TITLE: Emergence of drug resistant bacteria at the Hajj: a systematic review

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Abstract

Background: Hajj is the annual mass gathering of Muslims, and is a reservoir and potential source of bacterial transmission. The emergence of bacterial transmission, including multi-drug resistance (MDR) bacteria, during Hajj has not been systematically assessed.

Methods: Articles in Pubmed, Scopus, and Google scholar were identified using controlled words relating to antibiotic resistance (AR) at the Hajj from January 2002 to January 2017. Eligible studies were identified by two researchers. AR patterns of bacteria were obtained for each study.

Results: We included 31 publications involving pilgrims, Hajj workers or local patients attending hospitals in Mecca, Mina, and the Medina area. Most of these publications provided antibiotic susceptibility results. Ten of them used the PCR approach to identify AR genes. MRSA carriage was reported in pilgrims and food handlers at a rate of 20%. Low rates of vancomycin-resistant gram-positive bacteria were reported in pilgrims and patients. The prevalence of third-generation cephalosporin-resistant bacteria was common in the Hajj region. Across all studies, carbapenem-resistant bacteria were detected in fewer than 10% of *E.coli* isolates tested but up to 100% in *K. pneumoniae* and *A. baumannii*. Colistin-resistant *Salmonella enterica*, including *mcr-1* colistin-resistant *E.coli* and *K.pneumoniae* were only detected in the pilgrim cohorts.

Conclusion: This study provides an overview of the prevalence of MDR bacteria at the Hajj. Pilgrims are at high risk of AR bacterial transmission and may carry and transfer these bacteria when returning to their home countries. Thus, pilgrims should be instructed by health care practitioners about hygiene practices aiming at reducing

traveler's diarrhea and limited use of antibiotics during travel in order to reduce the risk of MDR bacterial transmission.

Keywords

Hajj; multidrug resistant bacteria; pilgrims; bacterial carriage; bacterial transmission; systematic review; Saudi Arabia

1. Introduction

Hajj (pilgrimage to Mecca) is the largest annual mass gathering of Muslims with more than two million participants every year from more than 184 countries gathering in Saudi Arabia. During their journey, pilgrims visit the Holy Mosque in Mecca, stay in a tented camp in Mina and usually travel to Medina [1]. This mass gathering has a high potential for an outbreak due to the transmission of infectious diseases among pilgrims via person-to-person contact, contaminated foods or water, and the environment [1]. During the Hajj season, pilgrims are required to follow time-sensitive religious rituals at specific times at different places simultaneously for a week. This intensely crowded situation has the potential for outbreaks of meningococcal disease [2], for the transmission of tuberculosis [3] other bacterial and viral respiratory tract infections [4] and for diarrheal diseases [5]. Additionally, many pilgrims travel to the Hajj in a group, sharing transport and accommodation including airlines and buses, food, tents, and toilets for a week, which constitutes an additional risk for transmission of communicable diseases. Nowadays, the global spread of antibiotic-resistant (AR) bacteria, such as extended spectrum beta-lactamase Enterobacteriaceae (ESBL-E), through international travelers is common [4,5]. The acquisition of carbapenem-resistant bacteria has also been described in travelers, including NDM-1 in travelers returning to the UK from India or KPC-producing bacteria in travelers returning to France from the United States [6]. AR bacteria are

prevalent in Saudi Arabia [7–11]. Hajj pilgrims therefore have the potential to disseminate or acquire AR bacteria during their stay in Saudi Arabia and to spread these bacteria when returning to their home country. Here, we review the available literature on the prevalence of major gram-positive and gram-negative AR bacteria isolated in pilgrims or other populations living in the area where pilgrims stay, including Mecca, Mina, and Medina.

