EVALUATION OF ANTIBIOTIC PRESCRIBING TRENDS, KNOWLEDGE, SELF-CONFIDENCE AND IMPACT OF EDUCATIONAL INTERVENTION ON IMPROVING ANTIBIOTIC PRESCRIBING IN UPPER RESPIRATORY TRACT INFECTIONS (URTIs) AT KOTA SETAR DISTRICT PUBLIC HEALTH CLINICS, MALAYSIA

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by

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LIST OF ABBREVIATIONS

Abbreviation	Terms
AAP	American Academy of Paediatrics
AMO	Assistant Medical Officer
AMR	Antimicrobial Resistance
ASP	Antimicrobial stewardship program
BNF	British National Formulary
CDC	Centre for Disease Control and Prevention
CME	Continuous medical education
DTC	Drug and Therapeutic Committees
FMS	Family Medicine Specialist
GARP	Global Antibiotic Resistance Partnership
GDP	Gross domestic product
ID	Infectious disease
LMIC	Low and middle income countries
MCH	Maternal Child Health Clinic
MO	Medical Officer
MTAC	Medication Therapy Adherence Clinic
NAB	National Antibiotic Guideline
NICE	National Institute for Health and Clinical Excellence
OPD	Outpatient Department
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
SNF	Sudan National Formulary
STRAMA	Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance
URTI	Upper respiratory Tract Infection
WHO	World Health Organization

PENILAIAN POLA MEMPRESKRIB ANTIBIOTIK, PENGETAHUAN , KEYAKINAN DIRI DAN IMPAK INTERVENSI PENDIDIKAN UNTUK MEMPERBAIKI PENGGUNAAN ANTIBIOTIK DALAM JANGKITAN SALURAN PERNAFASAN ATAS (URTI) DI KLINIK KESIHATAN AWAM DAERAH KOTA SETAR, KEDAH, MALAYSIA

ABSTRAK

Penambahbaikan dalam amalan penggunaan antibiotik dalam penjagaan primer merupakan satu tugas yang mencabar. Dalam konteks ini, pengamal perubatan di Malaysia perlu diberi pendidikan tentang penggunaan ejen-ejen ini secara rasional. Kajian ini meneroka pola penggunaan antibiotik, dan menilai kesan intervensi mudah di kalangan preskriber terhadap amalan pemberian ubat-ubatan. Kajian ini terdiri daripada gabungan beberapa fasa termasuk kajian asas kadar penggunaan antibiotic, soal selidik untu menilai tahap pengetahuan dan keyakinan diri pengamal perubatan, diikuti dengan kajian intervensi bagi menilai kadar penggunaan antibiotic sebelum dan selepas intervensi. Seramai lima puluh tujuh prescriber memberi maklum balas terhadap kaji selidik ini, dengan kadar respons sebanyak 68.7%. Majoriti peserta mempunyai pengetahuan yang baik tentang punca URTI adalah disebabkan oleh virus, 84% (n=48) dan bersetuju bahawa antibiotik tidak berkesan untuk merawat URTI (77%). Walau bagaimanapun, 47% responden menyatakan antibiotik boleh mengurangkan berlakunya komplikasi penyakit, manakala 33% menyatakan bahawa tempoh penyakit akan berkurangan dengan penggunaan antibiotik. Kebanyakan preskriber yakin terhadap pengetahuan mereka tentang antibiotik (n = 47, 85.9%), bagaimanapun 56.2% menghadapi kesukaran, dan 75.5% bergantung kepada pendapat rakan-rakan mereka dalam memilih antibiotik

yang betul untuk pesakit. Ini menunjukkan bahawa tahap pengetahuan preskriber adalah tidak mencukupi dan terdapat salah faham dalam penggunaan antibiotik. Seterusnya, 123,524 preskripsi daripada 1 Januari 2014 hingga 31 Mac 2014 telah disaring untuk menilai pola penggunaan antibiotic dalam URTI. Dalam tempoh ini, 7129 preskripsi telah ditulis untuk URTI, dengan 31.8% (n = 2270) daripadanya mengandungi antibiotik. Antibiotik paling banyak diberikan kepada pesakit tonsillitis, otitis media, dan sakit tekak (91.3%, 89.8%, dan 84.2%). Macrolides (erythromycin ethyl succinate) yang tidak dicadangkan oleh garis panduan adalah antibiotik yang paling kerap diberikan, terdiri daripada 61% (n = 1404) daripada jumlah keseluruhan antibiotik, diikuti dengan penisilin (n = 794; 35%). Penolong pegawai perubatan (AMO) telah dikenalpasti memberikan lebih banyak antibiotik berbanding pegawai perubatan (MO) dan pakar perubatan. Fasa akhir kajian ini melibatkan penghasilan modul pendidikan untuk preskriber, melaksana, dan akhirnya menilai kesannya ke arah mengurangkan kadar pemberian antibiotik. Analisis kuantitatif digunakan untuk menilai kadar penggunaan antibiotik sebelum dan selepas intervensi. Corak penggunaan antibiotik telah dipantau selama 3 bulan selepas intervensi. Penggunaan antibiotik didapati berkurangan sebanyak 27% pada bulan pertama. Penggunaan antibiotik, terutamanya erythromycin telah berkurangan. pada tonsillitis (12.6%) dan sakit tekak (10.9%). Walaubagaimanapun, penggunaan antibiotik didapati meningkat kembali seperti kadar kajian asas pada akhir bulan ketiga. Kesimpulannya, pendidikan perubatan adalah sangat perlu untuk meningkatkan pengetahuan dan membina keyakinan diri di kalangan preskriber, bagi menggalakkan penggunaan antibiotik yang betul. Pengenalan program pengawasan antibiotik (antibiotic stewardship program) diharapkan akan dapat mengawal dan menambah baik penggunaan antibiotik di Malaysia pada masa hadapan.

