ANTIBIOTIC RESISTANCE DURING COVID-19 PANDEMIC AND PERSPECTIVE OF HEALTHCARE PROVIDERS TOWARDS ANTIBIOTIC RESISTANCE: A MIXED-METHOD STUDY

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by

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LIST OF SYMBOLS

e.g.	Example given
et al.	And others
α	Alpha
Q	Quartile
χ^2	Chi-square
>	More than
<	Less than
$\geq$	Equal or more than
$\leq$	Equal or less than
=	Equal to
&	And
%	Percentage
$	Dollar
^{o}C	Degree Celsius
H_1	Alternative hypothesis

LIST OF ABBREVIATIONS

AR	Antibiotic Resistance
ATCC	American Type Culture Collection
A. baumannii	Acinetobacter baumannii
ASP	Antimicrobial stewardship program
AHWO	Animal Health World Organization
B-lactam	Beta-lactam
B-lactamase	Beta-lactamase
CDC	Centers for Disease Control and prevention
COVID-19	Novel Coronavirus Disease 2019
CRE	Carbapenem-Resistant Enterobacteriaceae
CAUTI	Catheter Associated Urinary Tract Infection
CLABSI	Central Line- Associated Bloodstream Infection
CLSI	Clinical Laboratory Standards Institute
CI	Confidence Interval
DA-HAI	Device associated Healthcare-Associated Infection
E. coli	Escherichia coli
ESBL	Extended-Spectrum Beta Lactamase
ER	Emergency room
GLASS	Global Antimicrobial Resistance and Use Surveillance System
FAO	Food and Agriculture Organization
IPA	Interpretative phenomenological analysis
HAI	Hospital Acquired Infection
HREC	Human Research Ethical Committee
HCW	Healthcare Worker
ICU	Intensive Care Unit
IPC	Infection Prevention and Control
IRB	Institutional Review Board
IQR	Interquartile range
K. pneumoniae	Klebsiella pneumoniae
KSA	Kingdom of Saudi Arabia
KAP	Knowledge, Attitude, and Practice

MERS	Middle East Respiratory Syndrome Corona Virus
KKH	King Khalid Hospital
MOH	Ministry of Health
MRSA	Methicillin-resistant Staphylococcus aureus
MDR	Multidrug Resistance
MDRO	Multidrug Resistance Organism
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PDR	Pan Drug Resistance
PPE	Personal Protective Equipment
P. aeruginosa	Pseudomonas aeruginosa
P. value	Probability value
PHCC	Primary healthcare center
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
STI	Sexually Transmitted Infection
S. aureus	Staphylococcus aureus
S. pneumoniae	Streptococcus pneumoniae
SSI	Surgical Site Infection
S. maltophilia	Stenotrophomonas maltophilia
SPSS	Statistical Package for Social Sciences
US	United States
USM	Universiti Sains Malaysia
UTI	Urinary Tract Infection
UK	United Kingdom
VAP	Ventilator-Associated Pneumonia
V. Cholera	Vibrio cholerae
WHO	World Health Organization
XDR	Extensive Drug-resistance

LIST OF APPENDICES

KERINTANGAN ANTIBIOTIK SEMASA PANDEMIK COVID-19 DAN PERSPEKTIF PENYEDIA PENJAGAAN KESIHATAN TERHADAP RINTANGAN ANTIBIOTIK: KAJIAN KAEDAH CAMPURAN.

ABSTRAK

Sewaktu pandemik Novel coronavirus 2019 (COVID-19), terdapat penggunaan antibiotik yang berlebihan di hospital. Pelbagai kajian telah melaporkan penggunaan antibiotik yang tidak betul semasa COVID-19 yang mana telah meningkatkan kerintangan antibiotik (AR). Objektif utama kajian ini adalah untuk mengkaji rintangan antibiotik semasa COVID-19 dan perspektif penyedia penjagaan kesihatan terhadap rintangan antibiotik. Penyelidikan ini menggunakan reka bentuk kaedah campuran sepanjang dua fasa. Kajian fasa I (i): Kajian keratan rentas retrospektif digunakan untuk mengenalpasti pesakit yang mempunyai bakteria AR positif sebelum, semasa dan selepas COVID-19 serta pengasingan bakteria; Kajian Fasa I (ii): Reka bentuk keratan rentas telah digunakan untuk menilai KAP HCW di Najran, KSA. Kajian fasa II: Kajian berbilang pusat kualitatif telah dijalankan di KSA untuk meneroka pengalaman pesuruhjaya kesihatan berhubung AR semasa COVID-19. Keputusan kajian Fasa I (i) menunjukkan prevalens Pan Drug Resistant (PDR) semasa pandemik COVID-19 (85.7%) adalah lebih tinggi berbanding masa sebelum (0%) dan selepas (14.3%), p= 0.001. *S. aureus* menunjukkan rintangan yang boleh diabaikan selepas wabak, manakala rintangan bakteria Gram-negatif berkurangan semasa dan selepas wabak berbanding dengan masa sebelumnya. Keputusan kajian Fasa I (ii) Kajian mendedahkan pengetahuan yang lemah, sikap negatif dan amalan HCW yang lemah. Faktor yang dikaitkan secara signifikan dengan pengetahuan yang baik ialah kewarganegaraan, kader, kelayakan, dan tempat bekerja. Sikap positif