2. Methods

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (http://www.prismastatement.org). The electronic literature search was conducted in three electronic databases, Pubmed, Scopus, and Google Scholar, for articles about the emergence of antibiotic resistant bacteria during the Hajj. Searches were specified only in Hajj areas including Mecca, Mina, and Medina. Papers published from January 2002 to January 2017 and written in English were included. MeSH terms included “Gram positive bacteria”, “Streptococcus”, “Staphylococcus”, “Enterococcus”, “Gram negative bacteria”, “Acinetobacter”, “Enterobacteriaceae”, “Campylobacter”, “Escherichia”, “Klebsiella”, “Neisseria”, “Pseudomonas”, “Salmonella”, “Shigella”, “Yersinia”, “methicillin”, “MRSA”, “vancomycin”, “VRSA”, “VRE”, “carbapenem”, “Extended spectrum”, “ESBL”, “colistin”, “drug resistant”, “ colonization”, “susceptibility”, “Hajj”, “pilgrims”, “Makkah”, “Mecca”, “Mina”, “Madinah”, and “Medina” (see Appendix). The search results were imported into the Mendeley references manager and de-duplicated. The articles were independently screened based on titles and abstracts by two researchers (Leangapichart and Gautret) and any discord was discussed between the two researchers. In addition, the Saudi epidemiology bulletin

(http://fetp.edu.sa/Bulletin.html) was hand searched for additional papers for inclusion. Studies were eligible for inclusion if they reported on phenotypic and/or genetic antibiotic resistance patterns and provided prevalence data. We excluded case reports. Reference lists of selected papers were screened to retrieve additional relevant studies. The following data were extracted from each study: year of study, geographical area, study setting, demographics, bacterial species investigated, and antibiotic resistance patterns. Prevalence of bacteria resistant to a given antibiotic was calculated from the number of AR bacteria divided by the total number of isolates tested.

3. Results

3.1 Study selection

A total of 275 papers resulted from the initial search. After de-duplication, 185 studies were screened based on abstract content and 148 were excluded. Subsequently, 37 full-text articles were assessed for eligibility and 31 were included in the qualitative synthesis of the systematic review with the first publication in July 2002 (Figure 1). Most of the publications provided antibiotic susceptibility results. Eleven of them used the PCR approach to identify AR genes. The main findings are presented in Tables 1 and 2.

3.2 Studies conducted in pilgrims and Hajj workers (Table 1).

A total of 14 publications were retrieved [12–25]. Studies were conducted during the Hajj season from 2000 through 2015. Most studies were conducted in Mecca and Medina, and one study was conducted in the Mina area. Study designs included cross-sectional surveys enrolling ill pilgrims attending health care structures in Saudi Arabia and food handlers and kitchen workers from Mecca. Other studies were prospective-cohort studies and were conducted in group of pilgrims before and after

participating in the Hajj or the Umrah. The number of individuals in each study varied from 80 to 374. Participants originated from different continents and countries (the Gulf region, Europe, Asia, Africa, America), with the majority from Saudi Arabia and France. Participants were selected through travel agencies, food facilities in Mecca and various Saudi health care structures. Studies conducted involving ill pilgrims included patients suffering from skin infections [12], respiratory tract infections [23] and urinary tract infections [25]. In two studies, the syndromic classification of infectious diseases was not documented [14,24]. Most samples were collected using nasal swabs (for respiratory pathogens), and rectal swabs (for intestinal pathogens). Clinical infections in ill pilgrims were documented in five studies while nine studies reported on asymptomatic bacterial carriage in pilgrims and Hajj workers (5 respiratory carriage studies and 4 digestive carriage studies). Only one study analyzed risk factors for CTX-M acquisition by PCR detection in French pilgrims, during 2013-2014 Hajj. Shortness of breath, diarrhea, and β-lactam use were significantly associated with high CTX-M acquisition. By contrast, the use of macrolide was associated with low CTX-M acquisition.

3.2.1 Studies investigating MRSA colonization and resistant *Streptococcus pneumoniae*

Several studies addressed oxacillin or methicillin-resistant *Staphylococcus aureus* (MRSA) carriage, starting from the 2000 Hajj.

Ill pilgrims consulting hospitals during the Hajj

The proportion of MRSA in positive isolates reported in patients varied according to the type of infection, reaching 2% in pilgrims suffering from pyoderma in 2000 [12], 7% in patients suffering from various types of infection in 2004, 28% in pilgrims

suffering from sinusitis in 2014 and 63% in pilgrims with community acquired infections in 2015 [14,23,24].