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ABSTRACT

Improving antimicrobial use practice in primary care is a challenging task. Within this context, primary care practitioners in Malaysia need to be well educated on rational prescribing of these agents. This study explored the antibiotic prescribing trends, and evaluated the impact of simple intervention among prescribers towards their prescribing practice. The study comprised of combination of several phases including a baseline study of the antibiotic prescribing rates, a questionnaire survey assessing knowledge and self-confidence of the practitioners, followed by a single group interventional study for the antibiotic use pre- and post-educational program. A total of fifty-seven prescribers responded to the survey, with a response rate of 68.7%. Majority of the participants had good knowledge of the viral-aetiology of URTIs, 84% (n=48) and agreed antibiotics are not useful as a treatment (77%). However, 47% said it can reduce the complications and duration of the disease episodes (33%). Majority of the prescribers were confident with their knowledge regarding antibiotics (n=47, 85.9%), however 56.2% faced difficulties, and 75.5% relied on the opinion of their colleagues in selecting correct antibiotic for patients. The result revealed that prescribers had inadequate knowledge and misconceptions about antibiotic prescribing. Subsequently, 123,524 prescriptions from 1st January 2014 to 31st March 2014 were screened to assess the trends of antibiotic prescribing. During this period, there were 7129 of prescriptions were for URTI, with 31.8%

(n=2270) involved antibiotics. Tonsillitis, otitis media, and pharyngitis were listed as major conditions for which antibiotics were prescribed (91.3%, 89.8%, and 84.2%). Macrolides (erythromycin ethyl succinate), which are not recommended by the guidelines constituted 61% (n=1404) of total antibiotics prescribed, followed by the penicillins (n=794; 35%). It was also found that AMOs prescribed more macrolides compared to MOs and specialists. The final phase of the study involved creating a module for educating the prescribers, implementing it, and finally evaluates the impact towards reducing the rate of antibiotic prescribing. The impact concerning the educational session was elicited through the analysis of antibiotic prescribing rates pre-and post-intervention. Overall antibiotic prescribing reduced 27% during the first month post-intervention. Antibiotics use in tonsillitis (12.6%) and pharyngitis (10.9%) were also reduced, most notably the use of erythromycin. However, antibiotic prescribing rates have increased to the similar rate of the baseline at the end of third month post-intervention. In conclusion, successions of medical education are needed to develop confidence among the prescribers, in order to encourage the correct use of antibiotics. A comprehensive development of national antibiotic stewardship program with more extensive interventional module is expected to improve future antibiotic prescribing and ensure organised and regulated control of antibiotic use in Malaysia.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Antimicrobial drug resistance is well known as a serious long standing problem faced by the healthcare system. In the early years of antimicrobial use, resistance was only seen in the hospitalized patients, particularly in the intensive care units causing high number of morbidity and mortality in patients (Alanis, 2005). Recently, the spread of resistant bacteria outside the hospitals, i.e. in primary care settings are increasingly reported in many countries worldwide (Helena, 1997, Cheong, 1995). The issue of antibiotic resistance in common infections, namely nosocomial and community-acquired infections in primary care settings is not new, as reported by the World Health Organization (WHO) in their surveillance in 2014 (WHO, 2014). Escalation of resistance in common-infections caused difficulties in selecting effective treatments for patients, subsequently may lead to complications, and will take a longer time to recover (WHO, 2014, Costelloe et al., 2010, Butler et al., 2006). This is something to be worried.

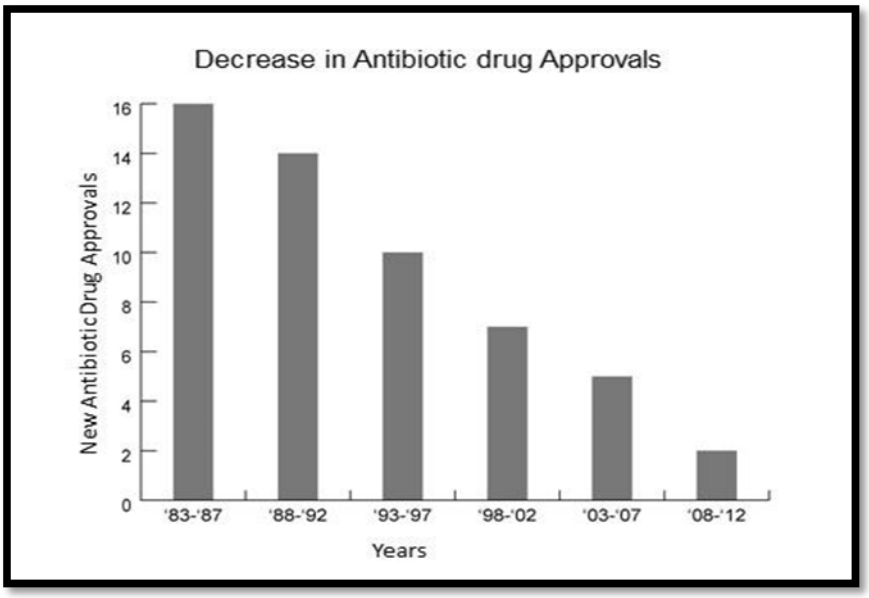
One of the major contributions to this problem is the uncontrolled and redundant use of antibiotics in primary health care sectors (Kumarasamy et al., 2010, Costelloe et al., 2010, Costelloe et al., 2010, Dowell et al., 1998, Mimi et al., 2011). For many years the widespread use of antibiotics in treating common infections, included upper respiratory tract infections is the main cause for excessive use of antibiotics in primary healthcare centres. In general, the concept of appropriate prescribing of

antibiotics advocates patients to receive the drug appropriate to their clinical needs for a sufficient period of time, with right dosage and duration when it is proven to be beneficial to patients; while targeting only to the desired pathogens (Owens et al., 2004). Instead, majority of antibiotics in primary care centres are used for the treatment of non-bacterial infection, such as viral respiratory tract infections where treatments with antibiotics are meaningless (Karabay et al., 2011, Mohan, 2004).

