Vol. 13(8), pp. 151-157, 28 February, 2019
DOI: 10.5897/AJMR2019.9048
Article Number: 031E56060337
ISSN: 1996-0808

http://www.academicjournals.org/AJMR

ACADEMIC JOURNALS
expand your knowledge

African Journal of Microbiology Research

Review

Antibiotic resistance in Saudi Arabia and some Middle Eastern countries: Current status

Shadi Ahmed Zakai

Department of Medical Microbiology and Parasitology, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

Received 3 January, 2019; Accepted 14 February, 2019

Antibiotic resistance has become a major threat to human health worldwide, especially for serious infections, leaving limited choices for antimicrobials to be used. The World Health Organization (WHO) launched several strategies to control the spread of this resistance. However, in the Middle East the problem can become worse if these strategies are not applied due to the geographical location between developed and developing worlds, and the heavy misuse of antibiotics in the region. The current picture of antibiotic resistance in Saudi Arabia and some of the Middle Eastern countries represents high resistance rates among other regions to penicillin, erythromycin, fluoroquinolone, carbapenem and anti-tuberculosis drugs. Misuse of antibiotics is one of the major factors that contribute to the increase in antimicrobial resistance (AMR). This includes self-medication, incomplete dosage of the medication, missing doses, and re-use of excess antibiotics from previous prescription. Moreover, lack of adherence to infection control practice by healthcare professionals can contribute in spreading antibiotic resistance. An action plan has already been set by the WHO to limit antibiotic resistance. Application of this plan requires efforts of stakeholders from all regional countries to successfully stop the spread of AMR in the Middle East. Actions should include spreading public awareness of antibiotic resistance, as well as educational programs for healthcare professionals on infection prevention and control. National surveillances of antibiotic resistant bacteria that cause nosocomial infections are essential to identify outbreaks. Strict regulations regarding dispensing antibiotics should be imposed. Each country should take action to limit the spread of antibiotic resistance. If resistance is left uncontrolled, the region may face a time in which treatments of minor infections may become impossible.

Key words: Antimicrobial resistance, Saudi Arabia, Middle East, antibiotic misuse, penicillin, erythromycin, fluoroquinolone, carbapenem.

INTRODUCTION

Antibiotics have been known to be the most effective method for the treatment of bacterial infections for decades. The discovery of penicillin in early 19th century has contributed in saving millions of lives by its ability to treat infectious diseases that were considered as the main killers in the pre-antibiotics ages. However, the

E-mail: szakai@kau.edu.sa.

rapidly increasing development of multi-drug resistant (MDR) bacteria to a large number of antibiotics is now becoming a global concern, causing increased morbidity and mortality worldwide, an increase in health care bills, failure of treatments, and increased hospitalization and visits to out-patient clinics (Abobotain et al., 2013; Ricciardi et al., 2016). The World Health Organization (WHO) refers to the fast development of MDR bacteria as one of the major threats to public health internationally, as it severely limits the option of treating infectious diseases (Brookes-Howell et al., 2012; World Health Organization, 2014).

For this reason, the WHO sets many strategies to limit antibiotic resistance (World Health Organization, 2015). The key strategies are to improve public awareness and understanding of the correct use of antibiotics, to support the knowledge and evidence base, to minimize infection rates, to control antibiotic use in human and animals, and to develop the economic case for sustainable investment (World Health Organization, 2015).

Misuse of antibiotics is one of the main factors for the increase of antibiotic resistance worldwide. The concept of misuse involves self-medication, incomplete dosage of the medication, missing doses, taking insufficient doses, and re-use of left-over antibiotics from previous prescription (Abobotain et al., 2013).

Kardas et al. (2005) carried out a large systematic review to evaluate the frequency of compliance with treatment and the re-use of leftover antibiotics, as two main factors of antibiotic misuse in the community covering all continents with emphasis on North America and Europe. They reported that the mean compliance with antibiotics was 62.2% and mean use of leftover antibiotics was 28.6%.

According to the WHO, self-medication means selecting and using medicines by people to treat self-identified diseases or symptoms' (Aljadhey et al., 2015; World Health Organization, 1998). Over the Counter (OTC) medication is the drugs that can be bought, safely and effectively being used by the general public without requiring medical consultation by a healthcare professional, as defined by the US Food and Drug Authority (US Food and Drug Authority, 2015). Responsible self-medication is consumption of OTC medications, and it is an internationally appropriate practice, whereas buying prescription-medications without prescription from a healthcare professional is unsafe self-medication (World Health Organization, 1998). The OTC medication use can be valuable to reduce the frequency and the cost of visits to clinics. However, even misuse of OTC medications can be accompanied by antagonistic reactions, drug-drug interactions, overdosing, and other medication-related problems (Austin et al., 1999). Therefore, it is recommended to increase public awareness and education on the use of OTC medications, as well as to control dispensing OTC medication, in order to facilitate responsible self-care.