Cohorts of pilgrims and food handlers

The acquisition of MRSA by pilgrims was also investigated through longitudinal surveys in 2009. The prevalence of MRSA among positive isolates was 15-20% in Hajj pilgrims and 10-11% in Umrah pilgrims with no significant difference before and after participating in the events [15]. Additionally, food handlers working in restaurants in Mecca were screened for MRSA carriage during the Hajj 2001-2002 and 2014 resulting, respectively, in 0 and 20% MRSA identification in positive isolates [13,22]. One study addressed the carriage of resistant *S. pneumoniae* in a multinational cohort of pilgrims and showed that 23% of isolates were resistant to multiple antibiotics (resistant to three or more classes of antibiotics) [17].

3.2.2 Studies investigating ESBL colonization

Cohorts of pilgrims

Five studies were prospectively conducted in cohorts of French pilgrims before, during and after the Hajj with the aim of evaluating the carriage of resistant pathogens[16,18–21]. During the 2013 and 2014 Hajj seasons, studies were conducted using rectal and/or and nasal samples obtained before and after the Hajj. The prevalence of the $bla_{\text{CTX-M}}$ gene in rectal samples was 10% before-Hajj compared to 33% after-Hajj in 2013 [18] and 7% before-Hajj compared to 34.83% after-Hajj in 2014 [19]. There was also a significant increase in the number of pilgrims harboring *E. coli* which was resistant to ceftriaxone and ticarcillin-clavulanic acid [18].

3.2.3 Studies investigating carbapenem-resistant bacteria colonization

Cohorts of pilgrims

Screening of carbapenemase genes by qPCR in rectal samples of pilgrims before and after Hajj showed the acquisition of *A. baumannii* with $bla_{\text{OXA-72}}$ and *E. coli* with $bla_{\text{NDM-5}}$ in a French cohort traveling to the 2014 Hajj [21].

Ill pilgrims consulting hospitals during the Hajj

During the 2014-2015 Hajj, the $bla_{\text{CTX-M}}$ gene in *E. coli* isolates was reported among 47% of pilgrims attending hospitals for urinary tract infections [25]. The 3GC-resistant *A. baumannii* were observed at 91% during the 2014 Hajj [21] and 77% in ill pilgrims during the 2015 Hajj [24]. Overall, imipenem-resistant bacteria were reported during the 2014-2015 Hajj at a rate ranging from 1 to 90% in *A. baumannii*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa* [21,23,24].

3.2.4 Studies investigating colistin resistant bacteria colonization

Cohorts of pilgrims

Salmonella enterica which were resistant to ceftriaxone, gentamycin and colistin were isolated from two pilgrims [16]. Screening for the *mcr-1* plasmid-mediated colistin resistance gene directly from rectal swabs was conducted in 2013 and 2014, and showed a prevalence of 1-2% before-Hajj and 9% after-Hajj. Rectal swabs from positive individuals allowed culturing *mcr-1* producing *E. coli* and *K. pneumoniae* [20].

3.3 Studies conducted in patients attending hospitals in Mecca and Medina (Table 2).

A total of 17 studies presented the prevalence of AR bacteria in local patients as shown in Table 2 [26–42]. Studies were conducted from 2003 through 2015. Fifteen studies were conducted in Mecca, while two studies were conducted in the Medina area. All studies were cross-sectional surveys conducted on patients attending general hospitals in Saudi Arabia and one was conducted on clinical isolates obtained

from clinical laboratories. The numbers of patients in each study varied from 43 to 1,626 [26–42]. The patients' origin was not documented in 12 studies. In studies with available data, the origin of patients was primarily Saudi Arabia. Studies were conducted on patients suffering from various diseases due to bacterial infection including skin infections [34], blood infections [28,36], digestive tract infections [27], and diarrhea [42]. The type of infection was not documented in most studies [26,29–33,35,37,40,41]. Several types of samples were collected depending on the type of bacterial infection using wound swabs, ear swabs, eye swabs, blood, sputum, urine, and stool samples. Two studies did not document the type of samples used [35,39]. Six studies reported the prevalence of MRSA in septicemic patients, diabetic patients and patients with undocumented types of infections which ranged from 38.9-57.7% in 2003-2015 [26,28,30,34,35]. Identification of the Panton-Valentine leucocidin (PVL) toxin by PCR was done in two studies, and PVL rose to 19% in 2012 [35] but was 0% in 2016 [40]. However, a later study reported the *fnBPA*-encoding gene in MRSA isolated from wound swabs at a rate of 8% and no vancomycin-resistant genes were detected in this study [40].