In primary care centres, almost all visits with an infection or suspected infection usually resulted with the administration of antibiotics, regardless of their actual needs (Chiappini et al., Gonzales et al., 2001a, Grijalva et al., 2009). Large number of patients, coupled with busy clinical schedules have been involuntarily motivated the prescribers to provide treatment according to patients' expectations, thus missed the opportunity to provide appropriate information regarding antibiotics to the patients (Mangione-Smith et al., 1999, Cockburn and Pit, 1997, Mangione-Smith et al., 2001). This practice has led to the public perceptions that antibiotics are the preferred treatment for any infections, subsequently induces patients to demand antibiotics on their following visits (Gonzales et al., 2001). Several factors have contributed to this practice, including physicians' non-adherence to the treatment guidelines, uncertainty of the diagnosis, fear of clinical failure, lack of diagnostic facilities for diagnosis confirmation, lack of knowledge regarding antibiotic, and pressure from patients or family members (Fakih et al., 2003, Hassali et al., 2013, Kotwani et al., 2010, Holloway et al., 2015, Li et al., 2012, Park et al., 2005, Radyowijati and Haak, 2003, Schwartz et al., 1989, Trap and Hansen, 2002).

A shift to newer and broader spectrum antibiotics are essentially needed when the standard treatments are no longer effective (Laxminarayan and Heymann, 2012, Van Nguyen et al., 2013). Newer generations of antibiotics are more specific and targeted, however are more expensive, and caused more side-effects (Fagnan, 1998, Falagas et al., 2008, World Health Organization, 2001, World Health Organization, 2014). Furthermore in the past few years the number of newly approved antibiotics continues to decline as the pipeline of new antibiotics has dried up (Gupta and Nayak, 2014, Spellberg et al., 2004) (Figure 1.1).

Figure 1.1 Decreased in antibiotic drug approval in the United States (Adapted and modified from Spellberg et al., 2004)



Lack of new antibiotic discoveries and developments, coupled with resource depletion has resulted in a diminished number of new antimicrobial agents being introduced into healthcare practice (Spellberg, 2012, Spellberg et al., 2004). High pharmaceutical research and development costs, which are estimated to be $400–$800 million per approved agent, pose a considerable barrier to this (DiMasi et al.,

2003). Some large pharmaceutical companies are curtailing—or abandoning completely—anti-infective research due to factors such as greater demand towards the agents to treat chronic medical conditions such as hypercholesterolemia, hypertension, mood disorders, dementia, and arthritis (Projan, 2003, Gilbert and Edwards, 2002). On the other hand, antibiotics are merely used just for short-course therapies. Management of deadly resistance infections will be tougher in the future if this problem is not addressed immediately. Besides, treatments guided by limited and biased information may increases the unnecessary use of broad spectrum antibiotics, thus leading to the resistance of the remaining resort of antibiotics (WHO, 2001, WHO, 2014).

In connection to the issue of antimicrobial resistance (AMR) in common infections, antibiotic prescribing in primary care has drawn significant interest among researchers. Reported rates of antibiotic prescribing in the public primary care clinics in Asia-Pacific countries have varied from 11.6% to 67% (Chalker, 2001, Chang et al., 2001, Lim and Yap, 1999, Teng et al., 2004, Van Nguyen et al., 2013). Numerous factors may have exacerbated the widespread prescription of antibiotics in this region. For example, many Asian countries such as China, Hong Kong, Japan, South Korea, Taiwan, Thailand, and Malaysia allow physicians to both prescribe and dispense drugs (Bhavnani et al., 2007, Hassali et al., 2015). High accessibility of these drugs, consequently, has been causing inappropriate use and led to a steadily increased of antibiotic resistance throughout the region (Radyowijati and Haak, 2003). Furthermore, in some countries like Thailand, the rate of antibiotic prescribing can be as high as 82%, due to the availability of antibiotics at cheaper price and can be obtained easily without a properly diagnosed condition or prescription (Bhavnani

et al., 2007). Several surveys in Hong Kong and Taiwan have shown that antibiotics are being prescribed for approximately 60-80% of cold and flu outpatient visits (Chou et al., 2003). As a result, the prevalence of antibiotic resistance in Asia-Pacific countries was found to be much higher than in Western countries (Hsueh et al., 2002, Hsueh and Luh, 2002). In Taiwan, about 50-70% of S. *pneumoniae* was penicillin-resistant, compared to the United States (40%), and Germany, where the rates were less than 10% (Schmitz et al., 1999, Harbarth et al., 2002, Pradier et al., 1997).

The use of broad-spectrum has to be controlled, especially in the treatment of acute common infections without clear justifications, thereby minimizing the pressures driving towards resistance (Lederberg et al., 2003, Shlaes and Moellering, 2002, Gilbert and Edwards, 2002). To overcome this issue, stringent criteria for diagnosing URTIs have been recommended by the Centres for Disease Control and Prevention (CDC) in collaboration with the American Academy of Paediatrics (AAP) and the American Academy of Family Physicians (CDC, 2011). Guidelines for prescribing antibiotics for respiratory tract infections were also introduced in the United Kingdom by the National Institute for Health and Clinical Excellence (NICE) in 2008 (Kennedy et al., 2010). In Malaysia, major references particularly in antibiotic prescribing are the National Antibiotic Guideline and MOH Drug Formulary.

It is now acknowledged that the rational use of antibiotics is one of the most important steps to slow down the development and spread of resistant bacteria (Earnshaw et al., 2013). Therefore, appropriate antibiotic use in primary care will have enormous implications towards AMR if practiced consistently (Van Nguyen et al., 2013). Consequently, a better understanding of the determinants of antibiotic

prescribing among physicians is essential for introducing and implementing targeted interventions to reduce future antibiotic prescribing and potential resistance (Thriemer et al., 2013). Physicians' prescribing behaviour plays a key role in the utilization of antibiotics. Hence, adequate knowledge and appropriate education are essential among these populations (WHO, 2001, Srinivasan et al., 2004). Physicians' understanding of when antibiotics are needed, and more importantly, when they are not, should subsequently reduce their prescribing (Smeets et al., 2009, Piddock, 2013). Since changes in prescribers' knowledge and behaviour are prerequisite for changes in the antibiotic prescribing patterns, it is important to understand what physicians know about antibiotics, how they acquire and maintain their knowledge, and what factors influence their prescribing practice (Srinivasan et al., 2004, Wahane et al., 2013, Md Rezal et al., 2015, Hassali et al., 2013). Understanding what shapes the prescribing choices and how this might be changed is one of many ways to address this situation, and could lead to the development of more effective interventions and strategies to promote the rational use of antibiotics.

