UNIVERSITI PUTRA MALAYSIA

KNOWLEDGE, ATTITUDES AND PRACTICES RELATED TO ANTIBIOTIC USE AND RESISTANCE PATTERNS AMONG OUTPATIENTS IN EASTERN PROVINCE, SAUDI ARABIA

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in Fulfillment of the Requirement for the Master of Science

KNOWLEDGE, ATTITUDES AND PRACTICES RELATED TO ANTIBIOTIC USE AND RESISTANCE PATTERNS AMONG OUTPATIENTS IN EASTERN PROVINCE, SAUDI ARABIA

By

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September 2015

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Antibiotic resistance is globally responsible for high numbers of morbidity and mortality. Methicillin-resistant *Staphylococcus aureus* and Extended-spectrum β-lactamases producing *Escherichia. coli* and *Klebsiella. pneumoniae* have high prevalence in many countries. Misuse of antibiotic is one major reason that has contributed to the emergence of antibiotic resistance. Knowledge and attitude of antibiotic were determined in some studies in order to determine the practice of antibiotic usage. There is scarce of studies in Saudi Arabia regarding surveillance of antibiotic resistance as well as regarding knowledge, attitude, and practice towards antibiotic usage.

The study was carried out to determine the prevalence of MRSA and ESBL-producing *E. coli* and *K. pneumoniae* in Qatif Central Hospital for five years. In addition, demographic and clinical characteristics of patients with MRSA and ESBL strains were determined in 2014. Furthermore, questionnaire was carried out to assess the level of knowledge, attitude, and practice towards antibiotics usage among outpatients in Qatif Central Hospital (QCH) and Dammam Medical Complex (DMC), Eastern Province, Saudi Arabia. Microsoft Excel and SPSS were used to analyze antibiotic resistance and the questionnaire.

Among the three organisms, the results showed that the prevalence of MRSA among *S. aureus* was the highest over the five years (2010-2014). The range of MRSA was 21.4% - 30.8%. ESBL-producing *E. coli* was the second highest prevalence over the five years with a range 14.2% - 26.7%. The prevalence of ESBL-producing *K. pneumoniae* was low with a minimum of 11.9% and maximum of 20.8%. In 2014, it was shown that majority of MRSA patients were female (59.8%), adults (20-59) years old (47.6%), from ICU (28.0%), and wound samples (38.4%). Likewise, many of ESBL-producing *E. coli* patients were female (66.7%) and adults (44.4%). Yet, most of patients were from Outpatient Department (34.0%) and urine sample (55.6%). Male patients with ESBL-producing *K. pneumoniae* were the greater (53.5%) and adults patients were the highest (51.2%). Many patients were from Outpatients Department (30.2%) and wound samples (32.6%). For the cross-sectional survey, out of the 300 respondents, males were 50.7%. Majority were married (73.3%), 18 - 29 years old (47%), college/university education (69.3%), and science field (33%). The findings showed that majority of respondents (79.6%) had low knowledge on antibiotic.

Although many respondents (71.7%) had a positive attitude, only few respondents (9.7%) had a good practice towards antibiotic usage. The study showed that level of education ($P = 0.002$) and field of education ($P < 0.0001$) were significantly associated with knowledge. Age ($P = 0.039$), level of education ($P = 0.001$), and field of education ($P < 0.0001$) were significantly associated with attitude. Gender ($P = 0.026$) and level of education ($P = 0.006$) had associated with practice towards antibiotic usage.

In conclusion, prevalence of MRSA and ESBL-producing *E. coli* was high over the past five years. Respondents in the study showed a low knowledge and poor practice towards antibiotic usage. Interventions are required in order to improve awareness of antibiotic and in turn to decrease antibiotic resistance.