didapati berkaitan secara signifikan dengan kader, kelayakan, dan tempat kerja. Amalan baik pula didapati berkaitan secara bererti dengan jantina, kader, kelayakan, dan tempat kerja. Dalam kajian Fasa II, tujuh tema telah muncul hasil temubual mendalam bersama pesuruhjaya kesihatan. Walaupun AR meningkat secara global semasa pandemik COVID-19, ia menurun secara beransur-ansur di wilayah Najran, KSA. Pengetahuan, sikap, dan amalan HCW di Najran, KSA mengenai AR semasa wabak memerlukan penambahbaikan, manakala pesuruhjaya penjagaan kesihatan menunjukkan pengetahuan saintifik dan terkini tentang AR. Preskripsi antibiotik harus dilaksanakan dengan ketat, bergantung pada program pengawasan antimikrob (ASP) dan garis panduan daripada Pertubuhan Kesihatan Dunia (WHO) atau Kementerian Kesihatan (MOH). Pelaksanaan program pendidikan dan latihan yang berkesan amat diperlukan. Dapatan kajian ini boleh digunakan untuk memaklumkan dasar dan amalan untuk HCW kerajaan dan orang ramai untuk mengurangkan kesan wabak ke atas AR.

ANTIBIOTIC RESISTANCE DURING COVID-19 PANDEMIC AND PERSPECTIVE OF HEALTHCARE PROVIDERS TOWARDS ANTIBIOTIC RESISTANCE: A MIXED-METHOD STUDY.

ABSTRACT

During the Novel coronavirus disease 2019 (COVID-19), there was an overuse of antibiotics in hospitals. The improper use of antibiotics during COVID-19 has increased the antibiotic resistance (AR), which was reported by multiple studies. The main objective of this study was to study the AR during COVID-19 and perspective of healthcare providers towards AR. This study employed a mixed method design throughout two phases. Phase I study (i): A retrospective cross-sectional study was employed to identify patients who had positive AR bacteria before, during and after COVID-19 as well as the bacterial isolates; Phase I study (ii): A cross sectional design was employed to assess the knowledge, attitude, and practice (KAP) of healthcare worker (HCWs) in Najran, Kingdom of Saudi Arabia (KSA); Phase II study: A qualitative multi-centre study was carried out in the KSA to explore the experience of health commissioners toward AR during COVID-19. Results of Phase I study (i) showed the prevalence of Pan Drug Resistance (PDR) during COVID-19 pandemic (85.7%) was higher as compared to the time before (0%) and after (14.3%), p= 0.001. *S. aureus* showed a negligible resistance after pandemic, while the resistance Gram-negative bacteria decreased during and after pandemic compared to the time before. Results of Phase I study (ii) revealed poor knowledge, negative attitude and poor practice of HCWs. The significantly associated factors with good knowledge were nationality, cadre, qualification, and working place. Positive attitude was significantly associated with cadre, qualification, and working place. Good practice was

significantly associated with gender, cadre, qualification, and working place. In Phase II, seven themes emerged from data. Therefore, despite the AR increased globally during COVID-19 pandemic, it dropped gradually in Najran region, KSA. Knowledge, attitude and practice of HCWs in Najran, KSA regarding AR during pandemic need improvement, whereas healthcare commissioners showed scientific and up to date knowledge about the AR. Antibiotics' prescription should be strictly implemented, relying on the antimicrobial stewardship programs (ASP) and guidelines from the world health organization (WHO) or ministry of health (MOH). Implementation of effective educational and training programs are urgently needed. Findings of this study could be used to inform policy and practice for governmental HCWs and public to reduce the impact of pandemics on the AR.

CHAPTER 1

INTRODUCTION

This chapter provides the major perspectives that lead to the problem statement. Perspectives of AR and how COVID-19 contributed to worsening the situation were provided and detailed on how both perspectives contribute to the evolution of the problem statement. In addition, this chapter provides an overview of AR bacterial infection. Significant advances and conceptual evolution in research on the topic of AR were identified, particularly in the context of concepts related to this study. To support the hypothesis constructed, problem statements were argued from both theoretical and practical aspects to mediate AR during COVID-19 and perspective of healthcare providers towards AR. Thus, research questions and objectives were formulated based on the problem statement.

1.1 Development of antibiotic resistance and contributory factors

AR is defined as the ability of microorganisms such as bacteria to resist antibiotics (WHO, 2021). Antimicrobial resistance (AMR) occurs when microorganisms, such as bacteria and fungi, evolve the capability to overcome drugs tailored to kill them. This means that these microorganisms are not killed and carry on growing. Such infections caused by AR are difficult and occasionally impossible to cure (CDC, 2022).

AR has been classified into three categories; Multidrug Resistance (MDR), Extensive drug-resistance (XDR), and PDR (Magiorakos et al., 2012).

There was an assumption that the development of AR is improbable. This justification was relied on previous assumption that mutation frequency producing bacterial resistance was slightly negligible (Davies, 1994). Regrettably, the opposite has proved over time. In the beginning, it was not anticipated that bacteria could resist to antibiotics through different mechanisms. Furthermore, it was also unexpected what is known as horizontal gene transfer by interchanging of genes. Subsequently, before characterizing the first antibiotic, penicillin, emerging of the resistance was discovered. Before releasing the penicillin to be used for treating patients, the primary Beta-lactamase (β-lactamase) was recognized in *Escherichia coli* (Abraham & Chain, 1940). Alongside Beta-lactams (β-lactams), one of the primary antibiotic groups that encountered the resistant challenges was aminoglycoside–aminocyclitol (Wright, 1999; Bradford, 2001).