1.2 Antibiotic prescribing in upper respiratory tract infection

High frequency of occurrence and transmissibility of respiratory infections within the family members implies the overwhelming burden of these infections in the community (Naghipour et al., 2007). Therefore, it is not surprising when URTIs accounted the highest proportion of ambulatory visits in most countries (McCaig and Hughes, 1995). In the United States, almost 75% of ambulatory antibiotic prescriptions are for the treatment of 5 specific RTIs: otitis media, sinusitis, pharyngitis, bronchitis, and upper respiratory tract infections (URTIs) (McCaig and

Hughes, 1995). A few studies have described URTI as a non-specific term representing infections in the upper region of the respiratory tract including nose, paranasal sinuses, pharynx, larynx, trachea, and bronchi (Dowell et al., 1998, Gonzales et al., 2001, Tonkin-Crine et al., 2011, Monto and Sullivan, 1993). Medical Research Council classified URTIs as common cold, otitis media, pharyngitis (including tonsillitis), laryngitis, croup, bronchitis, bronchiolitis, pneumonia, and influenza (Gonzales et al., 2001). Several viruses, such as rhinovirus, coronavirus, respiratory syncytial virus, and parainfluenza virus, cause URTIs (Heikkinen and Järvinen, 2003, Regamey and Kaiser, 2008). Small proportion of URTI cases are occasionally accompanied by bacterial complications, usually from Group A Streptococci with low percentage of incidents; ranging from 0.5% to 10% of all cases (Heikkinen and Järvinen, 2003).

In local perspective, antibiotic prescribing in the primary care centres are unduly common, owing to the fact that healthcare clinics are the first point of contact between communities and healthcare services to seek treatment for acute problems such as fever and URTIs. This has been shown in a few studies. Teng *et al.* (2004) revealed that half of all the antibiotic prescriptions in a Malaysian primary care setting were for URTIs. A more recent study in a Sarawak district hospital also showed a remarkably high percentage of URTI prescribing rate of more than 60% in the outpatient setting (Kho et al., 2013).

Many efforts have been made, including conducting intervention studies to promote the rational use of antibiotics, thus reducing the use, particularly for URTIs (Weissman and Besser, 2004, Matthys et al., 2009, Seager et al., 2006). According to

various literatures, the use of drugs is highly dependent on the demand of the patient and the willingness of prescribers whether to abide by the clinical evidence or to follow the request of the patient (Md Rezal et al., 2015). This certainly seems to be an area of exploration. The CDC has reported that patient's satisfaction is highly related to communication, rather than prescribing (Kuehn, 2014). In this case, prescribers must be proficient on how to discuss the illness and treatment needs with patients rather than giving antibiotic without justification (Kuehn, 2014). In many cases, URTI can simply be treated symptomatically with antipyretics, anti-inflammatory drugs and mouth gargles, with proper reassurance to the patients (Arroll, 2005, CDC, 2011). Furthermore, of all the factors leading to antibiotic prescribing, in addition to medical knowledge, physicians' concerns about retaining patients and patient satisfaction were often mentioned as a key (Mangione-Smith et al., 2001, Shapiro, 2002). Patient's demand for an antibiotic prescription may stem from a misunderstanding of the cause of viral respiratory infections, or from current medical opinion regarding appropriate treatment modalities. Therefore, education, whether to the prescriber or the patient has become one popular intervention tool as many believe that changing the misconceptions of patients regarding the effectiveness of antibiotics for viral infections and educating patients to become informed consumers could lead to a reduction in antibiotic use and the costs associated with that use (Kuzujanakis et al., 2003, Rodis et al., 2004, Md Rezal et al., 2015). When the patients are well informed and aware of the inappropriate of antibiotic use in viral infections, their demands will subsequently reduce. A trial study for the treatment of uncomplicated otitis media has shown while keeping patients' satisfaction at 78%, there was also a reduced of antibiotic use by 69% (Siegel et al., 2003).

1.3 Scope of the problem

Resistance in community-acquired respiratory infections, particularly in primary care settings are becoming more common (Dowell et al., 1998). The epidemic increase of antibiotic-resistant bacteria has led to the need to reduce excessive antibiotic use, especially in this sector, where many antibiotics are extensively prescribed (Gonzales et al., 2001a). Therefore any treatment decision in community-acquired respiratory tract infections must take account of the increasing prevalence of resistance among these major respiratory tract infections. The emergence of deadly illnesses caused by resistant pathogen in communities has led to growing national and international concern, thus raising efforts for the control of the resistance. One of the most important steps to slow down the spread of resistant bacteria is the rational use of antibiotics (Earnshaw et al., 2013). Therefore, efforts must be done to promote rational antibiotic prescribing practices in primary healthcare settings.

The fight against antimicrobial resistance (AMR) has also been identified as a priority by many countries and organizations, including the CDC, the American Society for Microbiology, the WHO, the American Academy of Family Physicians, and the American Academy of Society (WHO, 2001). In 2001, the WHO published its global strategy for containment of AMR report, focusing on several aspects of legislation, enforcement, improvement of utilization of antimicrobials, monitoring and surveillance, and promoting the development of new drugs (WHO, 2001). Many countries have also developed their national Antibiotic Stewardship Program (ASP) to promote the rational use of antibiotics while preventing the spread of resistance (Teo et al., 2012). Several methods have been adopted in this program, including

providing educational programs for stakeholders, patients and practitioners regarding the rational use of antibiotics (Chen et al., 2010, Pharmaceutical Service Division, 2014, Pulcini and Gyssens, 2013). Educational activities are widely known as one of the most important tools for combating antibiotic misuse and overuse, because it can change physicians' attitude and subsequently their prescribing practice (McCoy et al., 2011). However, in many countries the awareness of the importance of education is still low due to the lack of resources, access, and time to spend on educational activities; hence less practiced (Okeke et al., 1999).

