6	526
		2.25 g Q8	305
		2.25 g Q12	19
		2.25 g Q24	1
		1.5 g Q6	1
		1.5 g Q12	1

Key: g: gram; mg: milligram; Q24: every 24 hours; Q12: every 12 hours; Q8: every 8 hours; Q6: every 6 hours; Q4: every 4 hours.

Table 2.4: Type of prescriptions for Imipenem/cilastatin, meropenem and piperacillin/tazobactam

Variable	Antimicrobial agent		
	Imipenem/cilastatin	Meropenem	Piperacillin/ tazobactam
Total courses (n)	776	1021	3208
Total antimicrobial use (DDD)	5045.87	6492.25	15594.99
DDD per 100 bed-days	4.93	6.34	15.24
Type of prescriptions			
Empiric	476 (61.3%)	708 (69.3%)	2922 (91.1%)
Targeted	294 (38%)	292 (28.6%)	171 (5.3%)
Prophylaxis	6 (0.7%)	21 (2.1%)	115 (3.6%)

As illustrated in Figure 2.2, there was variability in the trend of the studied antimicrobial consumption during the study. It reached maximum in the last quarter of 2017 and minimum during the third quarter of 2016. The consumption of the studied antimicrobial during the second and third quarters of 2017 was very similar. Figure 2.3 illustrate the trends of Piperacillin/tazobactam, meropenem and imipenem/cilastatin consumption expressed as number of prescriptions.

The highest proportion of prescriptions were written for the patients treated in a medical ward (52%), followed by surgical wards (23.4 %), the ICU (15.3 %), and the ED (2.2%). Figure 2.4 illustrates the prescription distribution over the whole study period. Empiric and targeted therapy were the most common indications in the internal medicine wards, while prophylaxis therapy was most commonly prescribed in the surgical wards. Table 2.5 illustrates the numbers and percentages of antimicrobial prescriptions stratified by hospital wards.

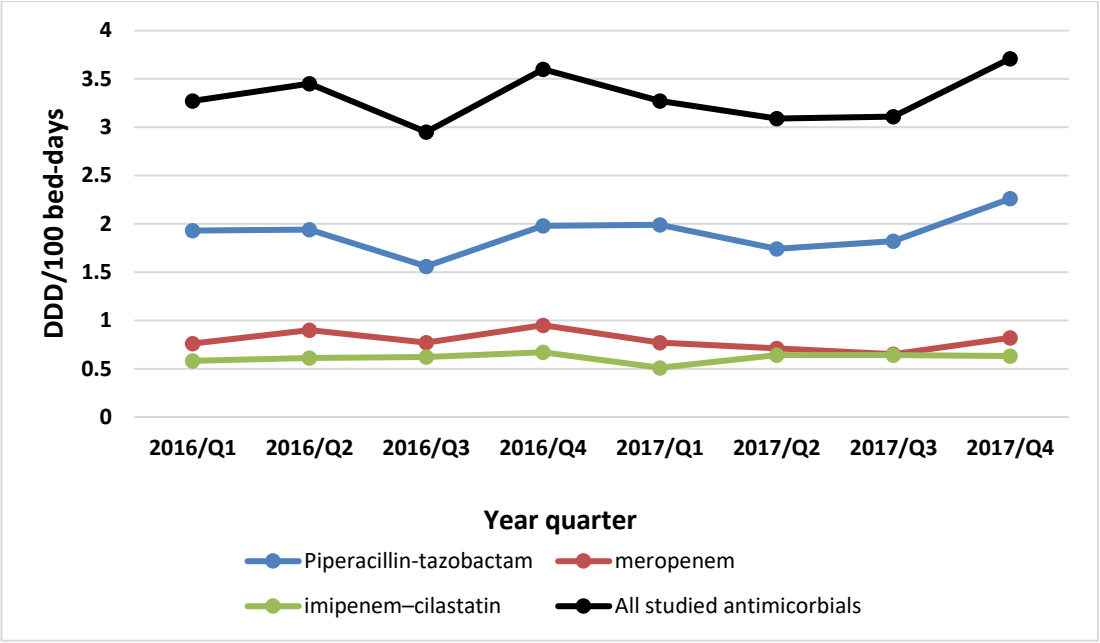


Figure 2.2: Trends of Piperacillin/tazobactam, meropenem and imipenem/cilastatin consumption, 2016-2017 (DDD per 100 bed-days)

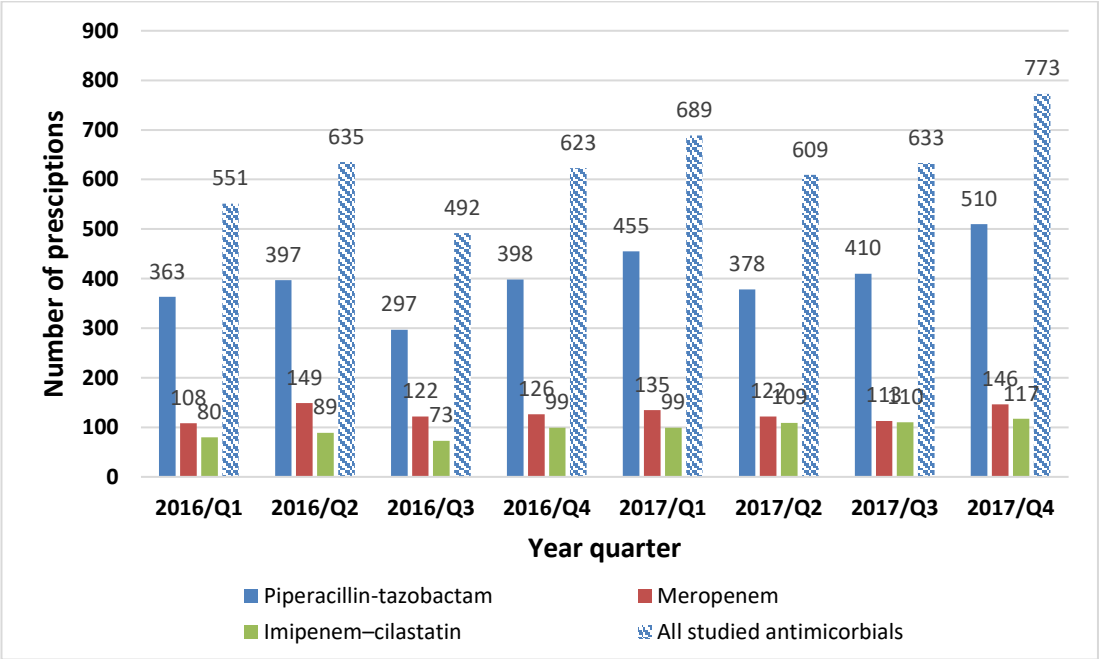


Figure 2.3: Trends of Piperacillin/tazobactam, meropenem and imipenem/cilastatin consumption, 2016-2017 (Number of prescriptions)

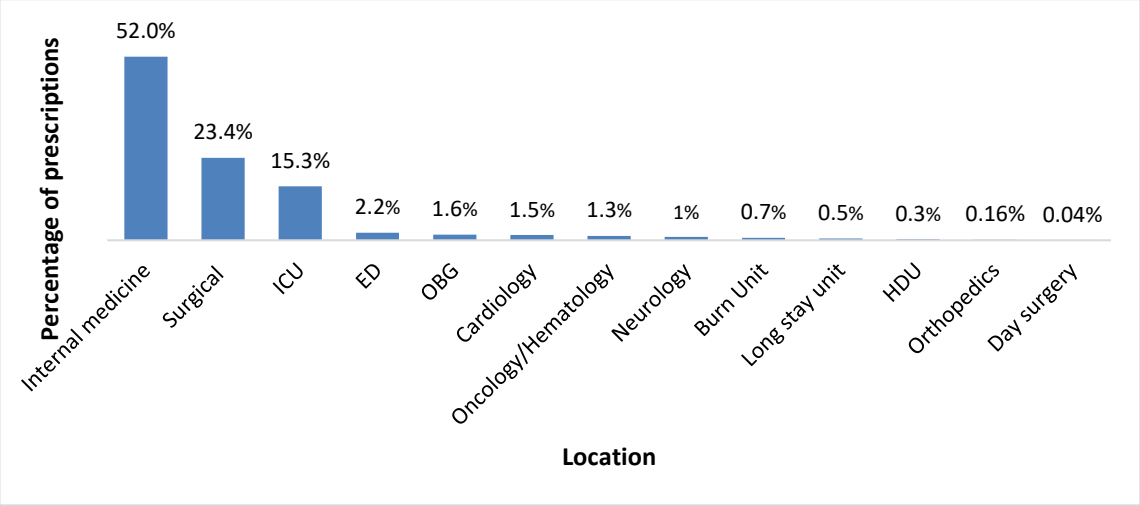


Figure 2.4: Prescriptions distribution over the whole study period

Table 2.5: Numbers and percentages of antimicrobial prescriptions stratified by hospital wards: Empiric, Targeted and Prophylaxis

Type of indication	Internal medicine	Surgical wards	ICU	ED	Others	Total
Empiric	2265 (55.2%)	851 (20.7%)	611 (14.9%)	96 (2.3%)	283 (6.9%)	4106
Targeted	328 (43.3%)	225 (29.7%)	135 (17.8%)	11 (1.5%)	58 (7.7%)	757
Prophylaxis	12 (8.5%)	94 (66.2%)	21 (14.8%)	1 (0.7%)	14 (9.8%)	142

Key: ICU: Intensive care unit; ED: Emergency department.

Pneumonia (26.6%) was the most common indication for initiation of antimicrobial therapy, followed by sepsis (24.9%), UTIs (17.3%), SSTIs (14.8%), intra-abdominal infections (8.6%) and febrile neutropenia (4%). Table 2.6 summarises the main indications for imipenem/cilastatin, meropenem and piperacillin/tazobactam. Medical residents prescribed the majority of antimicrobial therapy (64.7%), followed by internal medicine specialists (17%) and ICU specialists (11%). Table 2.7 illustrates the percentage of antimicrobials prescribed by different specialists. Culture and sensitivity tests were ordered on 3,934 (78.6%) occasions before prescribing antimicrobials; 3,177 (63.5%) were before initiating empiric antimicrobial therapy.

Table 2.6: Indications of antimicrobial therapy

Indication	Number N=5005	Imipenem/ cilastatin n=776	Meropenem n=1021	Piperacillin/ tazobactam n=3208
Febrile neutropenia	199	21 (2.7 %)	27 (2.6%)	151 (4.7%)
Gynaecological infection	5	0 (0%)	0 (0%)	5 (0.2%)
Intra-abdominal infection	431	54 (7%)	53 (5.2 %)	324 (10.1%)
Meningitis	8	0 (0%)	3 (0.2 %)	5 (0.2%)
Osteomyelitis	25	5 (0.6%)	9 (0.9 %)	11 (0.3%)
Pneumonia	1333	122 (15.7%)	203 (19.8%)	1008 (31.4%)
Sepsis	1248	257 (33.1%)	359 (35.2%)	632 (19.7%)
Skin and soft tissue infection	743	130 (16.8%)	130 (12.7 %)	483 (15.1%)
Urinary tract infection	864	181 (23.3%)	213 (20.9%)	470 (14.7%)
[a]Other	7	0 (0 %)	3 (0.3 %)	4 (0.1%)
Prophylaxis				
Surgical prophylaxis	102	3 (0.4 %)	8 (0.8%)	91 (2.8%)
[b]Other prophylaxis	40	3 (0.4 %)	13 (1.3%)	24 (0.7%)

[a] Other includes endocarditis and acute otitis externa

[b] Other prophylaxis includes trauma, burn and bite

Table 2.7: Percentage of antimicrobials prescribed by different specialists

Prescriber speciality	N (%)
Resident	3241 (64.8%)
[a]Internal medicine	854 (17.1%)
ICU	549 (11%)
Surgeon	157 (3.1%)
Cardiologist	96 (1.9%)
ED Physician	46 (0.9%)
Pulmonologist	36 (0.7%)
Orthopaedics	10 (0.2%)
Anaesthesiologist	8 (0.15%)
OBG	7 (0.13%)
Intern	1 (0.02%)
Total	5005

Key: ICU: Intensive care unit; ED: Emergency department; OBG: Obstetrics and gynaecology.

[a] Also include infectious disease specialist.

2.4.3 Appropriateness of antimicrobial therapy

Overall, 4,929 (98.5%) of the prescribed antimicrobials were assessed for their appropriateness of prescribing. A small number (76, 1.5%) of the prescribed antimicrobials could not be assessed as some patients were either discharged or died before culture results became available. The results showed that only 2,787 (56.5%)

of the antimicrobial orders were prescribed appropriately, with 2,142 (43.5%) being inappropriate. An empirical initiation of piperacillin/tazobactam was only appropriate in 52.3% of the total empiric piperacillin/tazobactam prescriptions. Almost all the carbapenem and piperacillin/tazobactam prescribed as prophylactic therapy was inappropriate. Table 2.8 illustrates the appropriateness of imipenem/cilastatin, meropenem and piperacillin/tazobactam prescriptions.

Table 2.8: Appropriateness of imipenem/cilastatin, meropenem and piperacillin/tazobactam prescriptions

Antimicrobial	Type of prescription	Appropriate	Inappropriate
Imipenem/cilastatin	Empiric (n=466)	63.5%	36.5%
	Targeted (n=294)	87%	13%
	Prophylaxis (n=6)	0%	100%
Meropenem	Empiric (n=691)	57.9%	42.1%
	Targeted (n=291)	79.4%	20.6%
	Prophylaxis (n=21)	0%	100%
Piperacillin/tazobactam	Empiric (n=2874)	52.3%	47.7%
	Targeted (n=171)	57.9%	42.1%
	Prophylaxis (n=115)	0.9%	99.1%

The most common reasons for inappropriate use of empiric prescriptions were: spectrum of activity was too broad 1029 (40%), antimicrobial used without a culture request 929 (36.2%), failure of suitable antimicrobial de-escalation 570 (22.2%), known allergy to the prescribed antimicrobial 29 (1%) and continuation of antimicrobial prescribing despite microbiology results indicating resistance 12 (0.5%). As some antimicrobial prescriptions had more than one reason for inappropriateness, the total number for the identified reasons were 2,870. Some of

the reasons were only applicable to one type of prescription, accordingly the total reasons under each type of prescription have different denominator. Figure 2.5 outlines the reason why antimicrobials were inappropriate for empiric, targeted and prophylaxis.

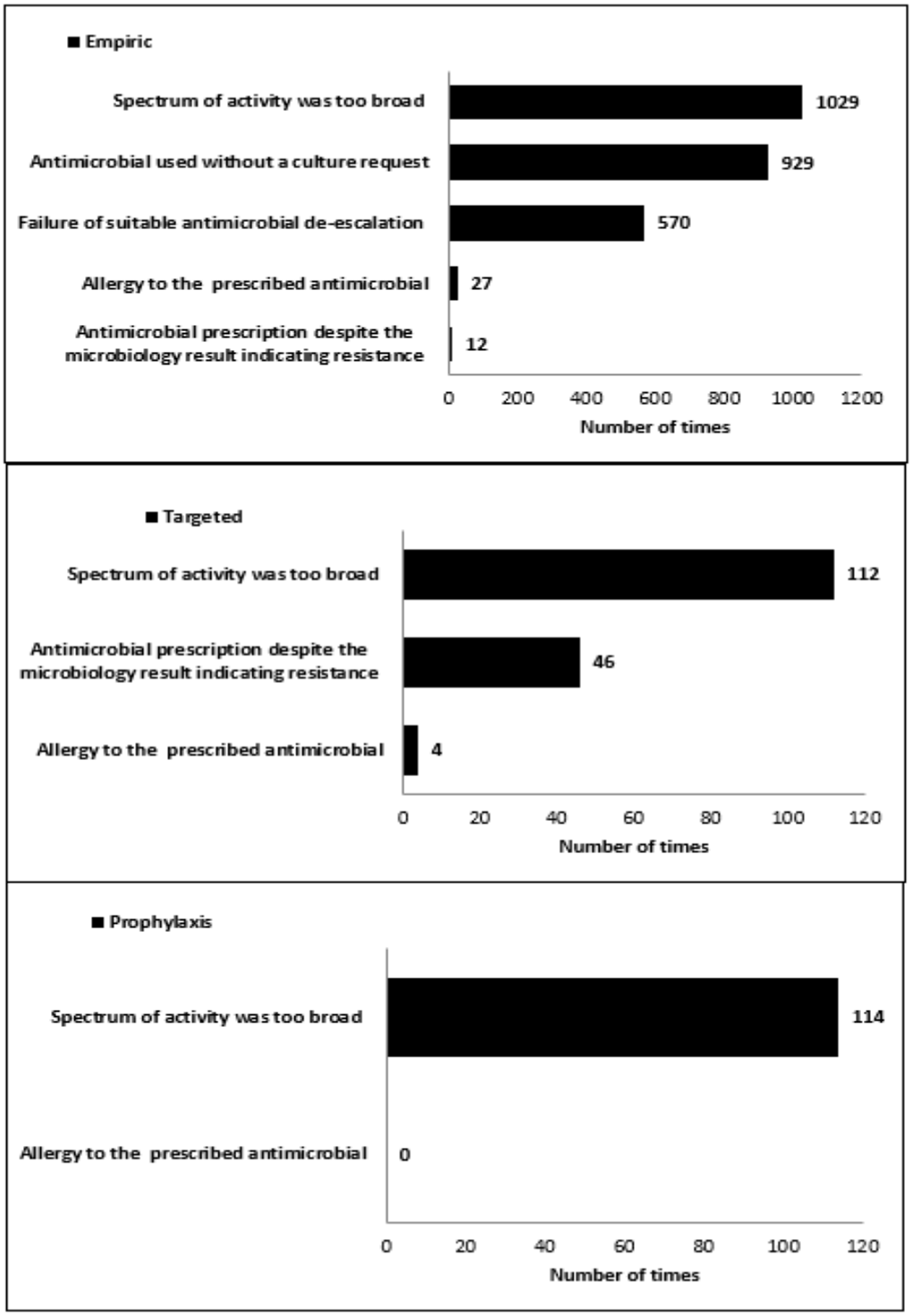


Figure 2.5: Reasons for the inappropriate prescribing according to the type of the prescription; empiric, targeted and prophylaxis

The percentages of appropriate prescriptions that were prescribed for sepsis, SSTI and UTIs were more than the percentage of the inappropriate prescriptions, while for pneumonia, febrile neutropenia and intra-abdominal infections prescriptions, the percentage of inappropriate prescriptions was more than the appropriate prescriptions. All the prescriptions that were for gynaecological infection and surgical prophylaxis were inappropriate. Table 2.9 illustrates the appropriateness of antimicrobials according to the indication. According to the prescriber speciality, 1396 (43%) of the prescriptions prescribed by the residents were inappropriate, 378 (44.3%) prescribed by internal medicine specialists were inappropriate and 217 (39.5%) prescribed by ICU specialists were inappropriate. Table 2.10 illustrates the appropriateness of antimicrobials according to prescriber speciality**.**

Table 2.9: Appropriateness of antimicrobials according to the indication

Indication	**Appropriate n (%)**	**Inappropriate n (%)**	**Not assessed n (%)**
Treatment (empiric and targeted)			
Febrile neutropenia	63/199 (31.7%)	134/199 (67.3%)	2/199 (1%)
Gynaecological infection	0/5 (0%)	5/5 (100%)	0/5 (0%)
Intra-abdominal infection	183/431 (42.5%)	243/431 (56.4%)	5/431 (1.1%)
Meningitis	3/8 (37.5%)	5/8 (62.5%)	0/8 (0%)
Osteomyelitis	17/25 (68%)	8/25 (32%)	0/25 (0%)
Pneumonia	612/1333 (45.9%)	703/1333 (52.7%)	18/1333 (1.4%)
Sepsis	873/1248 (70%)	340/1248 (27.2%)	35/1248 (2.8%)
Skin and soft tissue infections	492/743 (66.2%)	248/743 (33.4%)	3/743 (0.4%)
Urinary tract infection	539/864 (62.4%)	312/864 (36.1%)	13/864 (1.5%)
[a]Other	4/7 (57.1%)	3/7 (42.9%)	0/7 (0%)
Prophylaxis			
Surgical prophylaxis	0/102 (0%)	102/102 (100%)	0/102 (0%)
[b]Other prophylaxis	1/40 (2.5%)	39/40 (97.5%)	0/40 (0%)

[a] Other includes endocarditis and malignant otitis externa

[b] Other prophylaxis includes trauma, burn and bite

Table 2.10: Appropriateness of antimicrobials according to the prescriber speciality

Prescriber speciality	Total number of prescriptions (n)	Appropriate n (%)	Inappropriate n (%)	Not assessed n (%)
Resident	3241	1809 (55.8%)	1396 (43%)	36 (1.2%)
[a]Internal medicine	854	461 (54%)	378 (44.3%)	15 (1.7%)
ICU	549	312 (56.9%)	217 (39.5%)	20 (3.6%)
Surgeon	157	93 (59.3%)	63 (40.1%)	1 (0.6%)
Cardiologist	96	49 (51%)	45 (47%)	2 (2%)
ED Physician	46	27 (58.7%)	18 (39.1%)	1 (2.2%)
Pulmonologist	36	23 (64%)	12 (33.3%)	1 (2.7%)
Orthopaedics	10	5 (50%)	5 (50%)	0 (0%)
Anaesthesiologist	8	5 (62.5%) _	3 (37.5%)	0 (0%)
OBG	7	3 (43%)	4 (57%)	0 (0%)
Intern	1	0 (0%)	1 (100%)	0 (0%)
Total	5005	2787	2142	76

Key: ICU: Intensive care unit; ED: Emergency department; OBG: Obstetrics and gynaecology.
[a] Also include infectious disease specialist.

2.4.4 Appropriateness of antimicrobial therapy for pre-defined subgroups of patients and prescriptions

There were no significant differences in the incidence of inappropriate antimicrobial prescribing based on gender or patient location (ICU versus non-ICU). Patients aged >44 years had lower odds of inappropriate antimicrobial prescribing compared to those aged less than 44 years old. Patients with two or more co-morbidities had higher odds of inappropriate prescribing compared to those with one co-morbidity. Patients who had antimicrobial prescriptions for empiric treatment or prophylaxis had higher odds of inappropriate prescribing compared to those who had

prescription for targeted therapy. Table 2.11 shows the characteristics of the patients prescribed both appropriate and inappropriate antimicrobials.

Table 2.11: Appropriateness of antimicrobial therapy for pre-defined subgroups of patients and prescriptions

Characteristic	Appropriate n/N (%) N= (2787)	Inappropriate n/N (%) N= (2142)	Odds ratio (95%CI)	P value	Percentage risk difference (95%CI)
Age					
18-44	715/1345 (53.2%)	630/1345 (46.8%)	1.00	0.031	Reference
45-64	905/1553 (58.3%)	648/1553 (41.7%)	0.81 (0.70-0.94)		-5.1% (-8.7 to 1.5)
65-84	1016/1766 (57.5%)	750/1766 (42.5%)	0.84 (0.73-0.97)		-4.5% (-7.9 to 0.8)
≥ 85	151/265 (57.0%)	114/265 (43.0%)	0.86 (0.66-1.12)		-3.8% (-10.4 to 2.7)
Gender					
Female	1403/2445 (57.4%)	1042/2445 (42.6%)	1.00	0.238	Reference
Male	1384/2484 (55.7%)	1100/2484 (44.3%)	1.07 (0.956-1.198)		1.7% (-1.1 to 4.4)
Co-morbidities					
0	394/690 (57.1%)	296/690 (42.9%)	1.00		Reference
1	1155/1680 (68.8%)	525/1680 (31.3%)	0.61 (0.50-0.73)	<0.0001	-11.7% (-16 to 7.3)
2	281/576 (48.8%)	295/576 (51.2%)	1.40 (1.12-1.75)		8.3% (2.8 to 13.8)
≥3	957/1983 (48.3%)	1026/1983 (51.7%)	1.43 (1.20-1.70)		8.8% (4.5 to 13.1)
Location					
Non-ICU	2368/4203 (56.3%)	1835/4203 (43.7%)	1.00	0.491	Reference
ICU	419/726 (57.7%)	307/726 (42.3%)	0.946 (0.806-1.109)		-1.4% (-5.3 to 2.5)
Type of antimicrobial therapy					
Empiric	2200/4031 (54.6%)	1831/4031 (45.4%)	1.00	<0.001	Reference
Targeted	586/756 (77.5%)	170/756 (22.5%)	0.35 (0.29-0.42)		-22.9% (-26.3 to -19.5)
Prophylaxis	1/142 (0.7%)	141/142 (99.3%)	169.4 (23.7-1212.1)		53.9% (51.8 to 56)

2.4.5 The association between appropriate prescribing and patients' length of hospitalisation

A total of 2,695 patients during 3,453 visits were included in the study. A total of 506 patients had at least more than one visit during the study period. The total number of visits where patients were prescribed only one antimicrobial was 2,457 visits. During 996 admissions, there was at least more than one prescription during the same visit. For the total visits analysis, it was shown that the LOS was significantly higher related to appropriate therapy (17 days vs. 12 days (P=0.0001)). In the quantile regression model, there was a trend toward shorter LOS with inappropriate prescribing (adjusted median difference 5.7 (95% CI:4.4,7.1)). LOS reduced after adjusting of type of infection (adjusted median difference 3.8 (95% CI:2.3, 5.2)) (Table 2.12).

Sensitivity analyses were performed by including patients who had one prescription per admission and similar results were found. It was shown that the LOS was significantly higher related to appropriate therapy (14 days vs. 10 days (P=0.0001)). In the quantile regression model, it was shown that the LOS was significantly higher for therapy appropriateness (adjusted median difference 4 (95% CI:2.7,5.3)). LOS reduced after adjusting of type of infection (adjusted median difference 3.5 (95% CI:2.4, 4.7)) (Table 2.13).

An analysis of the cases with HAP showed that there were no significant differences in the LOS between the appropriate versus inappropriate group (15 days vs. 13 days (P=0.09)). In the quantile regression model, it was shown that the adjusted median difference was 0.4 (95% CI:-2.4, 3.3; Table 2.14).

Table 2.12: Length of stay by appropriateness and mortality (total visits analysis)

		Mortality		
Overall therapy appropriateness		No N=3105	Yes N=348	Total N=3453
No N=1698	Length of stay, Median [IQR]	11 [6-22] N=1542	26.5 [12.5-59] N=156	12 [6-24] N=1698
Yes N=1755	Length of stay, Median [IQR]	17 [9-32] N=1563	25 [11-43] N=192	17 [9-34] N=1755
P value*		0.0001	0.89	0.0001
Median difference (95% CI)**		6 (4.6, 7.4) P<0.0001	-2 (-8.7, 4.7) P=0.56	5 (3.6, 6.4) P<0.0001
Median difference (95% CI)***		5.9 (4.6, 7.2) P<0.0001	-1.2 (-8.4, 5.95) P=0.74	5.7 (4.4, 7.1) P<0.0001
Median difference (95% CI)****		4.1 (2.8, 5.5) P<0.0001	-1.9 (-9.3, 5.5) P=0.62	3.8 (2.3, 5.2) P<0.0001

*Mann-Whitney U test
**quantile regression model (unadjusted)
***adjusted for sex, age, ICU, no of co-morbidities.
**** adjusted for sex, age, ICU, no of co-morbidities, infection type.

Table 2.13: Length of stay by appropriateness and mortality (one prescription per admission)

		Mortality		
Overall therapy appropriateness		No N=2382	Yes N=75	Total N=2457
No N=1287	Length of stay, Median [IQR]	9 [6-17] N=1256	20 [9-54] N=31	10 [6-17] N=1287
Yes N=1170	Length of stay, Median [IQR]	14 [7-25] N=1126	21 [6.5-39.5] N=44	14 [7-26] N=1170
P value*		0.0001	0.47	0.0001
Median difference (95% CI)**		5 (3.7, 6.3) P<0.0001	2 (-19.9, 23.9) P=0.86	5 (3.6, 6.4) P<0.0001
Median difference (95% CI)***		4.6 (3.7, 5.6) P<0.0001	-0.9 (-18.3, 16.4) P=0.92	4 (2.7, 5.3) P<0.0001
Median difference (95% CI)****		3.5 (2.4, 4.6) P<0.0001	2.0 (-15.0, 19.1) P=0.81	3.5 (2.4, 4.7) P<0.0001

*Mann-Whitney U test
**quantile regression model (unadjusted)
***adjusted for sex, age, ICU, no of co-morbidities.
**** adjusted for sex, age, ICU, no of co-morbidities, infection type.

Table 2.14:**Length of stay by appropriateness and mortality (hospital-acquired pneumonia)**

		Mortality		
Overall therapy appropriateness		No N=365	Yes N=11	Total N=376
No N=205	Length of stay, Median [IQR]	13 [8-22] 201	74 [37.5-463] 4	13 [8-22] 205
Yes N=171	Length of stay, Median [IQR]	15 [8-29] 164	16 [10-42] 7	15 [8-30] 171

P value*	0.06	0.05	0.09
Median difference (95% CI)**	2 (-0.9, 4.9) P=0.17	-77 (678, 524) P=0.78	2 (-0.9, 4.9) P=0.17
Median difference (95% CI)***	0.4 (-2.6, 3.4) P=0.78	-29 (-842, 784) P=0.93	0.4 (-2.4, 3.3) P=0.76

*Mann-Whitney U test
**quantile regression model (unadjusted)
***adjusted for sex, age, ICU, no of co-morbidities.

2.5 Discussion

This study provides important insights into the current prescribing practices of carbapenems (imipenem/cilastatin or meropenem) and piperacillin/tazobactam at a tertiary hospital within Saudi Arabia.

The study found that these three broad-spectrum antimicrobials were commonly used for empiric indications and more than half of the prescriptions were ordered by medical residents. For the practice of taking a culture before starting antimicrobial therapy, culture and sensitivity tests were ordered in 78.6% of cases before prescribing antimicrobials. Assessment of the appropriateness of broad-spectrum antimicrobials showed that in 43.5% of cases, they were inappropriate.

It was found that appropriate broad-spectrum antimicrobial prescribing did not result in a shorter length of hospital stay, with the inappropriate prescriptions group spending less time in hospital. This section will discuss the results in details.

2.5.1 Antimicrobial use

In this study 245 (4.7%) prescriptions were excluded from the assessment due to a lack of documentation of the indication. Recording the indication for prescribing antimicrobial was higher (95.3%) compared with data from a PPS study in 26 Saudi hospitals (48.9%). This might reflect the recent adoption of electronic prescribing from 2015 onwards. KKUH is one of the oldest tertiary centre in KSA and have better infrastructure which may account for the differences observed in recording. The PPS survey data was noted to be collected on 2016 and this could reflect that the

electronic prescribing to theses hospital had not yet occurred and as a consequence the data records may have been less complete.

Antimicrobial consumption has been widely reported by measuring the DDD. Results have been used for benchmarking purposes; however, this methodology has its disadvantages (Kuster *et al.,* 2008). DDD and PDD can be over- or underestimated according to the underlying disease. Moreover, this measurement does not indicate the appropriateness of the antimicrobial therapy. DDD has the advantage of providing a better estimation than DOT, particularly in patients receiving one dose, such as surgical prophylaxis or a combination of antimicrobials. Therefore, in this study, for the purpose of quantifying antimicrobial consumption and assessment of the appropriateness of antimicrobial therapy, both the number of prescriptions and the DDD were used for reporting the results. In hospital settings, to overcome the variation and differences in occupancy rate and size, to allow benchmarking with other hospitals and organizations, it is recommended to measure the number of DDD per 100 bed-days (Birkett *et al.,* 2003). Thus, in this study, DDD was expressed per bed-days.

The consumption of piperacillin/tazobactam in this study was 15.24 DDDs per 100 bed-days, which was similar to that previously reported in Saudi (13.4 DDDs per 100 bed-days; Balkhy *et al.,* 2018). Unlike piperacillin/tazobactam, the consumption of carbapenem was 11.27 DDDs per 100 bed-days, which was less than previously reported in a Saudi hospital (25.6 DDDs per 100 bed-days; Balkhy *et al.,* 2018). This could be due to the differences in the local resistance pattern, prescribing policy. In this study, broad-spectrum antimicrobials were commonly prescribed in the internal medicine wards. The most common indication for prescribing carbapenems and piperacillin/tazobactam was pneumonia, followed by sepsis. A study conducted by

Youssif *et al.* (2018) found in a tertiary care hospital in Saudi Arabia found that the most common indication for prescribing carbapenems and piperacillin/tazobactam was SSTIs, followed by intra-abdominal infections. Reported differences in prescription indication may be due to the inclusion of surgical floors in the later study. This study showed that 64.8% of the prescribed broad-spectrum antimicrobials were prescribed by the resident physicians. This could be justified by shortage of senior physicians and the unavailability of ID physicians. . The lack or unavailability of ID physicians is considered to be a gap in the practice of antimicrobials prescribing, where physicians from different specialities can communicate and share the antimicrobial prescribing decisions. As the data were retrieved from the hospital system, it was not possible to obtain the percentage of antimicrobials prescribed by the ID physicians as they were in the internal medicine category (Pulcini *et al.,* 2014). Therefore, there is a need to conduct a study to further explore broad-spectrum antimicrobial prescribing practices.to identify ID physicians' prescribing patterns.

In this study, culture and sensitivity tests were ordered on 3,934 (78.6%) occasions before prescribing antimicrobials, while 1,071 (21.4%) antimicrobial prescriptions were started without culture and sensitivity tests orders. This could be because of several reasons. Some patients were prescribed antimicrobials as prophylaxis; however, in this study, only a few prescriptions were issued for prophylactic indications. Another reason could be organisational constraints due to limited capacity or opening hours (Schouten *et al.,* 2007; Om *et al.,* 2016). Failing to order a culture before the initiation of the therapy by some physicians where they decided to start the therapy based on the clinical signs and symptoms of the patient (Alharthi *et al.,* 2019) could also be a cause. Moreover, in some cases, taking culture is not possible due to reasonable reasons such as for patient with abdominal infections and

mild pneumonia. Further investigation is needed to probe the reasons behind not taking a culture at an institutional level.

2.5.2 Appropriateness of antimicrobial therapy

In this study, prescriptions were used as the unit of analysis instead of patients because 65.7% of the patients received more than one antimicrobial prescription during the evaluation period. The study found that the overall appropriate use of the three broad-spectrum antimicrobials was 56.5%. Most antimicrobials were prescribed for empirical indication (82%) and only 15.2% were prescribed post-culture. Empiric indication of piperacillin/tazobactam was appropriate in 52.3% of the empiric courses. The current results are similar to the study by Mekdad and AlSayed (2020), which was conducted in a cardiac unit of a tertiary care hospital in Saudi Arabia and found that piperacillin/tazobactam prescribing was appropriate in 55% of prescriptions. Moreover, a study conducted by Khan *et al*. (2012) to evaluate piperacillin/tazobactam use in an adult population in a tertiary care hospital in Qatar found that it was appropriately initiated in 57% of courses. In contrast, the results of the current study differ from other studies from countries in the locality, where it was calculated that piperacillin/tazobactam was appropriately initiated on 86% - 90% occasions (Raveh *et al.,* 2006; Zeenny *et al.,* 2014). The differences may be due to the variation in indication between paediatric versus adult populations, variations in prescriber education or the status of ASPs in each hospital. Moreover, different assessment criteria for the prescriptions could contributed to the identified differences in appropriateness. The rate of appropriateness of empiric indication of meropenem and imipenem was 57.9% and 63.5%, respectively. A study that evaluated the empiric prescriptions of imipenem/cilastatin conducted in a tertiary

care hospital over a 3-month period demonstrated a higher rate of appropriateness (97%) compared to the present study (Kabbara *et al.,* 2015). Furthermore, a study conducted by Raveh *et al. (*2006) reported that 82% f meropene prescriptions were appropriate. Similar justifications could be made about the reported differences in appropriates rates as described above

The most common diagnosis in the category of inappropriateness was pneumonia and sepsis. In sepsis, a delay in antimicrobial prescribing is associated with increased mortality (Levy *et al.,* 2018). The initial step in sepsis management is the identification of patients with sepsis, which can be clinically challenging. Sepsis diagnosis is extremely subjective and identification can be complex, particularly in the early stages when the presenting symptoms are non-specific and test results are pending. This means that a prescriber must make early decisions regarding antimicrobials usage (Vincent, 2016). In this period of uncertainty, prescribers need to act, balancing the risks of failing to treat sepsis versus over-prescribing, and the risk of increasing AMR.

The most common reason given for the assessment of inappropriateness for empiric prescriptions was that the spectrum of activity was too broad (40%). The high percentage of inappropriate initial selection of these broad-spectrum antimicrobials is concerning. Such over-prescribing is associated with an increased risk of AMR, adverse effects, opportunistic infections and increased healthcare costs (Tamma *et al.,* 2017). Therefore, there is a need for antimicrobial stewardship. Possible antimicrobial stewardship strategies include guideline implementation and staff education (Davey *et al.,* 2017).

In terms of de-escalation of therapy, the failure of de-escalation was shown in 19.9% of cases. The failure to de-escalate may be due to the reluctance of prescribers to

make modifications to a clinically unwell patient's therapy or the tendency toward continuation of a therapy that appears to be effective (Paterson, 2006). Nevertheless, the continuation of therapy while the culture indicated sensitivity to a narrower agent is concerning and this is considered a focus area for further explanation and future intervention in antimicrobial prescribing practice.

2.5.3 Appropriateness of antimicrobial therapy for pre-defined subgroups of patients and prescriptions

The analysis of antimicrobial appropriateness for pre-defined subgroups of patients and prescriptions showed that patients who had a higher number of co-morbidities were more likely to be prescribed inappropriate antimicrobials than those who had fewer or no co-morbidities. An assumption could be that for these patients, prescribers might prescribe broad-spectrum antimicrobials inappropriately to prevent the decompensation of co-morbidities related to sepsis.

Overall, the findings from this DUR study in terms of consumption and prescribing of broad-spectrum antimicrobials showed that there is inappropriate antimicrobial prescribing in terms of initial antimicrobial choice and/or continuation of therapy. These findings support Khan *et al.* (2012); Zeenny *et al.* (2014); Kabbara *et al.* (2015); and Mekdad and AlSayed (2020), who all reported different rates of inappropriate prescribing of at least one of the three studied antimicrobials. However, some of these studies used additional assessment criteria such as proper dosing (Khan *et al.,*2012; Zeenny *et al.,*2014; Kabbara *et al.,*2015) and may have been subject to different antimicrobial prescribing policies.

2.5.4 The association between appropriate prescribing and patients' length of hospitalisation

Appropriate broad-spectrum antimicrobial prescribing did not result in a shorter length of hospital stay, with the inappropriate prescriptions group spending less time in hospital, after controlling for cofounders such as sex, age, location (ICU- non-ICU), and number of co-morbidities.

Though it may seem logical that appropriate broad-spectrum antimicrobial prescriptions would lead to improved outcome such as the length of hospital stay, this association has not been identified in this study, where patients with appropriate prescriptions were shown to stay longer in hospital. . In this study, the use of a scoring system such as the Charlson co-morbidity index (Charlson *et al.,*1987) or the quick Sepsis-related Organ Failure Assessment (Seymour *et al.,* 2016) was considered; however, the required metrics to populate these datasets (i.e severity of liver disease, partial pressure of oxygen) were unavailable because they had not been captured electronically in the database that we had access to.

The first explanation for having longer hospital stay in the appropriately prescribed group may be that this group were experiencing more severe conditions as broad-spectrum seemed to be appropriately used in more severe cases. While patients who were prescribed broad-spectrum antimicrobials inappropriately were mainly because of the assessment that the spectrum was too broad where they can be treated with narrow-spectrum probably due to less severe infections which justified being discharged earlier (Garau *et al.,* 2008).

In observational retrospective studies, the potential for selection bias is considered a major limitation. In this case, the patients with less severe illness may be more likely

to receive unnecessary broad-spectrum antimicrobials and be categorised as receiving inappropriate prescriptions (Hulscher and Prins, 2017).

Moreover, in cases that broad-spectrum antimicrobials prescriptions were considered appropriate, there may have been a failure of initial therapy that led to the prescription of these antimicrobials, which had an impact on the LOS.

Another explanation may be that LOS is a variable that, in theory, should be affected by differences in quality of care; however, it is subject to several confounders, such as age, gender, co-morbidities, severity of illness and transfer (Garau *et al.,* 2008; Thom *et al.,* 2008; Baek *et al.,* 2018; Ofori-Asenso *et al.,* 2018). To reduce the chance of confounding, LOS was adjusted for sex, age, location (ICU- and non-ICU), and number of co-morbidities. However, there might be differences in severity between the two groups, which might justify the difference seen in LOS. Unfortunately, as it was mentioned earlier, there was no data on severity of illness score in this study.

In this study, we have looked at a range of ID and perhaps that is why interpretation is more difficult. When we looked at a subpopulation of the data, which was a large segment of the overall data, to see whether that same signal was maintained, we found that for HAP, there were no significant differences in LOS between the appropriate versus inappropriate groups.

In the literature, studies that have investigated the association between appropriate antimicrobial prescribing and LOS have either identified that appropriate antimicrobial prescribing is associated with a shorter LOS (Spoorenberg *et al.,* 2014; van den Bosch *et al.,* 2017; Wathne *et al.,* 2019) or no association was found (Thom *et al.,* 2008). These studies have used different methodology and criteria for the assessment of appropriateness. Wathne *et al.,* 2019 identified that appropriate antimicrobial prescribing in terms of guidelines adherence was associated with

decreased LOS. However, LOS for more than 21 days were excluded, which may limit the generalisability of the estimate. In addition, the severity of illness was not controlled for the analysis.

In some of these studies, LOS was stratified by disease indication (Spoorenberg *et al.,*2014; van den Bosch *et al.,* 2017; Thom *et al.,* 2008). Some studies used a comprehensive set of quality indicators (Spoorenberg *et al.,* 2014; van den Bosch *et al.,* 2017) in which only an IV to oral switch was associated with shorter hospital stay, which was not assessed in the present study (van den Bosch *et al.,* 2017). It is likely that LOS is prolonged for the reason that more days of hospitalisation are needed to continue receiving IV antimicrobial therapy.

A limitation of the study is the use of an international guideline for the assessment of the appropriateness of the antimicrobial prescriptions due to the unavailability of institutional guideline. While using institutional guideline would have been ideal, an ID specialised clinical pharmacists was consulted to assist where the decisions on appropriateness were not clear.

Other limitation is the impact of the classifications of inappropriate prescribing used in this study. The criteria that were used to assessed the inappropriateness may have an impact on the results of the assessment. For example, the inability to consider some patients factor such some patients may have antimicrobial before admission or in cases of not ordering culture due to the unavailability of a sample. Moreover, reasons for not ordering culture it could be for valid reasons such as in intra-abdominal infections and mild pneumonia. Consequently, this could explain the unexpected shorter LOS in inappropriate group. For example, culture may not take for a justifiable reason for a patient who had a shorter LOS and the prescription was categorised under inappropriate prescription.

Other limitation is that the LOS examined in the study was all-cause related LOS rather than infection-only related stay which may have an impact on the results of the study. For example, some patients who had appropriate prescriptions may need to stay longer due to nutritional management, surgeries or developing complications that are not related to the antimicrobial therapy.

Also, other limitation of this study is that we were unable to account for all the factors increasing LOS in hospitalised patients, such as the severity of illness. Consequently, this study provides justification for conducting a well-designed study that controls for further factors that may impact the LOS, such as information about the severity of infections and illness, to determine the benefit of appropriate broad-spectrum antimicrobials in hospitalised patients. Structured, accurate and accessible data on the severity of infections must be documented in the patient's electronic medical record to ensure and secure this data for quality improvement processes and research purposes.

2.6 Conclusion

This chapter presented the results from quantitative study related to physicians' broad-spectrum antimicrobial prescribing for adult patients in hospital setting. This study has provided important insights into the use and appropriateness of broad-spectrum antimicrobials.

We have identified that appropriate broad-spectrum antimicrobial therapy was associated with longer hospital stay. One hypothesis to justify this finding is that broad-spectrum antimicrobial prescriptions were considered to be prescribed appropriately for those who had severe infections, resulting in them staying longer in hospital. Another hypothesis is that there was no normalisation for individual patient health, which could lead to the positive outcome seen in the inappropriate group.

Overall, the results showed that the rate of inappropriate prescribing of broad-spectrum antimicrobials we 43.5%. Future research is needed to further explore factors associated with inappropriate antimicrobial prescribing practices.

3. Chapter 3: A qualitative study exploring physicians' views and perceptions on broad-spectrum antimicrobials and factors influencing antimicrobials prescribing

Overview: This chapter starts with a general introduction, including a summary of the key results of the quantitative study, and then illustrates the aims and objectives of the qualitative study. An explanation of the methodology adopted in the study is then presented, followed by the findings, discussion and a summary.

3.1 Introduction

International recommendations on ASPs are intended to improve the appropriateness of antimicrobial prescribing (Goff *et al.*, 2017; Morley and Wacogne, 2018). ASPs have been shown to reduce inappropriate antimicrobial use and resistance, reduce the length of hospital stay and decrease health care-associated costs (Ashiru-Oredope *et al*., 2012). The Saudi MOH has recognised the potential of these programmes through the initiation of an antimicrobial stewardship strategy as part of the national action approach to reduce the AMR threat (Alomi, 2017). Accordingly, the implementation of ASPs in Saudi hospitals has been endorsed to improve the rational use of antimicrobials, therefore reducing AMR (Alghamdi *et al*., 2019).

In Chapter 2, it was identified that there is considerable inappropriate prescribing of broad-spectrum antimicrobials in a hospital setting. The most common reasons for inappropriate prescribing of broad-spectrum antimicrobials were either the spectrum of activity was too broad, they were used without a culture request and there was a failure of suitable antimicrobial de-escalation. The study indicated the need for deep exploration of factors that drive inappropriate broad-spectrum

antimicrobial prescribing, which is the reason for conducting a qualitative study with the physicians.