It has been found that the overuse of the antibiotics participated in the emerging of AR among different species of bacteria (Mevius et al., 2009; De Greeff & Mouton, 2017). For example, methicillin-resistant *Staphylococcus aureus* (MRSA) appeared in 1960 and vancomycin-resistant enterococci (VRE) in 1988 (Jevons et al., 1963; Uttley, 1988).

The incorrect prescription of antibiotics and increased AR over time have been linked to several factors, including inexperienced doctors, knowledge gaps in the healthcare settings, improper practices of using antibiotics, lack of awareness towards AR, and low ASP efforts (Anwar et al., 2021; Gupta, 2018; Firouzabadi & Mahmoudi, 2020; Röing et al., 2020; Zetts et al., 2018).

1.2 Contribution of COVID-19 to antibiotic resistance

COVID-19 could effect the AR. For instance, AR likely elevate because of high proportions of patients, limited resources like personal protective equipment (PPE), disruption of ASP, and Infection Prevention and Control (IPC) program. However, AR may reduce because of implementation of strict instructions such as face masks and hand hygiene (Condes & Arribas, 2020; Subramanya et al., 2021; Tartari et al., 2020; Zhu et al., 2021).

During COVID-19, the AR carried on in the shadows as the pandemic rages on. The losses caused by AR on families and their patients are hugely invisible. However, lengthy hospital stays due to bacterial infections and needless deaths reflect that. Besides, AR affects poor people who have few choices of using second-line antibiotics, high-cost antibiotics that could be used when bacteria defeat the first- line antibiotics (Laxminarayan, 2022).

Heavy use of antibiotics among COVID-19 patients may contribute to the AR crisis. Overuse of the antibiotics was because of patients with respiratory diseases diagnosed initially with uncertainly and concern about secondary bacterial or co-infection in patients with positive COVID-19. Previous reviews indicated that there was antibiotic overprescribing for COVID-19 patients although the bacterial infections were low, particularly among non-intensive care unit (ICU) patients (Langford et al., 2022; Langford et al., 2021; Langford et al., 2020). Some studies found AR increased during COVID-19 while others reported differently.

1.3 Problem Statement

The ability of bacteria to resist the antibiotics has increased globally over time causing high proportions of morbidity, mortality, and economic expenses. Overuse, improper prescription, and injudicious use in agriculture of the antibiotics are the most revealed causes of the resistance (Larson, 2007; Ventola, 2015). The high percentages of AR alarm the dangerous situation of this issue.

New mechanisms of resistance are arising and disseminating globally, and the first-line antibiotic medications might be useless and entail using very expensive medication. There are also some common consequences such as increased in length of stay in hospitals and in the duration of the illness and treatment (Jacoby & Archer, 1991; Zhen et al., 2019).

Recently in the period of COVID-19, the AR increased and has been reported in some countries such as USA, China, Iran, Italy and Indonesia (Gomez-Simmonds et al., 2021; Sang et al., 2021; Sharifipour et al., 2020; Temperoni et al., 2021; Tiri et al., 2020; Wardoyo et al., 2021). More than 70% of COVID-19 patients who admitted to the hospitals have been treated with antibiotics whereas less than 9% of them had co-infections. Moreover, a wide range of broad-spectrum antibiotics such as Azithromycin, Amoxicillin-Clavulanic acid, Gentamicin, Vancomycin, and Piperacillin/Tazobactam were overused (Adebisi et al., 2021; Al-Hadidi et al., 2021). Consequently, the prevalence of AR during COVID-19 era was higher than before the pandemic (Bork et al., 2021; Gaspar et al., 2021).

Further, AR of Gram-negative bacteria was increased after COVID-19 pandemic compared to the era before COVID-19 (Gaspar et al., 2021). Consequently, the treatment of bacterial infections such as pneumonia, blood stream infection, urinary tract infection (UTI) will be harder and might be impossible. Patients infected by multidrug resistance organisms (MDROs) or other types of AR bacteria may die due to lenience of people regarding the importance of adherence to guidelines in using antibiotics (WHO, 2020).

Some factors encouraging AR, specifically during pandemic. First, improper use of antibiotic during COVID-19 pandemic (Elsayed et al., 2021). People in the community consume antibiotics without consultation of physicians as well as HCWs. Physicians in the healthcare settings prescribe antibiotics for patients as a prophylaxis while majority of the patients do not have secondary bacterial infections; they even do not have confirmed microbiological bacterial cultures (Dudoignon et al., 2020). Second, ASP is very important in the hospitals to guide physicians to prescribe antibiotics based on the common bacteria in the community where the patients come from and appropriate antibiotics. Some hospitals lack the ASP or implement it inappropriately. Previous studies found HCWs were not fully aware about the ASP. (Alghamdi et al., 2021; Herawati et al., 2021)

In addition, HCWs and health commissioners play an important role in the success of tackling the issue of AR. Through the intensive search, there was no studies focused on HCWs' KAP concerning AR during COVID-19. The previous studies covered the KAP of HCWs regarding the use of antibiotics and AR, which are not related to the time during COVID-19 and revealed low level of knowledge of the HCWs toward AR, however, some studies reported good knowledge. While it was reported low level of HCWs's knowledge about AR before COVID-19 (Alghamdi et al., 2021; Baraka et al., 2019; Sanneh et al., 2020; Tafa et al., 2017), in the KSA, it is expected that the knowledge of the HCWs toward AR during pandemic will be lower. Therefore, one of the key solutions is to assess the KAP of HCWs and to explore the experience of health commissioners. Then, defect factors can be identified, and therefore recommendations for further research will be highly recommended.