AMR can cause devastating consequences, including deaths, especially in resourced constrained region due to the failure of treatments and the lack of treatment options (O'Neill, 2014). In these countries where surveillance activities are not well established, it is difficult to assess the extent of the problem, as there is little reliable data available. Unless the issue of AMR is addressed immediately, AMR infections are feared to be the leading cause of death in the future (O'Neill, 2014, WHO, 2001). Although supportive data from developing countries are limited and scarce, the decisions on important intervention measures to be undertaken must be made at the local level. Similarly, in Malaysia there is a scarcity of data on antibiotic prescribing rates from Malaysian primary healthcare centres. Therefore, it is a challenge to convince policy makers and healthcare professionals to join the efforts of solving the problem. The establishment of the Antimicrobial Stewardship Program for Healthcare Facilities in the end of 2014 by the Ministry of Health may reinforce the surveillance and give valuable input in the future in managing antibiotic usage and resistance rate in this country. Surveillance programs through the antimicrobial

stewardship team is hoped to help in more comprehensive data gathering in the future thus helping to determine appropriate intervention to be undertaken.

In the present study, an analysis of the prescriptions of antibiotics for these conditions was undertaken in the public primary healthcare centres in Kedah. To accomplish this, simultaneously an assessment of knowledge regarding antibiotic resistance and review on antibiotic use in their daily practice was done. The results of these provided estimates of the rate of excess antibiotic use for URTIs, and based on this more current prescribing data, a targeted intervention was developed, and followed by evaluation of the differences of the antibiotic prescription rates after the intervention.

1.4 Objectives of the study

The objectives are:

1. To assess the knowledge of healthcare providers regarding antibiotic resistance and self-confidence and practice in antibiotic prescribing for URTIs.
2. To assess the trend of antibiotic prescribing patterns for URTIs at public primary healthcare clinics.
3. To develop and implement an educational intervention regarding antibiotic prescribing for URTIs.
4. To evaluate the impact of the educational intervention regarding antibiotic prescribing for URTIs.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Infectious diseases were the leading cause of morbidity and mortality before the discovery of antibiotics. This changed with their advent through researchers, including Paul Ehrlich and Alexander Fleming, turning once fatal diseases into more manageable health problems (O'Neill, 2014, Bosch and Rosich, 2008, Alharbi et al., 2014, Alanis, 2005). Advances in science and medical technology have resulted in the development of new antibiotics as well as generic antibiotics, with the latter in particular providing easy accessibility at affordable costs (Davies and Davies, 2010). Antibiotics are now commonly prescribed to patients in ambulatory care (Almeman et al., 2014, Kho et al., 2013, Larsson et al., 2000, Nash et al., 2002). However, greater accessibility has resulted in irrational and excessive use, leading to increasing antibiotic resistance (Barnett and Linder, 2014, Costelloe et al., 2010, Goossens et al., 2005, Kesselheim and Outterson, 2010, Davies and Davies, 2010, Conly, 1998). Increasing antimicrobial resistance is seen as one of the most critical problems facing healthcare systems (WHO, 2001), with estimates that antimicrobial resistance (AMR) infections currently cause approximately 50,000 deaths a year in Europe and the US alone (O'Neill, 2014). This increases to several hundred thousand deaths each year when other countries are included (O'Neill, 2014). The continual rise in AMR is envisaged to result in 10 million deaths annually by 2050 unless checked. As a consequence, AMR infections could be a leading cause of death by 2050. This death rate will reduce GDP by 2% to 3.5% by 2050 and costing the world up to US$100

trillion (O'Neill, 2014). Some common infections, especially those caused by antibiotic resistant bacteria, are becoming more difficult to treat, causing life-threatening illnesses and potentially death (Costelloe et al., 2010). The combination of overuse of antibiotics for minor infections, misuse and under use due to lack of access and financial support in certain settings, has been a key driver of resistance. This phenomenon has been termed selective pressure (WHO, 2001).

Increasing antibiotic resistance poses a threat to health and healthcare systems in both developed and developing countries (Van Nguyen et al., 2013). In high-income countries, continuing high rates of antibiotic use in hospitals, the community, and agriculture have contributed to selection pressure that has sustained resistant strains (Laxminarayan and Heymann, 2012), forcing a shift to more expensive and more broad spectrum antibiotics. In low-income and middle-income countries (LMICs), the high burden of infectious diseases and the unregulated access to antimicrobials has resulted in the emergence of antibiotic resistance (Van Nguyen et al., 2013). This is not helped by the increasing use of antibiotics to treat viral upper respiratory tract infections (URTIs), inappropriate prescribing of antibiotics for infections such as pneumonia, purchasing of antibiotics without a prescription as well as the challenges involved with determining current antimicrobial usage and AMR rates in LMICs to provide a baseline for future interventions and policies (Holloway et al., 2015, Holloway, 2011, Kotwani et al., 2010, Holloway et al., 2011b, Holloway et al., 2011a, Radyowijati and Haak, 2003, Holloway and Henry, 2014). Inappropriate use of antibiotics is also not helped by currently limited adherence to guidelines among physicians in LMICs; greater though among physicians in public (40%) than private-for-profit sector facilities at <30% (Holloway et al., 2013).

The inappropriate use of antibiotics has been attributed to a number of factors. These include physicians' non-adherence to treatment guidelines, lack of knowledge and training regarding antibiotics, lack of diagnostic facilities, and uncertainty over the diagnosis, pressure from pharmaceutical industry, fear of clinical failure, financial benefits for physicians, pressure from patients to prescribe antibiotics regardless of the indication coupled with lack of time of physicians to educate patients. In LMICs, there are also concerns with the extent and implementation of regulations surrounding the dispensing of antibiotics including self-purchasing (Schwartz et al., 1989, Fakih et al., 2003, Hassali et al., 2015, Kotwani et al., 2010, Radyowijati and Haak, 2003, Holloway and Henry, 2014, Holloway et al., 2015, Trap and Hansen, 2002, Li et al., 2012, Park et al., 2005). Moreover, antibiotic misuse or overuse has promoted the perception among the public that these medicines are the preferred treatment for instance for URTIs. This in turn induces patients to demand antibiotics, hastening the growth of resistant bacteria (Mohan et al., 2004, Holloway and Henry, 2014, Hassali et al., 2015). To help combat the irrational use of antibiotics, stringent diagnostic criteria for URTIs have been recommended by the Centers for Disease Control and Prevention (CDC) in collaboration with the American academy of Paediatrics (AAP) and the American Academy of Family Physicians (CDC, 2011). In United Kingdom, the National Institute for Health and Clinical Excellence (NICE) introduced in 2008 a guideline for antibiotic prescribing in respiratory tract infections (NICE, 2008). Despite these efforts and guidelines, physicians still manage URTIs with considerable variation (Mazzaglia et al., 1998, Chukwuani et al., 2002, Rosman et al., 2008, Holloway et al., 2015, Hassali et al., 2015, Holloway et al., 2011b).