The current status of antibiotic resistance in Saudi Arabia and some of the Middle Eastern countries

There is a remarkable increase in antibiotic resistance rates in common human pathogens in the Middle Eastern countries (Al-Tawfiq et al., 2009, 2010; Strahilevitz et al., 2007). Increased antimicrobial resistance was reported in several surveys in the last decade.

Penicillin and other β-lactams

The rate of penicillin resistance in the Arabian Peninsula and Egypt was investigated by a literature search by Shibl et al. (2009) covering 1990 to 2007. They found a range of resistance to penicillin from 0 to 78%. The same study also reported an increasing range of penicillin resistance over many decades from 0 to 20% between 1980s and 1990s; it reached 40% in early 2000s, 50–80% between 2003 and 2005 (Shibl et al., 2009). Increasing resistant *S. aureus* strains are becoming a big concern, especially those acquired from hospitals. The rate of both hospital-acquired (HA) methicillin-resistant *S. aureus* (MRSA) infection and colonization has increased from 2.17 cases in every 1000 admissions to 3.90 cases in every 1000 admission only between 2000 and 2004 in Saudi Arabia (Balkhy et al., 2007). In another study, the rate of community-acquired (CA) MRSA ranged from 10 to 30 per 100,000 patient-days (Al-Tawfiq, 2006b). Furthermore, MRSA rates reached 32.0% of all *S. aureus* isolates from 13 Kuwaiti hospitals (Udo et al., 2008). A national surveillance on Gram-positive cocci carried out in Saudi Arabia showed that MRSA counted 32% of *S. aureus*, and penicillin G-resistant *Streptococcus pneumoniae* (*S. pneumoniae*) were 33%, and 26% were erythromycin resistant (Shibl et al., 2014). A study from Jeddah showed that nasal colonization by *S. aureus* was 25.3% of the 150 tested participants who were all senior medical students and interns, of which 6.7% were colonized by MRSA (Zakai, 2015). Similar study done in Riyadh, showed that 40% of healthcare workers were colonized by *S. aureus,* of which 18 were MRSA carriers (Al-Humaidan et al., 2015). Another study in Jeddah showed remarkably higher rate of MRSA nasal colonization of healthcare workers (Iyer et al., 2014). They reported an incidence rate of 76% of MRSA nasal colonization among the tested group of healthcare workers.

Fluoroquinolones

The emergence of fluoroquinolone resistance in many regions in the Middle East has become a notable problem. In Saudi Arabia, from 2000 to 2006, resistance to ciprofloxacin by *Enterobacter cloacae* raised from 8.3 to 17.4% (Al-Tawfiq et al., 2009). Additionally, another

study in the same country showed a significantly increased resistant hospital-acquired isolates of *Klebsiella pneumonia* to ciprofloxacin. The resistance rate jumped from 2.6 to 23% in only six years (1998-2003) (Al-Tawfiq and Antony, 2007). Several other studies in the region were performed to examine the resistance rate to ciprofloxacin. In Oman, they reported ciprofloxacin resistance rate of 31% in urinary tract for *E. coli* isolates (Al-Lawati et al., 2000). In Lebanon, the resistance rate to ciprofloxacin in community isolates reached 25%, while it increased to 40–46% for hospital isolates (Fadel et al., 2004; Tohme et al., 2001). In Saudi Arabia, *E. coli* isolates were shown to be resistant to ciprofloxacin in 19% in outpatient urinary tract isolates, and 49% in inpatient urinary tract isolates (Al-Tawfiq, 2006a). Similar rates were found in Turkey, where ciprofloxacin resistance was reported in 42.1% of outpatients to *E. coli* (Yilmaz et al., 2009). Non-enteric species showed much higher rates of resistance. For instance, in the United Arab Emirates, resistance rate to ciprofloxacin was reported in 97.4% of *Pseudomonas aeruginosa* isolates (Al-Dhaheri et al., 2009).

Carbapenem

In Saudi Arabia, carbapenem-resistance was remarkably noted in Gram-negative bacilli (GNB). This resistance was reviewed in the last ten years and compared to those of the 1990s (Zowawi et al., 2013). The same review also reported an increased prevalence of extended spectrum beta-lactamase (ESBL) producing isolates in Saudi Arabia. Some institutes reported an ESBL rate of 29% among *Escherichia coli* (*E. coli*) and 65% among *K. pneumoniae* (Zowawi et al., 2013).