Given the uniqueness of the pandemic on increasing the AR, more than 29.400 idividuals died from infection caused by anitbiotic resistance at the beginnig of COVID-19 pandemic. Approximately 40% of them acquired the infection when they were in the hospital receiving the treatment. (CDC, 2022) As a result, previous studies highlighted some factors attributed to increase the AR, such as improper use of antibiotics, particularly in the healthcare settings, where physicians prescribe without guidelines (Albahooth et al., 2021; Althagafi & Othman, 2022; Dudoignon et al., 2020). In addition, as the ASPs are very important in controlling the issue of AR, the worsen situation of the pandemic has lead to suspend these programs and made the guidelines ambiguous (Comelli et al., 2022; Khan et al., 2022).

1.4 Significance of the study

This study aided us in exploring the status of AR before and after COVID-19 in the KSA as well as other parts of world. Throughout the current study, understanding the issue of AR during pandemic was expanded and more obvious for people in both the healthcare settings and the communities. This study reported the most common secondary bacterial infection among COVID-19 patients. The pattern of AR Gram-positive and negative bacteria prior, during and post COVID-19 era was determined. People in the community and health sectors will be shared with the significant findings of the changes in the AR, and then they will be informed about the threatening situation of the bacterial resistance to antibiotics especially during pandemics.

The level of KAP of HCWs was assessed and associated factors for poor knowledge and practice were identified. HCWs are deemed the group who can manage using antibiotics either during pandemics or normal situation like getting common cold viruses as well as convincing people at homes and in the communities about the proper uses of antibiotics and negative outcomes for improper uses such as increase of AR, particularly during pandemics. The findings of the current study about the level of KAP of HCWs in the KSA will be shared in educational programs and conferences related to pandemics, antibiotics, and microbiology. The weak points of the HCWs will be discovered and addressed by both educational programs and further studies. The experience of the health commissioners regarding AR during the pandemic was explored as well as their point of views toward talking about this issue. This study will highlight the key points from the experience of the commissioners in the health facilities toward AR during COVID-19. Proposals to combat the problem of AR during future pandemics will be recommended for consideration and development.

Consequently, people in the KSA and other countries will go through the findings of this study and will establish the issue of AR as serious. Its findings will enable evolutionary approaches to help in controlling AR. Policy makers will take an action in terms of using antibiotics in case of future pandemics. A suggestion of the intervention programs will be highly recommended to be launched immensely to raise the KAP of HCWs and fill the gap of this study.

1.5 Research questions

1- Is there any difference in the pattern of AR among Gram-positive and Gram-negative bacteria before, during, and after COVID-19 in KSA?

2- Is there any association between sociodemographic factors (patient location in the hospital, gender, multiple admission, nationality, COVID-19 infection, chronic disease, and time classification; before, during, and after) and AR (MDR, XDR, and PDR) classification in KSA?

3- Is there any association between sociodemographic factors (age, gender, nationality, COVID-19 infection, chronic disease, type of bacteria, AR classification (MDR, XDR, and PDR), time classification, and number of associated bacteria) and death of patients with AR in KSA?

4- What is the level of KAP of HCWs toward AR during COVID-19 in KSA?

5- Is there any association between sociodemographic factors (age, gender, nationality, cadre, qualification and place of work) and level of KAP towards AR among HCWs in KSA?

1.6 Objectives

1.6.1 Main objective

To study the antibiotic resistance during COVID-19 and perspective of healthcare providers towards AR.

1.6.2 Specific objectives

The specific objectives of this study, depending on the study phases:

1.6.2(a) Phase I

1- To evaluate the difference in the pattern of AR among Gram-positive and Gram-negative bacteria before, during, and after COVID-19 in KSA.

2- To evaluate the association between sociodemographic factors (patient location in the hospital, gender, multiple admission, nationality, COVID-19 infection, chronic disease, and time classification; before, during, and after) and AR (MDR, XDR, and PDR) classification in KSA.

3- To assess the association between sociodemographic factors (age, gender, nationality, COVID-19 infection, chronic disease, type of bacteria, AR classification; MDR, XDR, and PDR, time classification, and number of associated bacteria) and death of patients with AR in KSA.

4- To evaluate the level of KAP toward AR during COVID-19 among HCWs in KSA.

5- To determine the association between sociodemographic factors (age, gender, nationality, cadre, qualification and place of work) and level of KAP towards AR among HCWs in KSA.

1.6.2(b) Phase II

To explore the experience of healthcare commissioners towards AR during COVID-19 pandemic, challenges, and provide recommendations for combating AR during pandemic.

1.7 Research Hypothesises

The followings are the research hypothesis:

H_1 1: There is a difference in the pattern of AR among Gram-positive and Gram negative bacteria before, during, and after COVID-19 in KSA.

H_1 2: There is association between demographic factors (patient location in the hospital, gender, multiple admission, nationality, COVID-19 infection, chronic disease, and time classification; before, during, and after) and AR classification (MDR, XDR, and PDR) in KSA.

H_1 3: There is association between demographic factors (age, gender, nationality, COVID-19 infection, chronic disease, type of bacteria, AR classification; MDR, XDR, and PDR, time classification, and number of associated bacteria) and death of patients with AR in KSA.