From the literature, it was found that physicians are supportive of ASPs (Bannan *et al.,* 2009). However, one of the challenges to ASPs is an absence of consensus among physicians on what is considered an appropriate antimicrobial selection when deciding whether to prescribe a broad-spectrum antimicrobial as the initial therapy (Tarrant *et al.,* 2020). Moreover, physicians' views and perceptions about antimicrobial use and resistance differ across countries and settings (Md Rezal *et al.,* 2015; Kaae *et al*., 2017). A systematic review of studies on antimicrobial prescribing in hospital settings recommended that ASP sustainability could be enhanced with a greater understanding and consideration of the determinants of antimicrobial prescribing (Charani *et al.*, 2011). Behavioural, contextual and cultural factors which impact the antimicrobial use must be identified (Hulscher *et al*., 2010). To implement effective interventions to improve the appropriateness of broad-spectrum antimicrobial prescribing, it is crucial to explore and addressed physicians' views about broad-spectrum antimicrobials and identify how they make their antimicrobial prescribing decisions (Warreman *et al*., 2019). From the literature, several qualitative studies have been conducted regarding physicians' views about antimicrobials (Teixeira Rodrigues *et al.,* 2013; Warreman *et al.,* 2019). Nevertheless, little is known about why and how physicians decide to prescribe particular antimicrobials, particularly those which are broad-spectrum (Wood *et al.,* 2007; Tarrant *et al.,* 2020). Furthermore, no qualitative study has been conducted in the KSA to explore physicians' views about antimicrobial prescribing where differences in healthcare systems may contribute to different views and perceptions. Therefore, this study seeks to understand physicians' perceptions and views about broad-spectrum

antimicrobials and factors that impact upon their prescribing decisions. Part of this study was published (Appendix 11).

Enhancing the design of evidence-based practice relies on behaviour change (Michie *et al.,* 2011). Therefore, behaviour change interventions (BCIs) are essential to the effective and useful practice of public health and clinical medicine (Michie *et al.,* 2011). According to Michie *et al.,* BCIs are *"coordinated sets of activities designed to change specified behaviour patterns"*. The steps of designing BCIs generally includes the determination of the holistic approach that will be implemented, followed by the focus on the details of the intervention design (Michie *et al.,* 2011).

The BCW is a holistic and validated framework for designing interventions through the integration of behaviour theory to recognise the mechanisms of action of the intervention (Michie *et al.,* 2011; Michie *et al.,* 2014).

The BCW contains three layers; the first layer has the COM-B model, including capability, opportunity and motivation. Capability is defined as *"the individual's psychological and physical capacity to engage in the activity concerned"*; opportunity is defined as *"all the factors that lie outside the individual that make the behaviour possible or prompt it"* and motivation is defined as *"all those brain processes that energise and direct behaviour, not just goals and conscious decision-making".* The COM-B model is illustrated in Figure 3.1 These three factors have been developed to understand and target behaviours as a foundation for intervention design. The COM-B model is supported by the Theoretical Domains Framework (TDF) that consists of 14 domains and 84 constructs generated from 33 behavioural change theories under the capability, opportunity and motivation categories (Cane *et al.,* 2012). The TDF, with definitions and component constructs, is presented in Table 3.1.

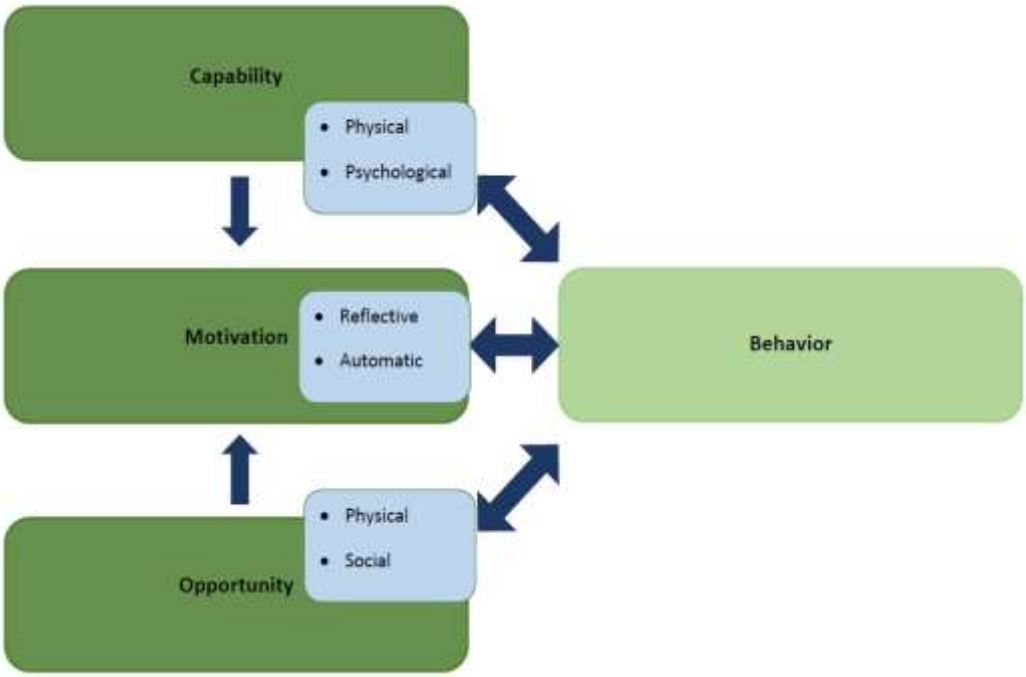


Figure 3.1: The COM-B model of behaviour (Michie *et al.,* 2011)

Table 3.1: The TDF with definitions and component constructs (Cane *et al.,* 2012)

Domain name	Definition	Constructs
Knowledge	An awareness of the existence of something	Knowledge (including knowledge of condition/scientific rationale) Knowledge of task environment Procedural knowledge
Skills	An ability or proficiency acquired through practice	Ability Competence Interpersonal skills Practice Skill assessment Skills Skills development
Social/ professional role and identity	A coherent set of personal qualities and behaviours displayed by an individual in a work or social setting	Group identity Identity Leadership Organisational commitment Professional boundaries Professional confidence Professional identity Professional role Social identity
Beliefs about capabilities	Acceptance of the truth, reality or validity of an ability, talent	Beliefs Empowerment Perceived behavioural control

	or facility that a person can put to constructive use	Perceived competence Professional confidence Self-confidence Self-efficacy Self-esteem
Optimism	The confidence that things will happen for the best or that desired goals will be attained	Identity Optimism Pessimism Unrealistic optimism
Beliefs about consequences	Acceptance of the truth, reality, or validity of outcomes of a behaviour in a given situation	Anticipated regret Beliefs Characteristics of outcome expectancies Consequents Outcome expectancies
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	Consequents Contingencies Incentives Punishment Reinforcement Rewards (proximal/distal, valued/not valued, probable/improbable) Sanctions
Intentions	A conscious decision to perform a behaviour or a resolve to act in a certain way	Stability of intentions Stages of change model Trans-theoretical model and stages of change
Goals	Mental representations of end states or outcomes that an individual wants to achieve	Action planning Goal priority Goal/target setting Goals (autonomous/controlled) Goals (distal/proximal) Implementation intention
Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives	Attention Attention control Cognitive overload/tiredness Decision-making Memory
Environmental context and resources	Any circumstance of a person's situation or environment that encourages or discourages the development of abilities and skills, social competence, independence and adaptive behaviour	Barriers and facilitators Environmental stressors Organisational culture/climate Person × environment interaction Resources/material resources Salient events/critical incidents

Social influences	Those interpersonal processes that can cause individuals to change their behaviours, thoughts or feelings	Alienation Group conformity Group identity Group norms Intergroup conflict Modelling Power Social comparisons Social norms Social pressure Social support
Emotion	A complex reaction pattern, involving physiological, experiential and behavioural elements, by which the individual attempts to deal with a personally significant event or matter	Affect Anxiety Burn-out Depression Fear Positive/negative affect Stress
Behavioural regulation	Anything aimed at changing or managing objectively observed or measured actions	Action planning Breaking habit Self-monitoring

The second layer includes nine intervention functions: coercion, education, enablement, environmental restructuring, incentivisation, modelling, persuasion, restrictions and training. The last layer contains seven policy categories: communication/marketing, environmental/social planning, fiscal, guidelines, legislation, regulation and service provision, which may be used to assist and enable the delivery of the intervention. Table 3.2 illustrates the definitions of the nine interventions functions and seven policy categories. The BCW enables designers and developers to recognise, in a clear and systematic way, intervention functions and policy categories that may possibly make a change. The system is increasingly applied to design interventions that aim to change antimicrobial prescribing practices (Lorencatto *et al.,* 2018). Figure 3.2 illustrates the BCW.

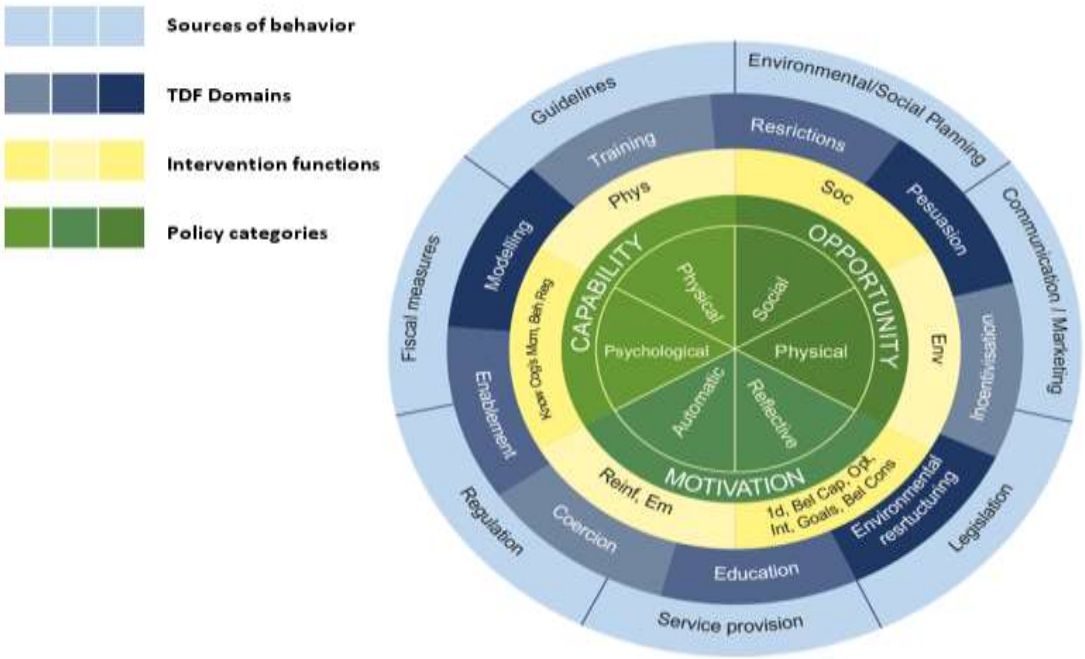


Figure 3.2: The BCW (Michie *et al.,* 2014)

Key: SOC: Social influences; Env: Environmental Context and Resources; Id: Social/Professional Role and Identity; Bel Cap: Beliefs about Capabilities; Opt: Optimism; Int: Intentions; Bel Cons: Beliefs about Consequences; Reinf: Reinforcement; Em: Emotion; Know: Knowledge; Cog: Cognitive and interpersonal skills; Mem: Memory, Attention and Decision Process; Beh Reg: Behavioural Regulation; Phys: Physical skills.

Table 3.2: Definitions of intervention functions and policy categories (Michie *et al.,* 2011)

Definition	
Intervention functions	
Coercion	Creating an expectation of cost or punishment
Education	Increasing understanding or knowledge
Enablement	Increasing means/reducing barriers to increase opportunity or capability
Environmental restructuring	Changing the social or physical context
Incentivisation	Creating expectation of reward
Modelling	Providing an example for people to imitate or to aspire to
Persuasion	Using communication to induce negative or positive feelings or stimulate action
Restriction	Using rules to reduce the opportunity to engage in the target behaviour (or to increase the target behaviour by reducing the opportunity to engage in competing behaviours)

Training	Imparting skills
Policy categories	
Communication/marketing	Using electronic, print, telephonic or broadcast media
Environmental/social planning	Designing and/or controlling the social or physical environment
Fiscal	Using the tax system to increase or reduce the financial cost
Guidelines	Creating documents that mandate or recommend practice. This includes all changes to service provision
Legislation	Making or changing laws
Regulation	Establishing principles or rules of behaviour or practice
Service provision	Delivering a service

3.2 Aims and objectives

3.2.1 Aims

To investigate physicians' views, perceptions and experiences regarding broad-spectrum antimicrobial prescribing in a hospital setting.

3.2.2 Objectives

1. Explore physicians' perceptions and views about broad-spectrum antimicrobials.
2. Identify factors that influence physicians' broad-spectrum antimicrobial prescribing for hospitalised patients.
3. Identify barriers to appropriately prescribing broad-spectrum antimicrobials to hospitalised patients.
4. Obtain physicians' recommendations to improve the appropriateness of broad-spectrum antimicrobial prescribing.

5. Map themes to COM-B framework to support behaviour change to improve the appropriateness of broad-spectrum antimicrobial prescribing.

3.3 Methodology

3.3.1 Study design

The study involved holding semi-structured interviews, conducted over 11 weeks between 5 April and 21 June 2020. The justification for choosing qualitative methods for this study was explained in Chapter 1. The semi-structured interview is the most common type of qualitative research data collection method in the qualitative research and healthcare context (Kallio *et al.,* 2016). It provides exploration and investigation of both the participants' and researchers' agendas (Pope and Mays, 2020). Moreover, it provides an opportunity for a deep understanding of the participants' perspective, knowledge, or experiences in an area of interest (Ritchie *et al.,* 2014).

Initially, the interviews were planned to be conducted as individual, face-to-face semi-structured interviews with selected physicians. However, due to the emergence of the COVID-19 pandemic, a decision was made to conduct all interviews via telephone. Evidence suggests that, in comparison with face-to-face interviews, telephone interviews could generate data of similar quality (Opdenakker, 2006; Novick, 2008).

3.3.2 Setting, sampling strategy and sample size

The study included a sample of physicians who were working at KSUMC and prescribing broad-spectrum antimicrobials for adult hospitalised patients. In this study, two fundamental considerations guided the recruitment of participants: appropriateness and adequacy. Appropriateness referred to the identification of

participants with the related knowledge and experience to best inform the study, while adequacy referred to sufficient related information being created by the participants (Fossey *et al.,* 2002), Thus, purposeful sampling was used as the sampling strategy in which the participants were approached based on their experience in broad-spectrum antimicrobial prescribing for adult hospitalised patients. A snowball sampling strategy was also used as enrolled participants were asked if they had colleagues who were interested in participating in the study. The sample size was decided when data saturation was attained, i.e., when no new ideas or views emerged (Pope *et al.,* 2000). In the literature, qualitative studies relevant to antimicrobial prescribing for adult hospital patients typically have sample sizes range from 5 to 30 (Velasco *et al.,* 2012; Broom *et al.,* 2014; Livorsi *et al.,* 2015; Skodvin *et al.,* 2015; Ravi *et al.,* 2017).

3.3.3 Inclusion and exclusion criteria

To capture the diversity of insights and views regarding physicians' prescribing, the inclusion criteria were set with a range of characteristics which included any physicians with a degree in medicine regardless of age, of either gender and regardless of years of practice. Physicians who prescribed for paediatric and neonates were excluded from the study because their prescribing differs from adult prescribing.

3.3.4 Participants' recruitment

Recruitment was conducted over 11 weeks between 2 March and 16 May 2020. To increase awareness about the research, several approaches for recruiting participants were used. Initially, an email was sent to the head of each speciality department at KSUMC, asking any physician who was interested and willing to participate in the study to contact the researcher through email or phone to arrange

a convenient date and time for a telephone interview. In addition, an email was sent to several residency training programme directors asking any resident who was interested in participating in the study to contact the researcher via email or phone to arrange a convenient date and time for a telephone interview. Furthermore, a direct email was sent to consultants at several departments asking them if they were interested in participating in the study and to reply with the appropriate date and time for the interview. The email included the research title, a brief description of the research, the research aims and the anticipated interview length. The researcher's contact details were provided for those who agreed to participate so they could contact the researcher for further details (Appendix 12).

When the interview date and time were agreed upon and confirmed, an email, including a participant's information sheet, was sent**.** The participant's information sheet provided full information and details about the study, including an overview, the procedure involved in the telephone interview and the participants' rights. It included the title of the study, the study background, the aim of the research, the recruitment criteria, a brief explanation of the interview process, the withdrawal policy, possible benefits and risks of participating, the participants' data confidentiality, and the researcher's contact information (Appendix 13). An email reminder was sent to all participants 24 hours before the interview.

3.3.5 Consent form

All participants were asked to sign and date an electronic consent form after providing a brief description of the study and the interview process. The consent form was sent before conducting the interview. It was signed through the DocuSign© website, which is an electronic, user-friendly platform for signing and handling documents securely. Once signed, two electronic copies were dispatched

automatically: one to the researcher and the other to the participant. The consent form can be seen in Appendix 14.

3.3.6 The interview topic guide

The interview topic guide is a document that illustrates the key topics to be discussed during the interviews (Ritchie *et al.,* 2014). It helps to ensure consistency in data collection across all the participants, while allowing for flexibility to follow issues that are salient to each of them (Ritchie *et al.,* 2014). The interview topic guide was developed following a review of the previously published and related qualitative research, as recommended by Ritchie *et al.* 2014. Studies on antimicrobial prescribing in hospitalised patients were used to design the interview topic guide questions (Charani *et al.,* 2013; Livorsi *et al.,* 2015; Skodvin *et al.,* 2015; Broom *et al.,* 2017). In addition to consideration of the key findings of the quantitative study reported in Chapter 2, all questions were reviewed and discussed by the researcher and supervisory team to best fit with the research aim and objectives. The interview topic guide has two main parts, as illustrated in Figure 3.3. The first set of questions was about the physicians' demographics, including their age, gender, speciality, current position, attended university, qualifications and number of years of experience. The second set comprised the main questions, divided into three sections. The first section included introductory questions relevant to the physicians' broad-spectrum antimicrobial prescribing practice, such as 'What is your understanding of appropriate broad-spectrum antimicrobial prescribing?' And 'In your daily practice, how do you plan or decide on prescribing broad-spectrum antimicrobials?'.

The second section included questions related to the barriers and challenges of appropriate broad-spectrum antimicrobial prescribing. The aim of these questions was to provide an in-depth understanding of the barriers and challenges of

appropriate broad-spectrum antimicrobial prescribing and to identify who was responsible for these barriers and challenges. The third section included recommendations to improve antimicrobial prescribing practice. These questions aimed to induce the physicians to state their opinions about guidelines and electronic tools and to suggest recommendations to improve broad-spectrum antimicrobial prescribing practice. The interview topic guide can be found in Appendix 15.

3.3.7 Pilot interviews

The interview guide was reviewed, re-drafted and revised several times by the supervisory team (ABM, HA and AM). Furthermore, it was reviewed by one clinical pharmacist who specialised in ID (AA) and a researcher who had experience in qualitative research (NAA). All the necessary comments and amendments were taken into account. Before conducting the pilot interview, the researcher NA received training in qualitative research interviewing. The final draft of the interview guide was tested in pilot interviews with two healthcare professionals. The first was a consultant clinical pharmacist and the second was a mixed methodology researcher with knowledge of and experience in qualitative research. The length of the first interviews was 27 minutes and the length of the second interview 21 minutes. Both interviews were recorded and transcribed. The audio recordings of the two interviews, along with their transcripts, were checked by one member of the supervisory team (HA). This allowed for an assessment of the participants' responses to the questions provided identification of any misunderstandings. Moreover, it offered additional interviewing techniques. It also provided an assessment of the estimated length of the interviews. The two pilot interviews were not included in the study analysis or findings.

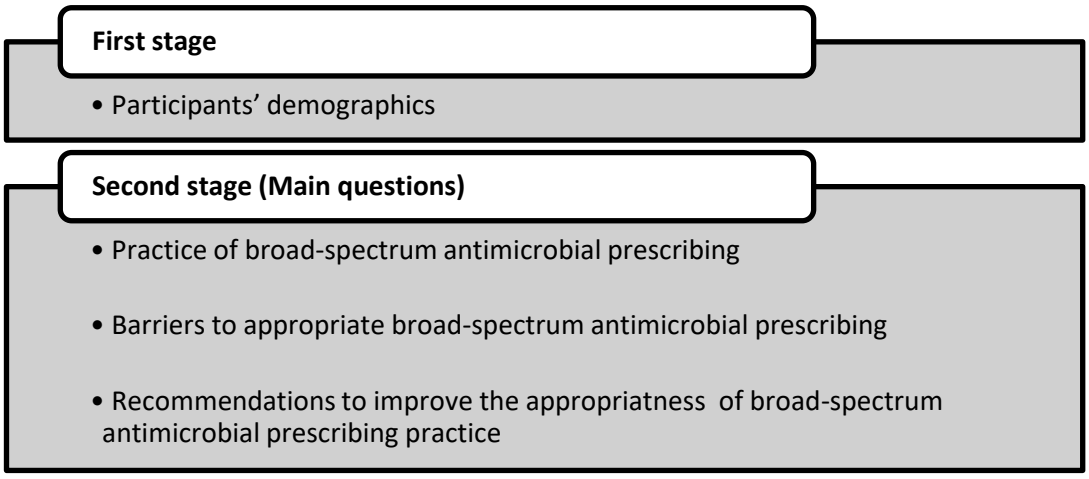


Figure 3.3: The two stages of the interview topic guide

3.3.8 Ethical approval

Before the study, an ethics application was submitted to KSUMC Institutional Review Board and permission for the study was granted (Appendix 3).

3.3.9 Data storage

All the audio recordings of the interviews were transcribed by the researcher. To retain anonymity, the recorded interviews were destroyed at the end of the study, but the transcripts were stored electronically for two years in an encrypted file using an encrypted format.

3.3.10 Data analysis

The interview audio recordings were transcribed into Microsoft® Word documents by the researcher NA. An intelligent verbatim style was used in transcribing; such a style omits all hesitation fillers, e.g., "uh" and "um", pauses and laughter during the interview and involves minor grammatical editing (Salonga, 2019). A random 20% of the transcribed files were screened, by comparing them to the digital recordings, by two researchers and only minor issues related to prepositions and articles were identified. The interview transcript files were uploaded into NVivo®12 (QSR International. 2018), a computer software programme that is used to store, organise and manage qualitative data (Appendix 16). The thematic approach to analysing

qualitative data was used, following the six-step phases recommended by Braun and Clarks (Braun and Clarke, 2006), discussed in more detail in Chapter 1. To assess the reliability of the coding, a random 20% sample was checked by a researcher who is experienced in qualitative research. A comparison between the codes was made. The majority of the codes were similar and only minor differences were identified. These were discussed and resolved. The study reporting followed the consolidated criteria for reporting qualitative research (COREQ) guidelines (Tong *et al.,* 2007) and Braun and Clarke's checklist (Braun and Clarke, 2006). The checklists are presented in Appendix 17 and Appendix 18. The results were mapped to the relevant TDF and COM-B components to identify intervention functions and policy categories.

3.4 Findings

3.4.1 Characteristics of interview participants

Sixteen physicians participated in the study, 13 (81%) of whom were male. The participants' mean age was 30.6 ± 5.8 and the interviews lasted for an average length of 30 minutes. Participant specialities included internal medicine (n=4), orthopaedics (n=4), infectious disease (n=3), emergency medicine (n=2), surgery (n=1), neurosurgery (n=1), and ear, nose and throat (n=1). The participants' positions included junior resident (n=6), senior resident (n=3), fellow (n=2) and consultant (n= 5). Table 3.3 summarises the demographics and professional characteristics of participants.

3.4.2 Qualitative analysis

Four main themes emerged from the interview data. These were views on broad-spectrum antimicrobials, factors influencing broad-spectrum antimicrobial prescribing, antimicrobial stewardship: practices and barriers and recommendations

to improve appropriate broad-spectrum antimicrobial prescribing. The themes and subthemes are shown in Table 3.4.

Table 3.3: Demographics and professional characteristics of participants

Participant number	Age (years)	Gender	Speciality	Working position	Working experience (years)	Working experience outside of the KSA, duration	Length of interview (minutes)
1	32	Male	Surgery	Fellow	8	No	21
2	26	Female	Internal medicine	Junior resident	1.5	Canada, 1 month	33
3	25	Male	Orthopaedics	Junior resident	2	No	22
4	27	Male	Orthopaedics	Senior resident	5	No	31
5	25	Male	Neurosurgery	Junior resident	1	Canada, 1 month USA, 1 month	32
6	27	Male	Orthopaedics	Senior resident	4	No	27
7	26	Male	Internal medicine	Junior resident	1	No	56
8	28	Male	Internal medicine	Senior resident	3	No	50
9	40	Male	Emergency medicine	Consultant	16	Australia, 7 years	24
10	26	Male	Ear, nose and throat	Junior resident	1	No	35
11	27	Male	Orthopaedics	Junior resident	1	Yes	38
12	37	Male	Emergency medicine	Consultant	9	USA, 5 years	41
13	43	Male	Infectious disease	Consultant	10	Canada, 8 years	17
14	30	Female	Infectious disease	Fellow	5	Canada, 1 month	29
15	36	Female	Infectious disease	Consultant	12	Canada, 3 years	41
16	35	Male	Internal medicine	Consultant	10	Canada, 8 years	31

Key: USA: United States of America.

Table 3.4: Themes and subthemes identified from thematic analysis

Theme	Subtheme
Views on broad-spectrum antimicrobials	✚ Physicians' perceptions of broad-spectrum antimicrobials ✚ Concern for AMR and other drawbacks associated with broad-spectrum antimicrobials
Factors influencing broad-spectrum antimicrobial prescribing	✚ Patient-related factors ✚ Physician-related factors ✚ External factors
Antimicrobial stewardship practices	✚ Taking culture before administering the antimicrobial therapy ✚ De-escalation therapy ✚ IV oral switch
Recommendations to improve appropriate broad-spectrum antimicrobial prescribing	✚ Education, awareness and training ✚ Guidelines implementation ✚ The stewardship programme ✚ Institution and technology-related recommendations

Key: IV: intravenous

3.4.2.1 Views on broad-spectrum antimicrobials

3.4.2.1.1 Perceptions of broad-spectrum antimicrobials

The absence of a standard definition of broad-spectrum antimicrobials and what is considered inappropriate prescribing was noted by the participants, regardless of their years of experience or speciality. This section will present their understanding and will give some enlightenment concerning their perceptions of broad-spectrum antimicrobials and inappropriate prescribing. Table 3.5 illustrates supporting quotes. Broad-spectrum antimicrobials were described as *"big guns"* that could target unknown organisms (Quote 1, Table 3.5). Some participants believed that broad-spectrum antimicrobials were antimicrobials that covered different groups of gram-negative, gram-positive and anaerobes bacteria (Quote 2, Table 3.5). Also, broad-spectrum antimicrobials could be referred to as antimicrobials that cover not only a single bacterium but could cover multiple bacteria (Quote 3, Table 3.5).

Some participants referred to broad-spectrum antimicrobials as agents that cover a suspected infection when the cause of the infection is unknown and where the patients are treated based on clinical assessment and vital signs (Quote 4, Table 3.5). Broad-spectrum antimicrobials were identified to be commonly prescribed in severe patient conditions that could be life-threatening, like meningitis or sepsis (Quote 5, Table 3.5). The participants gave examples of broad-spectrum antimicrobials including piperacillin-tazobactam, vancomycin, carbapenems, aminoglycosides and cephalosporins, as commonly used broad-spectrum antimicrobials in their clinical practice (Quote 6, Table 3.5). The appropriate prescribing of broad-spectrum antimicrobials was defined by some participants as those prescriptions that cover suspected organisms based on the location of the infection (Quote 7, Table 3.5).

Others considered the prescriptions appropriate when an ID team was involved in the decision of patient treatment, regardless of their choice, or when the treatment prevented a deterioration in the patient's condition (Quotes 8-9, Table 3.5).

Meanwhile, inappropriate prescribing was defined by participants as not covering a suspected infection. An example was prescribing antimicrobial therapy that has no coverage for *Pseudomonas* species or MRSA for a patient with HAP (Quotes 10-11, Table 3.5).

Some participants considered over coverage, which is the prescription of a broad-spectrum antimicrobial when it is not needed, like in tonsillitis cases. Also, the continuation of the broad-spectrum antimicrobial despite culture results indicating sensitivity to narrow-spectrum was also considered an inappropriate prescribing practice (Quotes 12-13, Table 3.5).

Table 3.5: Supporting quotations for Views on broad-spectrum antimicrobials theme

Subtheme	Supporting quotations
Physicians' perceptions of broad-spectrum antimicrobials	**1.** ''*Broad-spectrum agents, I would consider those that we call the big guns of antibiotics, that can actually target non-specific organism*." **(Physician 8: internal medicine, 3 years)** **2.** *''A broad-spectrum anything that covers more than one line of bacteria anaerobes and aerobes, gram-positive, gram-negative that exceeds two [organisms], to me is broad-spectrum.''* **(Physician 16: internal medicine, 10 years)** **3.** *''To cover more than one bacterium or more species of bacteria, to cover an infection that we don't know what the cause of this infection is.''* **(Physician 1: surgery, 8 years)** **4.** *''A broad-spectrum antimicrobial is the antimicrobial that would cover most organisms that we suspect the patient to have, based on their clinical signs and symptoms, and lab investigations while pending results of cultures.''* **(Physician 13: infectious disease, 10 years)** **5.** *"It's common to be prescribed in critically ill patients, patients we anticipate to have a critical disease like meningitis or sepsis, for example.''* **(Physician 8: internal medicine, 3 years)** **6.** *''Carbapenems, third and fourth generations of cephalosporin, some of the modified penicillin, like piperacillin-tazobactam.''* **(Physician 7: internal medicine, 1 year)** **7.** *"Appropriate, like, let's say, if we are treating a gastroenterology related infection, then I know that I should cover for the gram-negative bacteria, so that's why I use zocin [piperacillin-tazobactam] because zocin has good coverage for gram-negative. If I'm treating skin infections, I need to cover the gram-positive bacteria then I pick the appropriate one. If I'm going to treat outpatients, then I do clindamycin. If I'm going to treat, like, for inpatients, then I'm going to use vancomycin, especially if I'm concerned about methicillin-resistant bacterium. It depends on what the bacterium I suspect is and according to the system I'm treating. Then, I pick the coverage accordingly.''* **(Physician 12: emergency medicine, 9 years)** **8.** *"By involving the appropriate team, like infectious diseases …I think the most important thing is at least to involve the appropriate team that will follow the patient and they are more aware of antibiotics and these kinds of prescriptions."* **(Physician 6: orthopaedics, 4 years)** **9.** *"Appropriate, I would say that when you prescribe a broad-spectrum in a patient that you expect will deteriorate without this antibiotic."* **(Physician 8: internal medicine, 3 years)** **10.** *"Inappropriate would be to give an antimicrobial that would not cover all the possibilities of the infection of the patient."* **(Physician 13: infectious disease, 10 years)** **11.** *"If someone comes with hospital-acquired pneumonia and you're not covering for Pseudomonas or MRSA, you are not covering it properly."* **(Physician 12: emergency medicine, 9 years)** **12.** *"Covering organisms that do not need to be covered*". **(Physician 14: infectious disease, 5 years)** **13.** *"For example, like tonsillitis, if I start very broad amoxiclav when you can just do with just one antibiotic …Another inappropriate broad-spectrum practice is that you start broad and, even though you know the organisms, you still want to continue broad when you should actually consider narrowing as soon as possible if you have an organism that is sensitive to a narrow-spectrum antibiotic."* **(Physician 16: internal medicine, 10 years).**

Concern for AMR and other drawbacks associated with broad-spectrum antimicrobials	**14.** *''A lot of patients may develop resistance and we're not doing them any good because later on, we're going to go broader and broader till we have a resistant organism for every antibiotic and then we are stuck with nothing. I think this is the only drawback of prescribing broad-spectrum.''* **(Physician 11: orthopaedics, 1 year)** **15.** *"We are seeing a lot of different organisms that are developing resistance to specific antibiotics and which I think is due to the inappropriate antibiotic prescription."* **(Physician 8: internal medicine, 3 years)** **16.** *''I was surprised really when I came back that the penicillin family is almost not working in my country, so we need to go higher up, which means the big guns, like tazocin, meropenem and imipenem, and this is really a bad thing. But I think the biggest practice of prescribing lots of antibiotics for unnecessary things has led us to this point."* **(Physician 9: emergency medicine, 16 years)** **17.** *''As soon as possible, you have to narrow the antibiotic when you have like a bug or organism that is differentiated so you can monitor and minimise resistance. That's what I do."* **(Physician 16: internal medicine, 10 years)** **18.** *''The most concerning thing could be resistance. This is one. The other thing is the effect of the broad-spectrum antibiotics on other healthy normal flora."* **(Physician 5: neurosurgery, 1 year)** **19.** *"When you use a broad-spectrum that's usually IV or still can be oral, you will subject the patient to other infections by doing that. For example, C. diff."* **(Physician 16: internal medicine, 10 years)** **20.** *"They [broad-spectrum antimicrobials] can also have a lot of side-effects on other organs, kidney failure. Having an etiological side-effect that happens all time.''* **(Physician 16: internal medicine, 10 years)** **21.** *''Another challenge for the broad-spectrum, especially the IV ones, is that the patient has to stay in the hospital for a long time. For the IV antibiotics, and this issue by itself, it's sometimes affecting the patient.''* **(Physician 14: infectious disease, 5 years)** **22.** *"The unwanted side-effects of, basically, staying in a setting where you don't need to stay. So, being in a hospital for IV antibiotics, putting yourself and the patient at risk of catching other infections. For example, our time now is the pandemic of COVID-19.''* **(Physician 16: internal medicine, 10 years)** **23.** *"The other thing is the cost.''* **(Physician 16: internal medicine, 10 years)**

3.4.2.1.2 Concern for AMR and other drawbacks associated with broad-spectrum antimicrobials

Some participants raised concern regarding the potential effect associated with the use of broad-spectrum antimicrobials. They appeared aware of AMR and they recognised the contribution of inappropriate prescribing of broad-spectrum antimicrobials to this issue (Quote 14, Table 3.5). Participants reported having many organisms that developed resistance to some antimicrobials in their clinical setting, which could be due to the practice of prescribing unnecessary or inappropriate antimicrobials (Quote 15, Table 3.5). Consequently, the development of resistance to most penicillin group antimicrobials has led to the use of "big guns" like tazocin, meropenem and imipenem (Quote 16, Table 3.5). Some participants acknowledged optimising the use of broad-spectrum antimicrobial in their practice to decrease the AMR (Quote 17, Table 3.5). In addition to resistance, a concern was reported regarding the effect of broad-spectrum antimicrobials on the normal microbial flora (Quote 18, Table 3.5). Also, some participants expressed concern about an individual patient's risk of developing superinfections, like *C. difficile* (Quote 19, Table 3.5). Other consequences, such as kidney and liver damage, were highlighted, indicating that prescribing broad-spectrum antimicrobials can harm the patients (Quote 20, Table 3.5). Prolonging the hospital stay is another concern related to the use of broad-spectrum antimicrobials, particularly the IV antimicrobials, where the patient has to stay for a longer period in hospital (Quote 21, Table 3.5). Consequently, there is a risk of exposing the patient to infection while in the hospital. An example of this was the current pandemic resulting from COVID-19, where patients, if they stayed for a long period in the hospital, were put at risk (Quote 22, Table 3.5). Cost was

mentioned as a drawback associated with the inappropriate prescribing of broad-spectrum antimicrobials (Quote 23, Table 3.5).

3.4.2.2 Factors influence broad-spectrum antimicrobial prescribing

Several factors were reported by the physicians and were divided into patient-physician related factors and external factors. These factors are reported in this section. Table 3.6 illustrates supporting quotes.

3.4.2.2.1 Patient-related factors

Patient-related factors were mentioned as factors that influence broad-spectrum antimicrobial prescribing. These factors are discussed in detail in this section. Table 3.6 shows supporting quotes. Some participants considered age as a factor that might influence their broad-spectrum antimicrobial prescribing decisions. They reported that they tended to prescribe broad-spectrum antimicrobials for elderly patients. The reason was that elderly patients are at high risk of acquiring antimicrobial-resistant bacterial infections because they might have been exposed to multiple antimicrobials during their lives (Quote 1, Table 3.6). A patients' medical history seemed to play a crucial part in the judgement to prescribe broad-spectrum antimicrobials. Sick patients with co-morbidities, for example, a dialysis patient, experience the risk of aggressive progression or the deterioration of their illness; therefore, the participants would prescribe broad-spectrum antimicrobials to prevent any progress or deterioration of the patient's condition (Quote 2-3, Table 3.6). Also, the patient's immune status was considered as a factor that might influence the prescribing of broad-spectrum antimicrobials. It was reported that participants may consider adding another antimicrobial for immunocompromised patients (Quote 4-5, Table 3.6). A history of multiple admissions and long hospital stays were mentioned as

factors that influence participants to start broad-spectrum antimicrobials (Quote 6-7, Table 3.6). Previous cultures, prior antimicrobial exposure and the duration of the previous antimicrobial course are factors that might affect the broad-spectrum antimicrobial prescribing decision (Quote 8-10, Table 3.6).

The participants stated that the patients' clinical presentation and the type of infection play a significant part in the decision to consider and prescribe broad-spectrum antimicrobials. Severely sick patients suffering from severe infection or from sepsis that is affecting their haemodynamic instability are often aggressively treated with broad-spectrum antimicrobials, unlike stable patients with mild diseases, who are treated with narrow-spectrum antimicrobials (Quote 11-12, Table 3.6). Moreover, the participants stated that the sudden onset of patient deterioration is a factor for starting broad-spectrum antimicrobials or even an escalation of the current antimicrobial therapy to a broad-spectrum agent (Quote 13-14, Table 3.6). Conversely, it was reported that severity of illness had no influence on the decision to prescribe broad-spectrum antimicrobials (Quote 15, Table 3.6). The type of infection itself was considered an influence to prescribe broad-spectrum antimicrobials. Hospital-acquired infections are more severe than other types of infection; therefore, broad-spectrum antimicrobials tend to be prescribed for hospital-acquired infections (Quote 16, Table 3.6). Also, having polymicrobial infections like, for example, diabetic foot infections where there is a need to have a broader coverage including anaerobe, gram-negative, and gram-positive leads to broad-spectrum antimicrobial prescribing. However, infections caused by individual organisms, for example, cellulitis, where it is usually caused by *Streptococcus* or *Staphylococcus*, do not (Quote 17, Table 3.6).

Table 3.6: Supporting quotations for factors influencing broad-spectrum antimicrobial prescribing theme

Subtheme	Supporting quotations
Patient-related factors	**1.** *''Usually, we consider the age …To use some of the broad-spectrum antibiotics …I mean, if I have a patient who's elderly, I would think that this patient has had resistance before …He has been exposed to many antibiotics in his life, for a long time.''* **(Physician 7: internal medicine, 1 year)** **2.** *''For example, if we have patients on dialysis.''* **(Physician 7: internal medicine, 1 year)** **3.** *''The current condition of the patient, some patients with co-morbidities, we suspect very aggressive organisms or very aggressive progression of the disease, so we want to start something broad-spectrum to cover it. We didn't have any chance to start with something narrow-spectrum. This is one factor, the patient's condition.''* **(Physician 10: ear, nose and throat, 1 year)** **4.** *''First, I would say: ''Is the patient immunocompromised?'''* **(Physician 8: internal medicine, 3 years)** **5.** *''And I might add other antibiotics in immunocompromised patients.''* **(Physician 4: orthopaedics, 5 years)** **6.** *''Has the patient had multiple previous admissions?''* **(Physician 8: internal medicine, 3 years)** **7.** *''Like, if we have, for example, if we have a patient who was in hospital for a long time.''* **(Physician 7: internal medicine, 1 year)** **8.** *''If we have patients who have been exposed to the MRSA organism …There are, I would say, some antibiotics that have been used before, but they didn't work.''* **(Physician 7: internal medicine, 1 year)** **9.** *''Considering the previous microbiologic culture for the patient.''* **(Physician 14: infectious disease, 5 years)** **10.** *''Other factors that can affect my antimicrobial prescription, especially the broad-spectrum …The duration itself of the antibiotic usage.''* **(Physician 8: internal medicine, 3 years)** **11.** *''Any infection that is affecting the haemodynamic instability, for example, is just a simple UTI, but in a haemodynamically unstable patient, like a hypotensive patient, which is called urosepsis or UTI, causing septic shock at this stage, I would consider it a critical illness that needs a broad-spectrum antibiotic until I reach a definitive diagnosis, which I need a target therapy for.''* **(Physician 8: internal medicine, 3 years)** **12.** *''All comes within the signs and symptoms and clinical presentation of the patient. So, patients who come in with a mild disease don't necessarily need to be prescribed a broad-spectrum antimicrobial, I could give them more of a narrower spectrum compared to those who are sick. Those who present, for example, with a severe infection or septic shock, then it would be much more appropriate to prescribe them with a broad-spectrum antimicrobial until you have the results.''* **(Physician 13: infectious disease, 10 years)** **13.** *''The other factor, the patient deterioration, sometimes the patient gets sick suddenly.''* **(Physician 10: ear, nose and throat, 1 year)** **14.** *''The clinical scenario how sick is the patients, if the patient is hypotensive and if he's already covered by, let's say ceftriaxone, I definitely upgrade the antibiotic.''* **(Physician 2: internal medicine, 1.5 years)** **15.** *"But severity I don't think would change the antibiotic."* **(Physician 5: neurosurgery, 1 year)** **16.** *"The hospital admission, you know the hospital-acquired infections are more severe than the community-acquired infections.''* **(Physician 10: ear, nose and throat, 1 year)**

	17. *''For example, dealing with a diabetic foot, where it is known to have polymicrobial anaerobe, aerobe, gram-negative gram-positive, you need to have a broad-spectrum antibiotic. That's the ideal, when dealing with cellulitis, for example, as you are most likely dealing with a uniorganism - staph, strep.''* **(Physician 16: internal medicine, 10 years)**
Physician-related factors	**18.** *"We follow the IDSA guidelines with regard to the antimicrobial therapy.''* **(Physician 2: internal medicine, 1.5 years)** ***19.*** *''We use sometimes the guidelines. For example, in orthopaedics, we have two to three infections that we treat rather than the post-op. We have osteomyelitis and septic arthritis …To be honest, I can't remember, but it's related to the Orthopaedic Society not to the pharmacology or ID of the infectious disease …It's an international.''* **(Physician 1: surgery, 8 years)** **20.** *''We have actually a pocket antibiotic guide for any emergency which was made by the American Society of Emergency Medicine. I have had that from residency. So, I still have it and I try to buy the new updated version. Like, I have two different ones and I kind of use them for quick referencing.''* **(Physician 12: emergency medicine, 9 years)** **21.** *''It's all international, proven it is used mainly by the ID sub-speciality ID specialist and even clinical pharmacist.''* **(Physician 8: internal medicine, 3 years)** **22.** *''Usually, I don't have guidelines; we just have guidelines for our procedures in neurosurgery.''* **(Physician 5: neurosurgery, 1 year)** **23.** *''There are no clear guidelines that we are following except for the preoperative antibiotics …The guideline that we are using is international.''* **(Physician 6: orthopaedics, 4 years)** **24.** *''I use it if not backed up by senior or experienced doctors; in this case, I use guidance - mostly the applications on the phone."* **(Physician 11: orthopaedics, 1 year)** ***25.*** *''If I forget about specific dosage or selection of antibiotic, my first target is Stanford antimicrobial. The second thing is either UpToDate or the IDSA guideline.''* **(Physician 8: internal medicine, 3 years)** ***26.*** *''We use Stanford or John Hopkins. These are my references for starting broad-spectrum antibiotics if I have, like, clinical suspicion of something, and I can go back and check it."* **(Physician 14: infectious disease, 5 years)** **27.** *''And for difficult cases or cases that do not yield a positive culture and still I'm worried about the different diagnosis, I would review some articles, for example in the New England Journal of Medicine.''* **(Physician 8: internal medicine, 3 years)** ***28.*** *''There is no institutional guideline''* **(Physician 1: surgery, 8 years)** **29.** *''Generally speaking, we have local guidelines. For some diseases, we have hospital guidelines, like for febrile neutropenia, so they know what to do. Even if we are not involved, we need only, like, to approve the antibiotics for them but they know what the protocol is for like, febrile neutropenia. We have a local protocol, like, for example, malaria and we follow these local protocols.''* **(Physician 14: infectious disease, 5 years)** **30.** *''There are two types of guidelines by the way. There are clinical guidelines that are already available, either international or by our local hospital, for, like, treating pneumonia, treating bacteraemia, and there is the antimicrobial guidance of the drug itself, which we also do, like, for antimicrobial therapy, including ertapenem, meropenem, linezolid …We have few …We worked on the last few years on a few of them, including septic shock, pneumonia, bacteraemia.''* **(Physician 15: infectious disease, 12 years)**

	31. *''Myself, I'm following two things or three things, Stanford, the application or guidelines of antimicrobial therapy, UpToDate sometimes, and the pocket book that has been made by the pharmacy. Although not all the physicians know about it, I think there are a few. I mean, 10 to 20%, they know about the pocket books that are made by our institution."* **(Physician 7: internal medicine, 1 year)** ***32.*** *''I usually use the Ministry of Health antibiotics guidelines. It's an updated one, and I think the last issue was six months ago. This is my main source …I usually use the Ministry of Health local guideline.''* **(Physician 9: emergency medicine, 16 years)** ***33.*** *''If the infection that I'm dealing with is described and is well mentioned by a textbook or theory, I will go by the book, as I mentioned, because we go by the book.''* **(Physician 11: orthopaedics, 1 year)** ***34.*** *''If you mean a certain guideline we follow, no, it's not a single guideline that we follow but the general recommendations ...In terms of my speciality no, we don't use a certain guideline''* **(Physician 3: orthopaedics, 2 years)** **35.** *"I think we tend to prescribe the same regimen to a number of patients. So, like, anybody who comes in with, let's say, pneumonia, you immediately see us prescribing aziothro [azithromycin] and ceftriaxone. I think it [experience] heavily influences what I've seen in practice".* **(Physician 2: internal medicine, 1.5 years)** ***36.*** *''I depend more on evidence than my experience, but I'm sure my experience does play a part, but I always follow evidence-based medicine rather than my own.''* **(Physician 13: infectious disease, 10 years)** ***37.*** *''As time goes on, I get more experience and I get to know lots of information, lots of updated information, from the internet websites and that's changed me a lot from the time of residency till now. As a consultant, my prescription habits, my routine practice with antibiotics have changed. So, to be honest, initially, when I started as a resident, I used to give antibiotics, for example, to every sore throat, every upper respiratory tract infection. Now, almost zero. I don't give them unless it's very clear there is pus and the patient is sick. I will give them then. So, it's changed me a lot in my practice.''* **(Physician 9: emergency medicine, 16 years)** **38.** *''Actually, it increases it, especially in the areas that I was in - general surgery, neurosurgery and paediatrics. I saw many sick patients. I saw septic patients, actually, when they were haemodynamically unstable. They improved when they received the broad-spectrum antibiotic. It encouraged me to use more broad-spectrum antimicrobial therapies.''* **(Physician 10: ear, nose and throat, 1 year)** ***39.*** *''I make my own decision, at the end of the day, because I'm the consultant, you know.''* **(Physician 15: infectious disease, 12 years)** **40.** *''Sometimes, I think this is the main issue because they try to save time, they try to cut themselves some headache when calling up the ID team or the clinical pharmacist. So, I think this is one of the main points that contributes to this factor.''* **(Physician 11: orthopaedics, 1 year)** ***41.*** *''I will use the same antibiotic. It will not change my plan unless I didn't see an effect of my antibiotics. Then, I will consider changing the antibiotic".* **(Physician 5: neurosurgery, 1 year)** **42.** *''I saw a lot of physicians abuse the antibiotic, regardless of the infection.''* **(Physician 1: surgery, 8 years)** **43.** *''A lot of people just prescribe an antibiotic as if it is analgesia.''* **(Physician 12: emergency medicine, 9 years)** ***44.*** *"Usually, I come and see if the patient received tazocin [Piperacillin-tazobactam], even for a simple UTI. Why tazocin? Because it is the antibiotic that we usually prescribe."* **(Physician 8: internal medicine, 3 years)**