One of the most important steps to slow down the development and spread of resistant bacteria is to promote and practice rational use of antibiotics (Earnshaw et al., 2013). Consequently, a better understanding of what determined antibiotic prescribing among physicians is essential for introducing and implementing targeted interventions to reduce future antibiotic prescribing and potential resistance (Van Nguyen et al., 2013, Holloway et al., 2013, Kotwani et al., 2010, Holloway et al., 2011a), with physicians prescribing behaviour playing a key role in the utilization of antibiotics (Thriemer et al., 2013). Hence, adequate knowledge and appropriate education among these groups are essential. Physicians' understanding of when antibiotics are needed, and more importantly when they are not, should subsequently reduce their prescribing (Piddock, 2013, Sabuncu et al., 2009). However, there will be challenges especially in LMIC countries where resources are limited and enforcement efforts was lacking (Kotwani et al., 2010, Holloway et al., 2015, Park et al., 2005, Sabuncu et al., 2009, Li et al., 2012).

Changes in prescribers' knowledge and behaviour are prerequisite for changes in antibiotic prescribing patterns, it is important to understand what physicians know about antibiotics, how they acquire and maintain their knowledge, and what factors influence their prescribing practice. Understanding prescribers' perspectives could lead to the development of more effective interventions and strategies to promote the rational use of antibiotics. Consequently, the aim of this chapter is to systematically review the knowledge, perceptions, and behaviour of physicians regarding antibiotic prescribing to guide future strategies.

2.2 Methodology

An extensive literature search was performed to identify published studies related to medical practitioners' perceptions, knowledge, attitude, practice, belief, and behaviour regarding antibiotic prescribing and antibiotic use. The search strategy was to identify cross-sectional observational studies and experimental studies; applied either qualitative or quantitative methods or both. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and guidelines were followed when performing the search and the identification of possible studies (Moher et al., 2009) (Figure 2.1).

Relevant studies were identified by a comprehensive search of several electronic databases. These included Scopus, PubMed, ISI Web of Knowledge, Proquest, Science Direct online library and Google Scholar. The bibliography of the retrieved studies was also checked for potential studies. The search strategy involved using Boolean operators for combinations of several keywords to identify the relevant articles. The key words used in the search included (antibiotic(s) OR antimicrobials) AND (prescribing OR resistance) AND (knowledge OR practice) AND (attitude OR perception). For prescribers, the following keywords were used: prescriber(s), general practitioner(s), doctor(s) and physician(s). Articles related to antibiotic use in dental practices were excluded from the systematic review. It is acknowledged that particularly in LMIC, the prescribing and dispensing may be undertaken by non-physicians, e.g. pharmacists, even when this is not permitted (Kotwani et al., 2010, Godman et al., 2014). However, these papers have been excluded from the review as the study only focused on physicians.

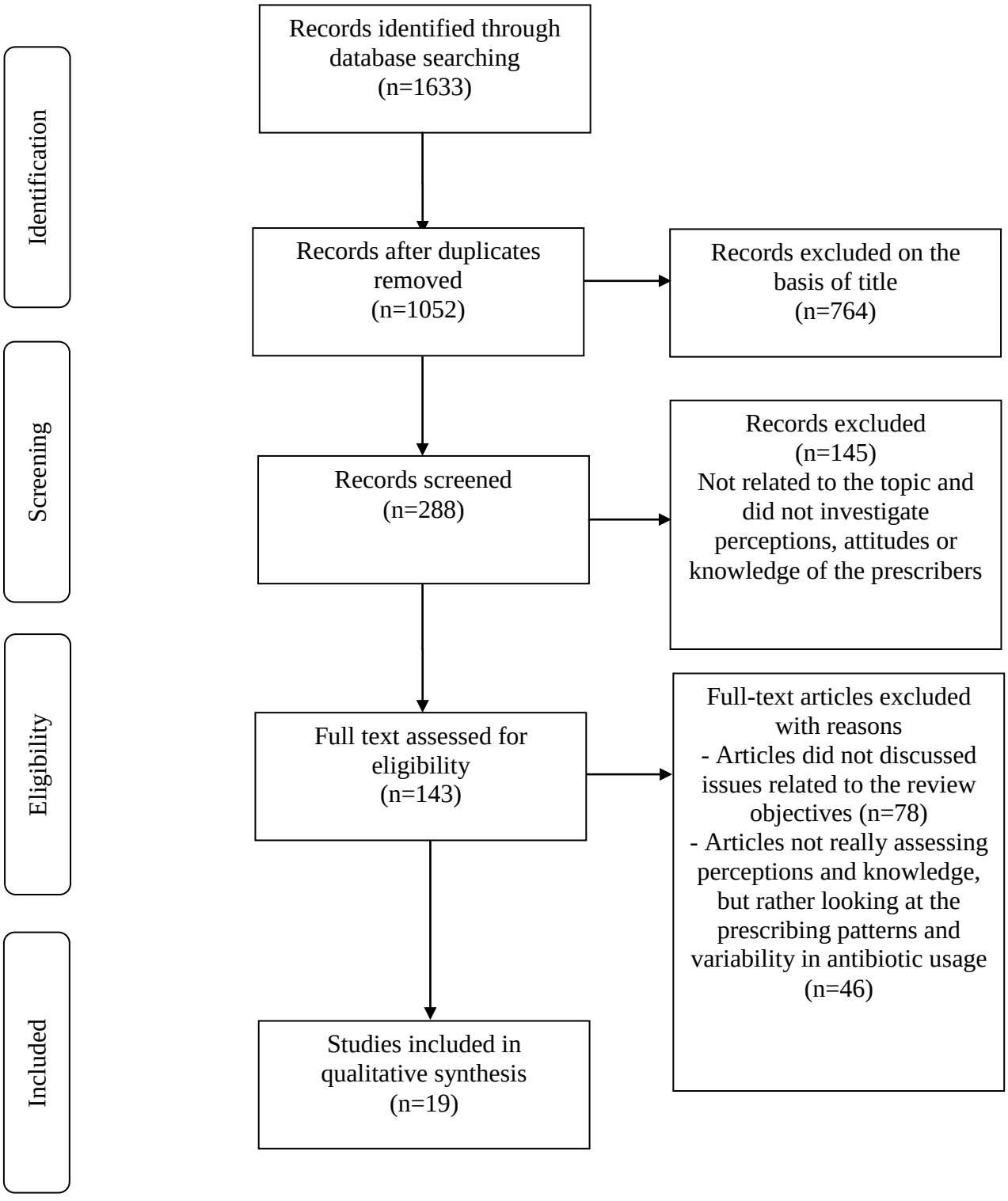


Figure 2.1: The PRISMA Diagram

(Template is adapted with modification from Moher et al. 2009).