H_1 4: There is association between demographic factors (age, gender, nationality, cadre, qualification and place of work) and level of KAP towards AR among HCWs in KSA.

1.8 Operational definitions

MDROs is defined as the ability of microorganisms, mainly bacteria, to resist more than three classes of agents (Magiorakos et al., 2012). XDR is defined as the susceptibility of bacteria to two or fewer antibiotic agents (Magiorakos et al., 2012). PDR is defined as the resistance of bacteria to all antibiotic agents (Magiorakos et al., 2012).

Before COVID-19 means the time from April 2019 to March 2020.-During COVID-19 means the time from April 2020 to March 2021.-After COVID-19 means the time from April 2021 to March 2022 (Bazaid et al., 2022; WHO, 2021; News, 2022).

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

This chapter provides an overview of relevant literature on AR in general and particularly during COVID-19. The literature review focused on five major aspects. The first aspect demonstrated common pathogenic bacteria, antibiotic classification based on the mechanism of action, and AR and AR classification. The second aspect demonstrated the antibiotic consumption and consequences of AR in healthcare settings and communities. The third aspect reviewed the history of global pandemic. The fourth aspect identified the AR during COVID-19 pandemic and the associated factor. The fifth aspect showed KAP of HCWs and perspective of health providers including HCWs and commissioners toward AR. A conceptual framework has been formulated according to the literature review.

2.2 History of antibiotics

Back in 1890, the term of antibiosis was earlier employed by Paul Vuillemin as an antonym to coexistence demonstrating the action of antagonistic among various microorganisms such as fungi vs bacteria, and bacteria vs parasite (Pegadraju et al., 2021; Roberts, 2010; Wallenfels, 1945).

The term antibiotic was subsequently used to depict secondary metabolites that are naturally created by fungi and bacteria, which might inhibit or kill bacteria or fungi. Nowadays, there is a wide meaning for the antibiotic term either the definition is narrow when there are designed molecules or using other terms like antifungal or antibacterial, to specify the mechanism of action against fungi and bacteria, respectively (Roberts, 2010).

One of the most significant breakthroughs in medical field is the evolution of antibiotics. Morbidity and mortality caused by bacterial infections have significantly declined as consequences of using antimicrobials (Andersson & Hughes, 2010).

In 1928, an antimicrobial agent was first identified by Alexander Fleming when he had discovered a mold produced by *Penicillium notatum* killing bacteria, mainly *S. aureus*. The mould yielded an active agent which was named penicillin, and considered a natural compound (Demain & Martens, 2017).

From that point onwards, an immense number of semi-synthetic and synthetic antibiotics have evolved, for example, B-Lactam antibiotics, aminoglycosides, and quinolones (Hauser, 2018; Rourke et al., 2020).

2.3 Common pathogenic bacteria, antibiotic classes, and development of antibiotic resistance and the resistant classifications

Based on the cell wall, the bacteria are classified into two groups (Gram-negative and Gram-positive). Figure 2.1 depicts the example of most common and medically critical bacteria. Gram-positive bacteria include *Streptococci*, *Staphylococci*, *Enterococci*, *Bacillus Anthracis*, while Gram-negative bacteria include *E. Coli*, *Klebsiella species*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (Alhumaid et al., 2021; Bandy & Almaeen, 2020; Gillespie & Hawkey, 2006).

Bacterial pathogen uses different mechanisms when encountering a host and these mechanisms help the pathogen to escape from the defence of the human host. Interaction between components of the bacteria and the host involves: A) Capsules;

protection for the bacteria from neutrophils and macrophage (phagocytosis), B) Septic shock caused by lipopolysaccharide and components of the cell wall, C) Toxin destroys the host cell and help invasion, and D) Adhesions that acts as a facilitator to bind the bacteria to surfaces of the host (Wilson et al., 2020).

Bacterial infections that cause the harm for both human and animal may attack respiratory tract, blood stream, and urinary tract as well as other sites such as gastrointestinal tract (Ahmed, 2020; Gajdács et al., 2021; Holmes et al., 2021).