	45. *''I think emergency room physicians are really generous with broad-spectrum antibiotics and I think that comes from our daily practice, dealing with the undifferentiated cases, trying to pick the right choice of antibiotic and starting wide …So, yes, I feel like this is really something related to my practice as an emergency room physician.''* **(Physician 12: emergency medicine, 9 years)** **46.** *"When you meet with them, the surgeons, I think you should ask them: 'Do you start the patient on medications based on your feeling that the patient is sick or because of knowledge?' and I'm sure that most of them will say it is based on their feeling that the patient needed the antibiotic, not because of their experience or knowledge with the antibiotic coverage or the bacteria.''* **(Physician 15: infectious disease, 12 years)** **47.** *''What I've seen is lack of knowledge in general. I mean, in our institution, lack of knowledge of using the broad-spectrum antibiotics, when it's indicated, risk factors and other things that we have to consider. The side-effect of using such antibiotics amikacin, vancomycin and other antibiotics.''* **(Physician 7: internal medicine, 1 year)** **48.** *''Well, there is probably, there's a lack of education, lack of knowledge, uh, not following our recommendations, not knowing that there is an existing policy and procedures in their regard, not reaching out to the antimicrobial stewardship team or the ID team. So, multiple reasons.''* **(Physician 13: infectious disease, 10 years)** **49.** *''This is the issue, like, in our institute there is a policy but we have reluctance from other teams to access it. Like, they don't want to open the ICT. They don't want to read the guidelines. So, they always call us to tell them what to do…But, unfortunately, most of them, they don't read the policy. So, they have to call us to know what's the policy.''* **(Physician 15: infectious disease, 12 years)** **50.** *''Lack of interest from others.''* **(Physician 13: infectious disease, 10 years)** **51.** *''I feel comfortable with most of the daily presentation's bacterial infection, yes, but I don't feel comfortable with the rare kind of infections, especially with what's happening now. Having too many patients with pneumonia and you're not sure if it's actually bacterial pneumonia or viral pneumonia or atypical pneumonia. So, it's, yeah, sometimes it feels like I just want to make sure that I'm not making wrong decisions.''* **(Physician 12: emergency medicine, 9 years)** **52.** *''I think ceftriaxone is enough but I started piperacillin/tazobactam …Because I'm not sure, I decided immediately to start tazo, I mean piperacillin-tazobactam, instead of ceftriaxone to save the patient's …Usually you cannot differentiate between acute chest syndrome and pneumonia. That's why I started piperacillin-tazobactam.''* **(Physician 7: internal medicine, 1 year)** **53.** *''Sometimes, if the patient is sick and we don't have a clear picture because we're at home on-call, for example, we just give them the green light.''* **(Physician 14: infectious disease, 5 years)** **54.** *''I think people tend to feel more comfortable the more the broad-spectrum the antibiotic is.''* **(Physician 2: internal medicine, 1.5 years)** ***55.*** *''We start broad-spectrum antibiotics just to be on the safe side.''* **(Physician 14: infectious disease, 5 years)** **56.** *''To face our fear."* **(Physician 10: ear, nose and throat, 1 year)** **57.** *''I think it's the safety of the patient.''* **(Physician 12: emergency medicine, 9 years)** **58.** *''In our hospital, tazocin is usually the first-line to use. We use tazocin because we don't have a lot of Hospital ESBL [Extended-spectrum beta-lactamase], but sometimes, when we get a patient from outside, he might present with septic shock and we start him*

	on tazocin and vancomycin. Then, we keep following the patient, and sometimes he's not improving because, like, we missed ESBL in the blood or in the urine. This is challenging.'' **(Physician 14: infectious disease, 5 years)** **59.** *''It's just a kind of feeling that you don't want to hurt the patient by just taking it lightly and it might be something serious."* **(Physician 12: emergency medicine, 9 years)** **60.** *"To me, as an emergency room physician, I think trying to be more of having a safe kind of zone of like coverage is really kind of hardest and, actually, the challenge for me, instead of going narrow …It's always this kind of concern from our side.''* **(Physician 12: emergency medicine, 9 years)** **61.** *''Most of them, while they are on overnight on-call, they just want to cover the patient for all the possibilities.''* **(Physician 14: infectious disease, 5 years)** **62.** *''I think, maybe, it's us emergency room physicians, it's our kind of feeling that I have one time to see this patient and the patient will be admitted or discharged so I better do the right thing, make the right choice. So, it's that feeling of I don't want to, like, miss this chance to treat the patient right because I'm not going to get that chance again.''* **(Physician 12: emergency medicine, 9 years)**
External factors	**63.** *"Usually we ask, regarding the use of broad-spectrum antibiotics, our seniors and the senior goes to the consultant to ask him about his opinion. Usually, we follow our consultant's recommendation, especially if that consultant is the primary physician.''* **(Physician 10: ear, nose and throat, 1 year)** **64.** *"Usually, my senior tries to explain why we are using this broad-spectrum rather than the other one, what the indications are, what the risk factors are, something like that.''* **(Physician 7: internal medicine, 1 year)** **65.** *"If the consultant said give broad-spectrum and we don't think it is correct, we will follow the consultant's, of course, order."* **(Physician 8: internal medicine, 3 years)** **66.** *"The ID team, usually they control it more. Sometimes they suggest we use it [a broad-spectrum antimicrobial], sometimes they suggest lowering it down to narrow-spectrum. So, I think they are very involved in the situation of using a broad-spectrum antibiotic.''* **(Physician 10: ear, nose and throat, 1 year)** **67.** *"It always, like, reinforces our knowledge and reinforces our guidelines that we use to go with in terms of what to prescribe and in terms of when to prescribe it.''* **(Physician 11: orthopaedics, 1 year)** **68.** *"If it's [infection] something more oriented, proven by cultures and does not need any ID consultation I would go with the antibiotics I prescribed.''* **(Physician 3: orthopaedics, 2 years)** **69.** *"If we are still at a point in the middle with no clear answer, we usually contacted the ID and ask them about their opinion.''* **(Physician 10: ear, nose and throat, 1 year)** ***70.*** *"I talked to them [the ID specialists] a few times about a very small number of cases but, in general, I really don't feel like I use their help a lot, …I never called them, except very rarely just to get their approval on giving the treatment, maybe because we are in the emergency room. It's not really making, like, big changes. If you are talking about inpatient service, like medicine or something, and treating some chronic infections, they probably would need help from the ID. But for us, in the emergency room, we kind of do one or*

	two doses maximum and the patient usually gets admitted or discharged on antibiotics. It's not really a big deal for us.'' **(Physician 12: emergency medicine, 9 years)** **71.** *"The ID consultants during ID rotation, they kind of open your eyes about things that you should be aware of. For example, we had a patient who had, like, infective endocarditis in our hospital, but he was previously managed in another hospital, so we had, like, a lack of information of what they were trying to treat because all the cultures in our hospital and our facilities were negative. So, the consultants were discussing, like, what antibiotics they should prescribe. I think that discussion kind of opened my eyes to a lot of things, why we should go for this medication, like, bacteriostatic versus bactericidal, that sort of, like, the effects of antimicrobials, like, why do they prefer a certain antimicrobial in this disease compared to the other disease.''* **(Physician 2: internal medicine, 1.5 years)** ***72.*** *"The ID team, they don't usually see the patient, they see the patient only once per week and they don't see the clinical improvement of the patient so, what I think is the clinical improvement is a significant indicator of the improvement, despite the clinical or microbiological evidence of positive organisms* **(Physician 8: internal medicine, 3 years)** **73.** *"Well, to be honest with you, in my institution, unfortunately, we don't have, like, an infectious disease round, so we don't know what they are doing.''* **(Physician 9: emergency medicine, 16 years)** **74.** *"To be honest, as a colleague, they didn't affect me much."* **(Physician 8: internal medicine, 3 years)** **75.** *"When I have more experienced colleagues in antibiotics and microbiology, I go with their advice, what they think the most suitable antibiotics for such infections, such organisms are. So, yeah, it has an impact when I have a colleague who is experienced in antibiotics …If I face an unusual infection, I take the opinion from an experienced colleague rather than revising a guideline.''* **(Physician 5: neurosurgery, 1 year)** **76.** *''Well, to be honest, it's kind of changed my practice a little bit. As I said, if they have a good reason that they can convince me about this antibiotic, very well-studied validated information is usually changing my practice."* **(Physician 9: emergency medicine, 16 years)** **77.** *"The issue is, when a medical on-call is responsible for patients, they don't discuss, actually they seek help from other colleagues if there are some colleagues in the hospital".* **(Physician 8: internal medicine, 3 years)** **78.** *"Always, 70% of the time.''* **(Physician 4: orthopaedics, 5 years)** **79.** *"We usually have the same antibiotics that we prescribe. So, with my colleagues in the same speciality, the same team, we didn't have a lot of differences in terms of antibiotics that should be used. I think we are usually on the same page in our neurosurgery practice."* **(Physician 5: neurosurgery, 1 year)** **80.** *"No, not always.''* **(Physician 10: ear, nose and throat, 1 year)** ***81.*** *"Usually I disagree with them but, unfortunately, that antibiotic is already being done and given to the patient. But, personally, I kind of disagree with some colleagues who prescribe antibiotics which I believe are maybe unnecessary to some stage. But it's almost like it is given to the patient and done."* **(Physician 9: emergency medicine, 16 years).**

	82. *"Before, I used to discuss with them, but with the time I found they become very offended and it was a very sensitive issue. I kind of stopped discussing with them about their practice. I kind of respect their opinion. So, I usually stop discussing.''* **(Physician 9: emergency medicine, 16 years)** ***83.*** *"Most of the time, I think the ID team make wiser choices because you have specialists. The primary team usually goes with what is safe …Prescribing broad-spectrum and not to be asked and to cover everything.''* **(Physician 10: ear, nose and throat, 1 year)** ***84.*** *"The primary physician, the one who is taking care of the patient, he will do, the final decision will be for the primary team.''* **(Physician 4: orthopaedics, 5 years)** ***85.*** *"We have sometimes disagreements and sometimes in the same team, in the primary team, they disagree between others: 'Why are you prescribing this? You have to give the patient the other one' and you have a lot of discussions sometimes when using such antimicrobial agents, but they are the ones, I would say, the judges. I would say the ID at the end, he will decide …We are asking the ID for such patients, approval for antibiotics. Most of the time, if the ID decides any antimicrobial, I mean broad-spectrum, I would say 70%-80% of the physician follow what they are recommending.''* **(Physician 7: internal medicine, 1 year)** ***86.*** *"Generally, we are going to have like a scientific discussion about the pros and cons and why they need a broad-spectrum antibiotic instead of something more tailored to whatever microorganism we're suspecting is causing the infection.''* **(Physician 2: internal medicine, 1.5 years)** **87.** *"I'll give you two examples: when I was in an ID team and when I was on the primary team calling the ID. So, in the primary team, I usually follow them most of the time If I don't follow them, it's based on our consultant in the primary team. For example, in general medicine, some consultant wanted to discharge the patient and the ID said 'No, keep the patient and repeat the cultures' and our team disagreed. So, usually, the issue is whether to discharge the patient or to keep the patient, and the primary team would usually discharge the patient, so they don't follow the ID team. The other example was when I was in the ID team. One patient I remember I was dealing with was having septic arthritis in the shoulder and we were giving vancomycin and the primary team stopped the vancomycin and discharged the patient, based on clinical improvement, on only oral clindamycin. So, is there are differences but, usually, we follow the ID, but there are some exceptions and the exceptions are mainly because of the decision to discharge.''* **(Physician 8: internal medicine, 3 years)** **88.** *"The clinical pharmacist is really very helpful. I personally ask them about antibiotics if I need them and they usually help me with prescription and alternatives, and they give me very good advice.''* **(Physician 9: emergency medicine, 16 years)** **89.** *"A clinical pharmacist is always our safety net because they monitored all the prescriptions, nearly all the prescriptions.''* **(Physician 11: orthopaedics, 1 year)** **90.** *"We wouldn't have been able to do it without our clinical pharmacist.''* **(Physician 13: infectious disease, 10 years)** **91.** *"We have an ID clinical pharmacist; she knows all the patient that are on very restricted antibiotics and she always gets us, like, if we don't have specific medication and we need it for a specific patient, she gets us back from our hospital. They help us, honestly, everything we want they are always available and they always provide us with it."* **(Physician 14: infectious disease, 5 years)**

	92. *"Yes, all the time. The clinical pharmacist is available in our hospital during the day time or during the on-call time. And, personally speaking, yes, I'm calling them, I'm taking the consult, I consult them. Not regarding the antimicrobial alone but also for all the types of medication.''* **(Physician 4: orthopaedics, 5 years)** **93.** *"The clinical pharmacy, they give us a lecture and give the other service departments lectures about this part of the practice of antibiotics, the antibiogram, and where we can find it actually, especially for those who are specialists, like infectious disease specialists or internal medicine residents, and those rotating in the infectious disease department.''* **(Physician 8: internal medicine, 3 years)** **94.** *"We have clinical pharmacist specialists on ID. We call them sometimes to help us decide which antimicrobial we can use. They made us a pocket guide for antimicrobial therapy or agents to use with such diseases."* **(Physician 7: internal medicine, 1 year)** **95.** *"In our practice, as neurosurgery, we usually don't have a direct encounter with clinical pharmacists until some situations arise. We are not like other specialities that have continuous encounters and discussions with the clinical pharmacists. So, in my practice, surgical specialities, we sometimes get the opinion and advice from clinical pharmacists in some situations, but not on a regular basis.''* **(Physician 5: neurosurgery, 1 year)** **96.** *"I remember seeing the clinical pharmacist about three times during the last year, they come sometimes and, if they are available, they try to help. So, I remember talking to him about one of my patients. He was really helpful when I asked him, but I'm not sure if they, like, it depends on if you recognise them because, like, he is not there all the time. When he is there or she is there, then we should at least make use of their presence in the emergency room.''* **(Physician 12: emergency medicine, 9 years)** **97.** *"In the ICU, they are around, but out of the ICU, no.''* **(Physician 10: ear, nose and throat, 1 year)** ***98.*** *"Unfortunately, in our institution, they only send us, like, students. As clinical pharmacists, they really, sometimes, they don't even know the families of antibiotics. I swear to God, it's super unhelpful that you cannot depend on them.''* **(Physician 16: internal medicine, 10 years)** ***99.*** *"Clinical pharmacists, their role comes with the doses usually. They follow the levels of the toxicity, like vancomycin. Yeah, that's it.''* **(Physician 10: ear, nose and throat, 1 year)** **100.** *"We are not calling them unless, I mean, for adjusting of medication and drug-drug interactions, but for approval, I mean for broad-spectrum antibiotics …If a patient, he was on vancomycin for a long time, I will not call the ID to approve it. I mean, vancomycin is already approved, but the stop date is today, for example, so I will call the clinical pharmacist and ask 'Please approve it again' just to give to the patient".* **(Physician 7: internal medicine, 1 year)** **101.** *"The number of people who need antibiotics is huge in a hospital. So, for you to have an ID team for all the cases that need antibiotic or broad-spectrum antibiotics is going to take a lot of time and effort to keep track of.* **(Physician 2: internal medicine, 1.5 years)** **102.** *"We don't have a good capacity; we are only a few. Numbers are very large and we leave it very late, 8-9 pm, to put orders for the patients in the hospital.''* **(Physician 14: infectious disease, 5 years)** **103.** *"The shortage of antibiotics can affect the antimicrobials or the broad-spectrum prescriptions.''* **(Physician 8: internal medicine, 3 years)**

	104. *"The main problem has always been lacking medications, lack of supply …Like, for example, we ran out of piperacillin/tazobactam then, like last month there was no more piperacillin/tazobactam in the whole hospital …Due to incompetency by storage.''* **(Physician 13: infectious disease, 10 years)** **105.** *"Depending on the availability."* **(Physician 16: internal medicine, 10 years)** ***106.*** *"Like for example, we don't have easy access to Keflex so we need to give, sometimes, ceftriaxone because we just don't have it and, to me, it's considered broad-spectrum. So, things like that …It's not available at the hospital formulary, this is one thing. Another thing is, for example, if you want to give it especially in cellulitis, they will tell you they don't have it so you have no choice and you will prescribe clindamycin and amoxiclav sometimes. To me, amoxiclav is broad-spectrum.''* **(Physician 16: internal medicine, 10 years)** **107.** *"We know about the shortage, the need for the antibiotic, for example, the broader spectrum like colistin, ceftazidime/ avibactam, currently tazocin in my hospital, which is in shortage, I would avoid the shortage. I would contact the clinical pharmacy and see what the options are. I can give them the options and they tell me what they suggest, usually if there is a mistake or if there is a shortage."* **(Physician 8: internal medicine, 3 years)** ***108.*** *"Yes, definitely I do.''* **(Physician 15: infectious disease, 12 years)** ***109.*** *"Sometimes if we are oriented about it, like, for example, imipenem, meropenem, they are always orienting us about the price; antifungals, they are always orienting us about micafungin and caspofungin and the difference in the price. If we are oriented about the price and we know, yes, we consider it.''* **(Physician 14: infectious disease, 5 years)** **110.** *"Never, we never consider the cost in our institution.''* **(Physician 1: surgery, 8 years)** **111.** *"I only think about the cost when I work in one of the private hospitals here in Saudi. I think I try to accommodate the patient with the cheapest antibiotic that would cover properly his or her infection.''* **(Physician 12: emergency medicine, 9 years)** **112.** *"I think this is something that we're going to work on in the future, with privatisation in Saudi.''* **(Physician 2: internal medicine, 1.5 years)** **113.** *"The system we use, the healthcare system, always raises red flags or raises rejection to the clinical pharmacist to review everything, if it's inappropriate.''* **(Physician 11: orthopaedics, 1 year)** **114.** *"We don't have the system in our phone or apps or laptops, unfortunately …There is room for improvement. The only disadvantage is sometimes, because, like, we don't have a laptop or system at home, so they call us for approval for an antibiotic. All the information is given over the phone and not everyone is able to deliver the right message for you or the right clinical picture for you, so, sometimes, you don't have the system, you don't have the data for the patient, you don't have the lab, you don't know anything and, like, the other physician consulting you during the on-call, the patient is very sick and in this situation, we need to give something broad because you don't know because he is not delivering the right message and he didn't know how to read microbiology. So, you will put all the consideration in your head and you will start empirically, even if you know you are wrong."* **(Physician 14: infectious disease, 5 years)** **115.** *"They prescribed it from the first dose and second dose, it depends. Sometimes we give them 24 hours. So, obstacle number one, that the system doesn't stop automatically because there is no restriction from the system itself. There is a restriction from the pharmacy*

	itself. Pharmacists, sometimes they don't have enough time to review all the antibiotics and to see that, 'Oh, this is, should we stop now? Where is the ID approval?' So, if no one picks it up, the patient will be on until they either finish the course or there is a new change. So, they call us to review." **(Physician 15: infectious disease, 12 years)** **116.** *"Sometimes, making sure that, like, everybody has authority. Sometimes there's miscommunication between the pharmacy and the team. I find, like, for example, an order has been saved by an ID specialist but, like, a rotating ID specialist, the pharmacy doesn't recognise me, so it drops from the system and the patient doesn't get the antibiotic. I could see that happening.''* **(Physician 2: internal medicine, 1.5 years)** **117.** *"We have a lot of issues with the IT department because we have requested multiple times from them that we need to have a few medications which are too broad-spectrum, like meropenem, imipenem, vanco, to be prescribed only for specific days and to drop from the system automatically, which has not yet been implemented. They said it needs a lot of power and money, financial support. So, this is what we need and we have asked them multiple times.''* **(Physician 15: infectious disease, 12 years)** **118.** *"During the past three years. I remember only two lectures by the clinical pharmacy given to the internal medicine residents about antimicrobial prescriptions and resistance. And the issue is not only the pharmacy, the residents themselves did not attend half of them or more which is, I think, very important. "* **(Physician 8: internal medicine, 3 years)** ***119.*** *"There are some seminars and physicians can, and clinical pharmacists and nurses as well, attend these sessions about the antibiotics and these things. But, I still, I believe it still didn't reach the expected limit. So, I think we are a little bit behind in this matter …we didn't have continuous updates in regard to antibiotics, antimicrobial prescribing on a regular basis. So, I think we have some deficiency.''* **(Physician 5: neurosurgery, 1 year)** **120.** *"From my institution, there is no educational support''* **(Physician 4: orthopaedics, 5 years)** ***121.*** *"We don't have any education with regards to antimicrobial stewardship."* **(Physician 2: internal medicine, 1.5 years)** **122.** *"Currently, no, it's just self-training, self-reading.* **(Physician 9: emergency medicine, 16 years)** **123.** *"Generally speaking, there is no institution role in stewardship on antibiotics. But personal efforts and education about stewardship, some are doing personal efforts. At the hospital, in general, there is no education about antimicrobial stewardship. It's only personal, one or two people, whoever is able to speak in general or to give a lecture about the stewardship.''* **(Physician 14: infectious disease, 5 years)** ***124.*** *"We don't interfere or interact with the microbiology lab in many cases of many diseases.''* **(Physician 4: orthopaedics, 5 years)** **125.** *"The micro lab, they don't give us the identification of the organism immediately or, I mean, in the next few days. Sometimes they delay identification of organisms giving us the sensitivity panel of using the antimicrobial."* **(Physician 7: internal medicine, 1 year)** **126.** *"We don't have an automated system for the antibiogram, MIC, other stuff. I mean that it is shown in our system. No, we have to call them and you have to go to them and discuss with them. What I mean is the MIC and other factors, we have to consider. Yeah; I think this is challenging.''* **(Physician 7: internal medicine, 1 year)** **127.** *"I didn't know the microbiology lab. How did they do the culture? Is it a technical issue? I don't know, but it's a clear infection.''* **(Physician 4: orthopaedics, 5 years)**

	128. *"Definitely, 100%.''* **(Physician 15: infectious disease, 12 years)** **129.** *"An example would be, let's say somebody presenting with acute pyelonephritis in the ER. We have a high rate of ESBL in the hospital and we would prescribe patients a carbapenem, like meropenem, as a broad-spectrum pending the urine and blood culture.''* **(Physician 13: infectious disease, 10 years)** **130.** *"Definitely but it not available all the time, and it is very helpful. Like, for example, C. diff guidelines at my institution. We have an understanding that metronidazole can still be superior to vancomycin and it's less expensive and people are responding to it. So, we definitely considered it.''* **(Physician 16: internal medicine, 10 years)** **131.** *"I don't know what the antibiogram is.''* **(Physician 6: orthopaedics, 4 years)** **132.** *"The biogram is not that widely available. I actually had to contact micro labs to get a biogram of each microorganism, and its susceptibility to different antibiotics. But I don't think that's widely available and, even if it's available, I don't think that everybody knows how to use the biogram in order to implement it into his or her practice.''* **(Physician 2: internal medicine, 1.5 years)** **133.** *"I've never seen them actually use it.''* **(Physician 11: orthopaedics, 1 year)** **134.** *"Some antibiotics are restricted to be approved by the ID, like meropenem. Also, tazocin, I can give only one dose, then I must take the approval from ID.''* **(Physician 10: ear, nose and throat, 1 year)** ***135.*** *"We are not really involved in this restriction much but, usually, if we are ordering, we will put in the comment that it's an order for the ID.''* **(Physician 6: orthopaedics, 4 years)** ***136.*** *"Obstacle number one, that the system doesn't stop automatically because there is no restriction in the system itself. There is a restriction from the pharmacy itself. Pharmacists, sometimes they do not have enough time to review all the antibiotics and to see that, 'Oh, this is, should we stop now? Where is the ID approval?' So, if no one picks it up, the patient will be on it until they either finish the course or a new change happens. So, they call us to review."* **(Physician 15: infectious disease, 12 years)** **137.** *"I don't think that [policy] impacted me. No, not really. I just do what is appropriate for my patients."* **(Physician 12: emergency medicine, 9 years)** ***138.*** *''The restriction regarding any big guns, any broad-spectrum antibiotics, that restriction made me think twice before I prescribed. What's the reason and how to explain it to the ID team, to pharmacy, to allow me to prescribe a medication? So, it helped me a lot and made me improve.''* **(Physician 4: orthopaedics, 5 years)** **139.** *"It restricts my use. I think it encourages me to contact the ID, the specialists to, to make it a wider decision.''* **(Physician 10: ear, nose and throat, 1 year)** **140.** *"It's not really helpful because the only restriction is for single like agents meropenem, Pip-tazo or tazocin, which is piperacillin/tazobactam so I don't know, like if it's helpful so much. They're just trying to keep certain antibiotics, but they are still being used very generously so I can't say that that's been helpful …Because this is not comprehensive, so it allows for other compensation or other physicians from the team to find ways to still prescribe a broad-spectrum."* **(Physician 16: internal medicine, 10 years)**

	141. *"I remembered facing a couple of issues with a couple of patients that, yes, me and the team, we saw that a certain antibiotic was more suitable for the patient and the patient was responding to it. However, it was restricted. So, we had trouble getting to an agreement between both the ID team and our team. So, if it was open, not restricted, it would have been offered from the beginning.***"** **(Physician 3: orthopaedics, 2 years)** **142.** *"Prescribing a broad-spectrum antibiotic needs ID's approval. That could delay appropriate antimicrobial therapy being administered in proper time. Like, there is a delay in patient care, which I think is a concern …For example, like I said, prescribing antibiotics without getting ID approval, like prescribing, like one dose of antibiotics. So, ID approve the dose or approve the regimen or whatever. If I don't do that, there's a delay in patient care. Like, the ID team maybe has, like, six, seven consults at the same time and they are getting all the pieces together. But, by the time they review all the cases, that's seven hours without being, without the patients being administered the proper medication.* **(Physician 2: internal medicine, 1.5 years)**

3.4.2.2.2 Physician-related factors

Physician-related factors were reported to influence broad-spectrum antimicrobial prescribing. This section will present these factors as reported by the participants.

Some participants reported the use of guidelines as an information source for broad-spectrum antimicrobial prescribing. They referred to the use of infection-related international guidelines, such as the IDSA practice guidelines (Quote 18, Table 3.6).

Other participants referred to the use of guidelines that are specialised in their area rather than general infection-related guidelines. Examples provided were the use of the Orthopaedic Society-related guidelines and the American Society of Emergency Medicine updated pocket guide (Quote 19-20, Table 3.6). Moreover, they reported that international guidelines were used by different levels of healthcare professionals, including ID specialists and clinical pharmacists (Quote 21, Table 3.6).

Some participants reported that they followed guidelines for procedures and preoperative indications only, while others reported the use of guidelines in situations where support from a senior or experienced physician was unavailable (Quote 22-24, Table 3.6). With respect to the use of clinical decision support tools, some participants reported the use of support tools, such as Stanford Guide, UpToDate, Lexi-Comp and John Hopkins antibiotic guide (Quote 25-26, Table 3.6). Participants referred to the use of other resources, such as the New England Journal of Medicine, for exceptional or undiagnosed cases (Quote 27, Table 3.6). Some participants reported the availability of institutional guidelines for certain infections like febrile neutropenia, septic shock, pneumonia and bacteraemia, while others were not aware of the availability of such guidelines at their institution (Quote 28-29, Table 3.6). Moreover, the participants reported having two types of antimicrobial guidelines: infection-related and drug-related. Some local guidelines were available

for common infections; for example, clinical guidelines for pneumonia and sepsis and drug guidelines for ertapenem and meropenem (Quote 30, Table 3.6).

The use of the Institutional Pharmacy Pocket Book in prescribing broad-spectrum antimicrobials was reported. However, it was noted that only a few physicians were aware of the pocket guide which was provided by the pharmacy (Quote 31, Table 3.6). The use of the updated MOH local antimicrobial guidelines was mentioned as a guide for prescribing broad-spectrum antimicrobials (Quote 32, Table 3.6). Text books as guidance for broad-spectrum antimicrobial prescribing was also reported (Quote 33, Table 3.6). The participants stated different degrees of awareness of certain guidelines as some were not familiar with specific guidelines for broad-spectrum antimicrobial prescribing (Quote 34, Table 3.6).

The participants had a general agreement that their experiences had had an influence on their broad-spectrum antimicrobial prescribing practices. Moving through the medical profession, individual experience became a predominant impact in broad-spectrum antimicrobial prescribing decisions (Quote 35, Table 3.6). Meanwhile, other participants reported that they rely on evidence more than their experience, although they still recognise the role of their experience in prescribing (Quote 36, Table 3.6). The participants who reported that their experiences had influenced their broad-spectrum antimicrobial prescribing practices stated two contradictory opinions. Some participants stated that, as they accumulated more experience, they became aware of not prescribing broad-spectrum antimicrobials when there were no indications (Quote 37, Table 3.6). Others stated that their experience has encouraged them to use more broad-spectrum antimicrobials (Quote 38, Table 3.6).

Senior physicians depend on their personal professional decisions and the desire to freely select what they think and decide to be the most suitable broad-spectrum

antimicrobial. This may include making broad-spectrum antimicrobial prescribing judgements that overrule the ID specialist's or clinical pharmacist's recommendations (Quote 39, Table 3.6). Another factor was that sometimes physicians failed to contact the ID team or the clinical pharmacist to save time and to avoid difficult professional discussions or confrontations (Quote 40, Table 3.6).

When a suspected infection did not respond to the prescribed antimicrobial therapy, the usual practice was to change the therapy to a broader spectrum (Quote 41, Table 3.6).

The participants mentioned that broad-spectrum antimicrobials were overused, regardless of the infection. It was reported that broad-spectrum antimicrobials being prescribed as "analgesia". An example provided was the common practice of prescribing piperacillin/tazobactam for a simple UTI (Quote 42-44, Table 3.6).

Emergency room physicians were described as being "generous" with the prescribing of broad-spectrum antimicrobials. They justified their liberal prescribing practice because of working in settings like the emergency room, where they faced undifferentiated cases on a daily basis (Quote 45, Table 3.6).

Concern was expressed regarding the surgeons' prescribing habits, where they tended to prescribe broad-spectrum antimicrobials because of their feelings that the patient needed them (Quote 46, Table 3.6).

A lack of knowledge about broad-spectrum antimicrobials was considered a factor that drove inappropriate prescribing. Some participants noted the physicians' lack of knowledge about indication and the side-effects of such agents (Quote 47, Table 3.6).

In addition, it was highlighted that the physicians were not aware of the existing policy and procedures and were not following recommendations provided by ID specialists (Quote 48, Table 3.6).

Reluctance to access the policy, to read the guidelines and lack of interest in antimicrobial stewardship policies were considered factors that contributed to the overuse of broad-spectrum antimicrobials. ID specialists reported that most physicians tended to call them to ask about the policy instead of reading the policy from the hospital information system by themselves (Quote 49-50, Table 3.6).

Participants were confident in the diagnosis and treatment of most common presentations of bacterial infection. However, they stated there were some occasions where they tended to prescribe broad-spectrum antimicrobials as a result of lacking confidence. These occasions included being uncertain about the diagnosis of rare infections, dealing with ID that had similar presentations and facing difficulty distinguishing between bacterial and viral infections. An example provided was the current pandemic of COVID-19, where participants faced difficulty in differentiating between a viral or bacterial cause, leading them to prescribe broad-spectrum antimicrobials (Quote 51, Table 3.6). Another example was the difficulty in differentiating between acute chest syndrome and pneumonia (Quote 52, Table 3.6).

The participants described situations when they did not have clear information about their patients. Consequently, they had unclear or fewer data to evaluate and assess a clinical condition compared to conditions where clear data was available. This led and contributed to diagnostic uncertainty. An example was during on-calls, where the participants tended to prescribe broad-spectrum antimicrobials (Quote 53, Table 3.6).

Perceived risks of undertreatment by not prescribing broad-spectrum antimicrobials seemed to impact the prescribing decision. Participants used terms such as *''face our fear''*, *''safe''*, *''comfortable'' and ''benefit''* to justify their decisions to prescribe the antimicrobials (Quote 54-57, Table 3.6).

The participants reported several situations where they perceived the risk of undertreatment, which resulted in prescribing broad-spectrum antimicrobials. First, there may have been a perceived risk of under-covering the condition of a patient who came from outside the hospital where the patient was being treated, according to the hospital local antibiogram, and there was no improvement (Quote 58, Table 3.6). Second, there may have been a perceived sense of alarm where the participants felt concerned about the possibility of there being a severe infection (Quote 59, Table 3.6). Third, there may have been a perceived risk of undertreatment in challenging situations: like, for example, emergency room settings and during on-calls (Quote 60-61, Table 3.6). Fourth, there may have been a perceived risk of not treating the patient properly in the first instance, such as in an emergency room, where the patient gets the initial doses of the antimicrobial and is then admitted to the hospital (Quote 62, Table 3.6).

3.4.2.2.3 External factors

In daily practice, seniors are usually consulted regarding broad-spectrum antimicrobial prescribing, especially if a consultant is the primary physician who is responsible for the patient (Quote 63, Table 3.6). Junior participants recognised that their prescribing decisions were strongly impacted by their senior colleagues. Some participants agreed with the senior's decisions on broad-spectrum antimicrobial prescribing and acknowledged their role in explaining and justifying the reason behind these decisions (Quote 64, Table 3.6). Meanwhile, others described receiving pressure from their seniors to prescribe broad-spectrum antimicrobials. Therefore, they tended to prescribe broad-spectrum antimicrobials even if they disagreed with the need for the prescription (Quote 65, Table 3.6).

Working in a multidisciplinary hospital allows the participants to consult the ID specialist in any case of infection. However, different levels of ID specialist involvement were reported. Some participants talked about the involvement of the ID specialists in every prescription of broad-spectrum antimicrobials. They recognised the impact of their role on the control of broad-spectrum antimicrobials prescriptions and on the reinforcement of the participant's knowledge (Quote 66-67, Table 3.6).

Others reported that they tended to contact ID specialists in uncertain cases. Thus, having a clear infection that was proven by a culture would make them decide not to contact the ID specialists (Quote 68-69, Table 3.6).

Conversely, it was mentioned that participants contacted the ID specialist on rare occasions just to get approval for the prescribed broad-spectrum antimicrobials. The reason for having limited contact with the ID specialists was the result of being in a setting like the emergency room, where the patients suffering an emergency received one or two doses before they were admitted to the hospital or discharged (Quote 70, Table 3.6).

Having an ID rotation as a part of the residency programme was very helpful as it made the physicians more aware of how to deal with different cases that needed broad-spectrum antimicrobials and also made them aware of their different mechanisms that led to the preference of one antimicrobial in certain disease compared to others (Quote 71, Table 3.6). The ID rounds seemed to add very valuable and helpful discussions about the patient therapy and they helped to monitor their improvements. However, some participants reported raising concern about having only one round per week, where there was a lack of good tracking of the patients' improvements (Quote 72, Table 3.6). Others reported that there were no ID rounds, which affected the communication with the ID specialist team (Quote 73, Table 3.6).

There were different views regarding the influence of other colleagues in broad-spectrum antimicrobial prescribing. It was mentioned that colleagues had no influence (Quote 74, Table 3.6). Meanwhile, other participants reported that their colleagues had an impact, particularly if they had experience with antimicrobials. They reported the practice of taking the opinion from an experienced colleague rather than looking at a guide for uncommon infections (Quote 75, Table 3.6). Another participant noted the influence of experienced colleagues (Quote 76, Table 3.6). Seeking advice from other colleagues was reported in situations where limited physicians are available, like during on-calls (Quote 77, Table 3.6).

Seeking agreement with other colleagues or teams on prescribing practices varied between the participants. This section will present these variations and will consider the issue of disagreement on an individual and team level, as reported by the participants. On an individual level, participants reported various degrees of agreement with their colleagues broad-spectrum antimicrobial prescribing practices (Quote 78-80, Table 3.6).

Some participants found it difficult to talk about other physicians who prescribed unnecessary broad-spectrum antimicrobials. One reason was that, although their decision to prescribe broad-spectrum antimicrobials may seem questionable, the participant pointed out that the therapy had already been given to the patient (Quote 81, Table 3.6). Another reason was that some colleagues get “offended” and are “very sensitive” when questioned about their decisions. As a result, the participants stopped providing feedback to them about their prescribing practices (Quote 82, Table 3.6). On a team level, it was reported that the ID team makes wiser choices because they are the specialists, while the primary physician goes with what is safe

to cover everything (Quote 83, Table 3.6). Some participants stated that, if a disagreement arose between the primary team who was responsible for the patient and the ID team, usually, they would follow the primary team's decision (Quote 84, Table 3.6). In contrast, other participants mentioned that the ID team would decide if disagreement occurred between teams (Quote 85, Table 3.6). It was reported that sometimes when disagreements happened, both teams tried to discuss the pros and cons of the selected therapy (Quote 86, Table 3.6). Disagreement was reported to be common on either to continue the patient on broad- spectrum antimicrobials or discontinue them and discharge him or her (Quote 87, Table 3.6).

Other healthcare professionals may be influential, including clinical pharmacists. Several participants described the role of clinical pharmacists in broad-spectrum antimicrobial prescribing and there were mixed views on their role. Some participants perceived a positive role. They used terms such as "*very helpful"* and *"safety net"* to express this (Quote 88-90, Table 3.6). Having an ID clinical pharmacist was found to be very helpful in identifying and monitoring patients who were on restricted broad-spectrum antimicrobials (Quote 91, Table 3.6). Furthermore, the availability of clinical pharmacist during both daytime and on-call time was noted (Quote 92, Table 3.6).

Also, the clinical pharmacist has a role in providing lectures and antimicrobial pocket guides which contribute to the improvement in the appropriateness of broad-spectrum antimicrobial prescribing (Quote 93-94, Table 3.6).

In contrast, different experiences were reported by some participants who stated that they did not have direct or regular encounters with the clinical pharmacy, as other specialities do (Quote 95, Table 3.6). Also, others reported seeing the clinical pharmacist only a few times during the year. It was reported that the clinical pharmacist was involved in the rounds in ICU settings but not in non-ICU settings

(Quote 96-97, Table 3.6). There was a concern about having students who were under training in the Clinical Pharmacy Department instead of having the clinical pharmacist, which was considered unhelpful (Quote 98, Table 3.6). Other participants restricted their role in dosing and therapeutic drug monitoring for some broad-spectrum antimicrobials like vancomycin, leaving this to the clinical pharmacist (Quote 99, Table 3.6). It was added that there was no such role for the clinical pharmacist in the decision of prescribing broad-spectrum antimicrobials and that their role was usually to re-approve an antimicrobial that had automatically stopped in the system (Quote 100, Table 3.6).

Workload was stated as a factor that might influence broad-spectrum antimicrobial prescribing. It was reported that it is difficult for the ID specialists to submit all the orders for broad-spectrum antimicrobials for all the hospitalised patients (Quote 101-102, Table 3.6).

Antimicrobial shortages were mentioned by several participants as one of the factors that influences broad-spectrum antimicrobial prescribing. They used words such as *"lack", "run out", "shortage"* and *"availability"* to address this factor (Quote 103-105, Table 3.6). The influence of antimicrobial shortages was presented from two different viewpoints: broad-spectrum and narrow-spectrum antimicrobial shortage. Some participants reported prescribing broad-spectrum antimicrobials in some cases where it was not indicated due to the unavailability of narrower spectrum medication at the hospital formulary (Quote 106, Table 3.6). Another point of view was the situation involving the unavailability of broad-spectrum antimicrobials which ends up in contacting the clinical pharmacist to review the circumstances and discuss the best and optimal options, which may be a narrower spectrum medication (Quote 107, Table 3.6).

The cost was reported as a factor that might influence broad-spectrum antimicrobial prescribing. Some participants reported considering the cost in situations where they were aware of it (Quote 108-109, Table 3.6). On the other hand, those participants working in a governmental hospital reported that they did not consider the cost. However, working in a private hospital, some participants may consider the cost of the broad-spectrum therapy (Quote 110-111, Table 3.6). Some participants believed that they would consider the cost when prescribing in the future with the new vision of the KSA, which is privatisation (Quote 112, Table 3.6).

Participants identified different factors related to the hospital system that influence their broad-spectrum antimicrobial prescribing. They mentioned having red flags in the system, allowing further review by the clinical pharmacist if inappropriate prescribing was prevalent (Quote 113, Table 3.6). Some participants reported having no access to the system in their phones or laptop, which is considered to be a factor that influences their prescribing. They reported that they tended to prescribe broad-spectrum antimicrobials during on-calls just because they did not have access to the system where they could view the patient's information (Quote 114, Table 3.6).

The process of broad-spectrum antimicrobial restriction is done manually instead of being done by the system. Basically, the pharmacist will stop the order after the first or second dose until there is ID approval. However, sometimes they miss it and the patient goes onto the broad-spectrum antimicrobial without ID approval (Quote 115, Table 3.6). As a result of the manual restriction process, the participants reported that the order sometimes drops from the system as the pharmacist does not recognise the new resident, who has been rotated in the ID, as an authorised physician to prescribe broad-spectrum antimicrobial (Quote 116, Table 3.6). It was reported that the issue of manual restriction was requested several times from the

IT department while they stated that it needed power and financial support (Quote 117, Table 3.6).

Institutional support in terms of education and training is considered a factor that has impacted broad-spectrum antimicrobial prescribing. Some participants reported the usefulness of antimicrobial-related lectures. However, there were only a few lectures and few physicians attended them (Quote 118, Table 3.6). The participants who reported having a few seminars about antimicrobials believed that it still did not reach the expected level of educational support from the institution. Also, they pointed out the lack of continuous updates related to antimicrobials (Quote 119, Table 3.6). Some participants reported that there was no educational support at the institution (Quote 120, Table 3.6).

Moreover, some participants reported that there was no institutional role in antimicrobial stewardship education, and it was mainly a personal effort. Participants mentioned words like "*self*", "*personal efforts",* "*self-training" and "self-reading"* to describe how there was no institutional support (Quote 121-123, Table 3.6).

The participants reported that microbiology test results had an influence on their broad-spectrum antimicrobial prescribing. Having little interaction with the microbiology lab was also reported (Quote 124, Table 3.6). They stated three different issues related to microbiology test results. The first issue was the length of time needed to receive the culture results. Some participants reported delays in obtaining them, particularly during weekends, which led to the prolongation of the therapy (Quote 125, Table 3.6). The second issue was the way of reporting the results. The participants raised a concern about not reporting the minimum inhibitory concentration (MIC) in the system, meaning they have to phone the microbiology lab to get this information (Quote 126, Table 3.6). The third issue was related to the

reporting of negative results where some participants believed that the results should have been positive, indicating a technical issue related to the microbiology lab (Quote 127, Table 3.6).

The hospital antibiogram was considered to be a factor of influence. Some participants reported the use of hospital antibiograms for prescribing broad-spectrum antimicrobials. Prescribing meropenem for pyelonephritis according to the antibiogram was provided as an example for the use of the hospital antibiogram in the decision to prescribe the therapy (Quote 128-129, Table 3.6). Another example was the use of metronidazole for *C. difficile* instead of using vancomycin, which is more expensive (Quote 130, Table 3.6). While other participants stated that they had no idea about what the hospital antibiogram was (Quote 131, Table 3.6).

Several issues were reported related to the hospital antibiogram. First, it was not easily accessible. Second, some participants were unfamiliar with the integration of the antibiogram into practice. Third, it was not commonly used in the hospital (Quote 132-133, Table 3.6).

Participants mentioned having restrictive policies on some of the broad-spectrum antimicrobials which allows them only to prescribe the first and second doses, then they need to have an ID specialist's approval. Examples of the restricted broad-spectrum antimicrobials were meropenem, imipenem, piperacillin-tazobactam, vancomycin, ceftazidime and colistin (Quote 134, Table 3.6). Approval can be either by physicians entering the order under the name of the ID specialist themselves or it can be easily done by writing a comment that the dosage was approved by someone from the ID (Quote 135, Table 3.6). The process of restricting the broad-spectrum antimicrobials to an ID specialist was not done automatically but was done manually by a pharmacist. Therefore, if the pharmacist does not recognise the broad-spectrum

antimicrobial as a restricted agent, it will continue to be issued automatically (Quote 136, Table 3.6). There were mixed views on the impact of policy on broad-spectrum antimicrobial prescribing. Some participants reported that there was no impact (Quote 137, Table 3.6). Other participants reported being influenced by the policy both ways, positively and negatively. Some reported that the policy made them think before they prescribed the broad-spectrum medication (Quote 138, Table 3.6). Also, it was reported that the policy encouraged more discussion with the ID specialist (Quote 139, Table 3.6). Conversely, some participants viewed this policy as being unhelpful as these antimicrobials were still being overused (Quote 140, Table 3.6). Another concern is that in some cases, despite the need for the broad-spectrum antimicrobials, the participants faced difficulty sometimes in getting ID approval (Quote 141, Table 3.6). Moreover, delay in getting the approval sometimes was another concern which led to delay in the administration of the antimicrobials, therefore, delaying patient care (Quote 142, Table 3.6).

3.4.2.3 Antimicrobial stewardship practices

For antimicrobial stewardship practices, the identified practices were taking a culture before administering the antimicrobial therapy, de-escalation therapy and IV to oral. These practices are discussed in the following section. Table 3.7 illustrates supporting quotes.