One study conducted on patients belonging to 22 nationalities suffering from gram-positive bacterial infections reported a low rate of vancomycin-resistant *S. aureus* (VRSA) at 2%, vancomycin-resistant *Enterococcus faecalis* at 3.5% and vancomycin-resistant *Enterococci* (VRE) at 2%, but a high rate of ampicillin-resistant *S. pneumoniae*, at 21.1% [30]. Oxacillin-resistant coagulase-negative staphylococci (CoNS) were observed at a rate of 61% during 2004-2005, 82.4% during 2008-2009, and 93.6% during 2012-2013, mainly in patients with sepsis [28,30,36].

Some studies reported 3GC-resistant *E.coli*, *K. pneumoniae*, and *A. baumannii* in patients with different bacterial infections during 2005-2015, ranging from 18.8% to

94% [29,33,34,41]. ESBL genes, *bla*$_{\text{CTX-M}}$, *bla*$_{\text{TEM}}$, and *bla*$_{\text{SHV,}}$ were reported in two studies conducted in ICU patients. The proportion of *bla*$_{\text{CTX-M}}$ and *bla*$_{\text{TEM}}$ in *E.coli* and *K. pneumoniae* cases were similar at 18.5-30% but in *A. baumannii* was 71-81%, while the rate of *bla*$_{\text{SHV}}$ was 7.4% in *E. coli*, 17.2% in *K. pneumoniae*, and 0% in *A. baumannii* [31,38]. Overall, low rates of imipenem-resistant bacteria, *E. coli* and *K. pneumoniae* were reported to vary at around 4-11.9% during 2004-2015 [28,29,41]. A high prevalence of imipenem-resistant *A. baumannii* and *P. aeruginosa* were detected at varying rates of 4-60.5% and 4-43%, respectively. The prevalence of *bla*$_{\text{OXA-23}}$ was identified in 91% in *A. baumannii* isolates, causing infection in ICU patients during 2012-2013 [31]. The occurrence of metallo-β-lactamase genes among carbapenem-resistant *A. baumannii* isolates during 2004-2014 was 11.5-27.1% carrying *bla*$_{\text{VIM}}$ and 13.6% carrying *bla*$_{\text{IMP.}}$ For carbapenem-resistant *P. aeruginosa* isolated from patients, 4.1-18.4% carried *bla*$_{\text{VIM}}$ and 4.7-21.0% carried *bla*$_{\text{IMP}}$ [31,32,37]. One study conducted on patients with peptic ulcer disease during 2003-2004 reported 31% of *Helicobacter pylori* isolates as being resistant to metronidazole and 3% resistant to tetracycline and erythromycin [27]. In addition, shiga toxin-producing *E.coli* was investigated in patients suffering from diarrhea in the Medina area. The report indicated significant associations between human and sheep isolates, with 70% of human isolates being resistant to trimethoprim/sulfamethoxazole [42].

3.4 Assessment of antibiotic resistance patterns among bacterial isolates

When data were pooled from the 30 published reports, AR patterns of 28 studies were compared between pilgrims and healthy participants during Hajj seasons and local patients attending hospitals in Mecca, Mina, and Medina. Two studies reported AR genes only using the PCR method. The reported rates of AR bacteria vary between

studies and hospitals. The comparisons of AR patterns were arranged by group of species and year of study (Figure 2-4).

3.4.1 Antibiotic resistance in Gram-positive bacteria

The prevalence and AR pattern of gram-positive bacteria isolated from pilgrims and Hajj workers, including local patients, drawn from 13 studies are presented in Figure 2. The prevalence of resistance in patients with *S. aureus* isolated from Hajj seasons was <30% for oxacillin but up to 100% in general patients. VRSA was identified in six studies, of which one reported a 2% resistance rate in local patients. CoNS and *Enterococcus sp.* were not studied in pilgrims or Hajj workers but in patients from Hajj areas. Compared to CoNS *Enterococcus sp.*, and *Streptococcus sp*., vancomycin was the most active agent with a resistance rate of 0-4%. The resistance rate of CoNS increased from 26% to 82% for gentamicin during 2004-2012; >70% for erythromycin; and >50% to 63% for clindamycin. The resistance rate of *Streptococcus spp.* isolates to amoxicillin/clavulanic acid in pilgrims and patients was 1-7% and was 7-26% for penicillin.