To make the review relevant to current practice, the search was restricted to the studies published between 1990 and 2014. Only articles published in the English language were included. All results were listed and evaluated by reading the abstracts. To determine whether the studies met the required criteria, the lists of titles and abstracts from the searches were examined by two researchers independently. Where doubt remained, the full article was examined by two of the researchers to determine whether it is relevant, with the final inclusion of the article undertaken in a consensus meeting involving the authors. The methodology, including summarizing the quality and limitations of the studies, follows previously published studies (Wong et al., 2014, Hassali et al., 2014, Al-Gedadi NA, 2008).

2.3 Results

The search process resulted in 1633 titles and abstracts. After removing duplicates, 1052 studies were screened, of which 764 were excluded on the basis of title. Further assessment of title and abstracts led to the identification of 145 studies not meeting eligibility criteria, as they were not related to the topic and did not investigate perceptions, attitude or knowledge of the prescribers towards antibiotics. The remaining (n= 143) were full-text assessed for eligibility for inclusion in the study. Seventy eight studies were then excluded as their main findings did not discuss issues related to the review objectives. A further 46 studies were excluded as they did not assess physicians' perceptions and knowledge, but rather looking at the prescribing patterns and variability in antibiotic usage. This left 19 articles for inclusion in the review (Table 2.1).

Table 2.1 Description of studies reporting on knowledge, attitude, beliefs and practices among physicians regarding antibiotic prescribing

Author(s) and year	Country of study	Study design	Survey characteristics	Response rate/sample size	Study population
Butler et al. (1998)	South Wales, UK	Qualitative study with semi-structured interviews	- A sampling frame was constructed to identify the general practitioners (GPs) according to their size of practices. - Interviews were conducted with GPs and lasted 10-35 minutes. All questions were open-ended. Interviews conducted until saturation achieved	21 Ps recruited	-Primary care setting -17 of the GPs had qualified in Britain, 13 held MRCGP, working experience between one and 28 years.
Wester et al. (2002)	Chicago, USA	Cross-sectional self -completed questionnaire	- The survey was conducted in 4 Chicago hospitals. - A 94-item self-administered questionnaire was used to collect information. Questionnaires were distributed among prescribers. After 2 weeks, phone calls were made to remind non-respondents.	87% (n=424)	Physicians included: All internal medicine residents and attending physicians, who cared for a minimum of 60 inpatients in that year. (excluding cardiologist and neurologist)
Fakih et al. (2003)	Michigan, USA	Cross-sectional Self-completed questionnaire	- Institutional board reviews and program directors' approval were obtained from graduate medical education programs involved in internal medicine and family practice in south-eastern Michigan. Then, the survey was mailed to every program director to distribute it to their resident physicians. - Survey included 22 Likert scale-based questions and 9 multiple-choice answers.	- 48% (n=182) from 11 primary care programs responded. - They were from Internal medicine (IM) 61.6% (n=112), family practice (FP) 25.8% (n=47), emergency medicine (EM) 10.8% (n=19), and medicine-paediatrics (MP) 2.2% (n=4)	- Primary care setting - 52.5% male; 47.5% female - Participating resident physicians were in postgraduate years; Year 1 (63 residents [34.6%]) Year 2 (45 [24.7%]) Year 3 (57 [31.3%]) Year 4(8 [4.4%])

Table 2.1 continued

Author(s) and year	Country of study	Study design	Survey characteristics	Response rate/sample size	Study population
Cho et al. (2004)	Korea	Cross-sectional Self-completed questionnaire	- Using simple random sampling, 600 physicians from two specialties—family practice and paediatrics (300 from each specialty). - Questionnaire was pre-tested with 15 family physicians and 20 paediatricians. - Questionnaires were mailed three times with a pre-paid return envelope. Follow-up telephone calls were made to non-responders.	75% (n=409) (74.2% for family physicians and 75.4% for paediatricians)	- Primary care setting - 75.1% male; 24.9% female - > 90% was solo practitioners in urban areas. - They see approximately 80 patients in a usual day
Srinivasan et al. (2004)	Baltimore, USA	Cross-sectional Self-completed questionnaire	- A 75-item survey was developed, including 10-item antimicrobial quiz. - The survey was administered to the house staff physicians at John Hopkin Hospital. - Surveys were distributed on campus and by electronic mail to the participants. - Surveys were re-sent every 2 and 4 week for those who had not returned them.	- 67% (n=179) responded as follows: - General medicine 86 (83%), -Emergency medicine 23(64%) - Obe/Gyn 15 (50%) - Surgery 40 (48%) - Neurology 5 (33%)	- Hospital setting - 32% was in the first year of residency; 23% second year; 31% third year; 13% beyond that.
Mohan et al. (2004)	Trinidad and Tobago	Cross-sectional Self-completed questionnaire	- Questionnaires were distributed among GPs from central and east Trinidad, from the respective branches of the Trinidad and Tobago Medical Association. - Letters were mailed to the doctors followed by telephone calls inviting them to participate.	84.4% (n=92)	- Primary care setting - 88% male (81); 12% (11) female. - - Mean age: 52.55 years - 26.1% had >30 years of practice; 41.3% less than 20 years