3.4.2.3.1 Taking a culture before administering the antimicrobial therapy

For suspected infections, blood and urine cultures were requested before initiating the broad-spectrum antimicrobial therapy. However, there were some situations where cultures were not taken. For severely ill, hypotensive and haemodynamically unstable patients or if there was any difficulty in taking the cultures, for example, in

getting a line from the patient, some participants reported that they would not wait to take the culture and would start the patients on the therapy immediately (Quote 1-3, Table 3.7). Moreover, it was mentioned that a culture would not be requested for a patient who had already received the broad-spectrum antimicrobial therapy from other teams or departments (Quote 4, Table 3.7) Also, for common infections where the causative organisms are predicted, some participants may not take culture for cost-effectiveness (Quote 5, Table 3.7). Having a culture that had been taken on the same day or the day before was a reason for participants not to request one (Quote 6, Table 3.7). Having previous cultures that show the same bacteria several times is considered to be a factor that leads some participants not to request a culture (Quote 7, Table 3.7). In addition, some participants stated that during on-calls and weekends, they might face some delays in taking the culture (Quote 8, Table 3.7). Also, forgetting to order a culture for a patient is an issue that might happen sometimes (Quote 9, Table 3.7). For some infections, for example, CNS (Central nervous system) infection, broad-spectrum antimicrobials will be started before doing the lumbar puncture and the culture is sent. Another example is an infected joint prosthesis, where the culture is taken intraoperatively (Quote 10-11, Table 3.7). In the emergency room, it was reported that, according to recent updates in emergency medicine, it is recommended to start the broad-spectrum antimicrobial before taking culture. In addition, it was reported that it is the responsibility of the admission team to request a culture; thus, in settings like the emergency room, the participants reported that they did not take cultures before starting the broad-spectrum antimicrobials (Quote 12, Table 3.7)

Taking a sputum culture was not common practice, and was only seen in the ICU for intubated patients if requested. The participants reported such a practice in the

emergency room and for CAP (Quote 13-14, Table 3.7). Some participants justified the practice of not taking a culture being out of their control. They reported being dissatisfied with the nurses' practices of not taking a sputum culture, which they justified by saying that they could not take sputum from the patient. However, when the participants saw the patient, they complained of having sputum (Quote 15, Table 3.7)

3.4.2.3.2 De-escalation therapy

The participants acknowledged the practice of de-escalating the broad-spectrum antimicrobial therapy to narrow-spectrum therapy. They reported mixed views on de-escalation practices at their institution (Quote 16-17, Table 3.7). However, they felt uncertain about de-escalating broad-spectrum antimicrobial therapy to narrow-spectrum antimicrobial when a patient was severely ill. Even if the culture indicated sensitivity to narrow-spectrum, they would wait until their condition becomes stable (Quote 18, Table 3.7). Some patients spike a fever after de-escalating the therapy, leading to the re-initiation of the broad-spectrum antimicrobial therapy (Quote 19, Table 3.7). Also, the delay in getting the culture and sensitivity results must be considered; for example, a culture that was taken during the weekend is a factor for not de-escalating the broad-spectrum antimicrobial therapy. Some participants mentioned the situation where they needed to do more tests for antimicrobials that were not in the usual antimicrobials list, which would take additional time (Quote 20, Table 3.7). Antimicrobial-related issues were mentioned as reasons for not de-escalating the therapy. This included drug unavailability and there being side-effects to the sensitive antimicrobial. Also, in some cases, the pharmacokinetic properties of the sensitive antimicrobial make it unsuitable for certain organs such as the CNS (Quote 21, Table 3.7).

Table 3.7: supporting quotations for antimicrobial stewardship practices theme

Subtheme	Supporting quotations
Taking a culture before administering the antimicrobial therapy	**1.** *"Whenever I think I'm going to use a broad-spectrum antibiotic to cover for or, kind of, especially for cases with sepsis, I always consider a urine culture and blood culture …But I would never wait for that if they kind of have difficulty. I would start the antibiotic as soon as possible.''* **(Physician 12: emergency medicine, 9 years)** **2.** *''I think if the patient is very sick, hypotensive, haemodynamically unstable we will start even without taking the cultures …It will take time and the patient is unstable. So, we will start him on the antibiotic''* **(Physician 10: ear, nose and throat, 1 year)** **3.** *"Sometimes the nurses called me if there is a difficulty to get a line for a patient".* **(Physician 8: internal medicine, 3 years)** **4.** *"Sometimes, we receive a patient who has already received the antibiotic from emergency, from the medical team, from ICU, before taking our opinion."* **(Physician 1: surgery, 8 years)** **5.** *''Common infections with an expected organism, in such cases I usually don't send a culture …I don't send for the cost-effectiveness."* **(Physician 5: neurosurgery, 1 year)** **6.** *"The only condition that I wouldn't is if he already has had a culture taken within the day, the same day or the day before, and we don't have the results.''* **(Physician 2: internal medicine, 1.5 years)** **7.** *"If I know that the patient has this bacterium, he's always come with this bacterium multiple times …This is the only reason that I might give broad-spectrum antibiotics before taking a blood culture.''* **(Physician 6: orthopaedics, 4 years)** **8.** *"At times, when it's during on-calls and weekend, I might face a delay."* **(Physician 5: neurosurgery, 1 year)** **9.** *"Sometimes the order, for example, the physician didn't make an order for the culture.''* **(Physician 15: infectious disease, 12 years)** **10.** *"For the CNS, yeah, I would start the antibiotic then we would do the lumbar puncture and get the culture sent. But I would start the antibiotic first.''* **(Physician 12: emergency medicine, 9 years)** **11.** *"For an infected joint prosthesis, the culture is taken intra-op so we start the patient on antibiotics and we take an intra-op [intraoperative] culture, so we can know exactly what organism that we're dealing with.''* **(Physician 11: orthopaedics, 1 year)** **12.** *"Usually I don't, I start the broad-spectrum antibiotic and, if the patient is for sure for admission, the admitting team, they usually take a culture of the patient. But personally, I don't …Because of the recent updates and the emergency medicine research has shown antibiotics should start as soon as possible. So, I usually don't do the cultures before starting the antibiotics.''* **(Physician 9: emergency medicine, 16 years)** **13.** *"The sputum culture is not really common."* **(Physician 12: emergency medicine, 9 years)** **14.** **"***I only saw a sputum culture in the ICU for an intubated patient. They send an endotracheal tube if you request it.''* **(Physician 15: infectious disease, 12 years)** **15.** *"Unfortunately, they don't do it [sputum culture], either because they are not aware of it or it is out of their control. For example, always for pneumonia patients, we ask them to send a sputum culture before starting the antibiotic because we will de-escalate, or even up-escalate, the option of the antibiotic depending on the isolates. Most of the time, especially at our hospital, the nurses don't do sputum culture and always justify that by saying that the patient didn't have sputum. However, when you go to the patient, he complains of*

	sputum production. So who do I trust? Our problem is in the sputum. However, they like blood culture because it's easy - extract the blood samples and take the blood for culture …It is, most of the time, the nurses who are responsible …It's the biggest problem that we face at our hospital. Before, it was not an issue but now I noticed this practice without knowing the reason behind it. Is it because the nurses are busy? But this is a factor why they didn't send the sputum culture in a lot of cases.'' **(Physician 15: infectious disease, 12 years)**
De-escalation therapy	**16.** *"It is somehow [de-escalation] not common, I would say."* **(Physician 7: internal medicine, 1 year)** **17.** *''I would say I de-escalate probably, like, 75% of the time.''* **(Physician 15: infectious disease, 12 years)** ***18.*** *''Sometimes I don't de-escalate, for example, to ceftazidime, because he's still in septic shock …When the patient's situation stabilises, I will consider de-escalation to the narrowest targeted antibiotic option.''* **(Physician 15: infectious disease, 12 years).** **19.** "*We have cases that we downgrade and the patient spikes the fever so, we put them again on the broader spectrum.''* **(Physician 8: internal medicine, 3 years)** **20.** *''There are scenarios when the results take a while to come out, let's say during the weekend …And, if you have a drug that is not sensitive to the usual antimicrobials, they do have to run more tests to check for the sensitivity, so that, that takes extra time …There's just one day or like two days left for that antimicrobial, so sometimes, honestly, I don't change this, which I kind of know is wrong.''* **(Physician 2: internal medicine, 1.5 years)** **21.** *"Sometimes, we face difficulties with the pharmacy, not having some antibiotics, some antibiotics have some side-effects, some antibiotics are not suitable for such organs like the brain, for example. Not all antibiotics will cross to the brain cell, although an organism is sensitive to this antibiotic."* **(Physician 5: neurosurgery, 1 year)**
IV to oral switch	**22.** *"Whenever it's possible, if I have a patient who can swallow a tablet and has no vomiting and no issues and he's stable and conscious, I usually go with oral antibiotics.''* **(Physician 9: emergency medicine, 16 years)** **23.** *"85 to 90%, we are continuing the full dose IV antibiotic."* **(Physician 4: orthopaedics, 5 years)** **24.** *"Most of the time, if it's infection or prophylactic, it depends. If it's infection, not so much, if it's prophylactic, yes."* **(Physician 1: surgery, 8 years)** **25.** *"If the patient tolerates, usually we do it in GS [general surgery], paediatric surgery and also in the ICU, if the patient tolerates orally, we immediately encourage him to shift from the IV to oral …It is a very common practice, especially in surgical areas, where taking therapy orally is more favourable than IV.''* **(Physician 10: ear, nose and throat, 1 year)** **26.** *"As soon as possible, because, as I mentioned, we tend to like, we like our patients in orthopaedics, we like them to move, to be mobile as soon as possible."* **(Physician 11: orthopaedics, 1 year)** **27.** *"Sometimes, we do it for patient preference.''* **(Physician 3: orthopaedics, 2 years)** ***28.*** *"When we want the patient to go from the hospital, this is the only, the only reason that we change IV to oral. But usually, once the patient is an inpatient, IV is the one …Depends on if the patient will be discharged''* **(Physician 6: orthopaedics, 4 years)** **29.** *"A lot of times, from IV to oral, if the patient is for discharge …Probably yes. I never switched from IV to oral not necessarily because it's wrong practice, it's just that it's not something that I've done, switch to oral, usually on discharge …From IV to oral there's nothing*

	against the de-escalation from IV to oral, it's just something that we haven't done …It's just that, routinely, we only change it when the patient's ready for discharge. But, like I said, I probably, we should change it while the patient is already hospitalised. For example, azithro [azithromycin] can be given orally or through IV. We tend to give it by IV with pneumonia. There's nothing against giving it orally, it's just something we do." **(Physician 2: internal medicine, 1.5 years)** **30.** *"We tried just to avoid the oral, although we can switch to oral, but sometimes, the patient is sick so will not risk it and give oral while we can give IV.''* **(Physician 14: infectious disease, 5 years)** **31.** *"We think, we believe in and we studied that, that the efficacy of the IV antibiotic is much more than the oral antibiotic.''* **(Physician 1: surgery, 8 years)** **32.** *"Usually the infection disease consultation team, they have the authority to change the antibiotics whenever they think that it is indicated. Sometimes, they're not calling us as the primary team, they're changing it by themselves."* **(Physician 7: internal medicine, 1 year)**

3.4.2.3.3 IV to oral switch

Some participants reported making an IV to oral switch whenever possible for hospitalised patients unless there was no option for the oral forms. However, it was reported that an IV to oral switch was not common practice for hospitalised patients (Quote 22-23, Table 3.7). Reasons for IV to oral switch were multifactorial and the switch was not based on an antimicrobial perspective. With a prophylactic indication, participants may switch to an oral formulation (Quote 24, Table 3.7). Moreover, participants identified the role of patients' conditions in influencing their decision to convert from IV to oral therapy. They reported the common practice of conversion from IV to oral for surgical patients where the oral route was more favourable than IV, like in general surgery, where patients are encouraged to take oral forms of antimicrobials. Another example was where participants preferred switching to oral, such as in orthopaedics patients wishing to enhance their mobility (Quote 25-26, Table 3.7). Also, patient preferences were reported as another factor for considering an IV to oral switch (Quote 27, Table 3.7). Furthermore, it was reported that discharge was the only reason for IV to oral switch (Quote 28, Table 3.7)

Several reasons for not converting the IV to oral therapy, although indicated, were suggested. Some participants noted the habit of keeping the patient on an IV antimicrobial rather than switching to oral even if the oral form could be prescribed, and it was just something that they were used to doing in their practice. They gave an example of cases of pneumonia, where they tended to give IV azithromycin, although oral azithromycin could be given (Quote 29, Table 3.7). Another reason that was identified was that treating patients with IV antimicrobials provides some physicians with a feeling of security, particularly with severely ill patients (Quote 30,

Table 3.7). In addition, some participants expressed a belief and offered evidence that IV antimicrobials held additional efficacy over oral antimicrobials (Quote 31, Table 3.7). Furthermore, it was reported that the decision to switch from IV to oral therapy was the responsibility of the ID team (Quote 32, Table 3.7).

3.4.2.4 Recommendations to improve appropriate broad-spectrum antimicrobial prescribing

When asked about recommendations to improve appropriate prescribing of broad-spectrum antimicrobials, the participants identified several areas that they considered had the potential to improve the appropriate prescribing of broad-spectrum antimicrobials. These recommendations are discussed in the following section. Table 3.8 illustrates supporting quotes.

4.4.2.4.1 Education, awareness and training

The participants felt that it would be very useful to have educational sessions about broad-spectrum antimicrobials, such as lectures, seminars and workshops. These sessions may help them in the practice of appropriate prescribing of these antimicrobials (Quote 1, Table 3.8). The participants suggested having educational sessions about the pharmacokinetic and dynamics of broad-spectrum antimicrobials (Quote 2, Table 3.8). They further emphasised a desire for continuous and feasible education sessions that targeted all levels of physician, from juniors to consultants (Quote 3-4, Table 3.8). Some participants, however, felt that general education about antimicrobials was useless as they considered it a waste of their time and they did not want to know about other infections, justifying this point of view by saying that, even if they knew, they could not legally prescribe for any infections that were not under their specialities. They recommended having specific lectures that targeted each department, which would encourage them to attend because that would help them with prescribing in their specialities (Quote 5, Table 3.8). Some participants suggested that there was a need to increase the period of ID training during residency. They reported that there was a variation in the period of the training in ID

compared to other specialities (Quote 6, Table 3.8). Mandatory stewardship courses for every physician, regardless of his or her speciality, was recommended by the participants. This course may help them to gain insight into the importance of the practice of antimicrobial stewardship and prevent the misuse of broad-spectrum antimicrobials, therefore decreasing AMR (Quote 7, Table 3.8). The participants further expressed a need for the incorporation of antimicrobial stewardship education during medical school (Quote 8, Table 3.8). In addition to education about broad-spectrum antimicrobials, awareness about AMR for different levels including physicians, patients and other healthcare professionals, was suggested (Quote 9, Table 3.8).

4.4.2.4.2 Guidelines implementation

Guidelines were reported and considered to be the mainstay of practice. The participants highlighted the need to implement clinically-based local guidelines that should be widely distributed to help and guide them on broad-spectrum antimicrobial prescribing (Quote 10, Table 3.8). They pointed out the importance of updating these guidelines frequently (Quote 11, Table 3.8). The participants further stated a desire to have a quick and easy-to-use reference guide in the form of a phone application, pocket-sized pamphlets or printed charts for the treatment of common infections, causative organisms and the contraindications of using such antimicrobial agents (Quote 12-13, Table 3.8).

4.4.2.4.3 The stewardship programme

The participants expressed a need to implement a stewardship programme that would improve broad-spectrum antimicrobial prescribing. A stewardship programme was referred to as a *"cornerstone"* of practice (Quote 14, Table 3.8). It was suggested

that a stewardship programme should be comprehensive and not just limited to the use of broad-spectrum antimicrobials (Quote 15, Table 3.8). A suggested element of a stewardship programme was to have a multidisciplinary team which reviewed all the antimicrobial therapies in the hospital (Quote 16, Table 3.8). The participants recommended having rounds with the ID teams and the clinical pharmacists. Based on their experience, this type of round was very helpful in deciding the appropriate therapy for patients (Quote 17, Table 3.8). They further suggested that during the multidisciplinary rounds, there was a need to discuss the initiation and the continuation part of the therapy. Such discussions could prevent errors that emerged from miscommunication and, therefore, improve the practice of appropriate broad-spectrum antimicrobial prescribing (Quote 18, Table 3.8).

It was stated that audit and feedback are needed to improve the practice of broad-spectrum antimicrobial prescribing. Audit can be done through programmes to track physician prescribing (Quote 19, Table 3.8). The participants further expressed a need for the initiation of a multidisciplinary committee to provide feedback to them about their prescribing, which could play an important role in minimising unnecessary antimicrobial prescribing (Quote 20, Table 3.8).

4.4.2.4.4 Institution and technology-related recommendations

The participants recommended having a checklist with specific criteria in the system to be filled before starting broad-spectrum antimicrobial therapy (Quote 21, Table 3.8). Another suggestion was to have alerts in the system, after five days, as a reminder to change the antibiotic therapy or carry out an IV to oral switch, if indicated (Quote 22, Table 3.8). Having an application for contact numbers of the physicians covering the services during on-call was suggested as it is sometimes hard to get the number from the system (Quote 23, Table 3.8). Having remote access to the system

was recommended by some participants, when they reported the issues of not having clear information about the patient, while being on-call led them to prescribe antimicrobials which may be unnecessary (Quote 24, Table 3.8). The participants recommended having more clinical pharmacists to support them in broad-spectrum antimicrobial prescribing. They mentioned words such as "*support*", "*cooperation*" and "*help*" to express their need for this service (Quote 25-26, Table 3.8). Some participants highlighted a desire to have a specialised on-board clinical pharmacist who would facilitate easy discussion of issues related to prescribing broad-spectrum antimicrobials (Quote 27, Table 3.8).

Having quick culture results was suggested by some participants. They indicated that having the results more quickly could improve their broad-spectrum antimicrobial prescribing practices (Quote 28, Table 3.8).

Table 3.7: Supporting quotations for Recommendations to improve appropriate broad-spectrum antimicrobial prescribing theme

Subtheme	Supporting quotations
Education, awareness and training	**1.** *"We must have more educational sessions about the use of antibiotics, about dealing with a sick patient, when we should use a broad-spectrum, about the disadvantages of malpractice of the usage of broad-spectrum antibiotics.''* **(Physician 10: ear, nose and throat, 1 year)** ***2.*** *"A knowledge of the medication pharmacokinetics and dynamics can affect the practice. For example, if I know the pharmacodynamics and kinetics of some important medication, I know when to switch to oral, when to give this antibiotic and which antibiotic is better for this disease or the other, for example. If I give an example of MRSA infection, MRSA in the blood is different from MRSA in the tissue, and there are some antibiotics that have, like, a high volume of distribution and can go to the tissue and others stay in the blood as they have less volume of distribution. So, what I think is, when the physician knows more about the medications themselves and has read about them, they will get better with their prescription practice.''* **(Physician 8: internal medicine, 3 years)** **3.** *"These tools have to be feasible and continuous.''* **(Physician 16: internal medicine, 10 years)** **4.** *"It has to be tailored to each institution, to each level, so, you would start by targeting medical students, by giving them didactic lectures, let's say teaching clinical presentations, and then you move on to your residents, junior and senior residents also giving them, again, education and teaching and then you have to move on to higher-level consultants."* **(Physician 13: infectious disease, 10 years)** **5.** *"Education, to be honest, in the medical field, generally, if someone, for example, me, if there is an education in antibiotics, I will consider this waste of time to go there and attend an education session because I'm too busy. We have a lot of patients in the OR [operating room], we are busy in our on-call, busy in our clinics, we spend nine hours in the hospital daily. I don't have time to attend the lecture for 2-3 hours; surgeons will never attend. So, I don't think it will help unless it is departmental …This lecture, this teaching, will help us and we will attend this type of lecture. To attend an antibiotic lecture, I mean titled as antibiotic, no one will attend …For me there is no benefit in knowing the antibiotic treatment for pneumonia because I will never treat pneumonia. Legally, I cannot do it. Legally, I cannot treat pneumonia even if I knew how.''* **(Physician 1: surgery, 8 years)** ***6.*** *"When it comes to the other departments, like internal medicine …They rotate in infectious disease twice during the whole four years …While they rotate in other departments more than us …So, it's a training variance when it comes to antibiotic or infectious disease-related issues as compared to others.''* **(Physician 15: infectious disease, 12 years)** **7.** *"There should be like mandatory stewardship programmes …For example, webinar course.''* **(Physician 13: infectious disease, 10 years)** ***8.*** *"What I think is an important thing for the antimicrobial stewardship and the practice of prescribing a broad-spectrum antibiotic is actually the knowledge before, in the medical school.''* **(Physician 8: internal medicine, 3 years)** **9.** *"Awareness for the physician, for the patient and for the staff.''* **(Physician 4: orthopaedics, 5 years)**

Guidelines implementation	**10.** *"If there is any guideline, I would always go back to it. It says it is a mainstay of practice …If there is an institutional guideline that is backed up by international researchers or updated, I think it would be great.''* **(Physician 11: orthopaedics, 1 year)** **11.** *"I believe that institutions should have a regularly updated guideline regarding certain infectious diseases, so everyone is aware of what is the updated management guidelines for antimicrobial prescribing in this institute.''* **(Physician 5: neurosurgery, 1 year)** **12.** *"Maybe printing out charts, sometimes it can help. I mean, if we have a clear schedule, short and small schedule, of using such antimicrobial agents, the indications of using them, the contraindications."* **(Physician 7: internal medicine, 1 year)** **13.** *"Maybe, like, having, like, a small pocket-sized, like, pamphlet or something, like, really small …Specially for the common infections, like, a quick summary of what you probably need to cover and how …Maybe like making it into a software, like an application that might help, like, make it quick to access for anyone from his phone.''* **(Physician 12: emergency medicine, 9 years)**
The stewardship programme	**14.** *"Stewardship. I think stewardship still needs to be implemented …I think stewardship is the cornerstone."* **(Physician 7: internal medicine, 1 year)** **15.** *"Programmes like stewardship programme, to limit the use, a comprehensive programme is needed, not just restricted to antibiotics or to certain antibiotics. So, that would be a holistic approach and it has to be continuous throughout the year and people should be allocated to this service.''* **(Physician 16: internal medicine, 10 years)** ***16.*** *"We need an antibiotic stewardship programme where we have a dedicated nurse, physician and clinical pharmacist only to review all the antibiotics. We are still lacking this in our institute.''* **(Physician 15: infectious disease, 12 years)** ***17.*** *"I used to work, like, in a big hospital where we did the rounds in the ICU and with the ID team, with the clinic. The MD pharmacist kind of guided us with the treatment. So yes, I think that was helpful and listening to their recommendations was a big factor in successfully treating the patients.''* **(Physician 12: emergency medicine, 9 years)** **18.** *"And they will discuss every patient, whether they need antibiotics or not, they need IV, and what the duration is and if we can downgrade or not. These simple questions kind of improve the quality of care and prescribing of antibiotics."* **(Physician 8: internal medicine, 3 years)** ***19.*** *"Feeding back to people who are prescribing and empowering them …Using technology to track how many antibiotics, so how many appropriate antibiotics, that you've used and how many of the broad-spectrum that you've used causes a side-effect and that side-effect could be the patient you harmed by doing something …You need to report them to the person who prescribed that …So, these can be tracked by some sorts of a programme or something."* **(Physician 16: internal medicine, 10 years)** **20.** *"If we want to improve that, I believe we need team work, we need, like, in each institute, we need a very active committee made up of the pharmacy, the clinical pharmacist and the infectious disease department. A small committee that goes into the hot areas like the emergency department, ICU, internal medicine wards and surgical wards and, if they just roam around*

	and they follow, we need them to follow, the antibiotic prescriptions from different departments and question why you have prescribed something that doesn't work in these conditions, this antibiotic usually works better. So, we need the feedback of our practice from this committee. I believe this will help us a lot in minimising unnecessary antibiotic prescription.'' **(Physician 9: emergency medicine, 16 years)**
Institution and technology-related recommendations	**21.** *"For the ideas to improve the broad-spectrum, sometimes, in our system, there is an ad hoc tool …You have to fulfil these indications. I mean you have to answer the questions before prescribing the broad-spectrum antibiotic. I think this is a good idea."* **(Physician 7: internal medicine, 1 year)** ***22.*** *"I would like to say there should be an alert in our system after one week after using antibiotics, one week or five days. It would say, 'Please think about other antibiotics', just a very short message to think about other antibiotics or other broad-spectrum antibiotics. I think this will help. 'Switch the patient from IV to oral'. I think these messages, if they come, like, in a system, this will prevent a lot of resistance and abuse of antimicrobial agents*." **(Physician 7: internal medicine, 1 year)** **23.** *"It's sometimes very hard to get the number off the system of who's on-call or covering the services in terms of getting the on-call team …By having, like, a specific app, where all the designated numbers are provided in by it.''* **(Physician 2: internal medicine, 1.5 years)** **24.** *"We don't have a laptop or system at home …So I think this issue needs to be improved and I have addressed this issue multiple times: that people who are home on-call, they need to be given the system at home so they can review the patient, see the lab, give the right doses. Sometimes, I just approve the antibiotic without knowing what the creatinine clearance is or whatever this disadvantage we are suffering with is. This is the only thing, if we can access the system at home and review the patient, we can prescribe whatever we think is right.''* **(Physician 14: infectious disease, 5 years)** **25.** *"I would say more staff of clinical pharmacists"* **(Physician 7: internal medicine, 1 year)** **26.** *"We need full, need good support, more than what we have from clinical pharmacists, about antibiotic prescriptions.''* **(Physician 12: emergency medicine, 9 years)** **27.** *"I would say in, like, a couple of words if we are dividing it into wards, that there is a specialised clinical pharmacist that is always available in person with the knowledge to help us out because sometimes we find it challenging to call them up or during on-calls or when we have some trouble. I think it would be very helpful if we had someone on board to always, to always discuss the thing with them.* **(Physician 11: orthopaedics, 1 year)** **28.** *"I think if we have faster results …If we had a super excellent fast way of having cultures right away …If we sent routine cultures and they came out in the same day or early morning the day after, I think it would be perfect. I mean, as routine work, not an emergency, urgent or stat.''* **(Physician 11: orthopaedics, 1 year)**

3.4.3 Mapping of the results to the relevant TDF and COM-B components

The mapping of the results of this study to the relevant TDF and COM-B components has been applied to the BCW to identify intervention functions and policy categories, as outlined in Table 3.9. By recognising the main influential components, the BCW enables the determination of intervention functions and policy categories to provide recommended interventions to improve the appropriate prescribing of broad-spectrum antimicrobials. Several intervention functions and policy categories were recommended by the participants, thus increasing the possibility of acceptability in the future. Some of the recommended interventions are discussed in detail in the Chapter 4.

Table 3.8: Recommended interventions to improve the appropriate prescribing of broad-spectrum antimicrobials using the TDF and BCW

Findings	COM-B	TDF	Intervention functions	Policy categories
Challenges in the diagnosis of some infections leading to the prescribing of broad-spectrum antimicrobials Lack of Knowledge and awareness of the available local guidelines or local AMR rates Not referring to AMR as a consequence of inappropriate prescribing	Psychological capability	Knowledge	Education Training Enablement Restriction	Communication/ marketing Guidelines
The individual patient care and decision-making autonomy leads the decision process without the consideration of the public health risk of AMR		Memory, attention and decision process	Education Training	Communication/ marketing
Desire for audit and feedback on prescribing		Behavioural regulation	persuasion	Environmental/Social planning
Professional confidence in prescribing relying more on experiences than guidelines	Reflective motivation	Belief of capabilities	Persuasion	Communication/ marketing
On-call physicians are often more likely to prescribe broad-spectrum antimicrobials		Social/ professional role and identity	Education Enablement	Environmental/Social planning
Harm to patient when not prescribed broad-spectrum antimicrobial Lack of acknowledgement that inappropriate broad-spectrum antimicrobial prescribing contributes to AMR		Beliefs about consequences	Persuasion Education	Communication/ marketing Guidelines
Fear of harming the patient	Automatic motivation	Emotion	Persuasion	Communication/ marketing
Pressure from senior physicians	Social opportunity	Social influences	Enablement	Communication/ marketing
Remote access to medical records Delay in lab results	Physical opportunity	Environmental context and resources	Environmental restructuring	Environmental/Social planning
Desire for guidelines to assist the prescribing of board-spectrum antimicrobials			Enablement	Guidelines

3.5 Discussion

Qualitative interviews were conducted to explore physicians' views, perceptions and experiences regarding the prescribing practice of broad-spectrum antimicrobials in hospital settings to help optimal prescribing of broad-spectrum antimicrobials. The themes identified were views on broad-spectrum antimicrobials, factors that influence broad-spectrum antimicrobial prescribing, antimicrobial stewardship: practices and barriers and recommendations to improve appropriate broad-spectrum antimicrobial prescribing. This section discusses the major findings from these themes with respect to the literature.

3.5.1 Views on broad-spectrum antimicrobials

Different responses were identified when the participants were asked about their views about broad-spectrum antimicrobials and what they considered inappropriate prescribing. They defined broad-spectrum antimicrobials as *"big guns"* that cover different types of and multiple bacteria. The participants had different points of view concerning their responsibilities in their decision-making with regard to public health as it was identified that some participants were only concerned about an individual patient. It was noticed that their sense of inappropriate antimicrobial prescribing was determined more by missing or not covering a suspected infection than by avoiding negative consequences associated with over coverage, such as *C. difficile* or infection with AMR. There may be many explanations why such negative consequences were underestimated. These antimicrobials-associated negative consequences may have a delayed appearance or there could be many different reasons for them. It would be difficult to relate such consequences to an individual physician's prescribing decision, thus giving them anonymity and offering a lack of accountability. Being unaware of

such negative consequences may also be because physicians do not follow-up patients after discharge; therefore, they would not be aware of their patients' readmission due to *C. difficile* or an AMR infection (Livorsi *et al.,* 2015). Furthermore, the extent to which the physicians are oriented about AMR and the impact of inappropriate prescribing on wider society may also be considered a reason that has led to the underestimation of the negative consequences of inappropriate antimicrobial prescribing. Generally, research has identified that physicians realise and perceive AMR as more of a population health or theoretical problem and, thus, not directly related to individual patient care (Pulcini *et al.,* 2011; Livorsi *et al.,* 2015). A qualitative study using semi-structured interviews was conducted in South Africa, Sri Lanka, and the UK to explore prescribers' perceptions of inappropriate antimicrobial prescribing and the factors that impacted their decisions. The study showed ambiguities in views and thoughts about what was considered to be inappropriate broad-spectrum antimicrobial prescribing in hospital settings. It was concluded that appropriate prescribing judgement is shaped by prescribers' moral, clinical and contextual frames (Tarrant *et al.,* 2020). As recognised in an earlier study, this might differ according to prescriber experience, training and seniority, as well as the degree of concern regarding the influence of patient negative consequences, and the risk of reputational and individual damage (Krockow *et al.,* 2019).

3.5.2 Factors influencing broad-spectrum antimicrobial prescribing

Several factors have been highlighted as influences on physicians' broad-spectrum antimicrobial prescribing. These factors can be divided into three categories: patient-related, physician-related and external factors.

3.5.2.1 Patient-related factors

Several patient-related factors concerning broad-spectrum antimicrobial prescribing were mentioned as being influential in broad-spectrum antimicrobial prescribing. The participants indicated that older age could be a predictor for the decision to prescribe such antimicrobials to hospitalised patients. They reported that elderly patients had a risk of getting antimicrobial-resistant bacterial infections as they may have been exposed to multiple antimicrobials during their lives. This could lead to considering whether to prescribe broad-spectrum antimicrobials or not to prevent them from rapid deterioration. This is consistent with previous research, where physicians stated that the elderly, in particular, patients above the age of 60, influenced their prescribing decisions (Brookes-Howell *et al.,* 2012). This is contrary to another qualitative study, where physicians proposed a lower threshold to prescribe antimicrobials for elderly patients, justifying this by claiming it would avoid any possible worsening of the patient's conditions or subsequent secondary infections (Chan *et al.,* 2019).

Another patient related factor that was reported to influence broad-spectrum antimicrobial prescribing was a patient's medical history. This involves a range of factors, such as co-morbidities, a patient's immune status, previous admissions, long hospital stays, the previous culture, the history of antimicrobial use and the duration of the previous antimicrobial prescription. This is in line with the findings in Chapter 2 of this study, where patients with co-morbidities tended to be prescribed broad-spectrum antimicrobials inappropriately. Similarly, a study that was conducted at KSUMC to determine factors that influence physicians' choice for empiric therapy for UTIs found that age, history of antimicrobial use, co-morbidities and chronic illness have an impact on the decision to prescribe antimicrobials (AlOsaimi *et al.,* 2018). It

is important to note that, in the previously mentioned study, it was a self-reported questionnaire with predetermined and limited choices and that the included physicians were limited to the ED and primary care.

Patients' clinical presentations were considered a major factor. The participants stated that severely sick patients were often treated more aggressively with broad-spectrum antimicrobials, unlike stable patients with a milder infectious disease, who were treated with narrower spectrum medication. A qualitative study was conducted with 40 GPs (general medical practitioners) to explore factors that influenced their decisions to prescribe broad-spectrum antimicrobials, particularly fluoroquinolones, rather than a narrower spectrum antimicrobial. Of the factors that were reported to influence their decisions, it was found that a patient's presenting condition was considered a major factor, whereby GPs justified their decisions to prevent the severe clinical decline of the patient (Wood *et al.,* 2007).

Generally, the findings in this study are directly in line with previous findings of a systematic review of 35 studies that explored factors that influenced physicians' antimicrobial prescribing. In this systematic review, Teixeira Rodrigues *et al.* (2013) reported a direct association between antimicrobial prescribing and patient presenting signs and symptoms, as identified in 14 studies, in addition to co-morbidities, which were described in two studies.

3.5.2.2 Physician-related factors

Physician-related factors were found to be a major influence. The participants addressed several factors that were divided into three sub-categories: information sources in broad-spectrum antimicrobial prescribing, attitudes and perceptions

related to prescribing, and anxiety and fear leading to broad-spectrum antimicrobial prescribing.

The participants reported various sources of information that they used in their prescribing, including textbooks, guidelines, electronic tools and personal experiences. Guidelines are considered to be the standard tool that supports and assists antimicrobial prescribing. However, in this study, not all the participants stated the use of international or local guidelines as a guide in their prescribing practices. Some participants were not even aware of the availability of any local guidelines. Similar findings were reported in other studies, in which participants were not aware of the available hospital guidelines (De Souza *et al.,* 2006; Cortoos *et al.,* 2008). This could be due to autonomy and clinical experience (Armstrong and Ogden, 2006; Charani *et al.,* 2013). Moreover, the unfamiliarity with or unavailability of local guidelines for some cases could be for other reasons. The participants generally agreed that their experiences had an influence on their prescribing. Following career progression through the medical profession, individual experience became a predominant factor in broad-spectrum antimicrobial prescribing decisions. This is in agreement with other studies (Barlow *et al.,* 2008; Skodvin *et al.,* 2015).

In the current study, the participants acknowledged that broad-spectrum antimicrobials are being overused, regardless of the infection type. They reported physicians being generous in prescribing them in settings such as the emergency room, in line with findings from the quantitative study in Chapter 2 of this study. From the literature, previous surveys have reported that physicians agreed that antimicrobials were being overprescribed by other physicians (Abbo *et al.,* 2011; Thakolkaran *et al.,* 2017).

Diagnostic uncertainty was reported to be a factor that influences prescribing. In the current study, the participants reported that being unable to differentiate between viral and bacterial infections or having infectious cases that had similar presentations led them to frequently prescribe a broad-spectrum antimicrobial inappropriately (WHO, 2001; Horwood *et al.,* 2016; Om *et al.,* 2016). In some situations, the participants did not have clear information about the patients. Therefore, they had to assess a clinical condition with limited data, which contributes to diagnostic uncertainty. In the case of diagnostic uncertainty, the participants appreciated the reassurance of prescribing antimicrobials, particularly broad-spectrum antimicrobials. While such a decision is reasonable in the case of a patient with suspected sepsis, the participants also tended to prescribe broad-spectrum antimicrobials in stable patients where narrow-spectrum antimicrobials would be clinically justified. The impact of uncertainty avoidance on antimicrobial prescribing has been identified in other qualitative studies conducted in hospital settings (Björkman *et al.,* 2010; Livorsi *et al.,* 2015) as an approach to prevent the patient's condition from deteriorating (Tonkin-Crine *et al.,* 2011). This may justify the variability in antimicrobial prescribing that is identified between different countries (Borg, 2012; Borg, 2014).

The participants reported several situations where they perceived a risk of not prescribing broad-spectrum antimicrobials. They felt that prescribing these antimicrobials removed their fear and insecurity. This is what Kunin *et al.* (1973) identified many years ago. They termed antimicrobials the "drugs of fear"; this appears to have been identified and confirmed by qualitative research that has explored factors that influence antimicrobial prescribing (Livorsi *et al.,* 2015; Schouten *et al.,* 2007). Livorsi *et al.* (2015) conducted a qualitative study to identify

the factors that influence physicians' antimicrobial prescribing decisions in the inpatient setting. They found that physicians tended to prescribe broad-spectrum antimicrobials to alleviate their fear of missing any unidentified organism(s) (Livorsi *et al.,* 2015). Moreover, a qualitative multicentre study was conducted to explore barriers to appropriate antimicrobial prescribing in patients with CAP. In this study, when the participants were asked about factors that influenced their choice of empirical therapy, they reported that *"everyone feels safe with a broad-spectrum antibiotic"*, and that, "*we are afraid of missing things, afraid to take risks with our patients*." (Schouten *et al.,* 2007).

In this study, what was found was that the perceived risk of not prescribing broad-spectrum antimicrobials led to the prioritisation of instant clinical fears over long-term public health risks. Prior studies have described the implications of such direct pressures in antimicrobial decision-making (Broom *et al.,* 2014; Broom *et al.,* 2017). Such dynamics are considered to be significant in prescribing in hospital settings, strongly favouring antimicrobial over-prescribing over the long-term associated risk to public health.

Overall, physician-related-factors were characterised by three systematic reviews as physicians' fear of adverse consequences, uncertain diagnoses, indifference, complacency, confidence, and responsibility for others (Tonkin-Crine *et al.,* 2011; Teixeira Rodrigues *et al.,* 2013; Warreman *et al.,* 2019). These factors were similar to the majority of the factors identified in the current study.

3.5.2.3 External factors

The participants identified several external factors that exceeded the patient- and physician-related factors. Under the external factors, 13 were described by the participants as influencing their broad-spectrum antimicrobial prescribing practices.

They reported that senior physicians had a strong impact on their prescribing decisions. Qualitative studies from the UK, USA, Belgium, Norway and Ireland have also recognised seniors as a significant contributing factor, overruling the impact of guidelines and local policy (De Souza *et al.,* 2006; Cortoos *et al.,* 2008; Charani *et al.,* 2013; Livorsi *et al.,* 2015; Skodvin *et al.,* 2015). According to current findings, attempts to improve antimicrobial prescribing in inpatient settings have to acknowledge the influence of the decision-making hierarchy. Junior physicians are going to struggle in following the guidelines and policies if their recommendations are not supported by their seniors.

The influence of ID specialists was reported by the participants. However, some reported that not following the ID specialists' advice indicated that they are more familiar with and responsible for their patients' cases. A qualitative study described a "prescribing etiquette", where senior physicians did not follow the guidance and recommendations from the ID specialists (Charani *et al.,* 2013). In contrast, in the current study, some participants viewed the ID specialist as the superior adviser. Similar findings in a Swedish study showed that all physicians emphasised the importance of ID specialists' support in antimicrobial prescribing (Björkman *et al.,* 2010). Given that the participants recognised the importance of the advice, and several studies showed that ID specialists were identified as improving the appropriate prescribing antimicrobials, these specialists have to be involved in multidisciplinary antimicrobial stewardship teams.

Some participants stated that their colleagues had an impact on their broad-spectrum antimicrobial prescribing, especially if they had experience in antimicrobials and microbiology. Similar findings from qualitative studies showed that peers might have a greater impact on antimicrobial prescribing than policy and guidelines (Charani *et al.,* 2011).

It was identified that there was a reluctance by physicians to provide feedback to other colleagues on their prescribing decisions. A systematic review of nine studies that identified antimicrobial prescribing behaviour in in-hospital settings found in six studies physicians reluctant to critique their colleagues antimicrobial prescribing (Warreman *et al.,* 2019). This reluctance was reported as an indication of a lack of collaboration to tackle the problem of AMR. Moreover, the physicians' desire to maintain a good relationship with their colleagues was viewed as a higher priority (Livorsi *et al.,* 2015). Similarly, in this study, reluctance to provide feedback and critique other colleagues' practices were reported to maintain a positive work relationship.

In the present study, there were different experiences with clinical pharmacy services. Although seen as being helpful, several issues were reported to have restricted the utilisation of clinical pharmacists, such as the availability and the role of the clinical pharmacists. However, limited involvement of the clinical pharmacists in ward rounds and in the decision to prescribe board-spectrum antimicrobials were the major reported issues. The involvement of a clinical pharmacist leads to an increase in the rate of appropriate antimicrobial prescribing (Oxman *et al.,* 2015; Van *et al.,* 2020). Clinical pharmacists' power to support the decision of broad-spectrum antimicrobial prescribing and participate in clinical rounds could improve appropriate broad-spectrum antimicrobial prescribing practices.

Antimicrobial shortages were reported as a factor that impacts prescribing. The participants reported the impact of the shortage of both narrow-spectrum and broad-spectrum antimicrobials. Such shortages limited their antimicrobial options, therefore, exposing the patients to risk in cases of antimicrobial resistance and the general population to risk in the form of the use of broad-spectrum antimicrobials as a consequence of there being a narrow-spectrum shortage. Antimicrobial shortage as a factor that influences antimicrobial prescribing, to our knowledge, has not been explored, which highlights the need for further study.

Several studies have identified that antimicrobial cost has an influence (Carthy *et al.,* 2000; Krishnakumar and Tsopra, 2019). In the current study, some participants noted how cost was a factor that influenced prescribing, while others said they did not consider it. This could be explained by practicing in a governmental hospital, where physicians are not oriented by the cost of treatment. A study that evaluated cost-consciousness among physicians practising in different settings in the KSA found that physicians were not very confident regarding their familiarity and knowledge about healthcare costs (Al-Omar, 2020).

In this study, the participants reported the influence of microbiology tests on their prescribing practices. They stated several factors associated with the microbiology test results, including the length of time needed to get the results, particularly during the weekend, and they got information related to the results whereby they had to phone the laboratory instead of having the information stored in the system. Skodvin *et al.* (2015) who investigated factors impacting physicians' antimicrobial prescribing practice, reported that physicians highlighted the impact of microbiology test results on their practices and raised a concern about delayed results (Skodvin *et al.,* 2015). Action to enhance the delivery of the results, both in timing and means of reporting,

is important as it could enhance decision-making regarding broad-spectrum antimicrobial prescribing. Further study is needed to explore issues related to results timing and reporting to identify possible interventions that could improve the situation. Moreover, research has found that antimicrobial stewardship teams may improve the time to influence appropriate antimicrobial therapy through close tracking of microbiological results (Huang *et al.,* 2013; Pogue *et al.,* 2014). Thus, the establishment of such teams is of great importance.

A lack of physicians' trust in negative microbiology results was also reported where some participants stated that, in some cases, they got negative results, while the patient was clearly infected. A study conducted by Hamilton *et al.* (2020) found that negative results had little influence on decisions concerning antimicrobial de-escalation. They concluded that, in antimicrobial stewardship, to increase the involvement of diagnostic microbiology, there needed to be an improvement in the predictive negative value of the microbiology results (Hamilton *et al.,* 2020).

The hospital antibiogram was viewed as a factor that might influence broad-spectrum antimicrobial prescribing practice. In the present study, some participants stated the use of the hospital antibiogram in their prescribing practices, while others reported not considering it. Several issues arise when not considering the antibiogram. Being unfamiliar with the hospital antibiogram leads to issues related to accessibility and the integration of the antibiogram in their practices. Similar findings were found in a previous study that was conducted in a teaching hospital, where the majority of participants reported that they did not know how to access the hospital antibiogram and they had never used it (Mermel *et al.,* 2008). Hospital antibiograms are commonly used to promote the demand for improving antimicrobial prescribing practices. It may impact antimicrobial prescribing (Lacy *et al.,* 2004) where it

encourages physicians to prescribe appropriate empiric antimicrobials. Therefore, efforts to provide more education about antibiograms may be desired to enhance their utilisation and effectively impact antimicrobial prescribing decisions. In addition, antibiograms can be used as a tool to assist ASPs (Dellit *et al.,* 2007).

3.5.3 Antimicrobial stewardship: practices and barriers

ASP is one of the strategies to prevent AMR. ASPs are well recognised as improving antimicrobial prescribing practices. Several barriers to appropriate broad-spectrum antimicrobial prescribing have been identified. These include the practice of not taking cultures before starting the therapy, problems with de-escalation and with IV to oral switch.

It is crucial to obtain a culture before the initiation of antimicrobial therapy. This can improve the possibility of identifying the microorganism in question (Rojo, 2006). It is evident that taking blood cultures after the initiation of antimicrobial therapy leads to a significant loss of organism identification (Kirn and Weinstein, 2013). The present study reveals a range of reasons and barriers to taking cultures before starting the broad-spectrum antimicrobial therapy. Some of these included having severely ill patients, patients with a previous culture history, facing difficulty or delay in getting a sample from a patient, a lack of communication between the teams, and the nurses' practice of not taking a sputum culture. Similar findings were recorded in a qualitative study that was conducted in three hospitals to investigate the barriers of optimal antimicrobial prescribing where healthcare professionals reported several barriers related to not taking a culture before the initiation of the antimicrobial therapy (Schouten *et al.,* 2007). Among these barriers, they reported the nurses' lack of familiarity and awareness, a lack of prescribers' adherence to guidelines, a lack of

communication and coordination between healthcare professionals and a lack of motivation (Schouten *et al.,* 2007).

The de-escalation approach is suggested to avoid the development of bacterial resistance (Gonzalez *et al.,* 2013). This approach involves changing the empiric broad-spectrum antimicrobial therapy to a narrower spectrum one following the identification of positive microbiology results. It was found that this has no negative impact on a patient's clinical condition (Gonzalez *et al.,* 2013). A qualitative examination that explored the barriers to de-escalation of antimicrobial therapy found that physicians felt uncertain about this after obtaining the culture results, especially for severely ill patients, which was justified by their attitude of "never change a winning team". Moreover, organisational constraints were identified where there was a delay in obtaining the culture results. When a patient's condition is improved with the initial therapy, de-escalation is postponed until the senior's rounds, which leads to further delay in de-escalation, thus keeping the patient longer than required on broad-spectrum antimicrobials (Schouten *et al.,* 2007). The present study found similar findings, in addition to the unavailability of the narrow antimicrobial sometimes having side-effects related to the sensitive antimicrobial or the pharmacokinetics of the antimicrobial that makes it unsuitable for such organs like the CNS. All of these factors contribute to the practice of not considering de-escalation to narrow-spectrum antimicrobials.