Abstrak tesis yang dikemukakan Senat Univeristi Putra Malaysia
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PENGETAHUAN, SIKAP DAN AMALAN YANG BERKAITAN DENGAN PENGGUNAAN ANTIBIOTIK DAN CORAK KETAHANAN ANTARA PESAKIT LUAR DI KAWASAN TIMUR SAUDI ARABIA

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Ketahanan antibiotik merupakan punca global yang menyumbang kepada morbiditi dan jumlah kematian yang tinggi. *E. coli* dan *K. penumoniae* yang menghasilkan MRSA dan ESBL tersebar luas di banyak negara. Penyalahgunaan antibiotik merupakan salah satu sebab utama yang menyumbang kepada kemunculan masalah ketahanan antibiotik. Pengetahuan dan sikap terhadap antibiotik telah ditentukan dalam beberapa kajian bagi memastikan amalan penggunaan antibiotik. Kajian-kajian yang berkaitan dengan surveilans ketahanan antibiotik serta pengetahuan, sikap, dan amalan terhadap penggunaan antibiotik di Arab Saudi amatlah jarang.

Kajian ini telah dijalankan bagi menentukan prevelans MRSA dan ESBL penghasil *E. coli* dan *K. pneumoniae* Hospital Qatif Tengah untuk lima tahun. Di samping itu, maklumat-maklumat demografi dan klinikal para pesakit yang mempunyai tanda-tanda MRSA dan ESBL telah ditentukan pada tahun 2014. Tambahan pula, soal selidik telah dijalankan bagi menilai tahap pengetahuan, sikap, dan amalan terhadap penggunaan antibiotik dalam kalangan pesakit luar di Hospital Qatif Tengah (HQT) dan Kompleks Perubatan Dammam (KPD), Wilayah Utara Arab Saudi. Perisian *Microsoft Excel* dan SPSS telah digunakan untuk menganalis ketahanan antibiotik dan hasil soal selidik.

Antara ketiga-tiga organisma tersebut, hasil kajian menunjukkan bahawa prevalens MRSA antara *S. aureus* adalah yang tertinggi dalam tempoh lima tahun tersebut (2010-2014). Julat MRSA adalah antara 21.4% - 30.8%. *E. coli* penghasil ESBL mempunyai keluasan sebaran yang kedua tertinggi dalam tempoh lima tahun tersebut dengan julat antara 14.2% - 26.7%. Prevalens *K. Pneumoniae* penghasil ESBL adalah rendah dengan peratusan minimum 11.9% dan maksimum 20.8%. Pada tahun 2014, didapati bahawa kebanyakan pesakit MRSA adalah perempuan (59.8%), dewasa (berumur 20-59) (47.6%), dari ICU (28.0%), dan sampel luka (38.4%). Demikian juga, kebanyakan pesakit *E. coli* penghasil ESBL merupakan perempuan (66.7%) dan dewasa (44.4%). Akan tetapi, kebanyakan pesakit tersebut adalah dari Jabatan Pesakit Luar (34.0%) dan sampel air kencing (55.6%). Lebih banyak pesakit yang menghidapi *K. pneumoniae* adalah lelaki (53.5%) dan pesakit-pesakit dewasa adalah yang terbanyak (51.2%). Banyak pesakit adalah dari Jabatan Pesakit Luar (30.2%) dan sampel luka (32.6%).

Bagi kajian tinjauan keratan lintang, daripada 300 orang responden, 50.75% adalah lelaki. Kebanyakan mereka telah berumah tangga (73.3%), berumur 18 - 29 tahun

(47%), mempunyai pendidikan kolej/universiti (69.3%), dan berkecimpung dalam lapangan sains (33%). Hasil kajian menunjukkan bahawa majoriti daripada responden (79.6%) berpengetahuan rendah tentang antibiotik. Walaupun banyak responden (71.7%) bersikap positif, hanya sebilangan (9.7%) yang mengamalkan penggunaan antibiotik yang baik. Kajian tersebut menunjukkan bahawa tahap pendidikan (P = 0.002) serta bidang pendidikan (P < 0.0001) menunjukkan perkaitan yang penting dengan pengetahuan. Faktor umur (P = 0.039), tahap pendidikan (P = 0.001), serta bidang pendidikan (P < 0.0001) menunjukkan perkaitan yang bermakna dengan sikap. Jantina (P = 0.026) dan tahap pendidikan (P = 0.006) mempunyai perkaitan dengan amalan penggunaan antibiotik.