Resistance of *Acinetobacter baumannii (A. baumannii)* to carbapenem (CRAB) showed a dramatic increase in Saudi Arabia. A study from Riyadh (Al-Obeid et al., 2015) demonstrated a decrease in susceptibilities of *A. baumannii* to meropenem and imipenem from 64-81.2 to 8.3-11%, in only six years between 2006 to 2012. Additionally, a study from the same region showed that multidrug resistance was reported in 14–35.8% of *Acinetobacter spp*. isolates (Al-Tawfiq and Mohandhas, 2007). In 2002, an outbreak of MDR *A. baumannii* was reported in one of the intensive care units (ICUs) in Qatar (El Shafie et al., 2004). A total number of 21 patients were included in this outbreak, all their infection/colonization were hospital-acquired. In the same study, a similar strain was isolated from the hospital equipment, environment, and also from hands of the healthcare workers. Another study reported similar outbreak of an epidemic strain of *A. baumannii* in 87% of patients undergoing tracheostomy at a tertiary care hospital in Riyadh, Saudi Arabia (Mah et al., 2001).

Colistin is considered as the final antibiotic of choice to be used against many of carbapenem-resistant Gram Negative Bacilli (GNB). Nevertheless, resistance to colistin has already been reported (Zowawi, 2016). It has been known that resistance to colistin is chromosomally mediated, which means it is not transmissible between bacterial cells. In China, however, an emergence of plasmid-mediated colistin resistance (*mcr-1*) was reported in both human and animals (Liu et al., 2016). A study reported the presence of *mcr-1* gene in *E. coli* strains isolated from Saudi Arabia, Bahrain and United Arab Emirates, which suggests the possibility of spreading of *mcr-1* carrying GNB in more isolates and between other species in the Arabian Peninsula (Sonnevend et al., 2016).

Anti-tuberculosis drugs

Anti-tuberculosis (anti-TB) drug resistance is becoming a critical problem for many countries, especially in those where the infection is endemic. A Saudi national survey on anti-TB drug resistance reported that the MDR TB phenotype was demonstrated in only 1.6% of total TB (Al-Hajoj et al., 2013). The WHO Global Project investigated the MDR-TB across 79 countries worldwide between 1999 and 2003. They found MDR-TB in 1.1% of new cases and 6.9% of retreatment patients (Aziz et al., 2006). In contrast, the regional surveillance estimated the rates of MDR-TB, which ranged from 2.3% in new cases to 52% in retreatment cases (Shamaei et al., 2009).

Regional factors contributing to the increase in the emergence and spread of antibiotic resistance

In the Middle East, the scenario of antibiotic resistance is unique. The geographical location of the Middle East connects the developed and developing worlds, thus, it is exposed to a variety of resistant bacteria from both worlds. For instance, oxacillin-resistant *S. aureus,* penicillin-resistant *Streptococcus pneumoniae* and multi-drug resistant (MDR) *Mycobacterium tuberculosis* (Al-Tawfiq et al., 2010).

During Hajj pilgrimage, millions of Hajj pilgrims visit two major cities in the Kingdom of Saudi Arabia annually. The gathering of this large human population brings imported and endemic diseases to be well transmitted between pilgrims from different countries and local pilgrims and residents, and then exported across many countries later (Al-Tawfiq et al., 2010; Moore et al., 1988). International travel is an important risk factor for the acquisition and transmission of infectious diseases, including those caused by high diversity of antibiotic resistant bacteria. A study assessed the carriage status of diverse bacteria in Hajj pilgrims before and after they travelled to Hajj (Leangapichart et al., 2016). Interestingly, the diversity of bacteria isolated from samples that were collected after the return from Hajj was significantly higher than those

collected before, in particular, carbapenemase-producing *A. baumannii* and *E. coli*. The high acquisition rate of diverse bacteria in Hajj season may be referred to the overcrowded conditions of the pilgrims in small areas. An increase by 16.5% in septicaemia cases was reported in Makkah during Hajj season due to the arrival of external visitors (Zowawi et al., 2013). In a study executed to evaluate the prevalence of MRSA carriage among Hajj pilgrims, it was found that *S. aureus* was present in 20.6% of the tested samples (*n* = 411), of which 1.46% were MRSA (Memish et al., 2006). Another common infection among hospitalized Hajj pilgrims is tuberculosis. A study done during the Hajj season of 64 patients with pneumonia, it was found that *M. tuberculosis* was the most common causative bacterial agent of pneumonia (Alzeer et al., 1998).