The most common reason for IV to oral switch was for discharge; it was not common practice for hospitalised patients. The reasons for an IV to oral switch were multifactorial, including patient preferences, the desire for oral intake in surgical patients and mobility-related issues in orthopaedic patients. Nevertheless, most of them were not underpinned from an antimicrobial perspective. When asked about

the reasons for not switching IV to oral when indicated, several reasons were identified. These included the habit of maintaining the patients on IV antimicrobials, the feeling of security, particularly of ill patients, the belief that IV forms are more effective than oral forms and the opinion that changing the therapy from IV to oral is the responsibility of the ID physicians. The false belief among physicians that IV antimicrobials have additional efficacy and potency over oral antimicrobials is likely to impact their practice of not considering an IV to oral switch for hospitalised patients is based on a qualitative study that used semi-structured interviews with 20 physicians to identify barriers to IV to oral switch (Broom *et al.,* 2016). Another reported barrier of IV to oral switch is the impact of the medical hierarchy, where junior physicians are not comfortable or confident enough in switching IV antimicrobials to the oral dosage form. The unavailability of the senior physician in the daily rounds leads to a delay in the decision on antimicrobial therapy. Therefore, the duration of IV antimicrobials is unnecessarily prolonged (Broom *et al.,* 2016).

3.5.4 Recommendations to improve appropriate broad-spectrum antimicrobial prescribing

To improve the appropriate prescribing of broad-spectrum antimicrobials, several recommendations were made by the participants. These included education, awareness and training for physicians about appropriate broad-spectrum antimicrobial prescribing and antimicrobial stewardship. These recommendations are in line with the Saudi national action plan for minimising AMR (MOH. 2017a). The participants recommended education about appropriate antimicrobial prescribing (e.g., lectures, seminars and workshops). This finding is in line with previous research that suggests that prescriber education about appropriate antimicrobial use could improve appropriate antimicrobial prescribing (Yates *et al.,* 2018; Saleem *et al.,*

2019). Education is an important component of any programme aimed and implemented to impact prescribing practices and behaviours (Pulcini and Gyssens, 2013). It is evident that the education-based ASPs have led to an enhancement in antimicrobial prescribing practice and a reduction in inappropriate antimicrobial use, although there were no implemented restrictive measures (Cisneros *et al.,* 2014). Educational sessions regularly occur in the form of single or multiple seminars or courses in a didactic lecture structure, recognised by many healthcare professionals (Satterfield *et al.,* 2020). Continuous education on appropriate broad-spectrum antimicrobial prescribing was recommended by the study participants. The continuous and frequent educational sessions seem to have a greater impact than having a single education event annually, in terms of improving the appropriate use of antimicrobials (Chazan *et al.,* 2007). It has been shown that there was a reduction in broad-spectrum antimicrobial use among a continuous education group more than a reduction in an annual group: 20% vs 16.5% reduction, $p<0.0001$ (Chazan *et al.,* 2007). Another suggested method of education was one-on-one inter-professional discussions. Such a method has proved its usefulness in clinical practice (Foral *et al.,* 2016). It has been suggested that education about appropriate broad-spectrum antimicrobials prescribing practices and antimicrobial stewardship must be involved in the medical curriculum, consistent with the WHO, who recommend and highlight the value of medical student education about antimicrobial prescribing (WHO, 2012). A recent study that explored undergraduates' knowledge about antimicrobial stewardship in the KSA showed that medical students have a fair knowledge and highlighted the need to incorporate such teaching in the medical curriculum (Alsaleh *et al.,* 2020). The participants also endorsed that inappropriate use of broad-

spectrum antimicrobials can be minimised by raising the awareness of the public, the physicians and all healthcare professionals.

Reporting physician prescribing and providing feedback was recommended to improve appropriate prescribing. Recommendations for reporting prescribing to physicians involved providing information regularly (e.g., quarterly, monthly) in an accessible electronic format. A similar recommendation had been previously reported in other studies (Yates *et al.,* 2018), and it was found to be effective (Gerber *et al.,* 2014).

The implementation of local guidelines supported by local resistance patterns was recommended by the participants. Such guidelines have been found to optimise appropriate antimicrobial prescribing. It is evident that guideline implementation has been shown to increase the appropriateness of empirical antimicrobial therapy (Ibrahim *et al.,* 2001; Hauck *et al.,* 2004) and improve the use of narrow-spectrum antimicrobials (Marrie *et al.,* 2000; Jenkins *et al.,* 2011; Newman *et al.,* 2012).

Receiving quick culture results was suggested by the study participants. It was noticed during the interviews that participants claimed they sometimes did not de-escalate due to late test results as sometimes they arrived when the patient had only one day to finish their antimicrobial therapy course. Therefore, the physician decided to complete the course without de-escalation of therapy. Quicker microbiology results may have an impact on limiting and decreasing unnecessary exposure to empirical antimicrobial therapy (Hamilton *et al.,* 2020). The adoption of rapid diagnostic test in combination with ASP have been shown to reduce time to appropriate therapy and unnecessary antimicrobial use and optimise clinical and economic outcomes (Clerc and Greub, 2010; Bauer *et al.,* 2014; Reuter *et al.,*2019).

The participants recommended implementing a checklist in the system to be filled before starting the broad-spectrum therapy. It has been found that the implementation of an antimicrobial checklist improved appropriate antimicrobial prescribing (van Daalen *et al.,* 2017). A reminder to either de-escalate or IV switch was also another suggestion. Such a reminder has proved its effectiveness in optimising antimicrobial prescribing and promoting an earlier IV to oral switch, which leads to a decrease in the duration of the IV therapy (Beeler *et al.,* 2015; Berrevoets *et al.,* 2017). The participants also suggested and justified the need to have access to the system while they were out of the hospital. They felt that they tended to give broad-spectrum antimicrobials where it may not be indicated due to the lack of a clear picture about the patient and being uncomfortable with information given over the phone.

Expanding the clinical pharmacy service, implementing comprehensive antimicrobial stewardship and not only restricting broad-spectrum antimicrobial prescribing, and enhancing multidisciplinary team communication were recommended to improve the practices of appropriate broad-spectrum antimicrobial prescribing. From the literature, multidisciplinary ward rounds have been identified as a means of reducing the duration and use of broad-spectrum antimicrobials without increasing mortality (Rimawi *et al.,* 2013).

Generally, the study findings show some degree of physicians' awareness that may not justify the high rate of inappropriateness identified in DUR in Chapter two. This could be due to the time gap between the two studies. Since the interviews were conducted in 2020 and the drug utilisation study reported in Chapter 2 was conducted in 2016/2017 and as reported in Chapter 1, in September 2017 the

antimicrobial stewardship was established which could be a reason for the degree of awareness identified in the qualitative study.

3.6 Conclusion

This study has identified four main themes that are related to physicians prescribing of broad-spectrum antimicrobials in a hospital setting. The themes identified were views on broad-spectrum antimicrobials, factors influencing broad-spectrum antimicrobial prescribing, antimicrobial stewardship, and practices and barriers and recommendations to improve appropriate broad-spectrum antimicrobial prescribing. Under the perception of broad-spectrum antimicrobials and what was considered inappropriate prescribing, it was found that the participants' sense of inappropriate antimicrobial prescribing was determined more by missing or not covering a suspected infection than by avoiding negative consequences associated with over coverage, such as *C. difficile* or infection with AMR. A lack of general agreement among participants about what was considered inappropriate prescribing poses a challenge for antimicrobial stewardship efforts to be implemented in the KSA if these findings are more widely applicable. Therefore, ASPs should target clinical, contextual and moral frames.

The study identified a variety of factors that impacted broad-spectrum antimicrobial prescribing in a hospital setting, of which many may lead to inappropriate prescribing. These factors were divided into three categories: patient-related, physician-related and external factors. The patient factors include age, medical history and clinical presentation; the physician-related factors were relevant to the physicians' source of information and their attitude towards prescribing, and the external factors were related to communication between multidisciplinary teams and the institutional

context. This points to the desire for a multifaceted approach to consider the factors that drive inappropriate prescribing practices.

Taking a culture before the initiation of the antimicrobial therapy, de-escalation of the antimicrobial therapy according to the culture and sensitivity results and the IV to oral switch are essential elements of stewardship intervention as they may reduce the duration of the therapy as well as the length of hospital stay, thus reducing overall healthcare-associated costs. This study identified that broad-spectrum antimicrobial prescribing is not optimal and determined the key drivers of inappropriate prescribing which could enable the development of accessible and applicable programmes. Finally, the study findings highlight the need for quality improvement interventions in the broad-spectrum antimicrobial prescribing areas. Moreover, it provides information that supports the design of interventions that are tailored to a particular setting.

4. Chapter 4: Overall discussion

Overview: This final chapter consists of a summary of the main quantitative and qualitative findings of the research, an overall discussion, the research strengths and limitations, the contribution of this research to knowledge, followed by recommendations and suggestions for practice and further research.

4.1 Summary of research main findings

- The three broad-spectrum antimicrobials were commonly used for empiric indications and more than half of the prescriptions were ordered by medical residents.
- For the practice of taking a culture before starting antimicrobial therapy, culture and sensitivity tests were ordered in 78.6% of cases before prescribing antimicrobials.
- Assessment of the appropriateness of broad-spectrum antimicrobials showed that in 43.5% of cases, they were inappropriate. The three most common reasons for inappropriateness for empiric prescriptions were the use of broad-spectrum where a narrow-spectrum antimicrobial would have been enough, prescribing antimicrobials without taking a culture and the failure to de-escalate the therapy where it was indicated according to the culture and sensitivity results.
- The qualitative interviews revealed that physicians' sense of inappropriate antimicrobial prescribing was determined more by missing or not covering a suspected infection than by avoiding the negative consequences associated with over coverage, such as *C. difficile* or infection with AMR.

- The study identified a variety of factors that may impact broad-spectrum antimicrobial prescribing in a hospital setting. These factors were divided into three categories: patient-related, physician-related and external factors.
- The research identified the barriers to antimicrobial stewardship practices, including failure to take a culture before starting the therapy, reluctance to de-escalate the therapy and to complete an IV to oral switch.
- In response to recommendations to improve the appropriateness of prescribing of broad-spectrum antimicrobials, several recommendations were made by the physicians, including education, training, audit, guidelines implementation and other institutional-related suggestions.

4.2 Overall discussion

Before the start of this study, several gaps were identified in the literature concerning the knowledge related to physicians' broad-spectrum antimicrobial prescribing for adult hospitalised patients in the KSA. This motivated the initiation of this research. This is particularly relevant since the KSA is experiencing increasing levels of AMR and the development of rare and novel MDR strains. This may lead to the spread of these rare MDR strains to other regions across the world considering that the KSA hosts over nine million pilgrims and visitors throughout the year to the holy city of Mecca for Umrah and Hajj. A further encouragement to conduct the study was the concern of a consultant clinical pharmacist (AM) that broad-spectrum antimicrobials were being overused. Inappropriate prescribing of broad-spectrum antimicrobials, as discussed in Chapter 1, has been associated with many risks, including AMR, *C. difficile* infection and mortality.

The aim and objectives of this research have been reached using a mixed methodology approach. The first part of this thesis was a DUR which explored broad-spectrum antimicrobial prescribing by physicians for adult hospitalised patients, assessed the appropriateness of broad-spectrum antimicrobial prescribing, identified prescribing characteristics that were associated with inappropriate prescribing and identified the association between appropriate prescribing and patients' length of hospitalisation. The second part was qualitative research that identified and explored physicians' perceptions and views about broad-spectrum antimicrobials, factors that may influence physicians' broad-spectrum antimicrobial prescribing, barriers to appropriate prescribing and the physicians' recommendations to improve appropriate prescribing.

Overall, of the three studied broad-spectrum antimicrobials, piperacillin/tazobactam was the most commonly prescribed, with 3,208 (64.1%) prescriptions, followed by meropenem with 1,021 (20.4%). The most common indication for prescribing carbapenems and piperacillin/tazobactam was pneumonia, followed by sepsis. In this study, in terms of the initiation and contribution of the therapy, it was found that the overall appropriate use of the three broad-spectrum antimicrobials was 56.5%. The most common reason given for the assessment of inappropriateness for empiric prescriptions was that the spectrum of activity was too broad. The unnecessary use of broad-spectrum antimicrobial as the initial selection is of concern and should be avoided as it is associated with an increased risk of AMR, adverse effects, opportunistic infections and increased healthcare costs (Tamma *et al.,* 2017). The second reason prescribing was considered inappropriate was prescribing occurred without taking a culture first and the third reason was identified as the failure of suitable de-escalation of the therapy. These practices may lead to an increase in

healthcare costs and the development of AMR. These findings necessitate an exploratory study to identify reasons for such inappropriate prescribing practices, using the qualitative methodology explained in Chapter 3.

During the interviews, there was a lack of consensus among participants about what they considered inappropriate prescribing practices to be. Moreover, it was found that the physicians' sense of inappropriate antimicrobial prescribing was determined more by missing or not covering a suspected infection than by avoiding the negative consequences associated with over coverage, such as *C. difficile* or infection with AMR. This could be for several reasons, as explained in Chapter 3, including moral, clinical and contextual frames. These findings pose a challenge for antimicrobial stewardship efforts. Thus, to implement successful intervention, such as ASPs, all clinical, contextual and moral frames should be considered.

The findings reveal that broad-spectrum antimicrobial prescribing process is complex in hospital settings and is influenced by several and diverse factors. These factors fell into three main contexts: patient-related, physician-related and external factors. Under these factors, patient co-morbidities and clinical presentations, the unavailability of local guidelines, physician autonomy, the medical hierarchy, prescribing habits, and several institutional constraints that have been addressed in Chapter 3 were found to be the major contributing factors that drive inappropriate decisions to start broad-spectrum antimicrobials. These point to the desire for a multifaceted approach that considers drivers of inappropriate prescribing practices.

Taking a culture before the initiation of the antimicrobial therapy, de-escalation of the antimicrobial therapy according to the culture and sensitivity results and IV to oral switch are essential elements of antimicrobial stewardship intervention as they may reduce the duration of the antimicrobial therapy as well as the length of hospital

stay, thus reducing overall healthcare-associated costs. The findings reveal that these practices were suboptimal as identified from the DUR study explained in Chapter 2. Moreover, reasons for these suboptimal practices were reported by participants as including the patients' condition, a lack of communication and coordination between the teams, physician uncertainty and beliefs, and organisational constraints.

Overall, this study has identified that broad-spectrum antimicrobial prescribing is not optimal and has determined the key drivers of inappropriate prescribing practices. Managing these practices and behaviours through suitable and effective intervention is the follow-up step in this process. This could be achieved through the use of the behaviour change wheel (BCW) (Michie *et al*., 2014) as a tool to design and develop interventions to improve broad-spectrum antimicrobial prescribing. Recommended interventions will be discussed in section 4.5.

4.3 Strengths and limitations

This thesis adopted a mixed method research approach, using the explanatory sequential approach as a method of triangulation, which is the use of different sources of data or multiple methodological approaches to enhance the validity of a piece of research (Salkind, 2010), to obtain an in-depth understanding and exploration of physicians' views and perception of broad-spectrum antimicrobial prescribing and to increase the reliability and validity of the research findings. The use of this method has achieved the thesis aim and objectives. The method, data analysis and the results of this research have been reported and explained in detail to allow adoption of the research methodology and an assessment of the transferability of the research findings.

4.3.1 Quantitative study

To the best of the knowledge of the researcher, this is the first study in the Gulf countries that has evaluated the appropriateness of prescribing three broad-spectrum antimicrobials, including all hospitalised adult patients in a tertiary care hospital. The strength of the study was the large sample size and the inclusiveness of all the adult hospitalised patients. To allow a comparison of the obtained quantitative results with other studies in the literature, both percentages and DDD were used to report the units for antimicrobial prescribing. The study had several limitations. The inherent limitation lies in employing a retrospective study design, even though this is a common and acceptable method for evaluating the appropriateness of antimicrobial therapy in hospital settings. In addition, as the assessment did not occur at the time of prescribing, the degree of accuracy of interpretations of information extracted from the hospital electronic database in the assessment of prescriptions relies on how much information had been recorded. Although, the electronic chart did capture comprehensive information on the course during hospitalisation and the physicians' notes and reports on microbiological findings. Moreover, to compare between appropriate prescribing and LOS, we were unable to account for all the factors increasing LOS in hospitalised patients, such as severity of illness. A future plan is to see whether a prospective study could be undertaken to capture illness severity in an attempt to better understand disease severity on prescribing patterns. It could also be used to better qualify negative outcomes e.g. *C difficile* rates.

A further limitation is that the study was conducted in a single academic tertiary care hospital, which may limit the generalisability of the findings. However, hospitals in the KSA are operated in a similar manner. It is very common for physicians to undergo rotational residency training in all hospitals in the KSA. It is considered a referral

hospital where patient may be referred from any hospital over the country where there are broad population similarities. It should be noted, though, that all hospital wards were included, which ensured representative results being recorded across a range of disciplines.

Moreover, a lack of local guidelines prevailed. Hospital antibiograms were considered in the evaluation, involving the use of international guidelines. Therefore, the results can be compared with those in the literature.

4.3.2 Qualitative study

To the knowledge of the researcher, this is the first qualitative study to explore physicians' views and perceptions about broad-spectrum antimicrobials, and to identify factors influencing broad-spectrum antimicrobial prescribing practices in the KSA. The method of data collection, which was through semi-structured interviews, allowed for the understanding of the physicians' viewpoints through encouraging them to speak and express their opinions and perceptions about broad-spectrum antimicrobial prescribing within their hospital context. The study was validated in terms of the quality of the collected data and the data analysis, where it was reviewed by an external researcher who is an expert in the field. The trustworthiness of the qualitative study was also enhanced by using Braun and Clarke's checklist (Braun and Clarke, 2006) and the COREQ guideline (Tong *et al.,* 2007), as described in Chapter 3.

The study had some limitations. It was conducted in a single tertiary care hospital; similar arguments could be made about the qualitative research undertaken at the single tertiary care hospital as described above in section 4.3.1. While the participants have varying levels of seniority and thematic saturation was identified by 16 interviews, there is a possibility that minority views and perceptions may have been missed due to being unable to interview physicians from other specialities, like

intensive care or OBG. A broader exploration of physicians' views and perceptions from different hospitals, including private hospitals, would be valuable. Moreover, potential bias is possible as interested physicians may have been more likely to participate in the study. Finally, there is the question of bias associated with self-reporting. Although this bias has been minimised by the use of telephone interviews instead of face-to-face interviews, there is a risk of social desirability bias, where participants provide a more socially acceptable response (Collins *et al.,* 2005; Althubaiti, 2016). During the interview, it became evident that participants felt comfortable and they became aware that their prescribing practices were not being assessed or judged. Their statements that broad-spectrum antimicrobials are prescribed inappropriately is evidence of that.

4.4 Research contribution to knowledge

The research presented in this thesis has added to the knowledge about the utilisation patterns of broad-spectrum antimicrobials, the quality of physicians' broad-spectrum antimicrobial prescribing for adult hospitalised patients, the understanding of physicians' views and perceptions about AMR and broad-spectrum antimicrobials, the different levels of factors that may impact physicians' broad-spectrum antimicrobial prescribing practices for adult hospitalised patients in the KSA, the barriers to antimicrobial stewardship practices and the physicians' recommendations to improve the appropriateness of broad-spectrum antimicrobial prescribing.

4.5 Recommendations

4.5.1 Education and multi-professional approach

Based on findings from the DUR, the qualitative study and the use of the BCW, a key recommended intervention might be an educational intervention that addresses the knowledge and education gaps and would be an initial step. An example would be sessions providing CMEs, seminars, conferences and antimicrobial stewardship training courses. As identified in Chapter 2, broad-spectrum antimicrobials were commonly prescribed by junior physicians, while, findings from the qualitative study, explained in Chapter 3, found that junior physicians followed instructions from their seniors when prescribing broad-spectrum antimicrobials. Therefore, educational interventions should target both senior and junior physicians. Moreover, during the interviews, when physicians were asked to provide recommendations that could help and support them to optimise their prescribing practices, they recommended having a continuous stream of education on the procedure. Another suggested method of education was through one-on-one inter-professional discussions. Such a method has proved its usefulness in clinical practice (Foral *et al.,* 2016). An educational approach is also important for the dissemination of a local prescribing guideline, described in more detail in the following section. Another approach could be that teaching hospitals and higher education institutions are required to introduce the principle of antimicrobial stewardship into the undergraduate medical curriculum (Alsaleh *et al.,* 2020; Tripathi *et al.,*2020).

Multidisciplinary team decision-making may also considered as part of the multifaceted intervention. The concept of a multidisciplinary team in the KSA, where there is parity of opinion or professionalisms, may be different than other countries. In Chapter 3, physicians' autonomy was identified and therefore that may impact the

dynamic of a multidisciplinary team which might impact the prescribing patterns (Alghamdi *et al.,* 2019). There are still cultural/ professional barriers that is still need to be developed more.

4.5.2 Implementation of local guidelines

One of the multifaceted interventions should be the implementation of antimicrobial prescribing guidelines with the use of local resistance data, particularly those that include the use of broad-spectrum antimicrobials. As an initial step, the development of respiratory and urinary tract infections guidelines is recommended as these were of the most common diagnosis that indicates the use of broad-spectrum antimicrobials in this study.

In Saudi hospitals, lack of adherence to guideline was consider a barrier to ASP implementation. This could be due to three major factors. First, physicians unaware of the existed guidelines. Second, the guidelines are not accessed electronically. Third, poor implementation and enforcement of these guidelines (Alghamdi *et al*., 2019). Therefore, these guidelines should be implemented with multidisciplinary input from ID physicians, clinical pharmacists with infectious disease backgrounds and clinical microbiologists. Moreover, they should be flexible, accessible and tailored to the local practice context. In addition, there is a need to increase the physicians' awareness and uptake of these guidelines.

Enhancing the logistics of care should be also considered as part of the intervention to encourage appropriate antimicrobial prescribing. This includes providing remote access to physicians so they can review medical records during on-call periods. Another improvement could be reducing the time needed to get lab results which may help de-escalation of therapy.

As mentioned in chapter 2, the current study shares some similar objectives to the study by Robson *et al.* (2018), however, this journey is at the first start as we developed some baseline information, we might then be able to increase the sophistication like Robson *et al.* (2018). Table 4.1 shows the comparisons of key results and recommendations between Robson *et al.* (2018) and the current study.

Table 4.1: Comparing Robson *et al.* (2018) study to the current study

Robson *et al.* (2018)	**Current study**
National institution ➢ 32 acute Scottish hospitals ➢ 15 health boards	Single tertiary hospital
National antimicrobial prescribing policy	No national antimicrobial prescribing policy
Carbapenem restriction and carbapenem sparing agents policies are in place	No restricted carbapenem policies at the start of the study
To evaluate interventions that are in place	To get baseline information before starting interventions
Key results: • Good compliance with local prescribing policies • Decreased usage of carbapenems and piperacillin/tazobactam • Lack of confidence in de-escalating therapy • Poor documentation of a review or stop date • Low use of carbapenem-sparing antibiotics	**Key results:** • 43.5% of the prescriptions were inappropriate according to an international guideline • Failure to take a culture before starting the therapy • Reluctance to de-escalate the therapy and to complete an IV to oral switch
Recommendations: • There is a need to feature carbapenem-sparing antibiotics in local guidelines • Development of a system to allow a formal review process by infection specialists or/and the clinical team • Development of a national standard and toolkit to support review of IV antimicrobial therapy	**Recommendations:** • Education and multi-professional approach • Implementation of local guidelines

Finally, the findings of this research were shared with AUV committee at KSUMC. As a result, the committee have started to develop respiratory tract infections guidelines. Moreover, it should be shared with the KSUMC infection control department and all physicians as a positive reinforcement of physicians' broad-spectrum antimicrobial prescribing practices. Further, it will be shared with the national action plan committee to compact AMR.

4.6 Future research

This research raised a number of ideas that need further investigation. Further research could be the following:

- Conduct a DUR in other governmental hospitals in different regions, as well as in private hospitals, to gain a broader insight into the use of broad-spectrum antimicrobials across the Kingdom.
- Conduct a well-designed study that looks for further factors that may impact the LOS, such as information about the severity of infections and illnesses, to determine the benefit of appropriate broad-spectrum antimicrobials in hospitalised patients.
- Design and implement different interventions such as guideline implementation and education to improve broad-spectrum antimicrobial prescribing.
- Evaluate the impact of the implemented interventions on drug utilisation, antimicrobial cost, and length of hospital stay.
- Conduct a qualitative study that investigates physicians' prescribing behaviour over a larger number of physicians from different specialities and

different Saudi hospitals, perhaps using a different qualitative methodology and analysis.

- Explore the views and perceptions of other healthcare professionals, including pharmacists, clinical pharmacists and nurses, concerning broad-spectrum antimicrobials and AMR.
- Identify factors that influence the practices of taking culture from the nursing perspective.

4.7 Conclusions

This thesis aimed to explore how physicians prescribe broad-spectrum antimicrobials for adult hospitalised patients in the KSA using a mixed methods approach to provide recommendations to improve the appropriateness of prescribing.

Results from the DUR showed a high rate of inappropriate broad-spectrum antimicrobial prescribing in terms of initiation and continuation of the therapy. The three most common reasons for inappropriate empiric prescriptions were spectrum of activity was too broad, the practice of prescribing broad-spectrum antimicrobials without taking a culture before the therapy and the failure to implement suitable de-escalation of the therapy. These inappropriate practices could lead to increased risk of AMR, opportunistic infections, adverse effects and increased healthcare costs.

Findings from qualitative study identified a variety of factors that impact broad-spectrum antimicrobial prescribing in a hospital setting, of which many may lead to inappropriate l prescribing. Of these factors, the most common were patient medical history and clinical presentation; physician-related factors related to their sources of information and their attitude towards prescribing; and external factors related to communication with multidisciplinary teams and the institutional context. The

qualitative study identified that broad-spectrum antimicrobial prescribing is not optimal, which supports the DUR findings presented in Chapter 2, and determined the key drivers of inappropriate prescribing which could enable the development of accessible and applicable practices.

This research has added to the insight and knowledge regarding physicians' broad-spectrum antimicrobial prescribing for adult hospitalised patients. Moreover, it has contributed to strategies and recommendations to improve appropriate prescribing through the use of a BCW. It is important to highlight that no framework was used when designing the qualitative study to allow for the emergence of unprompted and unanticipated matters during the interviews, it was only considered to provide recommended interventions to improve broad-spectrum antimicrobial prescribing.

The findings that have been found in KKUH confirms and reflects some of the existing data from an international perspective knowing that KSA is a very high prescribing country (Klein *et al.*,2018; WHO, 2021) This reinforces the fact that there is a need for effective interventions.

From the results of this research, it would appear that the most effective and suitable intervention could be that focused on educating physicians about the importance of antimicrobial stewardship practices. Moreover, introducing antimicrobial prescribing guidelines should be part of the intervention. Both education and guidelines should consider the factors that influence physicians prescribing and involve physicians through multifaceted interventions that aim to improve the broad-spectrum antimicrobial prescribing practices for adult hospitalised patients and to impact effectively and positively on physicians' inappropriate prescribing practices, thus reducing the risk of AMR.

5. References

ABBO, L., SINKOWITZ-COCHRAN, R., SMITH, L., ARIZA-HEREDIA, E., GÓMEZ-MARÍN, O., SRINIVASAN, A. & HOOTON, T. M. 2011. Faculty and resident physicians' attitudes, perceptions, and knowledge about antimicrobial use and resistance. *Infect Control Hosp Epidemiol*, 32, 714-718.

ABDALHAMID, B., HASSAN, H., ITBAILEH, A. & SHORMAN, M. 2014. Characterization of carbapenem-resistant Acinetobacter baumannii clinical isolates in a tertiary care hospital in Saudi Arabia. *New Microbiol,* 37, 65-73.

ABDALLAH, M., BADAWI, M., AMIRAH, M. F., RASHEED, A., MADY, A. F., ALODAT, M. & ALHARTHY, A. 2017. Impact of carbapenem restriction on the antimicrobial susceptibility pattern of Pseudomonas aeruginosa isolates in the ICU. *J Antimicrob Chemother,* 72, 3187-3190.

ADZITEY, F. 2015. Antibiotic Classes and Antibiotic Susceptibility of Bacterial Isolates from Selected Poultry; A Mini Review. *World 's Veterinary Journal*, 5, 36-41.

AHMED, O. B. 2016. Incidence and Antibiotic Susceptibility Pattern of Pseudomonas aeruginosa Isolated from Inpatients in Two Tertiary Hospitals. *Clinical Microbiology: Open Access*, 5, 248.

AKPAN, M. R., AHMAD, R., SHEBL, N. A. & ASHIRU-OREDOPE, D. 2016. A Review of Quality Measures for Assessing the Impact of Antimicrobial Stewardship Programs in Hospitals. *Antibiotics (Basel),* 5, 5.

ALGHAMDI, S., ATEF-SHEBL, N., ASLANPOUR, Z. & BERROU, I., 2019. Barriers to implementing antimicrobial stewardship programmes in three Saudi hospitals: Evidence from a qualitative study. *Journal of global antimicrobial resistance*, 18, 284-290.

AL JOHANI, S. M., AKHTER, J., BALKHY, H., EL-SAED, A., YOUNAN, M. & MEMISH, Z. 2010. Prevalence of antimicrobial resistance among gram-negative isolates in an adult intensive care unit at a tertiary care center in Saudi Arabia. *Ann Saudi Med,* 30, 364-369.

ALSALEH, N., ALSMARI, A., ALANAZI, F., ALSALEH, A., ALSMARI, R. & AL-SWEDAN, N., 2020. Medical and dental students'knowledge and perceptions about antimicrobial stewardship: a call for educational enhancement. *MMSL*, 89, 207-214.

AL-HUMAIDAN, O. S., EL-KERSH, T. A. & AL-AKEEL, R. A. 2015. Risk factors of nasal carriage of Staphylococcus aureus and methicillin-resistant Staphylococcus aureus among health care staff in a teaching hospital in central Saudi Arabia. *Saudi Med J,* 36, 1084-1090.

AL-OBEID, S., JABRI, L., AL-AGAMY, M., AL-OMARI, A. & SHIBL, A. 2015. Epidemiology of extensive drug resistant Acinetobacter baumannii (XDRAB) at Security Forces Hospital (SFH) in Kingdom of Saudi Arabia (KSA). *J Chemother,* 27, 156-162.

AL-OMAR, H. A. 2020. Cost-conscious medications-prescribing behavior among physicians working in Saudi Arabia. *Arch Pharm Pract,* 1, 143.

ALBEJAIDI, F. M. 2010. Healthcare system in Saudi Arabia: An analysis of structure, total quality management and future challenges. *J Alt Perspect Soc Sci,* 2, 794-818.

ALDEYAB, M. A., HARBARTH, S., VERNAZ, N., KEARNEY, M. P., SCOTT, M. G., DARWISH ELHAJJI, F. W., ALDIAB, M. A. & MCELNAY, J. C. 2012. The impact of antibiotic use on the incidence and resistance pattern of extended-spectrum beta-

lactamase-producing bacteria in primary and secondary healthcare settings. *Br J Clin Pharmacol,* 74, 171-179.

ALGHAMDI, S., ATEF-SHEBL, N., ASLANPOUR, Z. & BERROU, I. 2019. Barriers to implementing antimicrobial stewardship programmes in three Saudi hospitals: Evidence from a qualitative study. *J Glob Antimicrob Resist,* 18, 284-290.

ALHARTHI, N. R., KENAWY, G. & ELDALO, A. S. 2019. Antibiotics' prescribing pattern in intensive care unit in Taif, Saudi Arabia. *Saudi J Health Sci,* 8, 47.

ALKHAMEES, O., ALNEMER, K., BIN MANEEA, M., ALSUGAIR, F., ALENIZI, B. & ALHARF, A. 2018. Top 10 most used drugs in the Kingdom of Saudi Arabia 2010–2015. *Saudi Pharm J*, 26, 211–216.

ALMALKI, M., FITZGERALD, G. & CLARK, M. 2011. Health care system in Saudi Arabia: an overview. *East Mediterr Health J,* 17, 784-793.

ALOMI, Y. A. 2017. National antimicrobial stewardship program in Saudi Arabia; initiative and the future. *Open Access J Surg,* 4, 555646.

ALOSAIMI, K. M., KAMBAL, A. M., ALOTAIBI, F. M., AL-ANAZI, A. B., ALMOTAIRI, A. R., ALGHAMDI, W. M. & ALTUJJAR, A. R. 2018. Factors Affecting Physicians' Choice of Antibiotics for Treatment of Community Acquired Urinary Tract Infections and Their Correlation with Antimicrobial Susceptibility Test Results in King Khalid University Hospital during 2013-2014. *Int J Pharm Res Allied Sci,* 7, 119-125.

ALTHUBAITI, A. 2016. Information bias in health research: definition, pitfalls, and adjustment methods. *J Multidiscip Healthc,* 9, 211-217.

ALTUNSOY, A., AYPAK, C., AZAP, A., ERGÖNÜL, Ö. & BALIK, I. 2011. The impact of a nationwide antibiotic restriction program on antibiotic usage and resistance against nosocomial pathogens in Turkey. *Int J Med Sci,* 8, 339-344.

ALY, M. & BALKHY, H. H. 2012. The prevalence of antimicrobial resistance in clinical isolates from Gulf Corporation Council countries. *Antimicrob Resist Infect Control,* 1, 26.

ARMSTRONG, D. & OGDEN, J. 2006. The role of etiquette and experimentation in explaining how doctors change behaviour: a qualitative study. *Sociol Health Illn,* 28, 951-968.

ASHIRU-OREDOPE, D., SHARLAND, M., CHARANI, E., MCNULTY, C., COOKE, J. & GROUP, A. A. S. 2012. Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: Start Smart--Then Focus. *J Antimicrob Chemother,* 67 Suppl 1, i51-63.

AUSTRALIAN DEPARTMENT OF HEALTH AND DEPARTMENT OF AGRICULTURE. 2015. *Responding to the threat of antimicrobial resistance: Australia's First National Antimicrobial Resistance Strategy 2015–2019* [Online]. Available: http://www.health.gov.au/internet/main/publishing.nsf/content/1803C433C71415CACA257C8400121B1F/$File/amr-strategy-2015-2019.pdf [Accessed 12 March 2018].

AYUKEKBONG, J. A., NTEMGWA, M. & ATABE, A. N. 2017. The threat of antimicrobial resistance in developing countries: causes and control strategies. *Antimicrob Resist Infect Control,* 6, 47.

AZEEM, M., TASHANI, M., BARASHEED, O., HERON, L., HILL-CAWTHORNE, G. A., HAWORTH, E., DWYER, D. E., RASHID, H. & BOOY, R. 2014. Knowledge,

Attitude and Practice (KAP) Survey Concerning Antimicrobial Use among Australian Hajj Pilgrims. *Infect Disord Drug Targets,* 14, 125-132.

BAEK, H., CHO, M., KIM, S., HWANG, H., SONG, M., & YOO, S. 2018. Analysis of length of hospital stay using electronic health records: A statistical and data mining approach. *PloS one*, 13, e0195901.

BALDWIN, C. M., LYSENG-WILLIAMSON, K. A. & KEAM, S. J. 2008. Meropenem: a review of its use in the treatment of serious bacterial infections. *Drugs,* 68, 803-838.

BALKHY, H. H., ASSIRI, A. M., MOUSA, H. A., AL-ABRI, S. S., AL-KATHEERI, H., ALANSARI, H., ABDULRAZZAQ, N. M., AIDARA-KANE, A., PITTET, D. & WORKSHOP, A. T. 2016. The strategic plan for combating antimicrobial resistance in Gulf Cooperation Council States. *J Infect Public Health,* 9, 375-385.

BALKHY, H. H., EL-SAED, A., AL JOHANI, S. M., FRANCIS, C., AL-QAHTANI, A. A., AL-AHDAL, M. N., ALTAYEB, H. T., ARABI, Y., ALOTHMAN, A. & SALLAH, M. 2012. The epidemiology of the first described carbapenem-resistant Klebsiella pneumoniae outbreak in a tertiary care hospital in Saudi Arabia: how far do we go? *Eur J Clin Microbiol Infect Dis,* 31, 1901-1909.

BALKHY, H. H., EL-SAED, A., ALSHEHRI, A., ALSHAALAN, M., HIJAZI, O., EL-METWALLY, A., ALJOHANY, S. M. & AL SAIF, S. 2019. Antimicrobial consumption in three pediatric and neonatal intensive care units in Saudi Arabia: 33-month surveillance study. *Ann Clin Microbiol Antimicrob,* 18, 20.

BALKHY, H. H., EL-SAED, A., EL-METWALLY, A., ARABI, Y. M., ALJOHANY, S. M., AL ZAIBAG, M., BAHAROON, S. & ALOTHMAN, A. F. 2018. Antimicrobial

consumption in five adult intensive care units: a 33-month surveillance study. *Antimicrob Resist Infect Control,* 7, 156.

BANNAN, A., BUONO, E., MCLAWS, M. L. & GOTTLIEB, T. 2009. A survey of medical staff attitudes to an antibiotic approval and stewardship programme. *Intern Med J,* 39, 662-668.

BANTAR, C., SARTORI, B., VESCO, E., HEFT, C., SAÚL, M., SALAMONE, F. & OLIVA, M. E. 2003. A hospitalwide intervention program to optimize the quality of antibiotic use: impact on prescribing practice, antibiotic consumption, cost savings, and bacterial resistance. *Clin Infect Dis,* 37, 180-186.

BARBOUR, R. 2007. *Doing focus groups (Qualitative Research kit)*, 1st ed., London: SAGE Publications.

BARBOUR, R. 2008. *Introducing qualitative research,* 1st ed., London, SAGE Publications.

BARLAM, T. F., COSGROVE, S. E., ABBO, L. M., MACDOUGALL, C., SCHUETZ, A. N., SEPTIMUS, E. J., SRINIVASAN, A., DELLIT, T. H., FALCK-YTTER, Y. T., FISHMAN, N. O., HAMILTON, C. W., JENKINS, T. C., LIPSETT, P. A., MALANI, P. N., MAY, L. S., MORAN, G. J., NEUHAUSER, M. M., NEWLAND, J. G., OHL, C. A., SAMORE, M. H., SEO, S. K. & TRIVEDI, K. K. 2016. Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. *Clin Infect Dis,* 62, e51-77.

BARLOW, G., NATHWANI, D., MYERS, E., SULLIVAN, F., STEVENS, N., DUFFY, R. & DAVEY, P. 2008. Identifying barriers to the rapid administration of appropriate antibiotics in community-acquired pneumonia. *J Antimicrob Chemother,* 61, 442-451.

BARON, S. 1996. *Medical Microbiology*, 4th ed., Galveston: University of Texas Medical Branch at Galveston.

BARTLETT, J. G., GILBERT, D. N. & SPELLBERG, B. 2013. Seven ways to preserve the miracle of antibiotics. *Clin Infect Dis,* 56, 1445-1450.

BAUER, K.A., PEREZ, K.K., FORREST, G.N. & GOFF, D.A., 2014. Review of rapid diagnostic tests used by antimicrobial stewardship programs. *Clin infect dis,* 59, S134-S145.

BEELER, P. E., KUSTER, S. P., ESCHMANN, E., WEBER, R. & BLASER, J. 2015. Earlier switching from intravenous to oral antibiotics owing to electronic reminders. *Int J Antimicrob Agents,* 46, 428-433.

BELL, B. G., SCHELLEVIS, F., STOBBERINGH, E., GOOSSENS, H. & PRINGLE, M. 2014. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis,* 14, 13.

BELONGIA, E. A., KNOBLOCH, M. J., KIEKE, B. A., DAVIS, J. P., JANETTE, C. & BESSER, R. E. 2005. Impact of statewide program to promote appropriate antimicrobial drug use. *Emerg Infect Dis,* 11, 912-920.

BERREVOETS, M. A. H., POT, J. H. L. W., HOUTERMAN, A. E., DOFFERHOFF, A. T. S. M., NABUURS-FRANSSEN, M. H., FLEUREN, H. W. H. A., KULLBERG, B. J., SCHOUTEN, J. A. & SPRONG, T. 2017. An electronic trigger tool to optimise intravenous to oral antibiotic switch: a controlled, interrupted time series study. *Antimicrob Resist Infect Control,* 6, 81.

BERTOLLO, L. G., LUTKEMEYER, D. S. & LEVIN, A. S. 2018. Are antimicrobial stewardship programs effective strategies for preventing antibiotic resistance? A systematic review. *Am J Infect Control*, 46, 824-836.

BESSESEN, M.T., MA, A., CLEGG, D., FUGIT, R.V., PEPE, A., GOETZ, M.B. AND GRABER, C.J., 2015. Antimicrobial stewardship programs: comparison of a program with infectious diseases pharmacist support to a program with a geographic pharmacist staffing model. *Hosp. Pharm*, *50*, 477-483.

BIRKETT, D., DE, SMET, P., OFORI-ADJEI, D., TROLIN, I., BERGMAN, U., STRØM, H., HARBØ, B., T., RØNNING, M., SJÖQVIST & F. 2003. *Introduction to drug utilization research,* Switzerland: World Health Organization.

BJÖRKMAN, I., BERG, J., RÖING, M., ERNTELL, M. & LUNDBORG, C. S. 2010. Perceptions among Swedish hospital physicians on prescribing of antibiotics and antibiotic resistance. *Qual Saf Health Care,* 19, e8.

BLAIR, J. M., WEBBER, M. A., BAYLAY, A. J., OGBOLU, D. O. & PIDDOCK, L. J. 2015. Molecular mechanisms of antibiotic resistance. *Nat Rev Microbiol,* 13, 42-51.

BORG, M. A. 2012. National cultural dimensions as drivers of inappropriate ambulatory care consumption of antibiotics in Europe and their relevance to awareness campaigns. *J Antimicrob Chemother,* 67, 763-767.

BORG, M. A. 2014. Prolonged perioperative surgical prophylaxis within European hospitals: an exercise in uncertainty avoidance? *J Antimicrob Chemother,* 69, 1142-1144.

BOWLING, A. 2014. *Research methods in health: investigating health and health services*, 4th ed., Maidenhead: McGraw-hill; Open University Press.

BRAUN, V. & CLARKE, V. 2006. Using thematic analysis in psychology. *Qual Res Psychol,* 3, 77-101.

BRICELAND, L. L., NIGHTINGALE, C. H., QUINTILIANI, R., COOPER, B. W. & SMITH, K. S. 1988. Antibiotic streamlining from combination therapy to monotherapy utilizing an interdisciplinary approach. *Arch Intern Med,* 148, 2019-2022.

BROOKES-HOWELL, L., HOOD, K., COOPER, L., COENEN, S., LITTLE, P., VERHEIJ, T., GODYCKI-CWIRKO, M., MELBYE, H., KRAWCZYK, J., BORRAS-SANTOS, A., JAKOBSEN, K., WORBY, P., GOOSSENS, H. & BUTLER, C. C. 2012. Clinical influences on antibiotic prescribing decisions for lower respiratory tract infection: a nine country qualitative study of variation in care. *BMJ Open,* 2, e000795.

BROOM, A., BROOM, J. & KIRBY, E. 2014. Cultures of resistance? A Bourdieusian analysis of doctors' antibiotic prescribing. *Soc Sci Med,* 110, 81-88.

BROOM, J., BROOM, A., ADAMS, K. & PLAGE, S. 2016. What prevents the intravenous to oral antibiotic switch? A qualitative study of hospital doctors' accounts of what influences their clinical practice. *J Antimicrob Chemother,* 71, 2295-2299.

BROOM, J., BROOM, A., KIRBY, E., GIBSON, A. F. & POST, J. J. 2017. Individual care versus broader public health: A qualitative study of hospital doctors' antibiotic decisions. *Infect Dis Health,* 22, 97-104.

BURKE, J. P. 1998. Antibiotic resistance--squeezing the balloon? *JAMA,* 280, 1270-1271.

BURNARD, P., GILL, P., STEWART, K., TREASURE, E. & CHADWICK, B. 2008. Analysing and presenting qualitative data. *Br Dent J,* 204, 429-432.

BUSH, K. & BRADFORD, P. A. 2016. β-Lactams and β-lactamase inhibitors: an overview. *Cold Spring Harb Perspect Med,* 6, a025247.

BUTLER, C. C., SIMPSON, S. A., DUNSTAN, F., ROLLNICK, S., COHEN, D., GILLESPIE, D., EVANS, M. R., ALAM, M. F., BEKKERS, M. J., EVANS, J., MOORE, L., HOWE, R., HAYES, J., HARE, M. & HOOD, K. 2012. Effectiveness of multifaceted

educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ,* 344, d8173.

CALFEE, D. P., BROOKS, J., ZIRK, N. M., GIANNETTA, E. T., SCHELD, W. M. & FARR, B. M. 2003. A pseudo-outbreak of nosocomial infections associated with the introduction of an antibiotic management programme. *J Hosp Infect,* 55, 26-32.

CANE, J., O'CONNOR, D. & MICHIE, S. 2012. Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implement Sci,* 7, 37.

CARLET, J., COLLIGNON, P., GOLDMANN, D., GOOSSENS, H., GYSSENS, I. C., HARBARTH, S., JARLIER, V., LEVY, S. B., N'DOYE, B., PITTET, D., RICHTMANN, R., SETO, W. H., VAN DER MEER, J. W. & VOSS, A. 2011. Society's failure to protect a precious resource: antibiotics. *Lancet,* 378, 369-371.

CARLING, P., FUNG, T., KILLION, A., TERRIN, N. & BARZA, M. 2003. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. *Infect Control Hosp Epidemiol,* 24, 699-706.

CARR, E. C. J. & WORTH, A. 2001. The use of the telephone interview for research. *NT Research,* 6, 511-524.

CARRATALÀ, J., GARCIA-VIDAL, C., ORTEGA, L., FERNÁNDEZ-SABÉ, N., CLEMENTE, M., ALBERO, G., LÓPEZ, M., CASTELLSAGUÉ, X., DORCA, J., VERDAGUER, R., MARTÍNEZ-MONTAUTI, J., MANRESA, F. & GUDIOL, F. 2012. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. *Arch Intern Med,* 172, 922-928.

CARTHY, P., HARVEY, I., BRAWN, R. & WATKINS, C. 2000. A study of factors associated with cost and variation in prescribing among GPs. *Fam Pract,* 17, 36-41.

CDC. 1999. *Achievements in Public Health, 1900-1999: Control of Infectious Diseases.* [Online]. Available: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4829a1.htm [Accessed 20 March 2020].

CDC. 2013. *Antibiotic resistance threats in the United States, 2013*. [Online]. Available: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf [Accessed 11 February 2018].

CDC. 2019. *ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES.* [Online]. Available: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf [Accessed 08 January 2021].