Kesimpulannya, prevalens *E. coli* penghasil MRSA dan ESBL adalah tinggi dalam tempoh lima tahun yang lalu. Para responden dalam kajian ini menunjukkan pengetahuan rendah dan amalan yang tidak sihat dalam penggunaan antibiotik. Intervensi diperlukan bagi meningkatkan kesedaran tentang antibiotik dan oleh itu, dapat mengurangkan ketahanan terhadap antibiotik.

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In the name of God (Allah), the most compassionate, the most merciful

"Recite in the name of your Lord who created - Created man from a clinging substance- Recite, and your Lord is the most Generous - Who taught by the pen - Taught man that which he knew not".

All praise is due to Allah, Lord of the worlds, and thank for Allah for willing me the chance to proceed further in my education, a thing that he asks humankind to embrace and possess. I am grateful to the God for the good health and wellbeing that were necessary to complete this study. I am grateful to my supervisor; Associate Professor Dr. Malina Osman for guiding me to the right path to reach the last stage of the study and for providing of much of her valuable time throughout my entire research. The grateful also to my Co-supervisor Associate Professor Dr. Rukman Awang Hamat for providing extra assistance and support in order to accomplish the work. I thank God for having such a great father and brothers whom support me financially for the entire of the study and thank also God for having such a kind mother and sisters whom never forget me in the pray. To my fiancée, Fatima, I thank her for being beside me and encourage me. Besides, I never forget Dr. Araf Al-Hamad, clinical microbiologist, whom providing me with data regarding antibiotic resistance. Thanks to respondents who took times answering the questionnaire in both Dammam and Qatif Hospitals. At last but not least, I am pleasant being a student in UPM, particularly in Parasitology Lab and I am thankful for the activities they were provided during my study. Thanks all.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

β	beta
kg	Kilogram
km^2	kilometer square
%	percentage
m	meter
≥	equal or more than
CDC	Center for Disease Control and Prevention
DMC	Dammam Medical Complex
DNA	Deoxyribonucleic acid
ECDC	European Center for Disease Prevention and Control
ESBL	Extended-spectrum β-lactamase
GCC	Gulf Cooperation Council
KAP	knowledge, attitude, and practice
MIC	minimum inhibitory concentration
MOH	Ministry of Health
MRSA	Methicillin-resistant *Staphylococcus aureus*
NIH	The National Institute of Health
PBPs	Penicillin binding proteins
PGN	Peptidoglycan
QCH	Qatif Central Hospital
SD	Standard deviation
URTIs	upper respiratory tract infections
VRSA	Vancomycin-resistant *Staphylococcus aureus*
WHO	World Health Organization

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CHAPTER 1

INTRODUCTION

1.1 Antibiotic Resistant Bacteria

Antibiotic resistance is globally responsible for high numbers of morbidity and mortality (Klevens *et al.,* 2007). Cases of antibiotic resistance have been recorded in more than 100 countries (World Health Organization, 2014). According to Center for Disease Control and Prevention (2013), cases of antibiotic resistance in United States exceed two million cases every year and more than 23,000 fatal cases. Similarly, European Center for Disease Prevention and Control (2011) stated that at least 25,000 patients with antibiotic resistance dies every year in Europe.

Staphylococcus aureus is a common micro-organism that has developed into highly resistant species. *S. aureus* has disseminated globally as methicillin-resistant *Staphylococcus aureus* (MRSA). MRSA is a common nosocomial pathogen which is related to health-care-associated MRSA (HA-MRSA) as well as community-associated MRSA (CA-MRSA) cases (DeLeo *et al.,* 2010). In US, there are more than 80,000 cases of MRSA every year (CDC, 2013). In addition, European Union (EU) countries showed a high prevalence with more than 25% of MRSA cases among *S. aureus* (ECDC, 2009). More current surveillance in Europe showed a decrease of MRSA, yet some countries are still recording a high prevalence of MRSA (ECDC, 2013).