3.4.2 Antibiotic resistance in Enterobacteriaceae

Twelve studies performed antibiotic susceptibility testing on *E.coli*, *Klebsiella sp*., *Enterobacter sp*., *Salmonella sp.*, and *Proteus sp.* (Figure 3).

Overall, resistance rates of *E.coli* in pilgrims and local patients were similar, varying from 5-100% for cephalosporins; <10% for imipenem, meropenem, and ertapenem; and 13-75% for gentamicin. Colistin-resistant *E.coli* was observed in one pilgrim study. Meanwhile, the occurrence of resistant *Klebsiella sp.* isolates among pilgrims and patients was high, at 16-64% for cephalosporins and 4-82% for imipenem. In addition, the resistance rate of *Enterobacter sp.* to ciprofloxacin and gentamicin was low at an early stage, but increased substantially during 2004-2015. Susceptibility

testing of *Salmonella* isolates was conducted in three studies. Most isolates were susceptible to many antibiotic groups, including amikacin, imipenem, and ciprofloxacin.

3.4.3 Antibiotic resistance in non-Enterobacteriaceae

The antibiotic resistance of *A. baumannii* isolated from pilgrims and local patients showed uniform resistance to cephalosporins with a resistance rate of 45-100%. Resistance patterns of *A. baumannii* to imipenem in patients or ill pilgrims ranged between 14-100% but were 2% in healthy pilgrims. However, the resistance rate of *P. aeruginosa* to imipenem decreased in local patients from 43% to 22%, from 42% to 20% for amikacin, and from 61% to 27% for gentamicin during 2004-2015 (Figure 4).

Discussion

The prevalence of AR bacteria has increased significantly worldwide over the past two decades. International travelers have been known for years to experience alterations in gut microbiota due to the change of nutritional factors [43,44] and the acquisition of AR bacteria through the use of antibiotics during travel [4]. By attending the Hajj, millions of pilgrims present a source of infectious disease transmission [1,45,46]. Pilgrims attending Hajj are an important reservoir for the spread and transmission of AR bacteria. Many factors, such as crowded conditions, airborne/droplet transmission, and lack of efficient personal hygiene, diarrhea, and use of antimicrobial medications could be associated with the spread of AR bacteria. Our review indicates the prevalence and increasing rate of AR bacteria in the Hajj area include MRSA, 3GC-Enterobacteriaceae, imipenem-resistant bacteria, and colistin-resistant bacteria. Resistance rates varied between studies, although comparison was difficult due to differences in the antibiotics tested.

Community-acquired MRSA has been associated with closed settings involving lots of people and travelers [47]. In Saudi Arabia, the rates of MRSA varied between different regions ranging widely from 0.06% to 94%, in studies conducted during 2002-2012 [48,49]. The personal hygiene of food-handlers and the sanitation of restaurants in Mecca were investigated in 2007, demonstrating that 67% of food-handlers do not wear gloves and 45% have dirty fingernails [50]. It is not surprising that MRSA isolated from the food-handlers increased from 0 during 2001-2002 to 20% during the 2014 Hajj [13,22] and to 63.2% in pilgrims during the 2015 Hajj. Cross contamination of bacteria from workers may occur between people through skin, hands and food. In addition, the presence of *S. aureus* in a water tank supplying the drinking water to private households' in Mecca has also been reported. The poor condition of these water stations can result in poor water quality [51].

Additionally, common diseases such as airborne transmission or respiratory tract infections are well-documented in pilgrims through the acquisition of respiratory viruses and bacteria [52], including *S. pneumoniae, K. pneumoniae* [53], and *A. baumannii* [21]. The possible effect of desert dust and other particles in the spread of airborne bacteria has been documented (24), which might be related to very common symptoms among pilgrims including the "Hajj cough" [54]. Several pilgrims have an increased rate of *S. pneumoniae* acquisition at the Hajj, rising from 1.2 times to 3.9 times during 2011-2013 [17,52,55,56].