CHAN, Y. Y., BIN IBRAHIM, M. A., WONG, C. M., OOI, C. K. & CHOW, A. 2019. Determinants of antibiotic prescribing for upper respiratory tract infections in an emergency department with good primary care access: a qualitative analysis. *Epidemiol Infect,* 147, e111.

CHAN, Y. Y., LIN, T. Y., HUANG, C. T., DENG, S. T., WU, T. L., LEU, H. S. & CHIU, C. H. 2011. Implementation and outcomes of a hospital-wide computerised antimicrobial stewardship programme in a large medical centre in Taiwan. *Int J Antimicrob Agents,* 38, 486-492.

CHARANI, E., CASTRO-SANCHEZ, E., SEVDALIS, N., KYRATSIS, Y., DRUMRIGHT, L., SHAH, N. & HOLMES, A. 2013. Understanding the determinants of antimicrobial prescribing within hospitals: the role of "prescribing etiquette". *Clin Infect Dis,* 57, 188-196.

CHARANI, E., EDWARDS, R., SEVDALIS, N., ALEXANDROU, B., SIBLEY, E., MULLETT, D., FRANKLIN, B. D. & HOLMES, A. 2011. Behavior change strategies to influence antimicrobial prescribing in acute care: a systematic review. *Clin Infect Dis,* 53, 651-662.

CHARLSON ME, POMPEI P, ALES KL, MACKENZIE CR. 1987. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis,* 40, 373-383.

CHATZOPOULOU, M., KYRIAKAKI, A. AND REYNOLDS, L. 2020. Review of antimicrobial resistance control strategies: low impact of prospective audit with feedback on bacterial antibiotic resistance within hospital settings. *Infect Dis*, 53, 159-168.

CHAZAN, B., TURJEMAN, R. B., FROST, Y., BESHARAT, B., TABENKIN, H., STAINBERG, A., SAKRAN, W. & RAZ, R. 2007. Antibiotic consumption successfully reduced by a community intervention program. *Isr Med Assoc J,* 9, 16-20.

CHITNIS, A. S., HOLZBAUER, S. M., BELFLOWER, R. M., WINSTON, L. G., BAMBERG, W. M., LYONS, C., FARLEY, M. M., DUMYATI, G. K., WILSON, L. E., BELDAVS, Z. G., DUNN, J. R., GOULD, L. H., MACCANNELL, D. R., GERDING, D. N., MCDONALD, L. C. & LESSA, F. C. 2013. Epidemiology of community-associated Clostridium difficile infection, 2009 through 2011. *JAMA Intern Med,* 173, 1359-1367.

CHOPRA, I., HESSE, L. & O'NEILL, A. 2002. Discovery and development of new anti-bacterial drugs. *Pharmacochem Libr,* 32, 213-225.

CHUNG, G. W., WU, J. E., YEO, C. L., CHAN, D. & HSU, L. Y. 2013. Antimicrobial stewardship: a review of prospective audit and feedback systems and an objective evaluation of outcomes. *Virulence,* 4, 151-157.

CISNEROS, J. M., NETH, O., GIL-NAVARRO, M. V., LEPE, J. A., JIMÉNEZ-PARRILLA, F., CORDERO, E., RODRÍGUEZ-HERNÁNDEZ, M. J., AMAYA-VILLAR, R., CANO, J., GUTIÉRREZ-PIZARRAYA, A., GARCÍA-CABRERA, E., MOLINA, J. & TEAM, P. 2014. Global impact of an educational antimicrobial stewardship programme on prescribing practice in a tertiary hospital centre. *Clin Microbiol Infect,* 20, 82-88.

CLARO, T., DANIELS, S. & HUMPHREYS, H. 2014. Detecting Clostridium difficile spores from inanimate surfaces of the hospital environment: which method is best? *J Clin Microbiol,* 52, 3426-3428.

CLERC, O., & GREUB, G. 2010. Routine use of point-of-care tests: usefulness and application in clinical microbiology. *Clin Microbiol Infect*, 16, 1054–1061.

CODJOE, F. S. & DONKOR, E. S. 2017. Carbapenem Resistance: A Review. *Med Sci (Basel),* 6, 1.

COLLINS, M., SHATTELL, M. & THOMAS, S. P. 2005. Problematic interviewee behaviors in qualitative research. *West J Nurs Res,* 27, 188-199.

CONNELLY, L. M. 2016. Trustworthiness in Qualitative Research. *Medsurg Nurs,* 25, 435-436.

CORTOOS, P. J., DE WITTE, K., PEETERMANS, W. E., SIMOENS, S. & LAEKEMAN, G. 2008. Opposing expectations and suboptimal use of a local antibiotic hospital guideline: a qualitative study. *J Antimicrob Chemother,* 62, 189-195.

COSGROVE, S. E. 2006. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis,* 42 Suppl 2, S82-89.

COSGROVE, S. E. & CARMELI, Y. 2003. The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis,* 36, 1433-1437.

COUNTRY REPORTS. 2018. *Saudi Arabia* [Online]. Available: http://www.countryreports.org/country/SaudiArabia.htm [Accessed 15 April 2018].

CRESWELL, J. W., & CLARK, V. L. P. 2017. *Designing and conducting mixed methods research.* 3 rd ed., Thousand Oaks: SAGE Publications.

CRESWELL, J. W. & POTH, C. N. 2016. *Qualitative inquiry and research design: Choosing among five approaches,* 4 th ed., Thousand Oaks: SAGE Publications.

CRESWELL, J. W. & CRESWELL J. D. 2017. *Research Design Qualitative, Quantitative, and Mixed Methods Approaches,* 5 th ed., California: SAGE Publications.

CURCIO, D. 2010. Antibiotic stewardship: the "real world" when resources are limited. *Infect Control Hosp Epidemiol,* 31, 666-668.

DANIEL, T. M. 2005. Selman Abraham Waksman and the discovery of streptomycin. *Int J Tuberc Lung Dis,* 9, 120-122.

DAVEY, P., MARWICK, C. A., SCOTT, C. L., CHARANI, E., MCNEIL, K., BROWN, E., GOULD, I. M., RAMSAY, C. R. & MICHIE, S. 2017. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev,* 2, CD003543.

DE SOUZA, V., MACFARLANE, A., MURPHY, A. W., HANAHOE, B., BARBER, A. & CORMICAN, M. 2006. A qualitative study of factors influencing antimicrobial prescribing by non-consultant hospital doctors. *J Antimicrob Chemother,* 58, 840-843.

DELLIT, T. H., CHAN, J. D., SKERRETT, S. J. & NATHENS, A. B. 2008. Development of a guideline for the management of ventilator-associated pneumonia based on local microbiologic findings and impact of the guideline on antimicrobial use practices. *Infect Control Hosp Epidemiol,* 29, 525-533.

DELLIT, T. H., OWENS, R. C., MCGOWAN, J. E., GERDING, D. N., WEINSTEIN, R. A., BURKE, J. P., HUSKINS, W. C., PATERSON, D. L., FISHMAN, N. O., CARPENTER, C. F., BRENNAN, P. J., BILLETER, M., HOOTON, T. M., AMERICA, I. D. S. O. & AMERICA, S. F. H. E. O. 2007. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis,* 44, 159-177.

DENZIN, N. K. 2001. *Interpretive interactionism (Applied Social Research Methods),* 2 nd ed.,Thousand Oaks: SAGE Publications.

DEPARTMENT OF HEALTH 2013. *UK Five Year Antimicrobial Resistance Strategy 2013 to 2018.* [Online]. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf [Accessed 15 April 2018].

DEVITO, J. M. & JOHN, J. F. 1985. Effect of formulary restriction of cefotaxime usage. *Arch Intern Med,* 145, 1053-1056.

DIAL, S., KEZOUH, A., DASCAL, A., BARKUN, A. & SUISSA, S. 2008. Patterns of antibiotic use and risk of hospital admission because of Clostridium difficile infection. *CMAJ,* 179, 767-772.

DREW, R. H. 2009. Antimicrobial stewardship programs: how to start and steer a successful program. *J Manag Care Pharm,* 15, S18-23.

DREW, R. H., WHITE, R., MACDOUGALL, C., HERMSEN, E. D., OWENS, R. C. & PHARMACISTS, S. O. I. D. 2009. Insights from the Society of Infectious Diseases Pharmacists on antimicrobial stewardship guidelines from the Infectious

Diseases Society of America and the Society for Healthcare Epidemiology of America. *Pharmacotherapy,* 29, 593-607.

DUBEY, R. & MAHESHWARI, D. 1999. *A Textbook of Microbiology,* 1 st ed., New Delhi: S. Chand & Cmpany Limited.

DULHUNTY, J.M., PATERSON, D., WEBB, S.A., LIPMAN, J., 2011. Antimicrobial utilisation in 37 Australian and New Zealand intensive care units. *Anaesth Intensive Care*, 39, 231–237.

ELABD, F. M., AL-AYED, M. S., ASAAD, A. M., ALSAREII, S. A., QURESHI, M. A. & MUSA, H. A. 2015. Molecular characterization of oxacillinases among carbapenem-resistant Acinetobacter baumannii nosocomial isolates in a Saudi hospital. *J Infect Public Health,* 8, 242-247.

ELLIGSEN, M., WALKER, S. A., PINTO, R., SIMOR, A., MUBAREKA, S., RACHLIS, A., ALLEN, V. & DANEMAN, N. 2015. Audit and feedback to reduce broad-spectrum antibiotic use among intensive care unit patients: a controlled interrupted time series analysis. *Infect Control Hosp Epidemiol,* 33, 354-361.

ELSEVIERS, M., ALMARSDÏ, A. B., ANDERSEN, M., BENKO, R., BENNIE, M., ERIKSSON, I., GODMAN, B., KRSKA, J., POLUZZI, E. & TAXIS, K. 2016. *Drug utilization research: methods and applications*, 1 st ed., West Sussex: John Wiley & Sons.

ENANI, M. A. 2016. The antimicrobial stewardship program in Gulf Cooperation Council (GCC) states: insights from a regional survey. *J Infect Prev,* 17, 16-20.

EVANS, H. L., LEFRAK, S. N., LYMAN, J., SMITH, R. L., CHONG, T. W., MCELEARNEY, S. T., SCHULMAN, A. R., HUGHES, M. G., RAYMOND, D. P., PRUETT, T. L. & SAWYER, R. G. 2007. Cost of Gram-negative resistance. *Crit Care Med,* 35, 89-95.

FAIR, R. J. & TOR, Y. 2014. Antibiotics and bacterial resistance in the 21st century. *Perspect Medicin Chem,* 6, 25-64.

FARRUGIA, B. 2019. WASP (write a scientific paper): Sampling in qualitative research. *Early Hum Dev,* 133, 69-71.

FEUCHT, C. L. & RICE, L. B. 2003. An interventional program to improve antibiotic use. *Ann Pharmacother,* 37, 646-651.

FISHMAN, N. 2006. Antimicrobial stewardship. *Am J Infect Control,* 34, S55-61.

FISHMAN, N. 2012. Policy statement on antimicrobial stewardship by the society for healthcare epidemiology of America (SHEA), the infectious diseases society of America (IDSA), and the pediatric infectious diseases society (PIDS). *Infection Control & Hospital Epidemiology,* 33, 322-327.

FLEMING, A. 1945. Penicillin's finder assays its future. *New York Times*, 21.

FORAL, P. A., ANTHONE, J. M., DESTACHE, C. J., VIVEKANANDAN, R., PREHEIM, L. C., GORBY, G. L., HORNE, J. M., DOBRONSKI, L. A., SYED, J. J., MINDRU, C., ALI, M. A., ALI, K. F., NEEMANN, K. A. & BITTNER, M. J. 2016. Education and Communication in an Interprofessional Antimicrobial Stewardship Program. *J Am Osteopath Assoc,* 116, 588-593.

FOSSEY, E., HARVEY, C., MCDERMOTT, F. & DAVIDSON, L. 2002. Understanding and evaluating qualitative research. *Aust N Z J Psychiatry,* 36, 717-732.

FRASER, G. L., STOGSDILL, P., DICKENS, J. D., WENNBERG, D. E., SMITH, R. P. & PRATO, B. S. 1997. Antibiotic optimization. An evaluation of patient safety and economic outcomes. *Arch Intern Med,* 157, 1689-1694.

FRIEDMAN, N. D., TEMKIN, E. & CARMELI, Y. 2016. The negative impact of antibiotic resistance. *Clin Microbiol Infect,* 22, 416-422.

FRIERI, M., KUMAR, K. & BOUTIN, A. 2017. Antibiotic resistance. *J Infect Public Health,* 10, 369-378.

GARAU, J. 2006. Impact of antibiotic restrictions: the ethical perspective. *Clin Microbiol Infect,* 12 Suppl 5, 16-24.

GARAU, J., BAQUERO, F., PEREZ-TRALLERO, E., PÉREZ, J.L., MARTIN-SANCHEZ, A.M., GARCIA-REY, C., MARTIN-HERRERO, J.E. AND DAL-RÉ, R., 2008. Factors impacting on length of stay and mortality of community-acquired pneumonia. *Clin Microbiol Infect*, 14, 322-329.

GASTAT. 2019. *Statistical Yearbook of 2019* [Online]. Available: https://www.stats.gov.sa/en/1006 [Accessed 20 December 2020].

GENSINI, G. F., CONTI, A. A. & LIPPI, D. 2007. The contributions of Paul Ehrlich to infectious disease. *J Infect,* 54, 221-224.

GERBER, J. S., PRASAD, P. A., FIKS, A. G., LOCALIO, A. R., BELL, L. M., KEREN, R. & ZAOUTIS, T. E. 2014. Durability of benefits of an outpatient antimicrobial stewardship intervention after discontinuation of audit and feedback. *JAMA,* 312, 2569-2570.

GILCHRIST, M. & GEOGHEGAN, O. 2018. Antimicrobial stewardship: from principles to practice. In*:* NATHWANI, D., ABBO, L., JAMIESON, C., GILCHRIST, M., PULCINI, C. & BAR, L. eds. *THE STEWARDSHIP TOOLKIT.* Birmingham: British society of antimicrobial chemotherapy.

GIROTTI, M. J., FODORUK, S., IRVINE-MEEK, J. & ROTSTEIN, O. D. 1990. Antibiotic handbook and pre-printed perioperative order forms for surgical antibiotic prophylaxis: do they work? *Can J Surg,* 33, 385-388.

GIVEN, L. M. 2008. *The sage encyclopedia of qualitative research methods,* 1st ed*.,* Los Angeles: SAGE Publications.

GOFF, D. A., KULLAR, R., GOLDSTEIN, E. J. C., GILCHRIST, M., NATHWANI, D., CHENG, A. C., CAIRNS, K. A., ESCANDÓN-VARGAS, K., VILLEGAS, M. V., BRINK, A., VAN DEN BERGH, D. & MENDELSON, M. 2017. A global call from five countries to collaborate in antibiotic stewardship: united we succeed, divided we might fail. *Lancet Infect Dis,* 17, e56-e63.

GONZALEZ, L., CRAVOISY, A., BARRAUD, D., CONRAD, M., NACE, L., LEMARIÉ, J., BOLLAERT, P. E. & GIBOT, S. 2013. Factors influencing the implementation of antibiotic de-escalation and impact of this strategy in critically ill patients. *Crit Care,* 17, R140.

GONZALEZ-GONZALEZ, C., LÓPEZ-VÁZQUEZ, P., VÁZQUEZ-LAGO, J. M., PIÑEIRO-LAMAS, M., HERDEIRO, M. T., ARZAMENDI, P. C., FIGUEIRAS, A. & GROUP, G. 2015. Effect of Physicians' Attitudes and Knowledge on the Quality of Antibiotic Prescription: A Cohort Study. *PLoS One,* 10, e0141820.

GOOSSENS, H., FERECH, M., VANDER STICHELE, R., ELSEVIERS, M. & GROUP, E. P. 2005. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet,* 365, 579-587.

GRIFFITH, M., POSTELNICK, M. & SCHEETZ, M. 2012. Antimicrobial stewardship programs: methods of operation and suggested outcomes. *Expert Rev Anti Infect Ther,* 10, 63-73.

GROSS, R., MORGAN, A. S., KINKY, D. E., WEINER, M., GIBSON, G. A. & FISHMAN, N. O. 2001. Impact of a hospital-based antimicrobial management program on clinical and economic outcomes. *Clin Infect Dis,* 33, 289-295.

GUMS, J. G., YANCEY, R. W., HAMILTON, C. A. & KUBILIS, P. S. 1999. A randomized, prospective study measuring outcomes after antibiotic therapy intervention by a multidisciplinary consult team. *Pharmacotherapy,* 19, 1369-1377.

HAMID-ULLAH & ALI, S. 2017. Classification of anti-bacterial agents and their functions. In Kumavath, R.N., ed. *Antibacterial Agents*, London: Intech, 1–16.

HAMILTON, C. D., DREW, R., JANNING, S. W., LATOUR, J. K. & HAYWARD, S. 2000. Excessive use of vancomycin: a successful intervention strategy at an academic medical center. *Infect Control Hosp Epidemiol,* 21, 42-45.

HAMILTON, W. L., PIRES, S. M., LIPPETT, S., GUDKA, V., CROSS, E. L. A. & LLEWELYN, M. J. 2020. The impact of diagnostic microbiology on de-escalation of antimicrobial therapy in hospitalised adults. *BMC Infect Dis,* 20, 102.

HARRIS, A. D., PERENCEVICH, E., ROGHMANN, M. C., MORRIS, G., KAYE, K. S. & JOHNSON, J. A. 2002. Risk factors for piperacillin-tazobactam-resistant Pseudomonas aeruginosa among hospitalized patients. *Antimicrob Agents Chemother,* 46, 854-858.

HAUCK, L. D., ADLER, L. M. & MULLA, Z. D. 2004. Clinical pathway care improves outcomes among patients hospitalized for community-acquired pneumonia. *Ann Epidemiol,* 14, 669-675.

HEINEMAN, H. S. & WATT, V. S. 1986. All-inclusive concurrent antibiotic usage review: a way to reduce misuse without formal controls. *Infect Control,* 7, 168-171.

HENSGENS, M. P., GOORHUIS, A., DEKKERS, O. M. & KUIJPER, E. J. 2012. Time interval of increased risk for Clostridium difficile infection after exposure to antibiotics. *J Antimicrob Chemother,* 67, 742-748.

HOFFMANN, K., WAGNER, G., APFALTER, P. & MAIER, M. 2011. Antibiotic resistance in primary care in Austria - a systematic review of scientific and grey literature. *BMC Infect Dis,* 11, 330.

HOLLOWAY, I. 1997. *Basic concepts for qualitative research,* 1 st ed., London: Blackwell Science.

HOLMES, A. H., MOORE, L. S., SUNDSFJORD, A., STEINBAKK, M., REGMI, S., KARKEY, A., GUERIN, P. J. & PIDDOCK, L. J. 2016. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet,* 387, 176-187.

HORWOOD, J., CABRAL, C., HAY, A. D. & INGRAM, J. 2016. Primary care clinician antibiotic prescribing decisions in consultations for children with RTIs: a qualitative interview study. *Br J Gen Pract,* 66, e207-213.

HUANG, A. M., NEWTON, D., KUNAPULI, A., GANDHI, T. N., WASHER, L. L., ISIP, J., COLLINS, C. D. & NAGEL, J. L. 2013. Impact of rapid organism identification via matrix-assisted laser desorption/ionization time-of-flight combined with antimicrobial stewardship team intervention in adult patients with bacteremia and candidemia. *Clin Infect Dis,* 57, 1237-1245.

HULSCHER, M. E., GROL, R. P. & VAN DER MEER, J. W. 2010. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. *Lancet Infect Dis,* 10, 167-175.

HULSCHER, M.E.J.L. AND PRINS, J.M., 2017. Antibiotic stewardship: does it work in hospital practice? A review of the evidence base. *Clin Microbiol Infect,* 23, 799-805.

HUWAIT, B., RAHMAN, B., RAMADAN, O., ALETREBY, W., MADY, A. & HARTHY, A. 2019. A Pilot Study to Evaluate Appropriateness of Empirical Antibiotic Use in Intensive Care Unit of King Saud Medical City, Riyadh, Saudi Arabia. *Gen Med (Los Angeles),* 7, 323.

IBRAHIM, E. H., WARD, S., SHERMAN, G., SCHAIFF, R., FRASER, V. J. & KOLLEF, M. H. 2001. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med,* 29, 1109-1115.

INFECTIOUS DISEASES SOCIETY OF AMERICA. 2018. *practice guideline* [Online]. Available: https://www.idsociety.org/practice-guideline/alphabetical-guidelines/ [Accessed 10 May 2018].

INSTITUTE OF MEDICINE. 2011. *Clinical Practice Guidelines We Can Trust.* Washington, DC: The National Academies Press. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK209539 [Accessed 29 May 2021].

IYER, H. V. 2008. History revisited-Prontosil red. *J Emerg Med,* 35, 209-210.

JANOWSKI, A. B., MICHAELS, M. G., MARTIN, J. M. & GREEN, M. D. 2016. Piperacillin-Tazobactam Usage at a Tertiary Pediatric Hospital: An Antimicrobial Stewardship Review. *J Pediatric Infect Dis Soc,* 5, 342-345.

JENKINS, T. C., KNEPPER, B. C., SABEL, A. L., SARCONE, E. E., LONG, J. A., HAUKOOS, J. S., MORGAN, S. J., BIFFL, W. L., STEELE, A. W., PRICE, C. S., MEHLER, P. S. & BURMAN, W. J. 2011. Decreased antibiotic utilization after implementation of a guideline for inpatient cellulitis and cutaneous abscess. *Arch Intern Med,* 171, 1072-1079.

JOHNSON, R. B. & ONWUEGBUZIE, A. J. 2004. Mixed methods research: A research paradigm whose time has come. *Educ Res,* 33, 14-26.

JUMP, R. L., OLDS, D. M., SEIFI, N., KYPRIOTAKIS, G., JURY, L. A., PERON, E. P., HIRSCH, A. A., DRAWZ, P. E., WATTS, B., BONOMO, R. A. & DONSKEY, C. J. 2012. Effective antimicrobial stewardship in a long-term care facility through an infectious disease consultation service: keeping a LID on antibiotic use. *Infect Control Hosp Epidemiol,* 33, 1185-1192.

KAAE, S., MALAJ, A. & HOXHA, I. 2017. Antibiotic knowledge, attitudes and behaviours of Albanian health care professionals and patients - a qualitative interview study. *J Pharm Policy Pract,* 10, 13.

KABBARA, W. K., NAWAS, G. T. & RAMADAN, W. H. 2015. Evaluation of the appropriateness of imipenem/cilastatin prescription and dosing in a tertiary care hospital. *Infect Drug Resist,* 8, 31-38.

KALLIO, H., PIETILÄ, A. M., JOHNSON, M. & KANGASNIEMI, M. 2016. Systematic methodological review: developing a framework for a qualitative semi-structured interview guide. *J Adv Nurs,* 72, 2954-2965.

KAPISZEWSKI, A. 2006. Arab versus Asian migrant workers in the GCC countries. In: Jain, P.C., & Oommen, G.Z. (eds.) *South Asian Migration to Gulf Countries: History, Policies,* Development, 1 st ed., India: Routledge, 46-70.

KAZANJIAN, P. 2016. Chapter 3: history of antimicrobial stewardship. *In:* K LAPLANTE ed. *Antimicrobial Stewardship Principles and Practice.* 1 st ed., Boston: CABI.

KHAN, F. Y., ELHIDAY, A., KHUDAIR, I. F., YOUSEF, H., OMRAN, A. H., ALSAMMAN, S. H. & ELHAMID, M. 2012. Evaluation of the use of piperacillin/tazobactam (Tazocin) at Hamad General Hospital, Qatar: are there unjustified prescriptions? *Infect Drug Resist,* 5, 17-21.

KHARDORI, N. 2006. Antibiotics--past, present, and future. *Med Clin North Am,* 90, 1049-1076.

KINSMAN, L., ROTTER, T., JAMES, E., SNOW, P., & WILLIS, J. 2010. What is a clinical pathway? Development of a definition to inform the debate. *BMC medicine*, 8, 31

KIRN, T. J. & WEINSTEIN, M. P. 2013. Update on blood cultures: how to obtain, process, report, and interpret. *Clin Microbiol Infect,* 19, 513-520.

KLEIN, E. Y., VAN BOECKEL, T. P., MARTINEZ, E. M., PANT, S., GANDRA, S., LEVIN, S. A., GOOSSENS, H. & LAXMINARAYAN, R. 2018. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci USA,* 115, E3463-E3470.

KOCH, T. 2006. Establishing rigour in qualitative research: the decision trail. 1993. *J Adv Nurs,* 53, 91-100.

KOENKER, R. 2005. *Quantile Regression*. Cambridge: Cambridge University Press

KOLLEF, M. H. 2000. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clin Infect Dis,* 31 Suppl 4, S131-8.

KRISHNAKUMAR, J. & TSOPRA, R. 2019. What rationale do GPs use to choose a particular antibiotic for a specific clinical situation? *BMC Fam Pract,* 20, 178.

KROCKOW, E. M., COLMAN, A. M., CHATTOE-BROWN, E., JENKINS, D. R., PERERA, N., MEHTAR, S. & TARRANT, C. 2019. Balancing the risks to individual and society: a systematic review and synthesis of qualitative research on antibiotic prescribing behaviour in hospitals. *J Hosp Infect,* 101, 428-439.

KROCKOW, E.M.; KURVERS, R.H.; HERZOG, S.M.; KÄMMER, J.E.; HAMILTON, R.A.; THILLY, N.; MACHEDA, G.; PULCINI, C. 2020. Harnessing the wisdom of crowds can improve guideline compliance of antibiotic prescribers and support antimicrobial stewardship. *Sci* Rep, 10, 1–12.

KSU. 2018. *Medical City King Saud University*. Riyadh, KSA. [Online]. Available: http://medicalcity.ksu.edu.sa/en/page/about-ksumc [Accessed 18 April 2018].

KSUMC 2018. *Scope of Services King Saud University Medical City.* Riyadh, KSA. [Online]. Available:

https://medicalcity.ksu.edu.sa/en/sites/cns/pages/scope-of-services [Accessed 18 April 2018].

KUNIN, C. M., TUPASI, T. & CRAIG, W. A. 1973. Use of antibiotics. A brief exposition of the problem and some tentative solutions. *Ann Intern Med,* 79, 555-560.

KUSTER, S. P., RUEF, C., LEDERGERBER, B., HINTERMANN, A., DEPLAZES, C., NEUBER, L. & WEBER, R. 2008. Quantitative antibiotic use in hospitals: comparison of measurements, literature review, and recommendations for a standard of reporting. *Infection,* 36, 549-59.

KYNE, L., HAMEL, M. B., POLAVARAM, R. & KELLY, C. P. 2002. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. *Clin Infect Dis,* 34, 346-353.

LACY, M. K., KLUTMAN, N. E., HORVAT, R. T. & ZAPANTIS, A. 2004. Antibiograms: new NCCLS guidelines, development, and clinical application. *Hosp pharm,* 39, 542-553.

LAKSHMANA GOWDA, K., MARIE, M. A., AL-SHEIKH, Y. A., JOHN, J., GOPALKRISHNAN, S., CHIKKABIDARE SHASHIDHAR, P. & DABWAN, K. H. 2014. A 6-year surveillance of antimicrobial resistance patterns of Acinetobacter baumannii bacteremia isolates from a tertiary care hospital in Saudi Arabia during 2005-2010. *Libyan J Med,* 9, 24039.

LANDSTEDT, K.; SHARMA, A.; JOHANSSON, F.; LUNDBORG, C.S.; SHARMA, M. 2017. Antibiotic prescriptions for inpatients having non-bacterial diagnosis at medicine departments of two private sector hospitals in Madhya Pradesh, India: A cross-sectional study. *BMJ Open*, 7, e012974.

LANGTON, K. P., HENDERSON, P. J. & HERBERT, R. B. 2005. Antibiotic resistance: multidrug efflux proteins, a common transport mechanism? *Nat Prod Rep,* 22, 439-451.

LAROCCO, A. 2003. Concurrent antibiotic review programs--a role for infectious diseases specialists at small community hospitals. *Clin Infect Dis,* 37, 742-743.

LAROSA, L. A., FISHMAN, N. O., LAUTENBACH, E., KOPPEL, R. J., MORALES, K. H. & LINKIN, D. R. 2007. Evaluation of antimicrobial therapy orders circumventing an antimicrobial stewardship program: investigating the strategy of "stealth dosing". *Infect Control Hosp Epidemiol,* 28, 551-556.

LARSSON, J. & HOLMSTRÖM, I. 2007. Phenomenographic or phenomenological analysis: Does it matter? Examples from a study on anaesthesiologists' work. *Int J Qual Stud Health Well-being,* 2, 55-64.

LAWES, T., LOPEZ-LOZANO, J.M., NEBOT, C.A., MACARTNEY, G., SUBBARAO-SHARMA, R., WARES, K.D., SINCLAIR, C. & GOULD, I.M., 2017. Effect of a national 4C antibiotic stewardship intervention on the clinical and molecular epidemiology of Clostridium difficile infections in a region of Scotland: a non-linear time-series analysis. *Lancet Infect Dis*, *17*, 194-206.

LEE, C. R., CHO, I. H., JEONG, B. C. & LEE, S. H. 2013. Strategies to minimize antibiotic resistance. *Int J Environ Res Public Health,* 10, 4274-4305.

LEE, N. Y., LEE, H. C., KO, N. Y., CHANG, C. M., SHIH, H. I., WU, C. J. & KO, W. C. 2007. Clinical and economic impact of multidrug resistance in nosocomial Acinetobacter baumannii bacteremia. *Infect Control Hosp Epidemiol,* 28, 713-719.

LEEKHA, S., TERRELL, C.L., EDSON, R.S. 2011. General principles of antimicrobialtherapy. *Mayo Clin. Proc*. 86, 156–167.

LELORIER, J., VANDER STICHELE, R. H., AVORN, J., BEARD, K., HALLAS, J. & HENRY, D. A. 2003. Bringing epidemiology into drug utilisation research. *Pharmacoepidemiol Drug Saf,* 12, 153-156.

LEUNG, L. 2015. Validity, reliability, and generalizability in qualitative research. *J Family Med Prim Care,* 4, 324.

LEVY, M. M., EVANS, L. E. & RHODES, A. 2018. The Surviving Sepsis Campaign Bundle: 2018 Update. *Crit Care Med,* 46, 997-1000.

LEWIS, G. J., FANG, X., GOOCH, M. & COOK, P. P. 2012. Decreased resistance of Pseudomonas aeruginosa with restriction of ciprofloxacin in a large teaching hospital's intensive care and intermediate care units. *Infect Control Hosp Epidemiol,* 33, 368-373.

LEWIS, K. 2013. Platforms for antibiotic discovery. *Nat Rev Drug Discov,* 12, 371-387.

LIMMATHUROTSAKUL, D., DUNACHIE, S., FUKUDA, K., FEASEY, N. A., OKEKE, I. N., HOLMES, A. H., MOORE, C. E., DOLECEK, C., VAN DOORN, H. R., SHETTY, N., LOPEZ, A. D., PEACOCK, S. J. & (SEDRIC), S. A. E. O. D. R. I. C. 2019. Improving the estimation of the global burden of antimicrobial resistant infections. *Lancet Infect Dis,* 19, e392-e398.

LINCOLN, Y. & GUBA, E. 1985. *Naturalistic Inquiry*. 1 st ed., CA: SAGE Publications.

LINCOLN, Y. S. & GUBA, E. G. 1986. But is it rigorous? Trustworthiness and authenticity in naturalistic evaluation. *New Dier Eval,* 1986, 73-84.

LINKIN, D. R., PARIS, S., FISHMAN, N. O., METLAY, J. P. & LAUTENBACH, E. 2006. Inaccurate communications in telephone calls to an antimicrobial stewardship program. *Infect Control Hosp Epidemiol,* 27, 688-694.

LIVERMORE, D. M., HOPE, R., REYNOLDS, R., BLACKBURN, R., JOHNSON, A. P. & WOODFORD, N. 2013. Declining cephalosporin and fluoroquinolone non-

susceptibility among bloodstream Enterobacteriaceae from the UK: links to prescribing change? *J Antimicrob Chemother,* 68, 2667-2674.

LIVORSI, D., COMER, A., MATTHIAS, M. S., PERENCEVICH, E. N. & BAIR, M. J. 2015. Factors Influencing Antibiotic-Prescribing Decisions Among Inpatient Physicians: A Qualitative Investigation. *Infect Control Hosp Epidemiol,* 36, 1065-1072.

LORENCATTO, F., CHARANI, E., SEVDALIS, N., TARRANT, C. & DAVEY, P. 2018. Driving sustainable change in antimicrobial prescribing practice: how can social and behavioural sciences help? *J Antimicrob Chemother,* 73, 2613-2624.

MACDOUGALL, C. & POLK, R. E. 2005. Antimicrobial stewardship programs in health care systems. *Clin Microbiol Rev,* 18, 638-656.

MACK, A., RELMAN, D. A. & CHOFFNES, E. R. 2011. *Antibiotic resistance: implications for global health and novel intervention strategies: workshop summary*, Washington: National Academies Press.

MALANI, A. N., RICHARDS, P. G., KAPILA, S., OTTO, M. H., CZERWINSKI, J. & SINGAL, B. 2013. Clinical and economic outcomes from a community hospital's antimicrobial stewardship program. *Am J Infect Control,* 41, 145-148.

MARCHAIM, D., CHOPRA, T., BHARGAVA, A., BOGAN, C., DHAR, S., HAYAKAWA, K., POGUE, J. M., BHEEMREDDY, S., BLUNDEN, C., SHANGO, M., SWAN, J., LEPHART, P. R., PEREZ, F., BONOMO, R. A. & KAYE, K. S. 2012. Recent exposure to antimicrobials and carbapenem-resistant Enterobacteriaceae: the role of antimicrobial stewardship. *Infect Control Hosp Epidemiol,* 33, 817-830.

MARRIE, T. J., LAU, C. Y., WHEELER, S. L., WONG, C. J., VANDERVOORT, M. K. & FEAGAN, B. G. 2000. A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-

Acquired Pneumonia Intervention Trial Assessing Levofloxacin. *JAMA,* 283, 749-755.

MARTIN, C., OFOTOKUN, I., RAPP, R., EMPEY, K., ARMITSTEAD, J., POMEROY, C., HOVEN, A. & EVANS, M. 2005. Results of an antimicrobial control program at a university hospital. *Am J Health-Syst Pharm,* 62, 732-738.

MASHWAL, F. A., EL SAFI, S. H., GEORGE, S. K., ADAM, A. A. & JEBAKUMAR, A. Z. 2017. Incidence and molecular characterization of the extended spectrum beta lactamase-producing Escherichia coli isolated from urinary tract infections in Eastern Saudi Arabia. *Saudi Med J,* 38, 811-815.

MCDONNELL NORMS GROUP 2008. Antibiotic overuse: the influence of social norms. *J Am Coll Surg,* 207, 265-275.

MCKINNELL, J. A., KUNZ, D. F., CHAMOT, E., PATEL, M., SHIRLEY, R. M., MOSER, S. A., BADDLEY, J. W., PAPPAS, P. G. & MILLER, L. G. 2012. Association between vancomycin-resistant Enterococci bacteremia and ceftriaxone usage. *Infect Control Hosp Epidemiol,* 33, 718-724.

MD REZAL, R. S., HASSALI, M. A., ALRASHEEDY, A. A., SALEEM, F., MD YUSOF, F. A. & GODMAN, B. 2015. Physicians' knowledge, perceptions and behaviour towards antibiotic prescribing: a systematic review of the literature. *Expert Rev Anti Infect Ther,* 13, 665-680.

MEENA, D. K. & JAYANTHI, M. 2019. Drug utilization research: a review. *Int J Basic Clin Pharmacol,* 8, 354.

MEKDAD, S. S. & ALSAYED, L. 2020. Prospective evaluating the appropriate use of piperacillin /tazobactam in cardiac center of a tertiary care hospital. *J Cardiothorac Surg,* 15, 70.

MEMISH, Z. A., SHIBL, A. M., KAMBAL, A. M., OHALY, Y. A., ISHAQ, A. & LIVERMORE, D. M. 2012. Antimicrobial resistance among non-fermenting Gram-negative bacteria in Saudi Arabia. *J Antimicrob Chemother,* 67, 1701-1705.

MERMEL, L. A., JEFFERSON, J. & DEVOLVE, J. 2008. Knowledge and use of cumulative antimicrobial susceptibility data at a university teaching hospital. *Clin Infect Dis,* 46, 1789-1789.

MICHIE, S., ATKINS, L. & WEST, R. 2014. *The Behaviour Change Wheel: A Guide To Designing Interventions,* London: Silverback.

MICHIE, S., VAN STRALEN, M. M. & WEST, R. 2011. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci,* 6, 42.

MLADENOVIC-ANTIC, S., KOCIC, B., VELICKOVIC-RADOVANOVIC, R., DINIC, M., PETROVIC, J., RANDJELOVIC, G. & MITIC, R. 2016. Correlation between antimicrobial consumption and antimicrobial resistance of Pseudomonas aeruginosa in a hospital setting: a 10-year study. *J Clin Pharm Ther,* 41, 532-537.

MOELLERING, R. C. 1995. Past, present, and future of antimicrobial agents. *Am J Med,* 99, 11S-18S.

MOH. 2017a. *Kingdom of Saudi Arabia national action plan on combating antimicrobial resistance*, Riyadh, Saudi Arabia [Online]. Available: http://extwprlegs1.fao.org/docs/pdf/sau171813.pdf [Accessed 13 March 2018].

MOH. 2017b. *WHO Publishes the Saudi National Action Plan for Combating Antibiotic-resistant Bacteria on its Portal,* Riyadh, Saudi Arabia [Online]. Available:

https://www.moh.gov.sa/en/Ministry/MediaCenter/News/Pages/News-2017-11-19-002.aspx [Accessed 13 March 2018].

MOH 2018. *Statistical Yearbook* [Online]. Available: https://www.moh.gov.sa/en/Ministry/Statistics/book/Pages/default.aspx [Accessed 19 December 2020].

MORLEY, G. L. & WACOGNE, I. D. 2018. UK recommendations for combating antimicrobial resistance: a review of 'antimicrobial stewardship: systems and processes for effective antimicrobial medicine use'(NICE guideline NG15, 2015) and related guidance. *Arch Dis Child Educ Pract ,* 103, 46-49.

MORRILL, H. J., CAFFREY, A. R., GAITANIS, M. M. & LAPLANTE, K. L. 2016. Impact of a Prospective Audit and Feedback Antimicrobial Stewardship Program at a Veterans Affairs Medical Center: A Six-Point Assessment. *PLoS One,* 11, e0150795.

MORRIS, A. M. 2014. Antimicrobial Stewardship Programs: Appropriate Measures and Metrics to Study their Impact. *Curr Treat Options Infect Dis,* 6, 101-112.

MUFTI, M. H. 2000. *Healthcare development strategies in the Kingdom of Saudi Arabia*, US: Springer Science & Business Media.

MULLER, A., LOPEZ-LOZANO, J. M., BERTRAND, X. & TALON, D. 2004. Relationship between ceftriaxone use and resistance to third-generation cephalosporins among clinical strains of Enterobacter cloacae. *J Antimicrob Chemother,* 54, 173-177.

MUNITA, J. M. & ARIAS, C. A. 2016. Mechanisms of Antibiotic Resistance. *Microbiol Spectr,* 4.

NEIDELL, M. J., COHEN, B., FURUYA, Y., HILL, J., JEON, C. Y., GLIED, S. & LARSON, E. L. 2012. Costs of healthcare-and community-associated infections with

antimicrobial-resistant versus antimicrobial-susceptible organisms. *Clinical Infectious Diseases,* 55, 807-815.

NEMETH, J., OESCH, G. & KUSTER, S. P. 2015. Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis. *J Antimicrob Chemother,* 70, 382-395.

NEWMAN, R. E., HEDICAN, E. B., HERIGON, J. C., WILLIAMS, D. D., WILLIAMS, A. R. & NEWLAND, J. G. 2012. Impact of a guideline on management of children hospitalized with community-acquired pneumonia. *Pediatrics,* 129, e597-604.

NIEDERMAN, M. S. 2003. Appropriate use of antimicrobial agents: challenges and strategies for improvement. *Crit Care Med,* 31, 608-616.

NOVICK, G. 2008. Is there a bias against telephone interviews in qualitative research? *Res Nurs Health,* 31, 391-398.

OFORI-ASENSO, R., ZOMER, E., CHIN, K. L., SI, S., MARKEY, P., TACEY, M., CURTIS, A. J., ZOUNGAS, S., & LIEW, D. 2018. Effect of Comorbidity Assessed by the Charlson Comorbidity Index on the Length of Stay, Costs and Mortality among Older Adults Hospitalised for Acute Stroke. *Int J Environ Res Public Health*, 15, 2532.

OHASHI, K., MATSUOKA, T., SHINODA, Y., MORI, T., YOSHIDA, S., YOSHIMURA, T. AND SUGIYAMA, T. 2019. Clinical outcome of pharmacist-led prospective audit with intervention and feedback after expansion from patients using specific antibiotics to those using whole injectable antibiotics. *Eur. J. Clin. Microbiol. Infect. Dis.* 38, 593-600.

OKEKE, I. N., KLUGMAN, K. P., BHUTTA, Z. A., DUSE, A. G., JENKINS, P., O'BRIEN, T. F., PABLOS-MENDEZ, A. & LAXMINARAYAN, R. 2005a. Antimicrobial resistance in

developing countries. Part II: strategies for containment. *Lancet Infect Dis,* 5, 568-580.

OKEKE, I. N., LAXMINARAYAN, R., BHUTTA, Z. A., DUSE, A. G., JENKINS, P., O'BRIEN, T. F., PABLOS-MENDEZ, A. & KLUGMAN, K. P. 2005b. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect Dis,* 5, 481-493.

OM, C., DAILY, F., VLIEGHE, E., MCLAUGHLIN, J. C. & MCLAWS, M. L. 2016. "If it's a broad spectrum, it can shoot better": inappropriate antibiotic prescribing in Cambodia. *Antimicrob Resist Infect Control,* 5, 58.

OPDENAKKER, R. 2006. Advantages and disadvantages of four interview techniques in qualitative research. Forum Qualitative Sozialforschung/ Forum: Qualitative Social Research, 7, art. 11.

OSTHOLM-BALKHED, A., TÄRNBERG, M., NILSSON, M., NILSSON, L. E., HANBERGER, H., HÄLLGREN, A. & SWEDEN, T. S. G. O. S. 2013. Travel-associated faecal colonization with ESBL-producing Enterobacteriaceae: incidence and risk factors. *J Antimicrob Chemother,* 68, 2144-2153.

OWENS, R. C., FRASER, G. L., STOGSDILL, P. & PHARMACISTS, S. O. I. D. 2004. Antimicrobial stewardship programs as a means to optimize antimicrobial use. Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy,* 24, 896-908.

OXMAN, D. A., ADAMS, C. D., DELUKE, G., PHILBROOK, L., IRELAND, P., MITANI, A., PANIZALES, C., FRENDL, G. & ROGERS, S. O. 2015. Improving Antibiotic De-Escalation in Suspected Ventilator-Associated Pneumonia: An Observational Study With a Pharmacist-Driven Intervention. *J Pharm Pract,* 28, 457-461.

O'NEIL, J. 2014. *Review on Antimicrobial Resistance. Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations 2014*. [Online]. Available: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf [Accessed 03 September 2019].

O'NEILL, J. 2016. The Review on Antimicrobial Resistance. TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS. [Online]. Available: https://amr review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf [Accessed 12 September 2019].

PAGEL, S. W. & GAUTIER, P. 2012. Use of antimicrobial agents in livestock. *Rev Sci Tech,* 31, 145-188.

PAKYZ, A. L., OINONEN, M. & POLK, R. E. 2009. Relationship of carbapenem restriction in 22 university teaching hospitals to carbapenem use and carbapenem-resistant Pseudomonas aeruginosa. *Antimicrob Agents Chemother,* 53, 1983-1986.

PANDEY, N. & CASCELLA, M. 2020. Beta Lactam Antibiotics. In: StatPearls. Treasure Island: StatPearls Publishing [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK545311/ [Accessed 06 August 2020].

PASKOVATY, A., PFLOMM, J. M., MYKE, N. & SEO, S. K. 2005. A multidisciplinary approach to antimicrobial stewardship: evolution into the 21st century. *Int J Antimicrob Agents,* 25, 1-10.

PATE, P. G., STOREY, D. F. & BAUM, D. L. 2012. Implementation of an antimicrobial stewardship program at a 60-bed long-term acute care hospital. *Infect Control Hosp Epidemiol,* 33, 405-408.

PATEL, N., MCNUTT, L. A. & LODISE, T. P. 2008. Relationship between various definitions of prior antibiotic exposure and piperacillin-tazobactam resistance among patients with respiratory tract infections caused by Pseudomonas aeruginosa. *Antimicrob Agents Chemother,* 52, 2933-2936.

PATERSON, D. L. 2006. The role of antimicrobial management programs in optimizing antibiotic prescribing within hospitals. *Clin Infect Dis,* 42 Suppl 2, S90-95.

PAUWELS, I., VERSPORTEN, A., DRAPIER, N., VLIEGHE, E. AND GOOSSENS, H. 2021a. Hospital antibiotic prescribing patterns in adult patients according to the WHO Access, Watch and Reserve classification (AWaRe): results from a worldwide point prevalence survey in 69 countries. *J Antimicrob Chemother*, 76, 1614-1624.

PAUWELS, I., VERSPORTEN, A., VERMEULEN, H., VLIEGHE, E. AND GOOSSENS, H. 2021b. Assessing the impact of the Global Point Prevalence Survey of Antimicrobial Consumption and Resistance (Global-PPS) on hospital antimicrobial stewardship programmes: results of a worldwide survey. *Antimicrob Resist Infect Control*, 10, 1-12.

PEERY, A. F., DELLON, E. S., LUND, J., CROCKETT, S. D., MCGOWAN, C. E., BULSIEWICZ, W. J., GANGAROSA, L. M., THINY, M. T., STIZENBERG, K., MORGAN, D. R., RINGEL, Y., KIM, H. P., DIBONAVENTURA, M. D., CARROLL, C. F., ALLEN, J. K., COOK, S. F., SANDLER, R. S., KAPPELMAN, M. D. & SHAHEEN, N. J. 2012. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology,* 143, 1179-87.e1-3.

PERRY, C. M. & MARKHAM, A. 1999. Piperacillin/tazobactam: an updated review of its use in the treatment of bacterial infections. *Drugs,* 57, 805-843.