In line with that, β-lactamases, enzymes that degraded β-lactam agents, spread worldwide and is now found in many different species of members of the family *Enterobacteriaceae* as well as *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae* (Bradford, 2001). However, many species have developed an extended resistance to third generation cephalosporins, forming strains of high resistance known as extended-spectrum β-lactamases (ESBLs) (Rawat *et al.,* 2010). Currently, ESBL is considered problematic among hospitalized patients worldwide; moreover, many hospitals have experienced outbreak of ESBL-producing organisms (Bradford, 2001). The prevalence of ESBL-producing *Enterobacteriaceae* varies; some countries such as France recorded a low prevalence, less than 10%, of ESBL producing *E. coli* while it reached to as high as 40% in Bulgaria (ECDC, 2013).

Accordingly, there are several risk factors that can emerge and spread both hospital and community of resistant bacteria, such as length of hospitalization, age of patient, severity of the illness, time in intensive care unit (ICU), poor infection control practices , poor compliance of antibiotic use, previous exposure to antibiotics, and excessive use of antibiotics (Bradford, 2001; Rao, 1998). Nonetheless, application of antibiotic abuse is considered the major derivers of resistance (Laxminarayan *et al*., 2013).

1.2 Global Consumption of Antibiotics

Antibiotics are commonly consumed worldwide, and known as one of the most often purchased and consumed drug. Unfortunately, the use of antibiotics has not been limited to health-care setting only. Communities have been excessively used these drugs without physicians' consultant and without prescription. In addition, the use of

antibiotics has been reached to agriculture, aquaculture and horticulture as well (Laxminarayan *et al.,* 2013).

The total annual production of antibiotics is estimated around 100 to 200 million kg (Laxminarayan *et al.,* 2013). In US alone, it has been estimated that the total consumption of antibiotic drugs is around 11 million kg per annum which only one million kg is used for human care purposes while the rest of 10 million kg were used for veterinary and agriculture purposes (Palaniappan & Holley, 2010).

In the same tone, despite the high price of carbapenems, the sales in some countries such as Egypt and Pakistan (Figure 1.2) have increased with over-the-counter availability (Laxminarayan *et al.,* 2013). ECDC reported that consumption of carbapenems significantly increased in EU countries between 2009 and 2013 (ECDC, 2014).

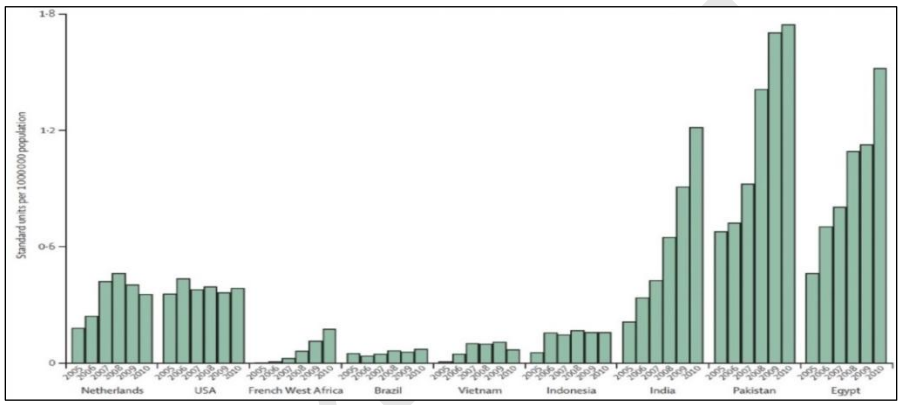

Figure 1.2 Trends in retail sales of carbapeneme antibiotics for Gram-negative bacteria
Adapted from (Laxminarayan, 2013)

The consumption of antibiotics is varied from country to country. European Surveillance of Antimicrobial Consumption (ESAC) which aims to collect reliable data on antibiotic use in Europe showed that penicillins, for example, represented the most frequently prescribed antibiotic in all countries, ranging from 28.7% in Germany to 66.0% in Slovenia of the total outpatient antibiotic use (ESAC, 2011).

1.3 The Consequences of Antibiotic Misuse

Despite the fact that the use of antibiotics has saved many lives, the efficacy of antibiotics has been decreased due its overuse (Smith & Coast, 2002). Accordingly, the time when antibiotics were still undiscovered (pre-antibiotic time), mainly before 1940, was known as "The Dark Age" while during the development of new antibiotics, specifically in 1950s, the time was known as "Golden Age"; ironically, the current time is being called "The time of disenchantment" by some scientists due to the disappointment it has created as resistant bacteria has been exacerbated by the slow pace in developing newer antibiotics (Davies & Davies, 2010).