Diarrhea is one of the most common problems among travelers, and is associated with the acquisition of ESBL bacteria. Twenty-one percent of travelers with ESBL acquisition had diarrhea [57]. ESBL-producing Enterobacteriaceae were detected in a single cohort study of pilgrims traveling to the 2013 Hajj, demonstrating the possibility that several bacterial species may carry CTX-M type ESBL genes [16,18].

A similar study was conducted on *E.coli* isolated from urinary tract infections in pilgrims attending hospital in Mecca during the 2014–2015 Hajj [25]. These two studies had the same circulating sequence type of *E.coli*, ST131 and ST648. The plasmid-mediated colistin resistance gene, *mcr-1* was screened in pilgrims during 2013-2014 and revealed the constant acquisition rate of *mcr-1* at 9% at return [20]. This may suggest an identical source of bacterial transmission among pilgrims during the Hajj season. The spread of clones and specific types of AR genes might be related to travel destination and food vehicles contaminated by MDR bacteria [58]. Thus, the detection of AR genes in Mecca residents or environments related to pilgrims may be a useful way of investigating the source of AR bacterial transmission. One limitation of this study is the lack of data about diarrhea prevalence and use of antibiotics in most included studies, which does not allow evaluating their possible impact on the prevalence of AR bacterial related infection or carriage.

Recently, our group reported CTX-M genes acquisition during the 2013 and 2014 Hajj showing rates of acquisition at 31.0% and 34.8%, respectively [19]. Diarrhea and use of β-lactam antibiotics during the Hajj were demonstrated to be independent risk factors of CTX-M gene acquisition. Moreover, shortness of breath in pilgrims was associated with CTX-M-gene acquisition and macrolide use was shown to be an independent protective factor against CTX-M-gene acquisition [19]. Most of pilgrims traveling to Hajj carry antibiotics from their home country or obtained from over the counter in Saudi Arabia [59,60]. Pilgrims overuse or misuse of antibiotics ranged from 34.9% to 94.7% at the Hajj, which likely contributes to increased resistance [54,59–64].

One study reported the negative association between macrolides and CTX-M acquisition. Thus, restricted use of antibiotics during the Hajj should be highly recommended.

In such a context, vaccination represents a key component in the fight against antibiotic resistance. Vaccination against bacterial pathogens or against viral agents including notably *S. pneumoniae* and influenza virus directly and indirectly reduces the need for antibiotics for both the control of primarily bacterial infections and super-infection of viral diseases [65]. In addition, it has been well demonstrated that the conjugate vaccine against *S. pneumoniae* targets the most virulent serotypes associated with invasive pneumococcal diseases (IPD) that are also associated with antibiotic resistance [66–68]. These arguments reinforce the need for compliance with current recommendations for vaccinating at-risk Hajj pilgrims against IPD and influenza [69].

The date of the Hajj changes from year to year and will fall in the summer season for the next 10 years [70], which may provide a favorable environment for AR bacteria and the spread of infectious diseases. In this review, we presented the prevalence of AR bacterial acquisition in pilgrims, including the prevalence of AR bacteria in food workers and patients living in the Hajj area, which saw an increase over the 2000-2015-period. In Hajj season, the number of food poisoning cases ranged from 44 to 132 for the last 12 years [71]. Pilgrims may acquire AR bacteria from contaminated food during preparation or storage, unpasteurized dairy products, raw unpeeled fruit and vegetables, or contaminated water. Thus, the personal hygiene of kitchen staff including sanitary of food preparation area and storage should be improved and monitored to reduce the rate of the transmission of foodborne infections. Moreover, pilgrims coming from different countries with different cultures and life style are