Uncontrolled use of antibiotics is one of the major factors that contribute to the increase of antimicrobial resistance (AMR). One means of antibiotic misuse is the uncontrolled use by patients, such as self-medication, noncompliance with antimicrobial therapy, taking sub-optimal dose, and consumption of leftover medication. The availability of OTC antibiotics that can be obtained without prescription was a major concern in Saudi Arabia before the Saudi Ministry of health set strict regulations in early 2018 for antibiotic prescription by the Executive Regulations of Health Practice Law, which prohibit pharmacists from dispensing any drug without a prescription issued by a doctor with a license to practice in the Kingdom. Self-medication was reported in 11.6% in a sample of Saudi parents (60.5% mothers and 39.5% fathers). Half of them claimed that antibiotics could be used for their children in cases of runny nose, cough, sore throat or fever. However, more than half (57.7%) believe that they can reduce severity and shorten duration of illness, 68.6% believe they can relieve viral infection, and 28.7% claim they can be stopped upon improvement (Abobotain et al., 2013). Another study in the Eastern region of Saudi Arabia reported that 67% of the parents tried self-medication once or more, and 37.7% of them used leftovers antibiotics (Al-Shawi et al., 2018). Misuse of antibiotics by patients is known to be common in the region. A Jordanian study reported self-medication rates of 23.1-39.5% (Al-Azzam et al., 2007; Al-Bakri et al., 2005). Higher rates (53%) were reported in Iran (Sarahroodi and Arzi, 2009). Another means of antibiotic misuse is the uncontrolled self-prescription by pharmacists. A Saudi study showed that 82% of pharmacists recommended self-prescription to treat symptoms of urinary tract infections, in which fluoroquinolone is the ordinarily dispensed antibiotic (Al-Ghamdi, 2001). A study in the Eastern region of Saudi Arabia revealed that only one out of 88 pharmacists refuse to sell antibiotics without prescription, while in Riyadh, 77.6% of pharmacists sell antibiotics without prescription (Zowawi et al., 2013). Physicians also have a role in antibiotic misuse in the area. An Iranian study showed that 37-40% of physicians prescribed antibiotics for cases that did not require antibiotic treatments. The Iranian physicians refer to patient pressure to prescribe more medication, particularly antibiotics (Amidi et al., 1975).

Another factor that contributes to the increase of antibiotic resistance is the lack of compliance of patients to the prescribed antimicrobial therapy. Comparing the status in the Middle East to elsewhere, data have shown better compliance in this region than somewhere else. A meta-analysis study revealed a rate of 72.4% of compliance with prescribed antibiotics, whereas internationally it was 58–68% (Kardas et al., 2005). Unfortunately, this is not the case with anti-TB agents. Data from Saudi Arabia have shown mixed results regarding compliance with anti-TB agents. In one study of 628 patients, noncompliance rate with the prescribed regimen was 43.8% (Al-Hajjaj and Al-Khatim, 2000). Another study found distinct gender variations showed a low noncompliance rate among females (15.3%), while a much higher rate among males (44%) (Samman et al., 2003).

Adherence to infection control practice by healthcare professionals is an essential factor in limiting the spread of antibiotic resistance. Hand hygiene of healthcare professionals was assessed in Makkah during the Hajj season in 2011 (Bukhari et al., 2011). The overall rate of compliance with hand hygiene was 50.3%, with highest rate among nurses (52.2%), followed by doctors (49.1%), and technicians (42.8%).

Antibiotic prescription and respiratory tract infections

Physicians prescribe antibiotics for upper respiratory tract infection (URTI) in children (Sa'ed et al., 2015). Nevertheless, URTI is most commonly caused by viruses (Harnden et al., 2007). Moreover, some bacterial infections causing URTI are self-limiting and do not require antimicrobial treatments, such as otitis media and sinusitis (Panagakou et al., 2011). Antibiotics are frequently misused by parents to treat upper respiratory tract infections, which are mainly caused by viruses. Parents believe they can reduce the severity of illness symptoms, although antibiotics have no effect on reducing symptoms nor shorten the time of recovery (Friedman et al., 2011). A Palestinian study addressed the parents' knowledge, attitude and practices on antibiotic use for children suffering from URTIs. Nearly 73% of parents choose antibiotics as a treatment for URTIs, 68% for earache, and 64% for fever (Sa'ed et al., 2015). A study done in a Jordanian community focused on the consumption of antibiotics, found that 46% of antimicrobial medications were dispensed without a prescription, either through self-medication (23.2%) or pharmacist recommendation (23.1%) (Al-Bakri et al.,

2005). Of dispensed antibiotics in this outpatient setting, almost one-third (29%) was inappropriate for prescribed and 34% for non-prescribed antibiotics. Most of these patients used these antibiotics to treat upper respiratory tract infections (URIs) symptoms. A study in Riyadh done on community pharmacies found that 49% of purchased medications were dispensed without prescription, in which antibiotics account for 22% of prescription medications that were dispensed without prescription. The commonest reasons for buying such medication without having a proper prescription from a physician were that symptoms were very minor to seek medical advice (54%), time saving (40%), and former consumer knowledge about the symptoms (40%) (Aljadhey et al., 2015). Another study carried out on an outpatient population in Alexandria found that 55% of oral antibiotics were inappropriately used (Koura et al., 1999). Additionally, in Kuwait a study examined antibiotic dispensing practices for children attending a primary healthcare center. They reported excessive prescription of antibiotics for 39% of the children, of whom 72% had respiratory tract infections (Najdi et al., 1988). Greater rates of inappropriate antibiotic prescribing were reported in Saudi Arabia. A study performed at a primary healthcare center in northern region of Saudi Arabia reported that antibiotics were prescribed to 87.8% of patients with upper respiratory infection (URI) (El-Gilany, 2000). In another study, antibiotics were prescribed to 51.6% of patients with URI symptoms in Bahrain (Senok et al., 2009).