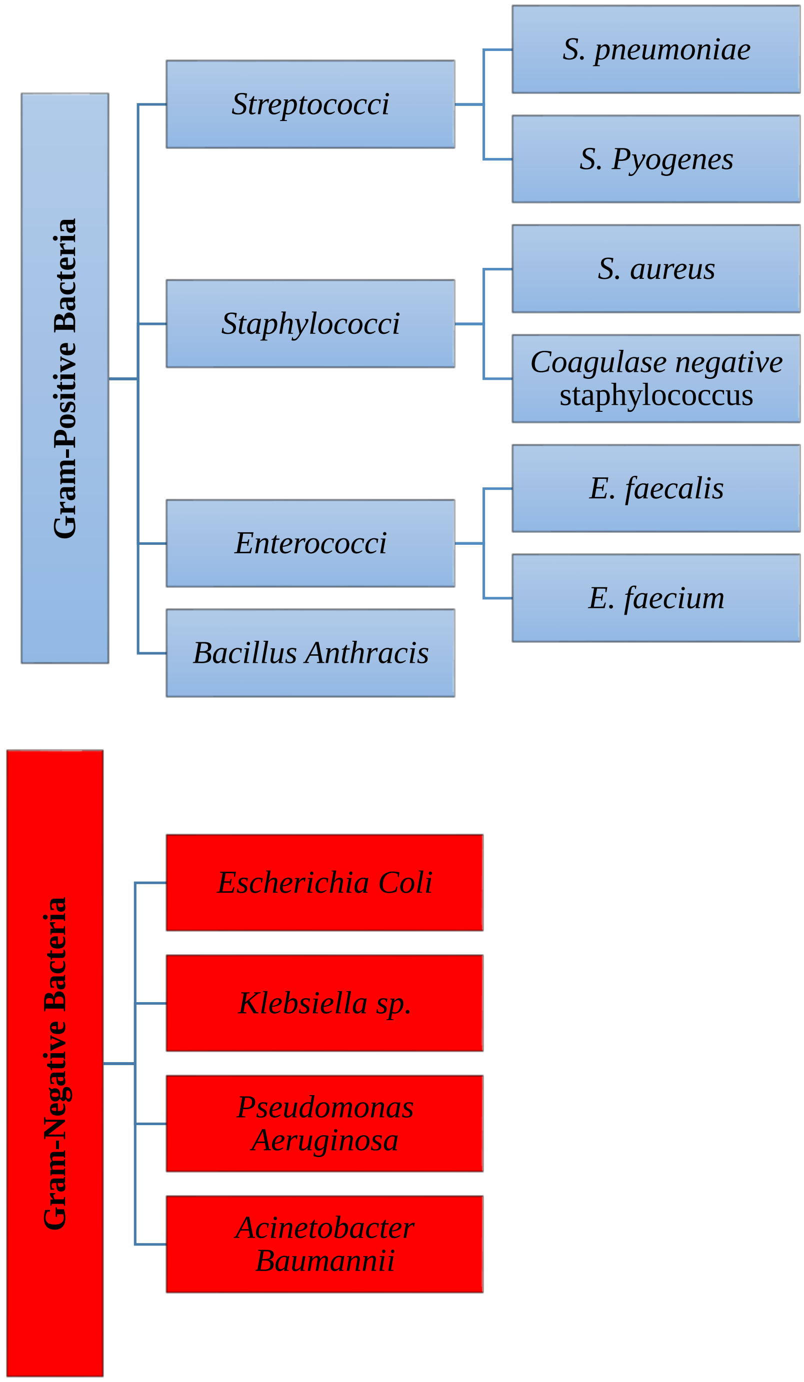

Figure 2.1 Example of some Gram-positive and negative bacteria.

Antimicrobial agents that cure and protect people from bacterial pathogenesis are classified into three wide groups. First, groups that target cell walls of the bacteria: B-Lactam Antibiotics; Glycopeptides, Daptomycin, and Colistin. Second, groups that stop proteins synthesis; Rifamycins, Aminoglycosides, Macrolides and Ketolides, Tetracyclines and Glycylcyclines, Chloramphenicol, Clindamycin, Streptogramins, Linezolid, and Nitrofurantoin. Third, groups that target bacterial DNA or multiplication of nucleic acid; Sulfa Drugs, Quinolones, and Metronidazole (Hauser, 2018; Moore, 2023), (Figure 2.2).

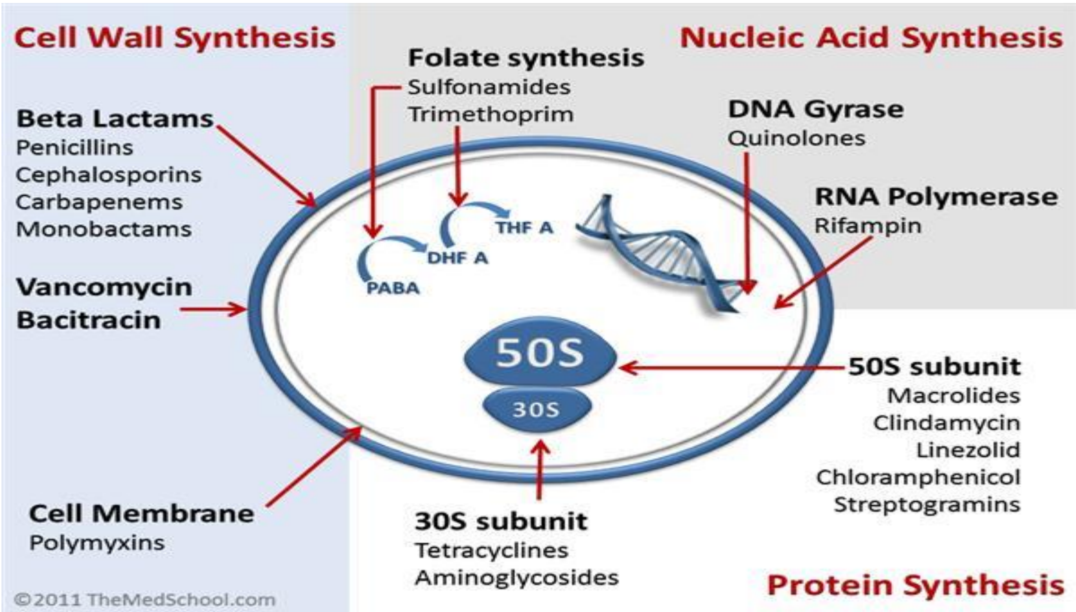

Figure 2.2 Mechanism of antibiotic action

AR is a part of the AMR, where the bacteria can defeat the antibiotics, which are essentially designed against them (WHO, 2021). Although the period between 1930s and 1960s is deemed a golden time of discovery of many antibiotics, misuse of antibiotics has resulted in emerging of AR, which has been threatening to end the golden time of antibiotics (Nathan, 2004).