PINDER, R., SALLIS, A., BERRY, D. & CHADBORN, T. 2015. *Behaviour change and antibiotic prescribing in healthcare settings Literature review and behavioural analysis.* Public Health England [Online]. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/774129/Behaviour_Change_for_Antibiotic_Prescribing_-_FINAL.pdf [Accessed 06 August 2020].

POGUE, J. M., MYNATT, R. P., MARCHAIM, D., ZHAO, J. J., BARR, V. O., MOSHOS, J., SUNKARA, B., CHOPRA, T., CHIDURALA, S. & KAYE, K. S. 2014. Automated alerts coupled with antimicrobial stewardship intervention lead to decreases in length of stay in patients with gram-negative bacteremia. *Infect Control Hosp Epidemiol,* 35, 132-138.

POLK, R. E., JOHNSON, C. K., MCCLISH, D., WENZEL, R. P. & EDMOND, M. B. 2004. Predicting hospital rates of fluoroquinolone-resistant Pseudomonas aeruginosa from fluoroquinolone use in US hospitals and their surrounding communities. *Clin Infect Dis,* 39, 497-503.

POPE, C. & MAYS, N. 2020. *Qualitative Research in Health Care,* 4 th ed., Hoboken, John Wiley and Sons.

POPE, C., ZIEBLAND, S. & MAYS, N. 2000. Qualitative research in health care: Analysing qualitative data. *BMJ*, 320, 114–116.

POPOVSKI, Z., MERCURI, M., MAIN, C., SNE, N., WALSH, K., SUNG, M., RICE, T. & MERTZ, D. 2015. Multifaceted intervention to optimize antibiotic use for intra-abdominal infections. *J Antimicrob Chemother,* 70, 1226-1229.

PUBLIC HEALTH AGENCY OF CANADA. 2015. *Federal action plan on antimicrobial resistance and use in Canada: building on the federal framework for action* [Online]. Available: http://healthycanadians.gc.ca/alt/pdf/publications/drugs-products-medicaments-produits/antibiotic-resistance-antibiotique/action-plan-daction-eng.pdf [Accessed 12 March 2018].

PULCINI, C., BOTELHO-NEVERS, E., DYAR, O. J. & HARBARTH, S. 2014. The impact of infectious disease specialists on antibiotic prescribing in hospitals. *Clin Microbiol Infect,* 20, 963-972.

PULCINI, C. & GYSSENS, I. C. 2013. How to educate prescribers in antimicrobial stewardship practices. *Virulence,* 4, 192-202.

PULCINI, C., WILLIAMS, F., MOLINARI, N., DAVEY, P. & NATHWANI, D. 2011. Junior doctors' knowledge and perceptions of antibiotic resistance and prescribing: a survey in France and Scotland. *Clin Microbiol Infect,* 17, 80-87.

QUALE, J., LANDMAN, D., SAURINA, G., ATWOOD, E., DITORE, V. & PATEL, K. 1996. Manipulation of a hospital antimicrobial formulary to control an outbreak of vancomycin-resistant enterococci. *Clin Infect Dis,* 23, 1020-1025.

RAHAL, J. J., URBAN, C., HORN, D., FREEMAN, K., SEGAL-MAURER, S., MAURER, J., MARIANO, N., MARKS, S., BURNS, J. M., DOMINICK, D. & LIM, M. 1998. Class restriction of cephalosporin use to control total cephalosporin resistance in nosocomial Klebsiella. *JAMA,* 280, 1233-1237.

RAHIM, K. A. A. A. & MOHAMED, A. M. A. 2014. Prevalence of extended spectrum β-lactamase-producing Klebsiella pneumoniae in clinical isolates. *Jundishapur J Microbiol,* 7, e17114.

RAMESH, K., SWAMINATH, M. S., DURAISINGH, L. B. & BALASUBRAMANI, V. 2020. Drug Utilization Evaluation of Meropenem in Surgical Patients in a Tertiary Trauma Care Hospital. *International Journal of Research and Review,* 7, 34-40.

RANJI, S. R., STEINMAN, M. A., SHOJANIA, K. G. & GONZALES, R. 2008. Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis. *Med Care,* 46, 847-862.

RAY, D. AND DATTA, S., 2018. A study on antimicrobial agents utilization pattern using anatomical therapeutic chemical/daily defined dose system and adverse drug reaction pattern in the intensive care unit of a tertiary care teaching hospital in North Eastern state of India. *Int J Basic Clin Pharmacol*, 7, 1612-1619.

RAVEH, D., MUALLEM-ZILCHA, E., GREENBERG, A., WIENER-WELL, Y., SCHLESINGER, Y. & YINNON, A. M. 2006. Prospective drug utilization evaluation of three broad-spectrum antimicrobials: cefepime, piperacillin-tazobactam and meropenem. *QJM,* 99, 397-406.

RAVI, N., LAHA, A., HMAR, L., CHATTERJEE, S., GOSWAMI, J., GOEL, G., DHAR, K., GHOSH, T., DATTA, S. S. & BHATTACHARYA, S. 2017. Exploring the prescribing behaviours and the mind of antibiotic prescribers is critical for a successful antibiotic stewardship programme: Results of a survey from Eastern India. *Indian J Med Microbiol,* 35, 299-301.

REUTER, C.H., PALAC, H.L., KOCIOLEK, L.K., ZHENG, X.T., CHAO, Y.Y., PATEL, R.M. & PATEL, S.J., 2019. Ideal and actual impact of rapid diagnostic testing and antibiotic stewardship on antibiotic prescribing and clinical outcomes in children with positive blood cultures. *Pediatr. Infect. Dis. J.,* 38, 131-137.

RIMAWI, R. H., MAZER, M. A., SIRAJ, D. S., GOOCH, M. & COOK, P. P. 2013. Impact of regular collaboration between infectious diseases and critical care

practitioners on antimicrobial utilization and patient outcome. *Crit Care Med,* 41, 2099-2107.

RITCHIE, J., LEWIS, J., NICHOLLS, C. M. & ORMSTON, R. 2014. *Qualitative research practice: A guide for social science students and researchers*, 2nd ed., London: SAGE Publications.

ROGERS, B. A., AMINZADEH, Z., HAYASHI, Y. & PATERSON, D. L. 2011. Country-to-country transfer of patients and the risk of multi-resistant bacterial infection. *Clin Infect Dis,* 53, 49-56.

ROJO, M. 2006. Collect before you treat: obtaining cultures before antibiotic treatment. *Drugs & Therapy Bulletin,* 20, 1-3.

RUPNIK, M., WILCOX, M. H. & GERDING, D. N. 2009. Clostridium difficile infection: new developments in epidemiology and pathogenesis. *Nat Rev Microbiol,* 7, 526-536.

RYAN, F., COUGHLAN, M. & CRONIN, P. 2009. Interviewing in qualitative research: The one-to-one interview. *Int J Ther Rehabil,* 16, 309-314.

SAGA, T. & YAMAGUCHI, K. 2009. History of antimicrobial agents and resistant bacteria. *JMAJ,* 52, 103-108.

SALE, J. E., LOHFELD, L. H., & BRAZIL, K. 2002. Revisiting the quantitative-qualitative debate: Implications for mixed-methods research. *Qual Quant*, 36, 43-53.

SALEEM, Z., HASSALI, M. A., GODMAN, B., HASHMI, F. K. & SALEEM, F. 2019. Antimicrobial prescribing and determinants of antimicrobial resistance: a qualitative study among physicians in Pakistan. *Int J Clin Pharm,* 41, 1348-1358.

SALKIND, N. J. 2010. *Encyclopedia of Research Design,* Thousand Oaks: SAGE Publications.

SALONGA, S. 2019. *Types of transcription explained: verbatim vs. Intelligent vs. Edited transcription* [Online]. Available: https://www.globalme.net/blog/verbatim-vs-intelligent-vs-edited-transcription/ [Accessed 13 October 2020].

SATTERFIELD, J., MIESNER, A. R. & PERCIVAL, K. M. 2020. The role of education in antimicrobial stewardship. *J Hosp Infect,* 105, 130-141.

SCHOUTEN, J. A., HULSCHER, M. E., NATSCH, S., KULLBERG, B. J., VAN DER MEER, J. W. & GROL, R. P. 2007. Barriers to optimal antibiotic use for community-acquired pneumonia at hospitals: a qualitative study. *Qual Saf Health Care,* 16, 143-149.

SEEMUNGAL, I. A. & BRUNO, C. J. 2012. Attitudes of housestaff toward a prior-authorization-based antibiotic stewardship program. *Infect Control Hosp Epidemiol,* 33, 429-431.

SETO, W. H., CHING, T. Y., KOU, M., CHIANG, S. C., LAUDER, I. J. & KUMANA, C. R. 1996. Hospital antibiotic prescribing successfully modified by 'immediate concurrent feedback'. *Br J Clin Pharmacol,* 41, 229-234.

SEYMOUR, C. W., LIU, V. X., IWASHYNA, T. J., BRUNKHORST, F. M., REA, T. D., SCHERAG, A., RUBENFELD, G., KAHN, J. M., SHANKAR-HARI, M., SINGER, M., DEUTSCHMAN, C. S., ESCOBAR, G. J., & ANGUS, D. C. 2016. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA, 315, 762–774.

SHAH, P. J. & RYZNER, K. L. 2013. Evaluating the appropriate use of piperacillin/tazobactam in a community health system: a retrospective chart review. *P T,* 38, 462-483.

SHALINI, S., RAVICHANDRAN, V., MOHANTY, B. K., DHANARAJ, S. K. & SARASWATHI, R. 2010. Drug utilization studies-an overview. *Int J of Pharm Sci Nanotechnol,* 3, 803-810.

SHARLAND, M., GANDRA, S., HUTTNER, B., MOJA, L., PULCINI, C., ZENG, M., MENDELSON, M., CAPPELLO, B., COOKE, G., MAGRINI, N. AND AZIZ, Z. 2019. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use—the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. *Lancet Infect. Dis*, 19, 1278-1280.

SHIBL, A. M., MEMISH, Z. A., KAMBAL, A. M., OHALY, Y. A., ISHAQ, A., SENOK, A. C. & LIVERMORE, D. M. 2014. National surveillance of antimicrobial resistance among Gram-positive bacteria in Saudi Arabia. *J Chemother,* 26, 13-18.

SKODVIN, B., AASE, K., CHARANI, E., HOLMES, A. & SMITH, I. 2015. An antimicrobial stewardship program initiative: a qualitative study on prescribing practices among hospital doctors. *Antimicrob Resist Infect Control,* 4, 24.

SMITH, F. 2002. *Research Methods in Pharmacy Practice*, 1 st ed., London: Pharmaceutical Press.

SMITH, R. & COAST, J. 2013. The true cost of antimicrobial resistance. *BMJ,* 346, f1493.

SOLOMON, D. H., VAN HOUTEN, L., GLYNN, R. J., BADEN, L., CURTIS, K., SCHRAGER, H. & AVORN, J. 2001. Academic detailing to improve use of broad-spectrum antibiotics at an academic medical center. *Arch Intern Med,* 161, 1897-1902.

SOMILY, A. M., ABSAR, M. M., ARSHAD, M. Z., AL ASKA, A. I., SHAKOOR, Z. A., FATANI, A. J., SIDDIQUI, Y. M. & MURRAY, T. S. 2012. Antimicrobial susceptibility patterns of multidrug-resistant Pseudomonas aeruginosa and Acinetobacter

baumannii against carbapenems, colistin, and tigecycline. *Saudi Med J,* 33, 750-755.

SONMEZER, M. C., ERTEM, G., ERDINC, F. S., KAYA KILIC, E., TULEK, N., ADILOGLU, A. & HATIPOGLU, C. 2016. Evaluation of Risk Factors for Antibiotic Resistance in Patients with Nosocomial Infections Caused by Pseudomonas aeruginosa. *Can J Infect Dis Med Microbiol,* 2016, 1321487.

SPIVAK, E.S., COSGROVE, S.E. AND SRINIVASAN, A., 2016. Measuring appropriate antimicrobial use: attempts at opening the black box. *Clin Infect Dis*, 63, 1-6.

SPOORENBERG, V., HULSCHER, M. E., AKKERMANS, R. P., PRINS, J. M. & GEERLINGS, S. E. 2014. Appropriate antibiotic use for patients with urinary tract infections reduces length of hospital stay. *Clin Infect Dis,* 58, 164-169.

STAMM, M., GRAYSON, M. L., NICOLLE, L. & AND POWELL, M. 2001. *WHO global strategy for containment of antimicrobial resistance, World Health Organization* [Online]. Geneva, Switzerland. Available: http://www.who.int/drugresistance/WHO_Global_Strategy_English.pdf [Accessed 21 March 2018].

STURGES, J. E. & HANRAHAN, K. J. 2004. Comparing Telephone and Face-to-Face Qualitative Interviewing: a Research Note. *Qualitative Research,* 4, 107-118.

SULLIVAN, C. & FORRESTER, M. A. 2019. *Doing qualitative research in psychology: A practical guide*, 2 nd ed., London: SAGE Publications.

SZUMILAS, M., 2010. Explaining odds ratios. *J Can Acad Child Adolesc Psychiatry*, 19, 227.

TAMMA, P. D., AVDIC, E., LI, D. X., DZINTARS, K. & COSGROVE, S. E. 2017. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. *JAMA Intern Med,* 177, 1308-1315.

TAMMA, P. D. & COSGROVE, S. E. 2011. Antimicrobial stewardship. *Infect Dis Clin North Am,* 25, 245-260.

TAMMA, P. D., HOLMES, A. & ASHLEY, E. D. 2014. Antimicrobial stewardship: another focus for patient safety? *Curr Opin Infect Dis,* 27, 348-355.

TANDON, A., MURRAY, C. J., LAUER, J. A. & EVANS, D. B. 2000. *Measuring overall health system performance for 191 countries.* Geneva: World Health Organization. [Online]. Available: https://www.who.int/healthinfo/paper30.pdf [Accessed 12 March 2018].

TARRANT, C., COLMAN, A. M., JENKINS, D. R., CHATTOE-BROWN, E., PERERA, N., MEHTAR, S., NAKKAWITA, W., BOLSCHER, M & KROCKOW, E. M. 2021. Drivers of Broad-Spectrum Antibiotic Overuse across Diverse Hospital Contexts—A Qualitative Study of Prescribers in the UK, Sri Lanka and South Africa. *Antibiotics*, 10, 94.

TARRANT, C., KROCKOW, E. M., NAKKAWITA, W., BOLSCHER, M., COLMAN, A. M., CHATTOE-BROWN, E., PERERA, N., MEHTAR, S. & JENKINS, D. R. 2020. Moral and Contextual Dimensions of "Inappropriate" Antibiotic Prescribing in Secondary Care: A Three-Country Interview Study. *Front. sociol,* 5, 7.

TAWFIK, A. F., SHIBL, A. M., ALJOHI, M. A., ALTAMMAMI, M. A. & AL-AGAMY, M. H. 2012. Distribution of Ambler class A, B and D β-lactamases among Pseudomonas aeruginosa isolates. *Burns,* 38, 855-860.

TEIXEIRA RODRIGUES, A., FERREIRA, M., PIÑEIRO-LAMAS, M., FALCÃO, A., FIGUEIRAS, A. & HERDEIRO, M. T. 2016. Determinants of physician antibiotic prescribing behavior: a 3 year cohort study in Portugal. *Curr Med Res Opin,* 32, 949-957.

TEIXEIRA RODRIGUES, A., FERREIRA, M., ROQUE, F., FALCÃO, A., RAMALHEIRA, E., FIGUEIRAS, A. & HERDEIRO, M. T. 2015. Physicians' attitudes and knowledge

concerning antibiotic prescription and resistance: questionnaire development and reliability. *BMC Infect Dis,* 16, 7.

TEIXEIRA RODRIGUES, A., ROQUE, F., FALCÃO, A., FIGUEIRAS, A. & HERDEIRO, M. T. 2013. Understanding physician antibiotic prescribing behaviour: a systematic review of qualitative studies. *Int J Antimicrob Agents,* 41, 203-212.

THAKOLKARAN, N., SHETTY, A. V., D'SOUZA, N. D. R. & SHETTY, A. K. 2017. Antibiotic prescribing knowledge, attitudes, and practice among physicians in teaching hospitals in South India. *J Family Med Prim Care,* 6, 526-532.

THE CENTER FOR DISEASE DYNAMICS ECONOMICS & POLICY. 2020a. *Resistance Map: Antibiotic Use* [Online]. Available: https://resistancemap.cddep.org/AntibioticUse.php [Accessed 11 December 2020].

THE CENTER FOR DISEASE DYNAMICS ECONOMICS & POLICY. 2020b. *Resistance Map: Antibiotic Resistance* [Online]. Available: https://resistancemap.cddep.org/AntibioticResistance.php [Accessed 11 December 2020].

THE PEW CHARITABLE TRUSTS 2021. *Tracking the Global Pipeline of Antibiotics in Development, March 2021.* [Online]. Available: https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development [Accessed 20 June 2021].

THE WHITE HOUSE. 2015. *National action plan for combating antibiotic-resistant bacteria* [Online]. Available: https://www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf [Accessed 12 March 2018].

THEURETZBACHER, U., OUTTERSON, K., ENGEL, A. & KARLÉN, A. 2020. The global preclinical antibacterial pipeline. *Nat Rev Microbiol,* 18, 275-285.

THOM, K. A., SCHWEIZER, M. L., OSIH, R. B., MCGREGOR, J. C., FURUNO, J. P., PERENCEVICH, E. N., & HARRIS, A. D. 2008. Impact of empiric antimicrobial therapy on outcomes in patients with Escherichia coli and Klebsiella pneumoniae bacteremia: a cohort study. *BMC Infect Dis*, 8, 1-9

TOBIN, G. A. & BEGLEY, C. M. 2004. Methodological rigour within a qualitative framework. *J Adv Nurs,* 48, 388-396.

TOMA, A. & DEYNO, S. 2015. Overview on mechanisms of antibacterial resistance. *Int J Res Pharm Biosci,* 2, 27-36.

TONG, A., SAINSBURY, P. & CRAIG, J. 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care,* 19, 349-357.

TONKIN-CRINE, S., WALKER, A. S. & BUTLER, C. C. 2015. Contribution of behavioural science to antibiotic stewardship. *BMJ,* 350, h3413.

TONER, E., ADALJA, A., GRONVALL, G.K., CICERO, A. and Inglesby, T.V., 2015. Antimicrobial resistance is a global health emergency. *Health secur,* 13, 153-155.

TONKIN-CRINE, S., YARDLEY, L. & LITTLE, P. 2011. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and meta-ethnography. *J Antimicrob Chemother,* 66, 2215-2223.

TRIPATHI, R., ALBARRAQ, A.A., MAKEEN, H.A., ALQAHTANI, S.S., TRIPATHI, P. & PANCHOLI, S.S., 2020. Knowledge and perceptions of antimicrobial stewardship program among health-care students in Saudi Arabia. *Saudi J Health Sci,* 9, 122-129.

UNDP. 2020. *Human Development Report 2020* [Online]. New York, USA. Available: http://hdr.undp.org/sites/default/files/hdr2020.pdf [Accessed 27 July 2021].

UNITED NATIONS. 2003. *World population 2002* [Online]. New York, US. Available: http://www.un.org/esa/population/publications/wpp2002/WorldPop2002.PDF [Accessed 15 April 2018].

VALDERAS, J. M., STARFIELD, B., SIBBALD, B., SALISBURY, C. & ROLAND, M. 2009. Defining comorbidity: implications for understanding health and health services. *Ann Fam Med,* 7, 357-363.

VAN, T. M., PHAM, N. H., HOANG, T. L. H., DANG, N. T., PHAM, T. N. A., NGUYEN, T. H., CAO, Q. T., PHAM, V. T. H., NGUYEN, N. & VASQUEZ, A. 2020. First-Time Use of Clinical Pharmacists to Improve Appropriate Antibiotic Prescribing in a Medical ICU in Viet Nam. Infect Control Hosp Epidemiol*,* 41, s236-s236.

VAN BOECKEL, T. P., GANDRA, S., ASHOK, A., CAUDRON, Q., GRENFELL, B. T., LEVIN, S. A. & LAXMINARAYAN, R. 2014. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis,* 14, 742-750.

VAN DAALEN, F. V., LAGERBURG, A., DE KORT, J., SÀNCHEZ RIVAS, E. & GEERLINGS, S. E. 2017. Implementation of an antibiotic checklist increased appropriate antibiotic use in the hospital on Aruba. *Int J Infect Dis,* 59, 14-21.

VAN DEN BOSCH, C., HULSCHER, M. E., AKKERMANS, R. P., WILLE, J., GEERLINGS, S. E., & PRINS, J. M. 2017. Appropriate antibiotic use reduces length of hospital stay. *J Antimicrob Chemother*, 72, 923-932.

VAN DE SANDE-BRUINSMA, N., GRUNDMANN, H., VERLOO, D., TIEMERSMA, E., MONEN, J., GOOSSENS, H., FERECH, M., GROUP, E. A. R. S. S. & GROUP, E. S.

O. A. C. P. 2008. Antimicrobial drug use and resistance in Europe. *Emerg Infect Dis,* 14, 1722-1730.

VANDERKOOI, O. G., LOW, D. E., GREEN, K., POWIS, J. E., MCGEER, A. & NETWORK, T. I. B. D. 2005. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis,* 40, 1288-1297.

VAUGHN, V.M.; FLANDERS, S.A.; SNYDER, A.; CONLON, A.; ROGERS, M.A.; MALANI, A.N.; MCLAUGHLIN, E.; BLOEMERS, S.; SRINIVASAN, A.; NAGEL, J. & KAATZ, S. 2019. Excess antibiotic treatment duration and adverse events in patients hospitalized with pneumonia: A multihospital cohort study. *Ann Intern Med* 171, 153–163.

VELASCO, E., ZIEGELMANN, A., ECKMANNS, T. & KRAUSE, G. 2012. Eliciting views on antibiotic prescribing and resistance among hospital and outpatient care physicians in Berlin, Germany: results of a qualitative study. *BMJ Open,* 2, e000398.

VENTOLA, C. L. 2015. The antibiotic resistance crisis: part 1: causes and threats. *P T,* 40, 277-283.

VERSPORTEN, A., ZARB, P., CANIAUX, I., GROS, M.F., DRAPIER, N., MILLER, M., JARLIER, V., NATHWANI, D., GOOSSENS, H., KORAQI, A. AND HOXHA, I. 2018. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob. Health* , 6, e619-e629.

VINCENT, J. L. 2016. The Clinical Challenge of Sepsis Identification and Monitoring. *PLoS Med,* 13, e1002022.

VINDIGNI, S. M. & SURAWICZ, C. M. 2015. C. difficile Infection: Changing Epidemiology and Management Paradigms. *Clin Transl Gastroenterol,* 6, e99.

WAKSMAN, S. & TISHLER, M. 1942. The Chemical Nature of Actinomycin, an Anti-microbial Substance Produced by Actinomyces Antibioticus, *J Biol Chem,* 142, 519-528.

WAKSMAN, S. A. 1953. Streptomycin: background, isolation, properties, and utilization. *Science,* 118, 259-266.

WALSTON, S., AL-HARBI, Y. & AL-OMAR, B. 2008. The changing face of healthcare in Saudi Arabia. *Ann Saudi Med,* 28, 243-250.

WARREMAN, E. B., LAMBREGTS, M. M. C., WOUTERS, R. H. P., VISSER, L. G., STAATS, H., VAN DIJK, E. & DE BOER, M. G. J. 2019. Determinants of in-hospital antibiotic prescription behaviour: a systematic review and formation of a comprehensive framework. *Clin Microbiol Infect,* 25, 538-545.

WATHNE, J. S., HARTHUG, S., KLEPPE, L. K. S., BLIX, H. S., NILSEN, R. M., CHARANI, E., & SMITH, I. 2019. The association between adherence to national antibiotic guidelines and mortality, readmission and length of stay in hospital inpatients: results from a Norwegian multicentre, observational cohort study. *Antimicrob Resist Infect Control*, 8, 1-10

WENISCH, J. M., SCHMID, D., TUCEK, G., KUO, H. W., ALLERBERGER, F., MICHL, V., TESIK, P., LAFERL, H. & WENISCH, C. 2012. A prospective cohort study on hospital mortality due to Clostridium difficile infection. *Infection,* 40, 479-484.

WETTERMARK, B., ELSEVIERS, M., ALMARSDÓTTIR, A. B., ANDERSEN, M., BENKO, R., BENNIE, M., et al. 2016. “Introduction to drug utilization research,” in *Drug Utilization Research: Methods and Applications*, eds M. Elseviers, B. Wettermark, A. B. Almarsdóttir, M. Andersen, R. Benko, M. Bennie et al. Chichester: John Wiley & Sons, Ltd, 1–12.

WHITE, A. C., ATMAR, R. L., WILSON, J., CATE, T. R., STAGER, C. E. & GREENBERG, S. B. 1997. Effects of requiring prior authorization for selected antimicrobials: expenditures, susceptibilities, and clinical outcomes. *Clin Infect Dis,* 25, 230-239.

WHO 2001. *WHO Global strategies for the containment of antimicrobial resistance.* Geneva, Switzerland [Online]. Available: http://whqlibdoc.who.int/hq/2001/WHO_CDS_CSR_DRS_2001.2.pdf [Accessed 03 August 2020].

WHO 2011. *Report on the Burden of Endemic Health Care-Associated Infection Worldwide.* Geneva, Switzerland [Online]. Available: https://apps.who.int/iris/bitstream/handle/10665/80135/9789241501507_eng.pdf?sequence=1&isAllowed=y [Accessed 11 January 2018].

WHO 2012. *The evolving threat of antimicrobial resistance—options for action.* Geneva, Switzerland. [Online]. Available: https://apps.who.int/iris/bitstream/handle/10665/44812/9789241503181_eng.pdf [Accessed 11 October 2020].

WHO. 2015. *Global action plan on antimicrobial resistance*. Geneva, Switzerland. [Online]. Available: http://www.who.int/antimicrobial-resistance/global-action-plan/en/ [Accessed 11 January 2018].

WHO 2016. *Critically Important Antimicrobials for Human Medicine, 5th Revision 2016: Ranking of Antimicrobial Agents for Risk Management of AMR Due to Non-Human Use.* Geneva, Switzerland. [Online]. Available: https://apps.who.int/iris/bitstream/handle/10665/255027/9789241512220-eng.pdf?sequence=1&isAllowed=y [Accessed 09 January 2018].

WHO. 2017a. *Antibiotic resistance* [Online]. Available: http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/ [Accessed 09 January 2018].

WHO. 2017b. *WHO publishes list of bacteria for which new antibiotics are urgently needed.* Geneva, Switzerland [Online]. Available: https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed [Accessed 09 January 2018].

WHO. 2018a. *Antibiotic resistance.* Geneva, Switzerland. [Online]. Available: http://www.who.int/news-room/fact-sheets/detail/antibiotic-resistance [Accessed 01 June 2018].

WHO 2018b. *Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2016-2017*. Geneva, Switzerland. [Online]. Available: https://apps.who.int/iris/bitstream/handle/10665/259744/9789241513449-eng.pdf?sequence=1 [Accessed 01 December 2018].

WHO. 2018c. *Guidelines for Surveillance of Antimicrobial Use.* Geneva, Switzerland [Online]. Available: http://www.who.int/medicines/areas/rational_use/AMU_Surveillance/en/ [Accessed 08 February 2018].

WHO 2018d. Critically Important Antimicrobials for Human Medicine, 6th Revision 2018: Ranking of Antimicrobial Agents for Risk Management of AMR Due to Non-Human Use. Geneva, Switzerland. [Online]. Available: https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf [Accessed 04 July 2021].

WHO. 2018f. WHO methodology for Point Prevalence Survey on Antibiotic Use in Hospitals. Geneva, Switzerland [Online]. Available: https://www.who.int/publications/i/item/WHO-EMP-IAU-2018.01 [Accessed 29 September 2021].

WHO. 2019. WHO Model List of Essential Medicines, 21st List, 2019. Geneva, Switzerland [Online]. Available: https://www.who.int/publications/i/item/WHOMVPEMPIAU2019.06 [Accessed 29 September 2021].

WHO. 2020. *ATC/DDD Index 2020* [Online]. Available: https://www.whocc.no/atc_ddd_index/ [Accessed 08 February 2018].

WHO 2021. *Global Antimicrobial Resistance and Use Surveillance System (GLASS)* Report. Geneva, Switzerland. [Online]. Available: https://www.who.int/publications/i/item/9789240027336 [Accessed 17 October 2021].

WHO COLLABORATING CENTRE. 2018. *ATC/DDD Index 2018.* Oslo, Norway [Online]. Available: https://www.whocc.no/atc_ddd_index/ [Accessed 08-February 2018].

WIEGAND, P. N., NATHWANI, D., WILCOX, M. H., STEPHENS, J., SHELBAYA, A. & HAIDER, S. 2012. Clinical and economic burden of Clostridium difficile infection in Europe: a systematic review of healthcare-facility-acquired infection. *J Hosp Infect,* 81, 1-14.

WILSON, A. P. R. 2017. Sparing carbapenem usage. *J Antimicrob Chemother,* 72, 2410-2417.

WINAU, F., WESTPHAL, O. & WINAU, R. 2004. Paul Ehrlich--in search of the magic bullet. *Microbes Infect,* 6, 786-789.

WINTERS, B. D., THIEMANN, D. R. & BROTMAN, D. J. 2010. Impact of a restrictive antimicrobial policy on the process and timing of antimicrobial administration. *J Hosp Med,* 5, E41-45.

WOOD, F., SIMPSON, S. & BUTLER, C. C. 2007. Socially responsible antibiotic choices in primary care: a qualitative study of GPs' decisions to prescribe broad-spectrum and fluroquinolone antibiotics. *Fam Pract,* 24, 427-434.

WOODRUFF, H. B. 2014. Selman A. Waksman, winner of the 1952 Nobel Prize for physiology or medicine. *Appl Environ Microbiol,* 80, 2-8.

YAM, P., FALES, D., JEMISON, J., GILLUM, M. & BERNSTEIN, M. 2012. Implementation of an antimicrobial stewardship program in a rural hospital. *Am J Health Syst Pharm,* 69, 1142-1148.

YATES, T. D., DAVIS, M. E., TAYLOR, Y. J., DAVIDSON, L., CONNOR, C. D., BUEHLER, K. & SPENCER, M. D. 2018. Not a magic pill: a qualitative exploration of provider perspectives on antibiotic prescribing in the outpatient setting. *BMC Fam Pract,* 19, 96.

YEO, C. L., CHAN, D. S., EARNEST, A., WU, T. S., YEOH, S. F., LIM, R., JUREEN, R., FISHER, D. & HSU, L. Y. 2012. Prospective audit and feedback on antibiotic prescription in an adult hematology-oncology unit in Singapore. *Eur J Clin Microbiol Infect Dis,* 31, 583-590.

YEZLI, S., SHIBL, A. M., LIVERMORE, D. M. & MEMISH, Z. A. 2014. Prevalence and antimicrobial resistance among Gram-negative pathogens in Saudi Arabia. *J Chemother,* 26, 257-272.

YOUNG, M. & PLOSKER, G. L. 2001. Piperacillin/tazobactam: a pharmacoeconomic review of its use in moderate to severe bacterial infections. *Pharmacoeconomics,* 19, 1135-1175.

YOUSSIF, E., ASEERI, M. & KHOSHHAL, S. 2018. Retrospective evaluation of piperacillin–tazobactam, imipenem–cilastatin and meropenem used on surgical floors at a tertiary care hospital in Saudi Arabia. *J Infect Public Health,* 11, 486-490.

YU, K., RHO, J., MORCOS, M., NOMURA, J., KAPLAN, D., SAKAMOTO, K., BUI, D., YOO, S. AND JONES, J., 2014. Evaluation of dedicated infectious diseases pharmacists on antimicrobial stewardship teams. *Am J Health Syst Pharm*, *71*,1019-1028.

YUSUF, N. 2014. Private and public healthcare in Saudi Arabia: future challenges. *Int J Bus Econ Dev,* 2, 114-118.

ZAHA, D. C., BUNGAU, S., UIVAROSAN, D., TIT, D. M., MAGHIAR, T. A., MAGHIAR, O., PANTIS, C., FRATILA, O., RUS, M. & VESA, C. M. 2020. Antibiotic Consumption and Microbiological Epidemiology in Surgery Departments: Results from a Single Study Center. *Antibiotics (Basel),* 9, 81.

ZEENNY, R., NASR, Z. & ADAIMY, I. 2014. Retrospective evaluation of the appropriate use of piperacillin/tazobactam in a tertiary care teaching hospital in Lebanon. *Acta Medica Mediterranea,* 30, 655-663.

ZHANG, D., CUI, K., LU, W., BAI, H., ZHAI, Y., HU, S., LI, H., DONG, H., FENG, W. & DONG, Y. 2019. Evaluation of carbapenem use in a tertiary hospital: antimicrobial stewardship urgently needed. *Antimicrob Resist Infect Control,* 8, 5.

ZOWAWI, H. M. 2016. Antimicrobial resistance in Saudi Arabia. An urgent call for an immediate action. *Saudi Med J,* 37, 935-940.

ZOWAWI, H. M., BALKHY, H. H., WALSH, T. R. & PATERSON, D. L. 2013. β-Lactamase production in key gram-negative pathogen isolates from the Arabian Peninsula. *Clin Microbiol Rev,* 26, 361-380.

Appendix

Appendix1. Published study (Quantitative)

Alsaleh NA, Al-Omar HA, Mayet AY, Mullen AB. 2020 Evaluating the appropriateness of carbapenem and piperacillin-tazobactam prescribing in a tertiary care hospital in Saudi Arabia. *Saudi Pharm J*, 28, 1492-1498.

Saudi Pharmaceutical Journal 28 (2020) 1492–1498

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Evaluating the appropriateness of carbapenem and piperacillin-tazobactam prescribing in a tertiary care hospital in Saudi Arabia

Nada A Alsaleh[a,b], Hussain A Al-Omar[c], Ahmed Y Mayet[c,d], Alexander B Mullen[b,*]

[a] Department of Pharmacy Practice, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh 84428, Saudi Arabia
[b] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE, United Kingdom
[c] Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
[d] King Khalid University Hospital, Riyadh 11451, Saudi Arabia

ARTICLE INFO

Article history:
Received 11 May 2020
Accepted 17 September 2020
Available online 25 September 2020

Keywords:
Carbapenem
Imipenem-cilastatin
Meropenem
Piperacillin-tazobactam
Prescribing patterns
Antimicrobial stewardship

ABSTRACT

Background: Antimicrobial resistance (AMR) is presently considered an emergent major global public health concern and excessive and/or inappropriate use of broad-spectrum antimicrobials contribute to the development of AMR.
Objective: To evaluate the appropriateness of carbapenems and piperacillin-tazobactam use in a tertiary care hospital.
Methods: A retrospective, observational, cross-sectional, drug-utilization study was conducted. The study included all adult hospitalized patients who had received at least one dose of the antimicrobials during their admission for the period between 1 January 2016 and 31 December 2017. The appropriateness of antimicrobial therapy was evaluated according to the Infectious Diseases Society of America (IDSA) guidelines with the consideration of the institutional antibiogram.
Results: Overall, 2731 patients received 5005 courses with one of the antimicrobials, for a total of 5045.9 defined daily doses (DDD) of imipenem-cilastatin, 6492.3 of meropenem and 15,595 of piperacillin-tazobactam (4.93, 6.34 and 15.24 DDD/100 bed days, respectively). The mean age of the patients who received either antimicrobial was 55.5 ± 20.3 years, with a 14-day average length of hospital stay. About half (52%) of the prescriptions were written for patients treated in the medical ward. Pneumonia (26.6%) and sepsis (24.9%) were the most common indication for the initiation of antimicrobial therapy. Of the assessed prescriptions, only 2787 (56.5%) were prescribed appropriately, with 2142 (43.5%) deemed inappropriate. The three most common reasons for inappropriate prescription were: the spectrum of activity was too broad (44.6%), followed by antimicrobial use without culture request (32.4%), and failure of suitable antimicrobial de-escalation (19.9%).
Conclusions: The study indicates that the overall rate of inappropriateness was high, emphasizing the need to develop initiatives to effectively improve broad-spectrum antimicrobial prescribing.

1. Introduction

In the last decade, there has been a substantial increase in bacterial organisms resistant to multiple antimicrobial drugs (World Health Organization, 2017). At present, the World Health Organization (WHO) considers AMR as a significant global public health crisis (WHO, 2017). Infections caused by resistant bacteria are not only difficult to treat (Frieri et al., 2017) but also can prolong patient hospitalization, increase mortality, morbidity, and the cost of care (Cosgrove, 2006). Excessive antimicrobial use has been associated with superinfection and also disease associated with antimicrobial use, for example, *Clostridium difficile*, both of which increase morbidity and mortality in hospitalized patients (Dial et al., 2008, Wenisch et al., 2012). There is no reliable estimation of AMR cases worldwide, primarily due to inadequate surveillance. Limitations of any surveillance system or AMR research are those characteristics associated with the assumptions, design, methodology and data used that influence the findings explana-

* Corresponding author.
E-mail addresses: Nada.alsaleh@strath.ac.uk (N.A Alsaleh), halomar@ksu.edu.sa (H.A Al-Omar), iymayet@ksu.edu.sa (A.Y Mayet), a.mullen@strath.ac.uk (A.B Mullen).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2020.09.015
1319-0164/

Appendix 2. Permission to include the published article in the thesis

Evaluating the appropriateness of carbapenem and piperacillin-tazobactam prescribing in a tertiary care hospital in Saudi Arabia

Author: Nada A Alsaleh,Hussain A Al-Omar,Ahmed Y Mayet,Alexander B Mullen

Publication: Journal of the Saudi Pharmaceutical Society

Publisher: Elsevier

Date: Available online 25 September 2020

Appendix 3. Ethical approval for the study

Kingdom of Saudi Arabia
King Saud University (0134)
P.O. Box 7805 Riyadh 1172
Tel. +966 11 4670011
Fax. +966 11 4671992
http://medicine.ksu.edu.sa

جامعة الملك سعود
King Saud University
المدينة الطبية الجامعية

15.02.18 (29.04.1439)
Ref. No. 18/0159/IRB

To: **Dr. Nada Alsaleh**
Department of Clinical Pharmacy
Prince Nora Bint Abdul Rahman University
Email: nada.alsaleh@strath.ac.uk
Principal Investigator

CC: Dr. Ahmed Mayet, Dr. Hussain Al-Omar
Co-Investigators

Subject: **Research Project No. E-18-2869**

Project Title: "Assessing Antimicrobial Prescribing in Tertiary Care Hospital in Kingdom of Saudi Arabia (KSA)"

Type of Review: Expedite
Date of Approval: 15 February 2018
Date of Expiry: 15 February 2019

Dear Dr. Nada Alsaleh,

I am pleased to inform you that your above-mentioned research project was reviewed and approved on 15 February 2018 (29 Jumada-I 1439). You are now granted permission to conduct study given that your study does not disclose patient identity and poses no risk to the patients.

As principal investigator, you are required to abide by the rules and regulations of the kingdom of Saudi Arabia and the research policies and procedures of the KSU IRB. If you make any changes to the protocol during the period of this approval, you must submit a revised protocol to the IRB for approval prior to implementing the changes. Please quote the project number shown above in any future correspondence or follow-ups related to this study.

We wish you success in your research and request you to keep the IRB informed about the progress and final outcome of the study in a regular basis. If you have any question, please feel free to contact me.

Thank you!

Sincerely yours,

Dr. Ayman Al-Eyadhy
Chairman, Institutional Review Board
King Saud University College of Medicine
King Saud University Medical City
P.O. Box 7805 Riyadh 11472 K.S.A.
E-mail: aleyadhy@ksu.edu.sa

كلية الطب
لجنة أخلاقيات البحوث الطبية
College Medicine
Institutional Review Board (IRB)

/braezell

Appendix 4. List of patient information extracted from the hospital database

1. Patient identifier
2. Financial Number
3. Antibiotic name
4. Date of birth
5. Sex
6. Age- Years
7. Admission Date & Time
8. Discharge Date & Time
9. Deceased Date & Time
10. LOS
11. Location
12. Allergy
13. Height
14. Weight
15. BMI
16. Surgical Case Specialty
17. Actual Procedure
18. Procedure level
19. Procedure Start Date and Time
20. Order Date & Time
21. Dispense Date & Time
22. Dose Strength
23. Dose Unit
24. Dose Frequency
25. Route of Administration
26. Dose Duration
27. Dose Duration Unit
28. Total Dispense Doses
29. Prescriber name
30. Prescriber position
31. Diagnosis Description
32. Diagnosis Date & Time
33. Culture request Date & Time
34. Susceptibility Result Date & Time
35. Organism
36. Antibiotic
37. Body Site
38. Detail Susceptibility Test
39. Micro Source Description
40. Susceptibility Result
41. Lab value
42. Lab test Date & Time

43. Specimen Type
44. Numeric Result Value
45. Result Value Unit

Appendix 5. Retrieved disease data recoded into new co-morbidities categories

Co morbidity category	Disease
Diabetes	Diabetes
Cardiovascular disease	Heart failure Left ventricular systolic dysfunction Ischaemic heart disease Rheumatic heart disease Ischaemic cardiomyopathy Atrial fibrillation Peripheral vascular disease
Respiratory disease	Asthma COPD Chronic Bronchitis Cystic Fibrosis Bronchiectasis
Dyslipidemia	Dyslipidemia
Psychiatric disorder	Depression Anxiety Generalised anxiety disorder Bipolar affective disorder Schizophrenia
Musculoskeletal disorder	Osteoporosis
Hypertension	Hypertension
Hematological disorder	Beta thalassemias Anemia Sickle cell anemia
Gastrointestinal disease	Irritable bowel syndrome Gastroesophageal Reflux Disease Gastric ulcer Crohn's disease
Liver disease	Hepatitis
Kidney disease	Chronic kidney disease End stage renal disease
Neurological disorders	Epilepsy Alzheimer's disease Seizure Dementia
Thyroid disorder	Hypothyroidism Hyperthyroidism
Cancer	Breast Cancer Bladder Cancer Lymphoma Colorectal Cancer Lung Cancer

	Ovarian Cancer Pancreatic Cancer Esophageal Cancer Thyroid Carcinoma Gastric Cancer Rectal cancer Acute myeloid leukaemia Brain cancer

Appendix 6. Retrieved location data recoded into new locations categories

Location in the retrieved data	Location Description according to the hospital	New location category
K W-25A Burn	K Ward-25A BURN UNIT	Burn Unit
K W-24A Cardio	K Ward-24A Cardio	Cardiology
K W-31A Cardio	K Ward-31A Cardio	Cardiology
K W- DSU	K Ward- Day Surgery Unit	Day surgery
K Adult ED Hold	K Emergency Department Adult Hold	ED
K ED Adult	K Emergency Department Adult	ED
A W-6B	A Ward 6B Female ENT	Internal medicine
A W-7A	A Ward 7A Male Ophtha / Cornea / External	Internal medicine
A W-6A	A Ward 6A Male ENT	Internal medicine
A W-7B	A Ward 7B Female Ophtha / Cornea / External	Internal medicine
K W-25 F MED	K Ward-25 F MED (CTU4,Pulmonology, Dermatology)	Internal medicine
K W-37 Med	K Ward-37 medicine	Internal medicine
K W-32A Med	K Ward-32A medicine	Internal medicine
K W-35 BC	K Ward-35 Business Center	Internal medicine
K W-31A Short Stay	K Ward-31A Short Stay	Internal medicine
K W-23 F MED	K Ward-23 F MED(CTU1,CTU2,Neurology,Gastroenterology)	Internal medicine
K W-42 Academic	K Ward-42 Academic Staff	Internal medicine
K W-34A Med	K Ward-34A medicine	Internal medicine
K W-39 Med	K Ward-39 medicine	Internal medicine
K W-24 F MED	K Ward-24 F MED (CTU4,Nephrology,Rheumatology)	Internal medicine
K W-32 M MED	K Ward-32 M MED(CTU1,CTU2,Nephro,Neuro,Derma)	Internal medicine
K W-33 M MED	K Ward-33 M MED(CTU3,CTU4,Gastro,Rheuma,Pulmo)	Internal medicine

K W-38 Med	K Ward-38 medicine	Internal medicine
K W-41 Academic	K Ward-41 Academic Staff	Internal medicine
K W-37 ISO	K Ward-37 Isolation Unit	Internal medicine
K W-25B Med	K Ward-25B medicine	Internal medicine
K W-39 ISO	K Ward-39 Isolation Unit	Internal medicine
K W-32BC ISO	K Ward-32BC Isolation Unit	Internal medicine
K W-32 M ISO	K Ward-32 Male Isolation Unit	Internal medicine
K W-38 Iso	K Ward-38 Isolation Unit	Internal medicine
K W-23AC Iso	K Ward-23AC Isolation Unit	Internal medicine
K W-23 F ISO	K Ward-23 Female Isolation Unit	Internal medicine
K W-02 M Psych	K Ward-02 Male Psychiatry	Internal medicine
K W-01 F Psych	K Ward-01 Female Psychiatry	Internal medicine
K W-15A MERS-CoV	K Ward-15A MERS-COV BAY Adult Medical Surgery	Surgical
K W-HDU	K Ward - High Dependency Unit	HDU
K W-22A Long Stay	K Ward-22A Long Stay Critical Care	ICU
K CCU	K 3rd Floor - Cardiac Care Unit	ICU
K CICU	K 2nd Floor - Cardiac Intensive Care Unit	ICU
K MICU	K 3rd Floor - Medical Intensive Care Unit	ICU
K SICU	K 2nd Floor - Surgical Intensive Care Unit	ICU
K W-32A LSCC F	K Ward-32A Long stay unit F	Long stay unit
K W-32B LSCC M	K Ward-32B Long stay unit M	Long stay unit
K W-32B Neuro	K Ward-32B Neurology	Neuro
K W-13 ANT	K Ward-13 Antenatal Patients	OBG
K W-15B Gynae	K Ward-15B Gynae Patients	OBG
K W-14A PN	K Ward-14A Post Natal Patients	OBG
K W-25B MODC	K W-25B Oncology/Hematology	Oncology/ Hematology
K W-44 M/F ONCO/HEMA	K Ward-44 M/F (Palliative/Iodine/Onco/Hema)	Oncology/ Hematology

K W-54 F ONCO/HEMA	K Ward-54 F Adult/Pedia(Onco/Hema)	Oncology/ Hematology
K W-34A Ortho	K Ward-34A Orthopedics	orthopedics
K W-31B PDDC – Adult	K Ward-31B PDDC - Adult	Internal medicine
K W-31B RDU	K Ward-31B Renal Dialysis Unit	Internal medicine
K W-21B-F CS/CARDIO	K Ward-21B-F Cardiac Surgery/Cardiology	Surgical
K W-36 Vas Sur Adult M	K Ward-36 Surgery	Surgical
K W-21A-M CS/CARDIO	K Ward-21A-M Cardiac Surgery/Cardiology	Surgical
K W-22A Vas Sur	K Ward-22A Surgery	Surgical
K W-33B Sur	K Ward-33B Surgery	Surgical
K W-36 M/F Surg	K Ward -36 M/F Surg Trauma & Acute Care	Surgical
K W-41 GS M	K Ward-41 GS M	Surgical
K W-21A CVD Sur	K Ward-21A CVD Sur	Surgical
K W-51 F Gen Surg	K Ward-51 F General Surgery (END,CRS,Acute,UGI,HBS)	Surgical
K W-52 F Surg	K Ward-52 F Surg (PED,Uro,Vas,ENT,FM,PM)	Surgical
K W-36 Adult M	K W-36 General Surgery Adult M	Surgical
K W-38 M Surg	K Ward-38 M URO,VASC,ENT,DM Foot,PM Surg	Surgical
K W-37 M GS	K Ward-37 M General Surgery	Surgical
K W-33A Sur	K Ward-33A General Surgery	Surgical
K W-25A P Sur M	K Ward-25A General Surgery	Surgical
K W-39 M Surg	K Ward-39 M Neuro-Thoracic,Facio,Plast,Burn Surg	Surgical
K W-53 F Surg	K Ward-53 F Surg (Neuro Surg, Thoracic, Plastic, Burn)	Surgical
K W-24A UroSurg	K Ward-24A UroSurgery	Surgical
K W-24A DSU M	K Ward-24A Day surgery unit	Surgical
K W-21B Nur Sur	K Ward-21B Neuro Sur	Surgical
K W-42 Male Peds Ortho	K Ward-42 Male Pediatrics Orthopedics	Surgical
K W-43 Fmale Peds Ortho	K Ward-43 Female Pediatrics Orthopedics	Surgical
K W-22B Ortho	K Ward-22B OrthoSurgery	Surgical

Key: ED: Emergency department; HDU: High dependency unit; Ortho: Orthopedics; OBG: Obstetrics and gynaecology; Neuro: Neurology.