Action plan is needed to limit the antibiotic resistance in the region

Antibiotic resistance shows a serious burden to the public health in the Middle East. For this, the WHO started the Global Action Plan on Antimicrobial Resistance (World Health Organization, 2015). This plan was committed by most of the region countries, including Saudi Arabia in the World Health Assembly in 2015. The plan addressed five main goals; to increase awareness, to strengthen knowledge through surveillance and research, to decrease the rate of infection, to control the use of antimicrobial agents, and to develop economic tools for sustainable investment to support the need in all countries in regards to new medicines, diagnostic tools, vaccines, and other interventions. To realize this action plan, some regional countries launched their own national AMR action plans, and their main common goal is to challenge the AMR in both human and animal sectors.

Spreading community awareness to AMR through different channels is necessary to tackle the AMR in the Middle East, particularly in Saudi Arabia as it is visited by large crowds during Hajj seasons with visitors from all over the world. Nationwide awareness campaigns should be initiated through different channels to ensure as wide delivery of the message as possible. Nowadays, this can be easily done via TV, radio, and social media channels (Zowawi et al., 2015). Governmental efforts can help to increase public awareness regarding antibiotic misuse. A good example is the French national 5-year program that reduced the antibiotic prescription by 26% between 2002-2007 (Sabuncu et al., 2009).

Educational program for healthcare professionals on infection prevention and control is crucial to limit the spread of AMR. Education on hand hygiene compliance can play an important role in limiting the spread of outbreaks in hospitals and community.

Due to the global increased prevalence of AMR bacteria, and the necessity for synchronized efforts for interventions, there should be matching between trends of resistance and amount of antibiotic consumption by local records to define the problem and allow appropriate interventions. Randomized regional studies can aid minimizing antibiotic resistance; however, expanded work is required in the Middle East region. Establishing national surveillance of AMR bacteria that cause nosocomial infections can help to identify outbreaks.

Last but not least, to limit the misuse and self-medication of antibiotics in the region, there should be strict regulation regarding selling these agents. Therefore, accessibility in all Middle Eastern countries must be restricted to antibiotics prescribed by physicians.

Conclusion

It is clear that AMR is a serious current global burden that threat public health, which requires focused attention, and the problem is also occurring in the Middle Eastern countries. If AMR is left uncontrolled, the region may face a ‘post-antibiotic era’, in which treatments of minor infections may become impossible, mortality rate may increase as well as the treatment costs and newer complex, more expensive antibiotics will be required. All countries should take action for limiting the spread of AMR. Prompt actions may embrace national surveillance of AMR at both hospital and community level. Educational programs of infection prevention and control should be initiated toward the same goal. Raising public awareness of AMR is also required to control misuse of antibiotics. Finally, the use of antibiotics should be controlled in hospital and community pharmacies.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES

Abobotain AH, Sheerah HA, Alotaibi FN, Joury AU, Mishiddi RM, Siddiqui AR, Saeed AB (2013). Socio-demographic determinants of antibiotic misuse in children. Saudi Medical Journal 34(8):832-840.

Al-Azzam S, Al-Husein B, Alzoubi F, Masadeh M, Ali M (2007). Self-medication with antibiotics in Jordanian population. International Journal of Occupational Medicine and Environmental Health 20(4):373-380.

Al-Bakri AG, Bustanji Y, Yousef AM (2005). Community consumption of antibacterial drugs within the Jordanian population: sources, patterns and appropriateness. International Journal of Antimicrobial Agents 26(5):389-395.

Al-Dhaheri AS, Al-Niyadi MS, Al-Dhaheri AD, Bastaki SM (2009). Resistance patterns of bacterial isolates to antimicrobials from 3 hospitals in the United Arab Emirates. Saudi Medical Journal 30(5):618-623.

Al-Ghamdi MS (2001). Empirical treatment of uncomplicated urinary tract infection by community pharmacist in the Eastern province of Saudi Arabia. Saudi Medical Journal 22(12):1105-1108.