To resist the antibiotics, bacteria use two fundamental strategies: First, to block reaching enough concentration of antibiotic to the target. Second, to alter the target on which the antibiotic works as shown in Figure 1.3, (Wistrand-Yuen et al., 2018). Bacteria have developed many ways to resist antibiotics over time.

A. To block reaching enough concentration of antibiotic to the target (Martínez & Baquero, 2014; Walsh, 2000):

1. Efflux pumps: Throughout the bacterial membrane or cell wall, the bacteria are capable to pump the antibiotic out of its cell.
2. The permeability of the antibiotic across the surrounding bacterial cell membrane is decreased. This happens because of specific modifications in the membrane of the bacteria.
3. Damage the antibiotic: bacteria produce enzymes that inhibit antibiotics. For example, the component of penicillin can be destroyed by β-lactamase.
4. Altering the antibiotic: Sometimes there is no binding between the target in the bacterial cell and the antibiotic, which occurs due to enzymes that are produced by bacteria and then add various chemical groups to the antibiotics.

B. To alter the target on which the antibiotic works (Martínez & Baquero, 2014; Walsh, 2000):

1. Camouflage the antibiotic target: modification in the structure of the site inside the bacterium can stop the effect of the antibiotic. This modification is consequence of mutations in the bacterial genetic material DNA.
2. Production of alternative proteins: bacteria are capable to producing new alternative proteins instead of the previously inhibited ones by the antibiotics.

3. Reprograming the target. Occasionally bacteria are capable to produce a different type of structure and need this structure. For instance, the bacteria that are resistant to Vancomycin build a various cell wall in comparison to the susceptible ones. Therefore, the antibiotic is not capable to interact with the newly built cell wall.

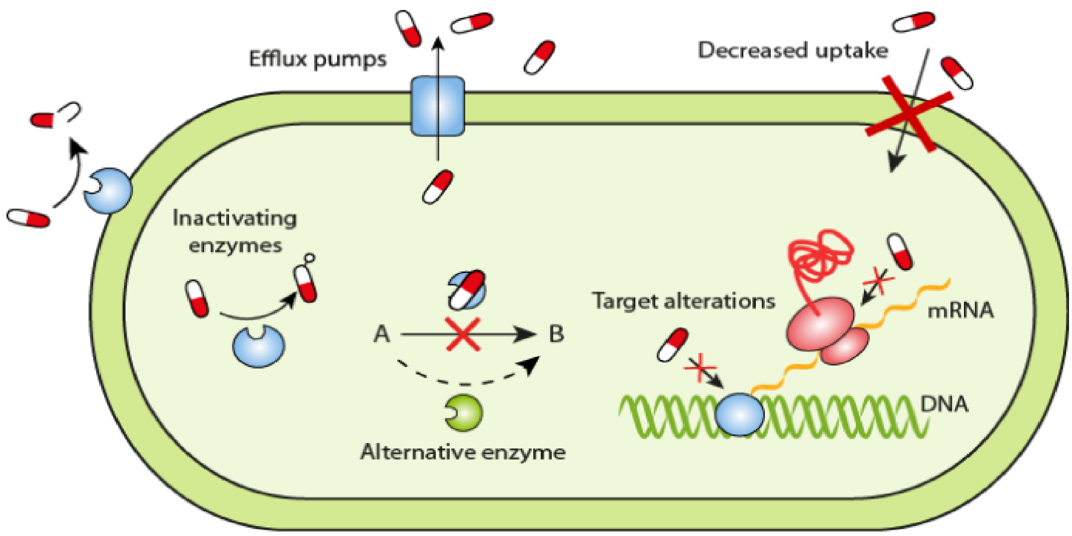

Figure 2.3 Mechanism of action for antibiotic resistanc

A crisis of AR has emerged due to misuse of antibiotics, and lack of development of new drugs throughout pharmaceutical industries, which are challenged by the decreased economic encouragement and regulations (Ventola, 2015). AR constitutes a serious public health issue worldwide affecting the health of human beings, animals, and the environment. MDR bacteria are the reason behind this public health issue because of their emersion, dispersion, and persistence (Davies & Davies, 2010). Consequently, interlink was found between human, animal, and the environment in terms of sharing AR among them (Rousham et al., 2018).

2.4 Antibiotic consumption

The WHO reports that there is an urgently golobal need to change the way of antibiotic uses and prescribes. Regardless of development of new drugs, without changing the behaviour, the issue of AR will stay a serious threat (CDC, 2023). Recently, the antibiotic prescription relys on the guidelines. Such guuidelinces explaind the proper uses of antibiotics for treatment the community and hospital acquired infections as well as empirical treatment. Noteworthy, there are five pillars of the ASP which include adherence, prevention, detection, improving use, and oversight, and the way of implementation (Ababneh et al., 2021; NICE, 2023; Saudi MOH, 2018).

COVID-19 pandemic has led to development of the remote medication prescription (Ita, 2021; Leite et al., 20202). Various health information technologies have been utilized for antibiotic prescription where physicians, for example order the antibiotics online without attending patients physically (Lim et al., 2021). Consequently, in some countries such as the UK, the remote prescription has been developed to become a standard practice (Lim et al., 2021). Currently in the KSA, the government has launched advanced technology for medication prescription using e-prescription platform “Anat”, where physician order the medication and patients receive it from the nearest pharmacy to him/her (Alhassoun & Aldossary, 2023).