As depicted in Figure 1.3, the identification of β-lactamases since the introductions of its antibiotics form has been escalated exponentially between 1970 and 2010 (Davies & Davies, 2010). Although resistant enzymes of bacteria are increasing, the discovery of new antibiotic agents is decreasing since the last two decades (CDC, 2013). It leads to the further consequence of antibiotic misuse, which is the higher cost of health-care treatment to eliminate the infection; patients infected with resistant bacteria need longer hospitalization, more advanced antibiotics and longer time of infection treatment (Stanton, 2013).

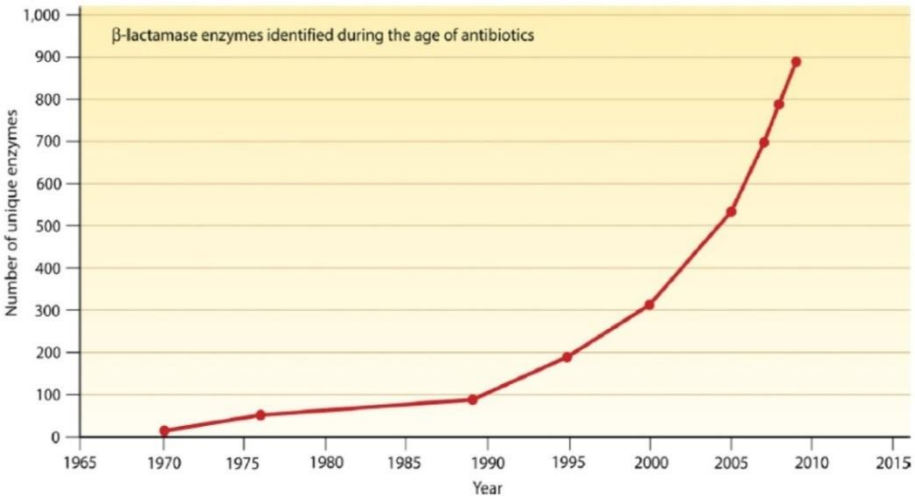

Figure 1.3 Numbers of β-lactamase enzymes identified from 1970 to 2010 (Source: Davies & Davies, 2010)

A study done by Huang *et al.,* (2013) investigated knowledge and attitude towards antibiotic use among students. The study compared knowledge, attitude, and practice (KAP) of non-medical students and medical students in China, and it was showed that medical students had better knowledge and attitude towards antibiotics than non-medical students (Huang *et al.,* 2013).

Low knowledge was also observed in another part of the world. In Saudi Arabia, for example, a study by Al-dossari (2013) showed that 60% of the parents did not have any knowledge that the upper respiratory tract infections (URTIs) are caused by viruses. In addition, the same study also showed around 64% of the participated parents asked their doctors for antibiotics when their children got flu like symptoms and half of the parents said that they expected antibiotics to be prescribed to their children for diagnosis of URTIs.

One of the reasons that can increase the probability of misuse of antibiotics or any medication is lack of knowledge about the effective of antibiotics (Kandakai *et al.,* 1996). Low knowledge of antibiotic can contribute to poor practice of antibiotic which in turn contribute the emergence of antibiotic resistance (Laxminarayan *et al.,* 2013). Besides, it is shown that some characteristics such as low level of education was significantly associated with poor practice (Panagakou *et al.,* 2012).

1.4 Problem Statement

The escalation of the global antibiotic usage, along with the irrational factors that caused it, such as self-medication, non-compliance, and misinformation are the major causes of antibiotic resistance (Laxminarayan *et al.,* 2013). According to WHO, antibiotic resistant bacteria is globally increasing and is disseminated in both developed and developing countries around the world (WHO, 2014). As a result, in order to limit the spread and development of resistance, it is critical to increase the awareness of its proper and improper use (CDC, 2013).