Al-Hajjaj MS, Al-Khatim IM (2000). High rate of non-compliance with anti-tuberculosis treatment despite a retrieval system: a call for implementation of directly observed therapy in Saudi Arabia. The International Journal of Tuberculosis and Lung Disease 4(4):345-349.

Al-Hajoj S, Varghese B, Shoukri MM, Al-Omari R, Al-Herbwai M, AlRabiah F, Alrajhi AA, Abuljadayel N, Al-Thawadi S, Zumla A, Zignol M (2013). Epidemiology of antituberculosis drug resistance in Saudi Arabia: Findings of the first national survey. Antimicrobial Agents and Chemotherapy, 57(5):2161-2166.

Al-Humaidan OS, El-Kersh TA, Al-Akeel RA (2015). Risk factors of nasal carriage of *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* among health care staff in a teaching hospital in central Saudi Arabia. Saudi Medical Journal 36(9):1084-1090.

Aljadhey H, Assiri GA, Mahmoud MA, Al-Aqeel S, Murray M (2015). Self-medication in Central Saudi Arabia Community pharmacy consumers' perspectives. Saudi Medical Journal 36(3):328-334.

Al-Lawati AM, Crouch ND, Elhag KM (2000). Antibiotic consumption and development of resistance among gram-negative bacilli in intensive care units in Oman. Annals of Saudi Medicine 20(3-4):324-327.

Al-Obeid S, Jabri L, Al-Agamy M, Al-Omari A, Shibl A (2015). Epidemiology of extensive drug resistant Acinetobacter baumannii (XDRAB) at Security Forces Hospital (SFH) in Kingdom of Saudi Arabia (KSA). Journal of Chemotherapy 27(3):156-162.

Al-Shawi MM, Darwish MA, Wahab MM, Al-Shamlan NA (2018). Misconceptions of parents about antibiotic use in upper respiratory tract infections: A survey in primary schools of the Eastern Province, KSA. Journal of Family and Community Medicine *25*(1):5-12.

Al-Tawfiq JA (2006a). Increasing antibiotic resistance among isolates of *Escherichia coli* recovered from inpatients and outpatients in a Saudi Arabian hospital. Infection Control and Hospital Epidemiology 27(7):748-753.

Al-Tawfiq JA (2006b). Incidence and epidemiology of methicillin-resistant *Staphylococcus aureus* infection in a Saudi Arabian hospital, 1999-2003. Infection Control and Hospital Epidemiology 27(10):1137-1139.

Al-Tawfiq JA, Antony A (2007). Antimicrobial resistance of *Klebsiella pneumoniae* in a Saudi Arabian hospital: results of a 6-year surveillance study, 1998-2003. Journal of Infection and Chemotherapy 13(4):230-234.

Al-Tawfiq JA, Antony A, Abed MS (2009). Antimicrobial resistance rates of Enterobacter spp.: a seven-year surveillance study. Medical Principles and Practice 18(2):100-104.

Al-Tawfiq JA, Mohandhas TX (2007). Prevalence of antimicrobial resistance in Acinetobacter calcoaceticus-baumannii complex in a Saudi Arabian hospital. Infection Control and Hospital Epidemiology 28(7):870-872.

Al-Tawfiq JA, Stephens G, Memish ZA (2010). Inappropriate antimicrobial use and potential solutions: a Middle Eastern perspective. Expert Review of Anti-infective Therapy 8(7):765-774.

Alzeer A, Mashlah A, Fakim N, Al-Sugair N, Al-Hedaithy M, Al-Majed S, Jamjoom G (1998). Tuberculosis is the commonest cause of pneumonia requiring hospitalization during Hajj (pilgrimage to Makkah). Journal of Infection 36(3):303-306.

Amidi S, Solter S, Rashidian B, Zokaian AR, Razmjoian F (1975). Antibiotic use and abuse among physicians in private practice in Shiraz, Iran. Medical Care 13(4):341-345.

Austin DJ, Kristinsson KG, Anderson RM (1999). The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. Proceedings of the National Academy of Sciences of the United States of America 96(3):1152-1156.

Aziz MA, Wright A, Laszlo A, De Muynck A, Portaels F, Van Deun A, Wells C, Nunn P, Blanc L, Raviglione M (2006). Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. Lancet 368(9553):2142-2154.

Balkhy HH, Memish ZA, Almuneef MA, Cunningham GC, Francis C, Fong KC, Nazeer ZB, Tannous E (2007). Methicillin-resistant *Staphylococcus aureus*: A 5-year review of surveillance data in a tertiary care hospital in Saudi Arabia. Infection Control and Hospital Epidemiology 28(8):976-982.

Brookes-Howell, L., Elwyn, G., Hood, K., Wood, F., Cooper, L., Goossens, H., Butler, C. C. (2012). 'The Body Gets Used to Them': Patients' Interpretations of Antibiotic Resistance and the Implications for Containment Strategies. Journal of General Internal Medicine *27*(7):766-772.