Regrettably, throughout the previous five decades, the consumption of antibiotics was high, then led to an increase in the selective pressure on the sensitive bacteria to antibiotics and resulted in supporting of survival of many strains of resistant bacteria (Arason et al., 2002). Such strains are resistant to more than two antibiotics. If people can limit the overuse of antibiotics, the resistant bacteria could become susceptible (Arason et al., 2006).

Global antibiotic consumption from 2000 to 2010 has been elevated by about 36%. This increased percentage is accounted for by some countries, for, example, Brazil, China, India, South Africa, and Russia. The consumption of the antibiotics was significantly varied with seasons in most countries. As for carbapenems and polymixins consumption, they were highly consumed by 45% and 13%, respectively (Van Boeckel et al., 2014).

Another study revealed that the global antibiotic consumption between 2000 and 2015 elevated by approximately 65%, which that mostly due to high levels of consumption in wealthy countries. Nevertheless, in developing countries, individual consumption was increasing rapidly due to growing better standards of life and affordability of care in health services. (Klein et al., 2018)

During COVID-19 pandemic there was a positive association between antibiotic sales and cases of COVID-19, particularly between 2020 and 2022. (Nandi et al., 2023). In terms of antimicrobial usage in food-producing animals, the global estimated usage in 2020 was roughly 99,502 tonnes. According to these trends, it was estimated to increase by about 107,472 tonnes (8%) in 2030. (Mulchandani et al., 2023).

2.5 Antibiotic resistance in healthcare settings and communities

MDROs are spreading dramatically in many countries producing critical medical and economic outcomes. Every few minutes a patient loses their life in both Europe and America due to MDR bacteria (Harbarth et al., 2015).

About 99,000 annual deaths in the USA are caused by MDROs associated with hospital-acquired infections (HAIs). In 2006, it was reported that about 50,000 deaths in America because of HAIs, specifically pneumonia and sepsis. Unfortunately, the

MDROs associated with HAIs cost the United States (US) roughly $8 billion (Infectious Diseases Society of America, 2011).

Additionally, patients infected by MDROs need to stay at the hospital for a minimum of thirteen days, which adds an extra eight million hospital stays yearly. It costs up to about $29,000 per patient cured with MDROs (Ventola, 2015). Comparing patients with no infection to those who infected by AR, risk of mortality was higher among patients infected by AR. For patients who acquired AR, the hospital length of stay ranged from three to about 45 days. The cost of hospital stay varied between US$238 to US$16,496 (Zhen et al., 2019).

One of the major causes of morbidity and mortality among hospitalized patients is HAIs, particularly associated with devices. Device-associated healthcare-associated infections (DA-HAIs) also lead to prolonged hospitalisation in the ICU as well as increased costs for hospitals. These high costs are much higher among low-income countries than high income (Rosenthal et al., 2011).

Roughly 4% of admitted patients in the hospitals experienced acquired infections at the hospitals (Monegro et al., 2020). During 2011, about 721,800 HAIs reported among 648,000 hospitalized individuals (Monegro et al., 2020). According to the reported findings, the HAIs were as the following; pneumonia, surgical site infections (SSI), gastrointestinal infections, UTIs, and bloodstream infection and the proportions were 21.8%, 21.8%, 17.1%, 12.9%, 9.9%, respectively. The most causative pathogens for the HAIs include *C. difficile*, *S. aureus*, *Klebsiella, and E. coli*, with the prevelance of 12.1%, 10.7%, 9.9%, and 9.3%, respectively (Monegro et al., 2020).

In Venezuela, surveillance data on DA-HAIs revealed that the rate of VAP per per1000 mechanical ventilator days was 7.2. The rate of central line-associated bloodstream infection (CLABSI) per 1000 central line days was 5.1, and catheter-associated urinary tract infection (CAUTI) was about 3.9 per 1000 days of using catheter (Empaire et al., 2017).

Regarding the information about DA-HAIs in developing nations, despite it is insufficient, about 43 countries in Asia, Africa, Europe, and Latin America have been involved in a study carried out by the International Nosocomial Infection Control Association between 2007 and 2012, and the CLABSI rate was five times higher than what has been reported in the USA. CAUTI and VAP also showed higher rates (Rosenthal et al., 2014). In the KSA, the DA-HAI rates were high. VAP was the highest (57.4%), and CAUTI and CLABSI ranked second and third at 28.4, and 14.2%, respectively (Gaid et al., 2018).

WHO has reported findings from various countries sharing their reports with the Global Antimicrobial Resistance and Use Surveillance System (GLASS) related to bacterial infections, involving UTIs, sepsis, Sexually Transmitted Infection (STI), and other types of infections causing diarrhoea, AR rates of antibiotics used to cure such infections were reported worldwide. For instance, ciprofloxacin is one of the common antibiotics used to treat UTIs, and the resistance to ciprofloxacin ranged between 8.4% and 92.9% for *E. coli* and *K. pneumonia* between 4.1% and 79.4% (WHO, 2021).

There was a global spread of *Klebsiella pneumoniae* against carbapenem antibiotics which are last-resort drugs. Among these countries, about 50% of patients who were treated for infections caused by *K. pneumoniae* did not respond because of resistance to carbapenem antibiotics (WHO, 2021). There was also spread of *E. coli* that are resistant to fluoroquinolone and some types of bacteria such as *E.coli* and *K.*