Supporting the above statements, out of many KAP studies that had been carried out in order to determine the level of awareness of people in different communities on antibiotics use, (André *et al.,* 2010; Huang *et al.,* 2013; Jose *et al.,* 2013; Kim *et al.,* 2011; McNulty *et al.,* 2007; Napolitano *et al.,* 2013; Oh *et al.,* 2011; Tenaiji *et al.,* 2008) low knowledge and attitude were recorded. Low level of knowledge in the form of ignorance or lack of education is a major reason that leads to poor application of antibiotics (Laxminarayan *et al.,* 2013). In turn, this might contribute to the increase of the number of antibiotic resistance which will eventually escalate the worldwide morbidity and mortality (CDC, 2013).

In the context of Saudi Arabia, studies on KAP towards antibiotic use as well as surveillance studies on antibiotic resistance were not so numerous up to the day this study was conducted. Nevertheless, the discoveries were in line with the global problems; it was revealed that 90% of the respondents used antibiotics as self-directed medication in order to help them get better when they feel ill (Emeka *et al.,* 2014). Access to antibiotics was reported to be easy for Saudi Arabians even without prescription due to the lack of pharmacists' adherence to regulations although it is forbidden to dispense drugs such as antibiotics without prescription (Bawazir & Ph, 1992).

In other words, it is critical to address the global misuse of antibiotics as a major problem. Therefore, it is also critical to address the global lack of knowledge and awareness related to the antibiotics misuse. Contextually, in order to solve this major problem in Saudi Arabia, a possible first step is to understand the actual current KAP. This knowledge might be a platform to conduct further actions to solve the aforementioned problem, both in Saudi Arabia and in larger population.

1.5 Significance of the Study

This study is intended to determine the prevalence of some selected antibiotic resistance in order to check whether the prevalence of the study area was high and whether there is actually an increase resistance over the past five years. In addition, demographic and clinical characteristics of patients with resistant bacteria were determined as risk factors for the study.

Furthermore, this study is meant to contribute a better knowledge and understanding towards the phenomenon of the misuse of antibiotics among outpatients in Dammam Medical Complex and in Qatif Central Hospital, Saudi Arabia. Furthermore, this study is expected to fill the gap of literature due to the limited numbers of research in the area.

As a result, findings of this study will contribute to the benefit of microbiological epidemiology regarding antibiotic resistance as well as public health considering the level of knowledge, attitude, and practice towards antibiotic use. As indicated by many studies that irrational use of antibiotic is the major drivers of resistance, this study will answer the questions about how respondents are dealing with antibiotics. It will also suggest whether it will be a demand for an intervention when the level of KAP becomes poor.

1.6 Study Objectives

1.6.1 General Objective

The main objective of this study was to assess the level of knowledge, attitude, and practice towards antibiotic use among outpatients as well as antibiotic resistance patterns in Eastern province hospitals in Saudi. This main objective is divided into several specific objectives to be chronologically achieved in order to solve the stated research problem.

1.6.2 Specific Objectives

Several specific objectives have been derived from the main objective, and they are as follows:

1. To determine the prevalence of MRSA and ESBL-producing *E. coli* and *K. pneumonia* in Qatif Central Hospital.
2. To determine the demographic and clinical characteristics of patients with MRSA and ESBL-producing *E. coli* and *K. pneumoniae* in 2014.
3. To identify the socio-demographic characteristics of the respondents
4. To determine the level of knowledge, attitude, and practice of respondents towards antibiotics
5. To determine the association between socio-demographic characteristics (such as gender, age, level of education, field of education) and knowledge, attitude, and practice towards antibiotic use.

1.7 Hypotheses

1. There is a significant association between socio-demographic characteristics (such as gender, age, level of education, field of education) and knowledge, attitude, and practice towards antibiotic use
2. Low knowledge and negative attitude of antibiotic lead unacceptable usage of antibiotics.