Bukhari SZ, Hussain WM, Banjar A, Almaimani WH, Karima TM, Fatani MI (2011). Hand hygiene compliance rate among healthcare professionals. Saudi Medical Journal 32(5):515-519.

El Shafie SS, Alishaq M, Garcia ML (2004). Investigation of an outbreak of multidrug-resistant Acinetobacter baumannii in trauma intensive care unit. Journal of Hospital Infection 56(2):101-105.

El-Gilany AH (2000). Acute respiratory infections in primary health care centres in northern Saudi Arabia. Eastern Mediterranean Health Journal 6(5-6):955-960.

Fadel R, Dakdouki GK, Kanafani ZA, Araj GF, Kanj SS (2004). Clinical and microbiological profile of urinary tract infection at a tertiary-care center in Lebanon. Infection Control and Hospital Epidemiology 25(1):82-85.

Friedman BC, Schwabe-Warf D, Goldman R (2011). Reducing inappropriate antibiotic use among children with influenza infection. Canadian Family Physician 57(1):42-44.

Harnden A, Perera R, Brueggemann AB, Mayon-White R, Crook DW, Thomson A, Mant D (2007). Respiratory infections for which general practitioners consider prescribing an antibiotic: a prospective study. Archives of Disease in Childhood 92(7):594-597.

Iyer A, Kumosani T, Azhar E, Barbour E, Harakeh S (2014). High incidence rate of methicillin-resistant *Staphylococcus aureus* (MRSA) among healthcare workers in Saudi Arabia. Journal of Infection in Developing Countries 8(3):372-378.

Kardas P, Devine S, Golembesky A, Roberts C (2005). A systematic review and meta-analysis of misuse of antibiotic therapies in the community. International Journal of Antimicrobial Agents 26(2):106-113.

Koura MR, Khairy AE, Abdel-Aal NM, Deghedi B, Sabra AA (1999). Quality assessment of the primary health care services provided for ARI control in Alexandria. Journal of the Egyptian Public Health Association 74(3-4):275-296.

Leangapichart T, Gautret P, Griffiths K, Belhouchat K, Memish Z, Raoult D, Rolain JM (2016). Acquisition of a High diversity of bacteria during the hajj pilgrimage, including *Acinetobacter baumannii* with blaOXA-72 and *Escherichia coli* with blaNDM-5 carbapenemase genes. Antimicrobial Agents and Chemotherapy 60(10):5942-5948.

Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, Doi Y, Tian G, Dong B, Huang X, Yu LF (2016). Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. Lancet Infectious Diseases 16(2):161-168.

Mah MW, Memish ZA, Cunningham G, Bannatyne RM (2001). Outbreak of *Acinetobacter baumannii* in an intensive care unit associated with tracheostomy. American Journal of Infection Control 29(5):284-288.

Memish ZA, Balkhy HH, Almuneef MA, Al-Haj-Hussein BT, Bukhari AI, Osoba AO (2006). Carriage of *Staphylococcus aureus* among Hajj pilgrims. Saudi Medical Journal 27(9):1367-1372.

Moore PS, Harrison LH, Telzak EE, Ajello GW, Broome CV (1988). Group-A Meningococcal carriage in travelers returning from Saudi-Arabia. Journal of the American Medical Association 260(18):2686-2689.

Najdi AN, Khuffash FA, R'Shaid WA, Ateeqi WA (1988). Antibiotic misuse in a paediatric teaching department in Kuwait. Annals of Tropical Paediatrics 8(3):145-148.

Panagakou SG, Spyridis N, Papaevangelou V, Theodoridou KM, Goutziana GP, Theodoridou MN, Syrogiannopoulos GA, Hadjichristodoulou CS (2011). Antibiotic use for upper respiratory tract infections in children: A cross-sectional survey of knowledge, attitudes, and practices (KAP) of parents in Greece. BMC Pediatrics 11(1):60.

Ricciardi W, Giubbini G, Laurenti P (2016). Surveillance and Control of Antibiotic Resistance in the Mediterranean Region. Mediterranean Journal of Hematology and Infectious Diseases 8(1):e2016036.

Sa'ed HZ, Taha AA, Araj KF, Abahri IA, Sawalha AF, Sweileh WM, Awang R, Al-Jabi SW (2015). Parental knowledge, attitudes and practices regarding antibiotic use for acute upper respiratory tract infections in children: a cross-sectional study in Palestine. BMC Pediatrics 15(1): 176.

Sabuncu E, David J, Bernède-Bauduin C, Pépin S, Leroy M, Boëlle PY, Watier L, Guillemot D (2009). Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. *PLoS* Medicine 6(6):e1000084.