Table 2.1 continued

Author(s) and year	Country of study	Study design	Survey characteristics	Response rate/sample size	Study population
Chamany et al. (2005)	USA	Cross-sectional self-completed questionnaire	- Questionnaires were distributed among American College of Obstetricians and Gynaecologists (ACOG) Fellows. - Questionnaires were sent by mail. Non-responders received second mailing after 6 weeks of first mailing.	48% (n=428)	Obstetricians and Gynaecologists in ambulatory settings within USA who manage upper respiratory tract infections (URIs) in non-pregnant patients.
Kotwani et al. (2010)	India	Qualitative study using focus group discussion (FGD)	- Three FGD conducted; 1 group composed exclusively doctors from private sectors, one group for public sector doctors and the third group contained doctors from both sectors. - The FGDs was conducted with the help of a topic guide. - Results from a completed antibiotic use and resistance study were given to participants at the beginning of FGDs.	36 doctors participated in 3 FGDs	Primary care doctors practicing in both private and public sectors
Pulcini et al. (2010)	France and United Kingdom	Cross-sectional Self-completed questionnaire	- Survey involved junior doctors in two public teaching hospitals; Dundee, Scotland, UK and Nice, France. - Participants were identified using data provided by Human Resource Department. - The questionnaire was developed in consultation with a group of experts, and was piloted with 10 junior doctors. - In Dundee, the questionnaires were distributed at the beginning of a compulsory training session. - In Nice, questionnaires were sent by email and could be returned by fax, E-mail or mail. Reminders emails were sent for non-responders.	73% (n=139)	- Hospital setting - 82 participants were from medical specialties, and 39 from surgical specialties.

Table 2.1 continued

Author(s) and year	Country of study	Study design	Survey characteristics	Response rate/sample size	Study population
Vazquez Lago et al. (2011)	Spain	Qualitative study using focus group discussion (FGD)	- The study used a theoretical model based on previous systematic review. - Participants were recruited with the support of Galician Association of Family and Community Medicine. Potential participants were contacted by telephone or email. - Each FG was made of 4-10 GPs, sessions were held in the meeting room at the respective health centres at the time reserved for teaching activities.	44% (n=33)	- GPs in the Spanish NHS in Galicia actively engaged in healthcare. - 14 female (42.4%) and 19 male (57.6%)
Garcia et al. (2011)	Peru	Cross-sectional Self-completed questionnaire	- The Survey was done with residents (physicians in training) and attending physicians (staff physicians) from two public hospitals, Cayetano Heredia (CHH) and Arzobispo Loayza (ALH), both are tertiary, teaching hospital located in urban areas. - Questionnaire content was based on a previous survey in US, adapted into Peruvian system. Prior to administration, it was reviewed by a team of 6 infectious disease physicians.	82% (n=260)	- Hospital setting - 53% (135) residents (physicians in training) and 47% (121) attending physicians (staff physicians after completing training and specialization) - 55% of respondents has less than 5 years working experience
Zaki et al. (2012)	Sudan	Cross-sectional hospital based interview study	- Participants were selected randomly from private and governmental hospitals. - The survey used a 16-item antimicrobial quiz questionnaire.	72.4% (n=181)	- 86.7% practitioners were from governmental hospital while 13.3% practitioners were from private hospitals.

Table 2.1 continued

Author(s) and year	Country of study	Study design	Survey characteristics	Response rate/sample size	Study population
Navarro-San Francisco et al. (2013)	Spain	Cross-sectional self-completed questionnaire	- The survey was conducted with all resident doctors in 5 teaching hospitals in 4 different cities (Madrid, Sevile, Murcia and Barakaldo) - This is an online survey. A link to the questionnaire was emailed to all participants. - Residents received 3 reminders during the 8 weeks of survey	33.05% (n=279)	844 residents in various specialties
Thriemer et al. (2013)	DR Congo	Cross-sectional Self-completed questionnaire	- A Purposive sample of last year medical students (who are prescribing as part of their practice) and prescribing medical doctors - Questionnaire was distributed and collected by trained collaborators - Medical students were recruited at the University Hospital of Kisangani. - Medical doctors were visited on site after making an appointment - The respondents filled in the questionnaire forms, with collaborators available for explanation.	94.4% (n=184)	- Hospital and health centres (outpatient) setting. - Medical doctors and medical students accounted for 78 (42.3%) and 106 (57.6%) of respondents respectively. - Among medical doctors, 11.5% (n=11) has less than 1 year work experience; 38.5% 1-3 years; 23.1% 4-6 years; 26.9% more than 10 years. - 54.4% prescribed antibiotics more than once a day; 15.2% 1-2 times; 17.4% 3-5 times per week.
Adorka et al. (2013)	Lesotho	Cross-sectional self-completed questionnaire	- The survey was conducted in 5 Health Service Areas in Lesotho. - Questionnaires were distributed and collected by the principal researcher.	76% (n=51)	All doctors and nurses who prescribed antibiotics.

Table 2.1 continued

Author(s) and year	Country of study	Study design	Survey characteristics	Response rate/sample size	Study population
Chandy et al. (2013)	South India, India	Qualitative study using focus group discussion (FGD)	- Recruitment was done through purposive sampling. Open invitations were given through respective associations, selection based on their willingness and ability to commit time for the FGD. - Discussion was guided by a moderator, who communicated the objective of the discussion, and used a semi-structured discussion guide with predefined themes.	Two groups of 6 doctor each, from urban and rural area.	- Doctors were mainly in private practice and hospital, from urban and rural areas. - Age range for urban doctors: 33-63 years, while 29-54 for rural doctors.
Woods et al. (2013)	A multi-country study from Europe	Qualitative study, using a semi-structured interview and a fixed category survey	- Primary care clinicians were selected randomly from Genomics to combat Resistance against community-acquired LRTI in Europe (GRACE). - Interviews were conducted by a trained interviewer. A pre-piloted interview topic guide was used to facilitate the interviews.	80 interviews were conducted.	- 41% were female participant. - Mean age 43 years. - Mean years in practice; 16 years
Sutradhar et al. (2014)	Bangladesh	Cross-sectional Self-completed questionnaire	- The survey was done in 24 Upazila Health Complexes and 112 Union Health Centres of Dhaka and Rajashi divisions. - Questionnaires were pilot-tested prior to the main survey. - The survey was done by interviewers, following a face-to-face interview protocol. - Questionnaires were given only to the spontaneously interested candidates during the survey.	580 physicians	- Outpatient setting (health centres) - Registered physicians practicing in the Upazila Health Complexes and Union Health Centres