1.8 Conceptual Framework

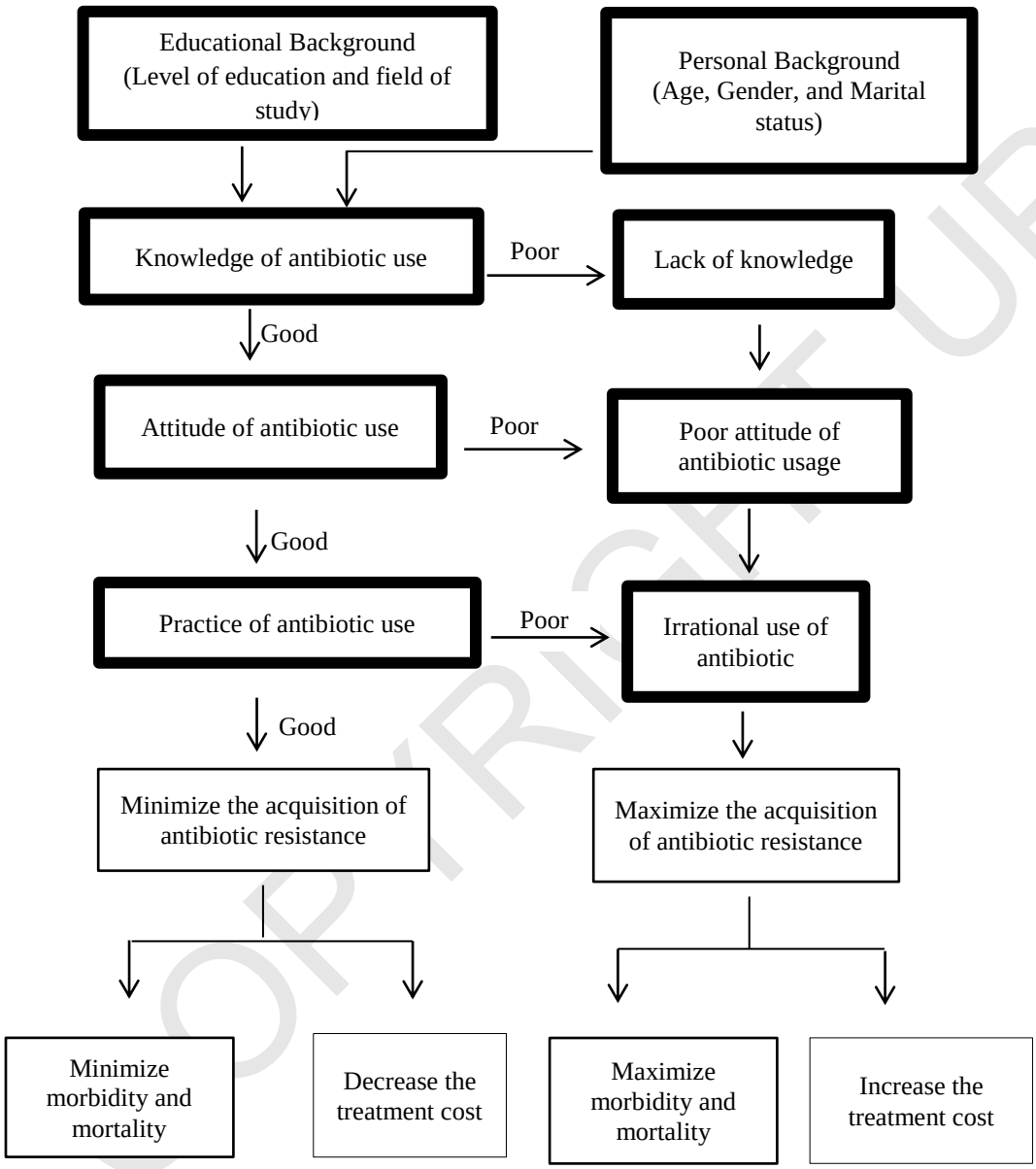

Figure 1.8 Conceptual Framework

Operational variables
Conceptual variables

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LIST OF PUBLICATIONS

Alramadhan W. H., Hamat R .A., Malina O. Knowledge, Attitude, and Practice towards Antibiotic Use among Patients in Two Hospitals in Eastern Province, Saudi Arabia (Poster). Infection 2015 Conference on Infectious Diseases and Microbial Genomics. (2015). Malaysia

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