Samman Y, Krayem A, Haidar M, Mimesh S, Osoba A, Al-Mowaallad A, Abdelaziz M, Wali S (2003). Treatment outcome of tuberculosis among Saudi nationals: role of drug resistance and compliance. Clinical microbiology and infection 9(4):289-294.

Sarahroodi S, Arzi A (2009). Self medication with antibiotics, is it a problem among Iranian college students in Tehran. Journal of Biological Sciences 9(8):829-832.

Senok AC, Ismaeel AY, Al-Qashar FA, Agab WA (2009). Pattern of upper respiratory tract infections and physicians' antibiotic prescribing practices in Bahrain. Medical Principles and Practice 18(3):170-174.

Shamaei M, Marjani M, Chitsaz E, Kazempour M, Esmaeili M, Farnia P, Tabarsi P, Amiri MV, Mirsaeidi M, Mansouri D, Masjedi MR (2009). First-line anti-tuberculosis drug resistance patterns and trends at the national TB referral center in Iran-eight years of surveillance. International Journal of Infectious Diseases 13(5):E236-E240.

Shibl A, Memish Z, Pelton S (2009). Epidemiology of invasive pneumococcal disease in the Arabian Peninsula and Egypt. International Journal of Antimicrobial Agents 33(5):410-e1.

Shibl AM, Memish ZA, Kambal AM, Ohaly YA, Ishaq A, Senok AC, Livermore DM (2014). National surveillance of antimicrobial resistance among Gram-positive bacteria in Saudi Arabia. Journal of Chemotherapy 26(1):13-18.

Sonnevend Á, Ghazawi A, Alqahtani M, Shibl A, Jamal W, Hashmey R, Pal T (2016). Plasmid-mediated colistin resistance in *Escherichia coli* from the Arabian Peninsula. International Journal of Infectious Diseases 50:85-90.

Strahilevitz J, Engelstein D, Adler A, Temper V, Moses AE, Block C, Robicsek A (2007). Changes in qnr prevalence and fluoroquinolone resistance in clinical isolates of *Klebsiella pneumoniae* and *Enterobacter* spp. collected from 1990 to 2005. Antimicrobial Agents and Chemotherapy 51(8):3001-3003.

Tohme A, Karam-Sarkis D, El-Rassi R, Chelala D, Ghayad E (2001). Agents and consequences of nosocomial infections in a Lebanese university hospital. Retrospective study over a two-year period. InAnnales de Medecine Interne (Paris) 152(2):77-83.

Udo EE, Al-Sweih N, Dhar R, Dimitrov TS, Mokaddas EM, Johny M, Al-Obaid IA, Gomaa HH, Mobasher LA, Rotimi VO, Al-Asar A (2008). Surveillance of antibacterial resistance in *Staphylococcus aureus* isolated in Kuwaiti hospitals. Medical Principles and Practice 17(1):71-75.

US Food and Drug Authority. (2015). Drug applications for over-the-counter (OTC) drugs. Retrieved from https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/over-the-counterdrugs/default.htm

World Health Organization (1998). The role of pharmacist in self-care and self-medication. Retrieved from http://apps.who.int/medicinedocs/en/d/Jwhozip32e/5.html

World Health Organization (2015). Global action plan on antimicrobial resistance. Retrieved from https://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/

World Health Organization. (2014). Antimicrobial resistance: Global report on surveillance 2014. Retrieved from https://www.who.int/drugresistance/documents/surveillancereport/en/

Yilmaz N, Agus N, Yurtsever SG, Pullukcu H, Gulay Z, Coskuner A, Kose S, Aydemir S, Gulenc N, Ozgenc O (2009). Prevalence and antimicrobial susceptibility of *Escherichia coli* in outpatient urinary isolates in Izmir, Turkey. Medical Science Monitor 15(11):161-165.

Zakai SA (2015). Prevalence of methicillin-resistant *Staphylococcus aureus* nasal colonization among medical students in Jeddah, Saudi Arabia. Saudi Medical Journal 36(7):807-812.

Zowawi HM (2016). Antimicrobial resistance in Saudi Arabia An urgent call for an immediate action. Saudi Medical Journal 37(9):935-940.

Zowawi HM, Abedalthagafi M, Mar FA, Almalki T, Kutbi AH, Harris-Brown T, Harbarth S, Balkhy HH, Paterson DL, Hasanain RA (2015). The potential role of social media platforms in community awareness of antibiotic use in the Gulf Cooperation Council States: Luxury or necessity? Journal of medical Internet Research 17(10):e233.

Zowawi HM, Balkhy HH, Walsh TR, Paterson DL (2013). β-Lactamase Production in Key Gram-Negative Pathogen Isolates from the Arabian Peninsula. Clinical Microbiology Reviews 26(3):361-380.