Appendix 7. King Saud University Medical City Antibiogram

المدينة الطبية الجامعية
University Medical City

جامعة الملك سعود
King Saud University

King Saud University Medical City Antibiogram (Percent-Susceptible Isolates)

2017

Facility:

King Saud University Medical City

(King Khalid University Hospital and King Abdulaziz University Hospital)

Inclusive Dates:

1st of January 2017 to 30th of June 2017

Acknowledgement & Contact Information:

Ph. Leen Ghonem- Msc, BCPS

Infectious Diseases clinical pharmacist specialist & Antimicrobial Stewardship Pharmacist

Deputy Chair of AUVS

Email: lghonem@ksu.edu.sa

Bleep: 1808

Ext: 92380

Prof. Ali M. Somily- MD, MBBS, FRCPC, D(ABMM), FCCM

Consultant Microbiologist

Chairman of Pathology and Laboratory Medicine & Head of Microbiology Department

Member of AUVS

Email: Ali.somily@gmail.com

Ext: 4672640

Reviewed by:

Antimicrobial Utilization/Stewardship and Vaccination Subcommittee

Endorsed by:

KSUMC Pharmacy and Therapeutics Committee

KSUMC Antimicrobial Utilization/Stewardship and Vaccination Subcommittee

Members:

Dr. Awadh Al-Anazi – Adult Infectious Diseases Consultant

Dr. Naif Al-Otaibi – Adult Infectious Disease Consultant

Dr. Fatma AlShahrani – Adult Infectious Disease Consultant

Dr. Sara AlSubei- Pediatric Infectious Diseases Consultant

Prof. Ali Smaily- Head of Pathology & Microbiology Department

Ph. Leen Ghonem- Infectious Diseases Clinical Pharmacist

Dr. Manal Abo Alkheir – Pediatric Clinical Pharmacist

Ph. Shereen AlDosoqi – Critical Care Clinical Pharmacist

Ph. Sheikha Alanazi- King Abdul-Aziz Hospital Clinical Pharmacist

Mr. Abba Elgujja – Infection Control Practitioner

Mr. Maher Titi- Quality Coordinator

Mrs. Mhardiya Alfad- Nurse representative

King Khalid University Hospital

January - June 2017 Cumulative Antibiogram for Gram-Negative Organisms - (Percent Susceptible)

Gram-Negative Organisms	No. of strains	β-lactams							Quinolones		Aminoglycosides		Others	
		AMP	CZ	CXM	CAZ	FEP	MEM	TZP	CIP	MXF	AN	GM	NIT	SXT
Acinetobacter baumannii	143	R	R	R	38	32	22	22	32	---	43	48	---	73
Citrobacter freundii§	28	R	R	R	---	85	93	---	67	54	100	85	---	59
Enterobacter aerogenes §	25	R	R	R	---	84	100	---	92	75	100	80	---	76
Enterobacter cloacae	120	R	R	R	---	80	96	---	93	85	97	96	49	91
Escherichia coli	1119	26	56	58	62	63	100	95	60	52	98	83	98	50
Klebsiella pneumoniae	562	R	61	58	63	65	96	90	76	60	95	82	60	62
Morganella morganii	36	R	R	R	---	80	94	---	60	36	97	69	R	37
Proteus mirabilis	80	48	64	77	---	84	96	---	65	55	87	67	R	52
Pseudomonas aeruginosa	550	R	R	R	75	76	62	77	82	---	94	85	R	R
Salmonella spp.	36	67	---	---	100	100	100	83	46	78	17	---	---	72
Serratia marcescens	52	R	R	R	---	90	96	---	94	88	94	96	R	98
Stenotrophomonas maltophilia	52	R	R	R	24	R	R	R	---	---	---	---	R	87

Note

* The percent susceptible for each organism antimicrobial combination was generated by including only the first isolate of that organism encountered on a given patient

** Nitrofurantoin data from urine isolates only

§ Organisms with less than 30 isolates, susceptibilities should be interpreted cautiously

(---) Drug not tested or drug not indicated

Abbreviations:

Amp (Ampicillin), **CZ** (Cefazolin), **CXM** (Cefuroxime), **CAZ** (Ceftazidime), **FEP** (Cefepime), **MEM** (Meropenem), **TZP** (Piperacillin-tazobactam), **CIP** (Ciprofloxacin) **MXF** (Moxifloxacin), **AN** (Amikacin), **GM** (Gentamicin), **NIT** (Nitrofurantoin), **SXT** (Trimethoprim-sulfamethoxazole), **R** (Resistant)

King Khalid University Hospital
January - June 2017 In-Patient Antibiogram for Gram-Negative Organisms
Percent Susceptible

Gram-Negative Organisms	No. of strains	β-lactams							Quinolones		Aminoglycosides		Others	
		AMP	CZ	CXM	CAZ	FEP	MEM	TZP	CIP	MXF	AN	GM	NIT	SXT
Acinetobacter baumannii §	27	R	R	R	30	30	16	13	30	---	40	59	---	78
Enterobacter cloacae	55	R	R	R	---	82	95	---	96	86	98	98	48	95
Escherichia coli	306	19	48	48	53	55	100	94	50	38	96	75	97	43
Klebsiella pneumoniae	198	R	53	53	58	52	97	89	70	84	94	82	56	58
Proteus mirabilis	20	30	40	45	---	65	95	---	45	30	65	65	R	45
Pseudomonas aeruginosa	200	R	R	R	73	73	66	74	83	---	96	88	R	R
Stenotrophomonas maltophilia	20	R	R	R	29	R	R	R	---	---	---	---	R	73

Note

* Inpatient includes all wards at King Khalid University Hospital except ICUs

** The percent susceptible for each organism antimicrobial combination was generated by including only the first isolate of that organism encountered on a given patient

*** Nitrofurantoin data from urine isolates only

(---) Drug not tested or drug not indicated

§ Organisms with less than 30 isolates, susceptibilities should be interpreted cautiously

Abbreviations:

Amp (Ampicillin), **CZ** (Cefazolin), **CXM** (Cefuroxime), **CAZ** (Ceftazidime), FEP (Cefepime), **MEM** (Meropenem), **TZP** (Piperacillin-tazobactam), **CIP** (Ciprofloxacin) **MXF** (Moxifloxacin), **AN** (Amikacin), **GM** (Gentamicin), **NIT** (Nitrofurantoin), **SXT** (Trimethoprim-sulfamethoxazole), **R** (Resistant)

King Khalid University Hospital

January - June 2017 Intensive Care Units (ICU) Antibiogram for Gram-Negative Organisms

Percent Susceptible

Gram-Negative Organisms	No. of strains	β-lactams							Quinolones		Aminoglycosides		Others	
		AMP	CZ	CXM	CAZ	FEP	MEM	TZP	CIP	MXF	AN	GM	NIT	SXT
Acinetobacter baumannii	39	R	R	R	34	32	24	46	34	---	31	41	---	77
Enterobacter cloacae §	27	R	R	R	---	86	100	---	93	89	100	96	---	93
Escherichia coli	68	9	34	34	43	49	97	82	50	---	96	82	91	41
Klebsiella pneumoniae	99	R	45	45	52	52	97	86	80	68	97	65	55	51
Pseudomonas aeruginosa	139	R	R	R	68	68	48	71	83	---	91	78	R	R

Note

* ICU include (CCU, CICU, SICU, MICU, PICU, and NICU) at King Khalid University Hospital

** The percent susceptible for each organism antimicrobial combination was generated by including only the first isolate of that organism encountered on a given patient

** Nitrofurantoin data from urine isolates only

(---) drug not tested or drug not indicated

§ Organisms with less than 30 isolates, susceptibilities should be interpreted cautiously

Abbreviations:

Amp (Ampicillin), **CZ** (Cefazolin), **CXM** (Cefuroxime), **CAZ** (Ceftazidime), **FEP** (Cefepime), **MEM** (Meropenem), **TZP** (Piperacillin-tazobactam), **CIP** (Ciprofloxacin) **MXF** (Moxifloxacin), **AN** (Amikacin), **GM** (Gentamicin), **NIT** (Nitrofurantoin), **SXT** (Trimethoprim-sulfamethoxazole), **R** (Resistant)

King Khalid University Hospital
January - June 2017 Community Isolates Antibiogram - Gram-Negative Organisms
Percent Susceptible

Gram-Negative Organisms	No. of strains	β-lactams							Quinolones		Aminoglycosides		Others	
		AMP	CZ	CXM	CAZ	FEP	MEM	TZP	CIP	MXF	AN	GM	NIT	SXT
Enterobacter cloacae §	24	R	R	R	---	71	92	---	88	82	92	88	36	83
Escherichia coli	638	33	64	64	72	72	100	97	68	63	98	88	98	56
Klebsiella pneumoniae	190	R	67	69	73	73	97	95	84	87	95	92	66	71
Proteus mirabilis	36	47	69	78	---	92	97	---	72	83	94	61	R	53
Pseudomonas aeruginosa	108	R	R	R	87	93	80	85	84	---	94	89	R	R

Note

* Community Isolates include Emergency department and Outpatient clinics at King Khalid University Hospital

** The percent susceptible for each organism antimicrobial combination was generated by including only the first isolate of that organism encountered on a given patient

** Nitrofurantoin data from urine isolates only

(---) drug not tested or drug not indicated

§ Organisms with less than 30 isolates, susceptibilities should be interpreted cautiously

King Khalid University Hospital
January - June 2017 Cumulative Antibiogram for Gram-Positive Organisms
Percent Susceptible

Gram-Positive Organisms	No. of strains	AMP	CLI	GM SYNERGY	ST SYNERGY	CZ	DAP	ERY	OXA	PEN	Van	LZD	SXT
Staph aureus MIC Breakpoint (µg/ml)			≤ 0.5						≤ 2	≤ 0.12	≤ 2	≤ 4	≤ 40
Coag-Neg Staph MIC Breakpoint (µg/ml)									≤ 0.25		≤ 4		
Enterococcus MIC Breakpoint (µg/ml)		≤ 8								≤ 8	≤ 4	≤ 2	
Methicillin-Susceptible Staph aureus (MSSA)	239	---	90	---	---	100	100	71	100	0	100	100	93
Methicillin-Resistant Staph aureus (MRSA)	180	---	74	---	---	0	100	67	0	0	100	100	92
Coagulase-Negative Staphylococcus	171	5	47	---	---	18	97	17	19	5	93	93	64
Enterococcus faecalis	114	100	R	67	79	R	---	---	---	98	100	100	R
Enterococcus faecium	59	12	R	84	58	R	---	---	---	12	46	96	R

Note:
* If susceptible , an aminoglycoside (gentamicin and streptomycin) may be used with a cell-wall active agent (ampicillin/vancomycin) for the treatment of serious Enterococci infections (such as endocarditis)
** Trimethoprim/sulfamethoxazole (Bactrim) should only be considered for treatment of skin and soft tissue infections due to these organisms
*** Daptomycin is a non-formulary antibiotic in KSUMC
(---) Drug not tested or drug not indicated

Abbreviations:
AMP (Ampicillin), **CLI** (Clindamycin), **CZ** (Cefazolin), **DAP** (Daptomycin), **ERY** (Erythromycin), **GM SYNERGY** (Gentamicin synergy), **LZD** (Linezolid), **OXA** (Oxacillin), **PEN** (Penicillin), **ST SYNERGY** (Streptomycin synergy), **SXT** (Trimethoprim-sulfamethoxazole), **VA** (Vancomycin), **R** (Resistant)

King Khalid University Hospital
January - June 2017 In-Patient Antibiogram for Gram-Positive Organisms
Percent Susceptible

Gram-Positive Organisms	No. of strains	AMP	CLI	CZ	DAP	ERY	GMS	LZD	OXA	PEN	Sts	SXT	Van
Staph aureus MIC Breakpoint (µg/ml)			≤ 0.5					≤ 4	≤ 2	≤ 0.12		≤ 40	≤ 2
Coag-Neg Staph MIC Breakpoint (µg/ml)									≤ 0.25				≤ 4
Enterococcus MIC Breakpoint (µg/ml)		≤ 8						≤ 2		≤ 8			≤ 4
Methicillin-Susceptible Staph aureus (MSSA)	92	---	88	100	100	69	---	100	100	5	---	91	100
Methicillin-Resistant Staph aureus (MRSA)	63	---	75	0	100	92	---	100	0	0	---	82	100
Coagulase-Negative Staphylococcus	66	2	50	18	100	24	---	100	18	2	---	77	100
Enterococcus faecalis	37	100	R	R	---	---	79	100	---	97	87	R	100
Enterococcus faecium §	23	5	R	R	---	---	88	93	---	5	56	R	48

Note:

* Inpatient includes all wards at King Khalid University Hospital except ICUs

** If susceptible , an aminoglycoside (gentamicin and streptomycin) may be used with a cell-wall active agent (ampicillin/vancomycin) for the treatment of serious Enterococci infections (such as endocarditis)

*** Trimethoprim/sulfamethoxazole (Bactrim) should only be considered for treatment of skin and soft tissue infections due to these organisms

*** Daptomycin is a non-formulary antibiotic in KSUMC

§ Organisms with less than 30 isolates, susceptibilities should be interpreted cautiously

(---) Drug not tested or drug not indicated

Abbreviations:

AMP (Ampicillin), **CLI** (Clindamycin), **CZ** (Cefazolin), **DAP** (Daptomycin), **ERY** (Erythromycin), **Gms** (Gentamicin synergy), **LZD** (Linezolid), **OXA** (Oxacillin), **PEN** (Penicillin), **Sts** (Streptomycin synergy), **SXT** (Trimethoprim-sulfamethoxazole), **VA** (Vancomycin), **R** (Resistant)

King Khalid University Hospital
January - June 2017 Intensive Care Units (ICU) Antibiogram for Gram-Positive Organisms
Percent Susceptible

Gram-Positive Organisms	No. of strains	AMP	CLI	CZ	DAP	ERY	GMS	LZD	OXA	PEN	Sts	SXT	Van
Staph aureus MIC Breakpoint (µg/ml)			≤ 0.5					≤ 4	≤ 2	≤ 0.12		≤ 40	≤ 2
Coag-Neg Staph MIC Breakpoint (µg/ml)									≤ 0.25				≤ 4
Enterococcus MIC Breakpoint (µg/ml)		≤ 8						≤ 2		≤ 8			≤ 4
Methicillin-Susceptible Staph aureus (MSSA)	34	---	94	100	100	68	---	100	100	2.9	---	94	100
Methicillin-resistant Staph aureus (MRSA)	49	---	51	0	100	51	---	100	0	0	---	92	100
Coagulase-negative Staph §	25	0	12	5	100	12	---	100	4	0	---	58	100
Enterococcus species €	30	60	R	R	---	---	57	100	---		63	R	77

Note:

* ICU include (CCU, CICU, SICU, MICU, PICU, and NICU) at King Khalid University Hospital

** If susceptible , an aminoglycoside (gentamicin and streptomycin) may be used with a cell-wall active agent (ampicillin/vancomycin) for the treatment of serious Enterococci infections (such as endocarditis)

*** Trimethoprim/sulfamethoxazole (B^{act}rim) should only be considered for treatment of skin and soft tissue infections due to these organisms

*** Daptomycin is a non-formulary antibiotic in KSUMC

§ Organisms with less than 30 isolates, susceptibilities should be interpreted cautiously

€ Susceptibilities to subgroups of Enterococcus was not possible due to small isolates pool. Please refer to cumulative Antibiogram for further details

(---) Drug not tested or drug not indicated

Abbreviations:

AMP (Ampicillin), **CLI** (Clindamycin), **CZ** (Cefazolin), **DAP** (Daptomycin), **ERY** (Erythromycin), **Gms** (Gentamicin synergy), **LZD** (Linezolid), **OXA** (Oxacillin), **PEN** (Penicillin), **Sts** (Streptomycin synergy), **SXT** (Trimethoprim-sulfamethoxazole), **VA** (Vancomycin), **R** (Resistant)

King Khalid University Hospital
January - June 2017 Community Isolates Antibiogram- Gram-Positive Organisms
Percent Susceptible

Gram-Positive Organisms	No. of strains	AMP	CLI	CZ	DAP	ERY	GMS	LZD	OXA	PEN	Sts	SXT	Van
Staph aureus MIC Breakpoint (µg/ml)			≤ 0.5					≤ 4	≤ 2	≤ 0.12		≤ 40	≤ 2
Coag-Neg Staph MIC Breakpoint (µg/ml)									≤ 0.25				≤ 4
Enterococcus MIC Breakpoint (µg/ml)		≤ 8						≤ 2		≤ 8			≤ 4
Methicillin-Susceptible Staph aureus (MSSA)	89	---	91	100	100	76	---	99	100	0	---	93	100
Methicillin-resistant Staph aureus (MRSA)	57	---	91	0	100	81	---	100	0	0	---	97	100
Coagulase-negative Staph	62	7	66	27	100	18	---	100	30	7	---	73	100
Enterococcus faecalis	45	100	R	R	---	---	62	100	---	98	74	R	100

Note:
Community isolates include Emergency department and Outpatient clinics at King Khalid University Hospital
** If susceptible , an aminoglycoside (gentamicin and streptomycin) may be used with a cell-wall active agent (ampicillin/vancomycin) for the treatment of serious Enterococci infections (such as endocarditis)
*** Trimethoprim/sulfamethoxazole (Bactrim) should only be considered for treatment of skin and soft tissue infections due to these organisms
*** Daptomycin is a non-formulary antibiotic in KSUMC
(---) Drug not tested or drug not indicated

Abbreviations:
AMP (Ampicillin), **CLI** (Clindamycin), **CZ** (Cefazolin), **DAP** (Daptomycin), **ERY** (Erythromycin), **Gms** (Gentamicin synergy), **LZD** (Linezolid), **OXA** (Oxacillin), **PEN** (Penicillin), **Sts** (Streptomycin synergy), **SXT** (Trimethoprim-sulfamethoxazole), **VA** (Vancomycin), **R** (Resistant)

King Abdulaziz University Hospital
January - June 2017 Cumulative Antibiogram
Percent Susceptible

Gram-Negative Organisms	No. of strains	β-lactams						Quino-lones	Aminoglycosides		Others	
		AMP	CZ	CXM	CAZ	MEM	TZP	CIP	AN	GM	NIT	SXT
Escherichia coli	208	43	59	81	81	100	99	74	97	86	98	59
Klebsiella pneumoniae	61	R	64	84	66	95	92	92	95	94	72	76
Pseudomonas aeruginosa	31	R	R	R	100	100	100	100	97	95	R	R

Note
* The percent susceptible for each organism antimicrobial combination was generated by including only the first isolate of that organism encountered on a given patient
** Nitrofurantoin data from urine isolates only (---) Drug not tested or drug not indicated

Gram-Positive Organisms	No. of strains	AMP	CLI	CZ	LZD	OXA	SXT	VA
Staph aureus €	77	---		---	---			
Coagulase-negative Staph	47	9	68	---	---	53	100	100

Note:
* If susceptible , an aminoglycoside (gentamicin and streptomycin) may be used with a cell-wall active agent (ampicillin/vancomycin) for the treatment of serious Enterococci infections (such as endocarditis)
** Trimethoprim/sulfamethoxazole (Bactrim) should only be considered for treatment of skin and soft tissue infections due to these organisms
*** Daptomycin is a non-formulary antibiotic in KSUMC
€ Susceptibilities to subgroups of Enterococcus was not possible due to small isolates pool (---) Drug not tested or drug not indicated

Abbreviations:
AMP (Ampicillin), **CZ** (Cefazolin), **CXM** (Cefuroxime), **CAZ** (Ceftazidime), **MEM** (Meropenem), **TZP** (Piperacillin-tazobactam), **CIP** (Ciprofloxacin) **MXF** (Moxifloxacin), **AN** (Amikacin), **GM** (Gentamicin), **NIT** (Nitrofurantoin), **SXT** (Trimethoprim-sulfamethoxazole), **R** (Resistant)
AMP (Ampicillin), **CLI** (Clindamycin), **CZ** (Cefazolin), **DAP** (Daptomycin), **ERY** (Erythromycin), **LZD** (Linezolid), **OXA** (Oxacillin), **PEN** (Penicillin), **SXT** (Trimethoprim-sulfamethoxazole), **VA** (Vancomycin), **R** (Resistant)

King Khalid University Hospital
January - June 2017 Cumulative Antibiogram for Streptococcus pneumoniae
Difference between meningitis and non-meningitis

Organism	No. of strains	PEN	CTX	CRO	ERY	CLI	LEVO	SXT	VA
Streptococcus pneumoniae	29	---	---	---	34.5	69	100	63	100
Meningitis	29	69.2	76.9	63	---	---	---	---	---
Nonmeningitis	29	100	96.2	100	---	---	---	---	---

Note:
- Breakpoints differ for cefotaxime, ceftriaxone, and penicillin based on diagnosis.
- Meningitis applies to the susceptibility of pneumococci for patients who have meningitis for cefotaxime, ceftriaxone, and penicillin
- Non-meningitis applies to the susceptibility of pneumococci for patients who do not have meningitis for cefotaxime, ceftriaxone, and penicillin

Abbreviations
PEN (Penicillin), **CTX** (Cefotaxime), **CRO** (Ceftriaxone), **ERY** (Erythromycin), **CLI** (Clindamycin), **LEVO** (Levofloxacin), **SXT** (Trimethoprim-sulfamethoxazole), **VA** (Vancomycin)

King Khalid University Hospital

January - June 2017 Combined Antibiogram for Selected Organisms from Blood cultures

Gram Negative Organisms (GN)€	Number of Strains	AN	AMP	CZ	CAZ	CRO	CIP	GM	MEM	TZP	SXT
Escherichia coli	66	79	21	40	62	64	61	82	100	91	49
Klebsiella pneumoniae	48	90	R	---	69	67	94	88	92	79	65
Pseudomonas aeruginosa	25	96	R	R	88	R	84	96	72	NA	R

Gram Positive Organisms (GP) €	Number of Strains	AMP	CZ	ERY	CLI	CLOX	LZD	SXT	VA
Gram positive Cocci in CLUSTERS	214	---	30	33	58	28	99	69	100
Gram-positive Cocci in CHAINS	62	53	---	29	49	---	99	61	75

Note:

€ Further stratification based on patient care areas were not possible due to small pool of isolates

Abbreviations:

GN table: **AMP** (Ampicillin), **CZ** (Cefazolin), **ERY** (Erythromycin), **CLI** (Clindamycin), **CLOX** (Cloxacillin), **LZD** (Linezolid), **SXT** (Trimethoprim-sulfamethoxazole), **VA** (Vancomycin)

GP table: **AN** (Amikacin), **AMP** (Ampicillin), **CZ** (Cefazolin), **CAZ** (Ceftazidime), **CRO** (Ceftriaxone), **CIP** (Ciprofloxacin), **GM** (Gentamicin), **MEM** (Meropenem), **TZP** (Piperacillin-tazobactam), **SXT** (Trimethoprim-sulfamethoxazole)

Appendix 8. Empiric and prophylactic indication of carbapenems and piperacillin-tazobactam according to IDSA (Infectious Diseases Society of America, 2018)

Indication of empiric therapy	
Sepsis	
Hospital-acquired Pneumonia	
Ventilator-associated Pneumonia	
Community-acquired pneumonia	if *P. aeruginosa* is a consideration (e.g., in patients with bronchiectasis, chronic oral steroid use, or late HIV infection, ICU)
Urinary tract infection	Recurrent UTI where microbiology indicated susceptibility only to those antimicrobials
Febrile neutropenia	
Diabetic foot infection	Moderate to severe diabetic foot infection
Intra-abdominal infection	Community-acquired acute cholecystitis of severe physiologic disturbance, advanced age, or immunocompromised state. Acute cholangitis following bilio-enteric anastamosis of any severity. Healthcare–associated biliary infection of any severity.
Skin and soft tissue infection	Incisional Surgical Site Infections if surgery of Intestinal or Genitourinary Tract. Necrotizing Fasciitis, Including Fournier Gangrene. Cellulitis with systemic signs of infection.

Note:

- Surgical prophylaxis for patients undergoing liver transplantation
- Piperacillin-tazobactam should be avoided for the treatment of infections caused by ESBL-E, even if susceptibility to piperacillin-tazobactam is demonstrated

Appendix 9. DDD and DDD per 100 bed – days calculations (WHO, 2020)

DDD= $\frac{\text{Total amount of consumption (grams)}}{\text{WHO antimicrobial specific average DDD}}$

DDD for imipenem= 2 g

DDD for meropenem= 3 g

DDD for piperacillin-tazobactam= 14 g

DDD per 100 bed-days= $\frac{\text{DDD}}{100\ \text{bed}-\text{days}}$

Appendix 10. Confidence interval calculation

Confidence Interval = $\text{Risk differences} \pm$ 1.96 x Standard error (SE) of the risk difference]

SE of the risk difference=$\sqrt{\frac{n1}{N}(1-\frac{n1}{N})(\frac{1}{m0}+\frac{1}{m1})}$

Below is an example of calculating CI:

n1= 2787

N= 4929

m0=2484

m1=2445

SE= $\sqrt{0.565 * 0.435 * 0.0008} = 0.01412$

The risk differences = 0.443-0.426 = 0.017

CI for gender is 0.017 -1.96* 0.01412= -0.011

CI for gender is 0.017 +1.96* 0.01412 = 0.044

Appendix 11. Published study (Qualitative)

Alsaleh NA, Al-Omar HA, Mayet AY, Mullen AB. 2021. Exploring Physicians' Views, Perceptions and Experiences about Broad-Spectrum Antimicrobial Prescribing in a Tertiary Care Hospital Riyadh, Saudi Arabia: A Qualitative Approach. *Antibiotics (Basel)*, 10, 366.

antibiotics

MDPI

Article

Exploring Physicians' Views, Perceptions and Experiences about Broad-Spectrum Antimicrobial Prescribing in a Tertiary Care Hospital Riyadh, Saudi Arabia: A Qualitative Approach

Nada A. Alsaleh [1], Hussain A. Al-Omar [2], Ahmed Y. Mayet [2,3] and Alexander B. Mullen [4,*]

1 Department of Pharmacy Practice, College of Pharmacy, Princess Nourah bint Abdulrahman University, Riyadh 84428, Saudi Arabia; naaalsaleh@pnu.edu.sa
2 Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia; halomar@ksu.edu.sa (H.A.A.-O.); iymayet@ksu.edu.sa (A.Y.M.)
3 King Khalid University Hospital, Riyadh 11451, Saudi Arabia
4 Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow G4 0RE, UK
* Correspondence: a.mullen@strath.ac.uk

Abstract: Antimicrobial resistance (AMR) is a global public health threat associated with increased mortality, morbidity and costs. Inappropriate antimicrobial prescribing, particularly of broad-spectrums antimicrobials (BSAs), is considered a major factor behind growing AMR. The aim of this study was to explore physician perception and views about BSAs and factors that impact upon their BSAs prescribing decisions. Qualitative semistructured telephone interviews over an eleven-week period were conducted with physicians in a single tertiary care hospital in Riyadh, Saudi Arabia. Purposeful and snowball sampling techniques were adopted as sampling strategy. All interviews were audio recorded, transcribed verbatim, uploaded to NVivo® software and analysed following thematic analysis approach. Four major themes emerged: views on BSAs, factors influencing BSA prescribing and antimicrobial stewardship: practices and barriers and recommendations to improve appropriate BSA prescribing. Recommendations for the future include improving clinical knowledge, feedback on prescribing, multidisciplinary team decision-making and local guideline implementation. Identification of views and determinants of BSA prescribing can guide the design of a multifaceted intervention to support physicians and policymakers to improve antimicrobial prescribing practices.

Keywords: qualitative research; broad-spectrum antimicrobial; physicians; prescribing behaviour

Citation: Alsaleh, N.A.; Al-Omar, H.A.; Mayet, A.Y.; Mullen, A.B. Exploring Physicians' Views, Perceptions and Experiences about Broad-Spectrum Antimicrobial Prescribing in a Tertiary Care Hospital Riyadh, Saudi Arabia: A Qualitative Approach. *Antibiotics* **2021**, *10*, 366. https://doi.org/10.3390/antibiotics10040366

Academic Editor: Seok Hoon Jeong

Received: 9 February 2021
Accepted: 24 March 2021
Published: 31 March 2021

1. Introduction

Antimicrobial resistance (AMR) is a global public health threat associated with increased mortality, morbidity and costs [1]. Inappropriate antimicrobial prescribing, particularly of broad-spectrums antimicrobials (BSAs), is considered a major factor behind growing AMR [2]. Implementing antimicrobial stewardships programmes (AMS) aimed to enhance the appropriate prescribing of antimicrobials may lower inappropriate or overuse of BSAs [3,4]. AMS have shown to decrease the inappropriate antimicrobial use, slow the development of AMR, reduce the length of hospitalisation and the health care-associated costs treating infectious disease [5]. The World Health Organization has recognised the potential of these programmes through endorsement of the antimicrobial stewardship policy and strategy as part of the global action plan to decrease AMR risk. [6] Consequently, implementation of AMS in a hospital setting has been endorsed by several countries and institutions to improve the appropriate use of antimicrobials, thus decreasing AMR [7,8]. Physicians are supportive of AMS [9]; nevertheless, one of the challenges and barriers to AMS is the lack of physician consensus on what is considered an appropriate choice when deciding to initiate prescribing of a BSA [10]. Furthermore, physician perception and views about antimicrobial use and AMR vary across different settings and countries [11,12]. A

Appendix 12. Participant's Invitation Letter

You are invited to participate in this study which is investigating the physicians' practices in broad-spectrum antimicrobials prescribing in KSUMC. It is concerned with determining physicians' practices of broad-spectrum antimicrobials and exploring what influences them when prescribing broad-spectrum antimicrobials. This study will help to inform future developments associated with the delivery of care in your hospital. The aim is to find measures that could help physicians' when prescribing broad-spectrum antimicrobials.

All physicians' prescribing broad-spectrum antimicrobial to adult patients and working in hospital wards are welcomed to take part in this research.

This is qualitative research; the interview will take approximately 30 minutes and will be digitally recorded.

If you are willing to participare, please email me and I will be happy to schedule a meeting with you at your convenience date and time. Kindly read the attached participant's information sheet, and if you require any further information or clarification, please contact me

Thank you for your time and consideration.

Yours faithfully,

Nada Alsaleh, MSc

PhD Research Student-external supervision joint programme

Institute of Pharmacy and biomedical Science

University of Strathclyde

Email:Nada.alsaleh@strath.ac.uk

Tel: 966555443885

Appendix 13. Participant's information sheet

Title of the study

A qualitative study exploring physicians' views and perceptions about broad-spectrum antimicrobials prescribing and factors influencing broad-spectrum antimicrobials prescribing

Purpose of the study

The aim of this study is to understand broad-spectrum antimicrobial prescribing practises among physician practicing in hospital settings, in order to find measures that could improve broad-spectrum antimicrobial prescribing practices.

Why am I being asked to participate in this research?

We are recruiting physicans who have prescribed broad-spectrum antimicrobails for adult hospitalized patients.

What will happen if I decide to participate?

If you decide to participate, a PhD student, Nada Alsaleh (NA), will conduct a short interview which will last approximately 30 minutes to explore your views, perceptions and practice in broad-spectrum antimicrobial prescribing. The interview will be conducted at your convenient date and time. You can stop the interview any time if you no longer want to participate or you can skip any question that you don't want to answer. The interview will be audio recorded. Before starting the interview, you will be given a consent form to sign. You can have a copy of the signed consent form and this information sheet.

Do I have to take a part?

No, your participation is voluntary and you are free to decide not to participate or to withdraw at any time without giving a reason.

Is there is any possible risk of participating?

All data will be confidential and will remain anonymous.

What are the possible benefits of participating?

Participating will provide information that will help to get better understanding of the broad-spectrum antimicrobial prescribing practices. In turn, this will help in developing a quality improvement plan that will improve patients' outcome and decrease antimicrobial resistance. The findings will be reported in the researcher's (NA) PhD thesis and may be published in journals.

Contact for further information: If you need more information, you can contact the researcher, Nada Alsaleh (who will conduct the interview) using the following contact details:

Nada Alsaleh

PhD Research Student-External Supervision Joint Programme

Institute of Pharmacy and biomedical Science

University of Strathclyde

Email:Nada.alsaleh@strath.ac.uk

Tel: 966555443885

You can also contact the research supervisors using the followin contact details:

Professor Ahmed Mayet

Professor in clinical pharmacy

College of Pharmacy

King Saud University

Email: iymayet@ksu.edu.sa

Tel: 966 14677487

966 14679519

Dr. Hussain A. Al-Omar

Assistant Professor of Pharmacoeconomics and Healthcare Professionals Behaviour

College of Pharmacy

King Saud University

Email: halomar@ksu.edu.sa

Tel: +966551113337

Thank you for reading this information sheet and for considering participating in this research.

Appendix 14. Consent Form

Study title: Physicians' views and perceptions about broad-spectrum antimicrobials and factors influencing broad-spectrum antimicrobial prescribing

I confirm that I have read the participant information sheet and fully understand the information provided

I confirm that I was given the opportunity to ask questions □

I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving reasons

I understand that the interview will be audio recorded then transcribed □

I understand that the data obtained from the interview will be anonymised

I understand that the results may be published □

I agree to take part in the study and participate in the interview □

_____	_ _ / _ _ / _ _ _ _	_____
Name of participant	**Date**	**Signature**
_____	_ _ / _ _ / _ _ _ _	_____
Name of researcher	**Date**	**Signature**

Appendix 15. Interview topic guide

Physicians' views and perceptions about broad-spectrum antimicrobials and factors influencing broad-spectrum antimicrobial prescribing

Qualitative evaluation of prescribers' views and behaviours (30-35 mins)

Interview introduction (3 mins)

Thank you for coming today to take part in this interview. As I explained to you in my original email, we are interested in antimicrobial prescribing behaviour and to understand levers and barriers faced by front-line clinicians such as yourself in ensuring safe, rational and effective prescribing of broad-spectrum antimicrobials.

As mentioned in the information sheet, so that I don't have to take long notes and can concentrate on what you are telling me I am going to record this meeting if you are still okay with that?

It is important to emphasise that there are no 'right' or 'wrong' answers so please speak freely. This interview will last for approximately 30 minutes, will be recorded and then anonymously transcribed before analysis by me and my academic supervisors.

I guarantee your confidentiality throughout the process and you can withdraw from participation at any time without giving a reason, until a report has been published.

- **Before we start, do you have any questions about the study?**
- **Could you please sign the consent form?**

Part A: Demographics

Age (years): _____

Gender: ☐ Male ☐ Female

Speciality: _____

Working position:

☐ Junior resident ☐ Senior resident

☐ Fellow ☐ Attending physician ☐ Other:___

Attended university: _____

Qualification: _____

Working experience (years): ____

Working experience outside KSA: Yes, ☐ (Country: _____ Duration :_____)

No ☐

Part B: Questions & prompts

1. Practice of broad-spectrum antimicrobial prescribing

- What would you consider a broad-spectrum agent?
- What is your understanding of appropriate broad-spectrum antimicrobial prescribing?
- What is your understanding of inappropriate broad-spectrum antimicrobial prescribing?
- In your daily practice, how do you plan or decide on prescribing broad-spectrum antimicrobials?
- In your daily practice, how often do you request cultures before starting broad-spectrum antimicrobial therapy? In which situation(s) do you decided not to request a culture prior to initiation of a broad-spectrum antimicrobial?
- In your daily practice, how do you plan or decide on prescribing broad-spectrum antimicrobials?
- What factors influence your decision to start broad- spectrum antimicrobial?
  - Infection severity
  - patient factors
  - Costs
  - peer or patient pressures
  - hospital antibiogram

- In your practice, have you ever prescribed broad-spectrum antimicrobial when you think you could prescribe a narrow-spectrum? Tell me about those circumstances?
- In your daily practice, how often do you subsequently narrow antimicrobial therapy based on culture/sensitivity results?
- In your daily practice, how often do you convert antimicrobial therapy from IV to oral?
- How has your clinical experiences shape your practice of prescribing broad-spectrum antimicrobials?
- How has the clinical experience of your colleagues' practice has impacted on your broad-spectrum antimicrobial prescribing?
- How has the institutional policy impacted your broad-spectrum antimicrobial prescribing practice?
- How has the institutional support i.e., infectious diseases specialist, clinical pharmacist and education impacted your broad-spectrum antimicrobial prescribing practice?

2. Barriers of appropriate broad-spectrum antimicrobial prescribing

- How do you view your broad-spectrum antimicrobial prescribing practices compared to your colleagues? Do you agree with their decision on broad-spectrum antimicrobial prescribing? how are disagreements on therapy discussed/concluded?
- In your own view and clinical experience, what could be the possible challenges/barriers associated with broad-spectrum antimicrobial prescribing?
- In your belief, who or what contribute to these challenges/barriers?

3. Strategies and interventions to improve broad-spectrum antimicrobial prescribing

- In your daily practice, do you use any antimicrobial guidelines to help you in your antimicrobial prescribing, if yes what is/are they?

- In your daily practice, do you use any electronic tools to help you in your antimicrobial prescribing, if yes what is/are they?
- Do you think you have had sufficient support, education and training on broad-spectrum antimicrobial prescribing?
- In your view, what could be the most useful tool(s), intervention(s) or measure(s) to improve appropriate broad-spectrum antimicrobials prescribing?

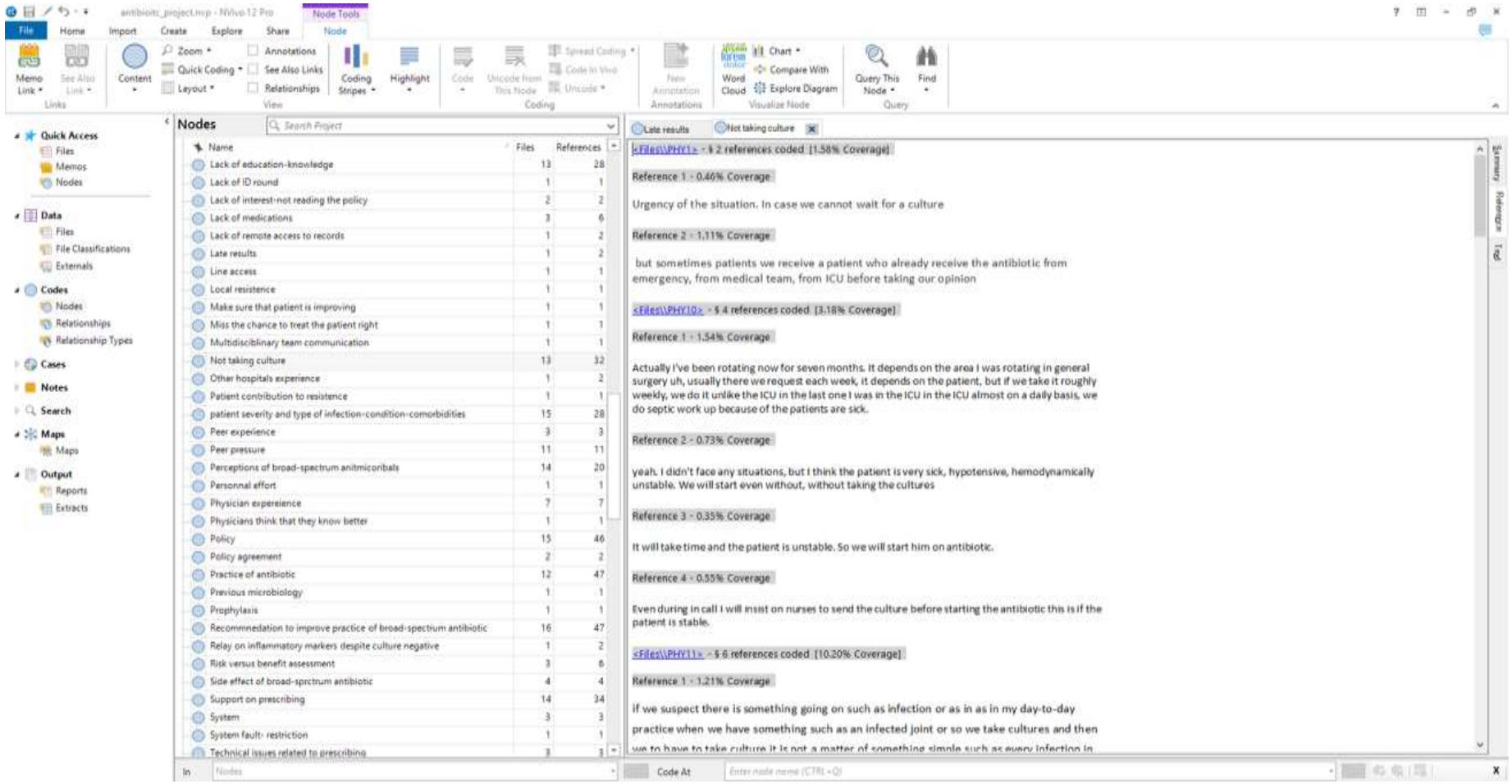
4. Summary

- Is there anything else you would like to add?

❖ **Probing and prompting**

- Can you tell me more about?
- What do you mean by that?
- Can you please give me an example?
- Could you explain more?
- Is there anything you want to say about this?

Appendix 16. Example of coding using NVivo®



Appendix 17. COREQ: Consolidated criteria for reporting qualitative research: a 32-item checklist for interviews and focus groups

Developed from:

Tong A, Sainsbury P, Craig J. 2007. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*, 19, 349 – 357.

Section/Topic	Item No	Checklist item	Reported on page No
Domain 1: Research team and reflexivity			
Personal Characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group? Interviewer/facilitator	Nada Alsaleh
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	MSc pharmacist
Occupation	3	What was their occupation at the time of the study?	PhD student
Gender	4	Was the researcher male or female?	Female
Experience and training	5	What experience or training did the researcher have?	The researcher participated in many qualitative research courses and workshops
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	No
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	Participant information sheet
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	Not reported
Domain 2: study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse	Methods

		analysis, ethnography, phenomenology, content analysis	
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	Purposive and snowball detail description in the methods
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	Email
Sample size	12	How many participants were in the study?	16
Non-participation	13	How many people refused to participate or dropped out? Reasons?	0
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	Data was collected via phone
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	No
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	Results Table 3.1 speciality and year of experience
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Yes
Repeat interviews	18	Were repeat interviews carried out? If yes, how many?	No
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	Audio recorded
Field notes	20	Were field notes made during and/or after the interview or focus group?	Yes
Duration	21	What was the duration of the interviews or focus group?	An average duration of 30 minutes [durations ranged from 17-56 minutes]
Data saturation	22	Was data saturation discussed?	Yes
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	No

Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	Methods
Description of the coding tree	25	Did authors provide a description of the coding tree?	Yes
Derivation of themes	26	Were themes identified in advance or derived from the data?	Derived from the data
Software	27	What software, if applicable, was used to manage the data?	Nvivo
Participant checking	28	Did participants provide feedback on the findings?	No
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes / findings? Was each quotation identified? e.g. participant number	Yes-results
Data and findings consistent	30	Was there consistency between the data presented and the findings?	Yes-discussion
Clarity of major themes	31	Were major themes clearly presented in the findings?	Yes-results
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	Yes-results

Appendix 18. A 15-Point Checklist of Criteria for Good Thematic Analysis Process

Developed from:

Braun, V., & Clarke, V. 2006. Using thematic analysis in psychology. *Qualitative research in psychology,* 3, 77-101.

Transcription	1.	The data have been transcribed to an appropriate level of detail, and the transcripts have been checked against the tapes for 'accuracy'.
Coding	2.	Each data item has been given equal attention in the coding process.
	3.	Themes have not been generated from a few vivid examples (an anecdotal approach) but, instead, the coding process has been thorough, inclusive and comprehensive.
	4.	All relevant extracts for all each theme have been collated.
	5.	Themes have been checked against each other and back to the original data set.
	6.	Themes are internally coherent, consistent, and distinctive.
Analysis	7.	Data have been analysed rather than just paraphrased or described.
	8.	Analysis and data match each other – the extracts illustrate the analytic claims.
	9.	Analysis tells a convincing and well-organised story about the data and topic.
	10.	A good balance between analytic narrative and illustrative extracts is provided.
Overall	11.	Enough time has been allocated to complete all phases of the analysis adequately, without rushing a phase or giving it a once-over-lightly.
Written report	12.	The assumptions about ThA are clearly explicated.
	13.	There is a good fit between what you claim you do, and what you show you have done – ie, described method and reported analysis are consistent.
	14.	The language and concepts used in the report are consistent with the epistemological position of the analysis.
	15.	The researcher is positioned as active in the research process; themes do not just 'emerge'.