exposed to crowded food outlets, toilets, and other accommodation and transportation facilities with different personal hygiene standards. Implementation of effective personal hygiene practices such as wearing a face mask, hand hygiene, can be effective approaches for reducing respiratory and digestive illness. Additionally, pilgrims should be instructed by travel medicine practitioners for guiding hygienic precautions, avoidance of diarrhea and unnecessary use of antibiotics before travels. Moreover, our review showed a high rate of resistance among gram-positive and negative bacteria including MRSA and 3GC-Enterobacteriaceae in local habitants; whereas, VRSA, VRE, carbapenem and colistin-resistant bacteria prevalence is still low. However, carbapenem resistance emergence in *A. baumannii* and *P. aeruginosa* is of concern in Mecca and Medina area. In Saudi Arabia, antibiotics are easily obtained from over the counter without legislation or restrictions on their use [72], which may lead to increase AR bacteria prevalence. High rates of AR bacterial infection in patients hospitalized in Saudi Arabia is worrying and physicians attending patients in this area should be aware of the situation and undertake adapted isolation measures. Therefore, controlling inappropriate use of antibiotics is the key for reducing antibiotic resistance. Moreover, public educational campaigns to discourage the use of antibiotics should be promoted. This may include country or global-wide surveillance to monitor antibiotic consumption and resistance trends among local population and international travelers including Hajj pilgrims.

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Conflict of interest

None to declare.

Appendix A. Supplementary data

Table legends

Table 1. Prevalence of antibiotic resistance bacteria in 13 studies conducted in pilgrims and Hajj workers

Table 2. Prevalence of antibiotic resistance bacteria in 17 studies conducted in patients hospitalized in Mecca and the Medina area.

Figure legends

Figure 1 Study selection. Flow diagram of identification and selection process included in systematic review.

Figure 2 Antibiotic susceptibility patterns of gram-positive bacteria from in-Hajj and out-Hajj periods. Blue highlights indicate the study was conducted during Hajj seasons. Prevalence of bacteria resistant to a given antibiotic were calculated from the number of AR bacteria divided by the total number of isolates tested, red, ≥ 67%; orange, < 67% and ≥ 33%; green, <33% are highlighted. Different numbers of isolates tested for resistance are marked with asterisk.

Figure 3 Antibiotic susceptibility patterns of Enterobacteriaceae from in-Hajj and out-Hajj periods. Blue highlights indicate the study was conducted during Hajj seasons. Prevalence of bacteria resistant to a given antibiotic were calculated from the number of AR bacteria divided by the total number of isolates tested, red, ≥ 67%; orange, < 67% and ≥ 33%; green, <33% are highlighted. Different numbers of isolates tested for resistance are marked with asterisk.

Figure 4 Antibiotic susceptibility patterns of *Acinetobacter sp.* and *Pseudomonas aeruginosa* from in-Hajj and out-Hajj periods. Blue highlights indicate the study was conducted during Hajj seasons. Prevalence of bacteria resistant to a given antibiotic were calculated from the number of AR bacteria divided by the total number of isolates tested, red, ≥ 67%; orange, < 67% and ≥ 33%; green, <33% are highlighted. Different numbers of isolates tested for resistance are marked with asterisk.

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678 **Appendix A. Supplementary data**

679 **Search strategy for the systematic review of the emergence of drug resistant**

680 **bacteria at the Hajj**

681 **Pubmed** ((Gram positive[tiab] OR streptococc*[tiab] OR staphylo*[tiab] OR

682 enterococc*[tiab] OR Gram negative[tiab] OR Acinetobact*[tiab] OR

683 Enterobacteri*[tiab] OR Entero bacteria*[tiab] OR Enteric bacteria*[tiab] OR

684 Enterobacter*[tiab] OR Escherichia*[tiab] OR e coli[tiab] OR Klebsiella*[tiab] OR

685 Campylobacter*[tiab] OR Salmonell*[tiab] OR Shigell*[tiab] OR Yersinia*[tiab] OR

686 Neisseria*[tiab] OR Pseudomonas*[tiab] OR methicillin*[tiab] OR MRSA*[tiab] OR

687 vancomycin*[tiab] OR VRSA*[tiab] OR VRE*[tiab] OR carbapenem*[tiab] OR

688 ESBL*[tiab] OR Extended spectrum*[tiab] OR colistin*[tiab])) AND ((resistan*[tiab]

689 OR coloni*[tiab] OR ((antibiotic*[tiab] OR antimicrob*[tiab]) AND sensitivit*[tiab])

690 OR susceptib*[tiab])) AND (hadj*[tiab] OR hajj*[tiab] OR pilgrim*[tiab] OR

691 Makkah[tiab] OR Mecca[tiab] OR Mina[tiab] OR Medina[tiab] OR Madinah[tiab])

692

693 **Scopus** TITLE-ABS-KEY ((("Gram positive") OR Streptococcus* OR

694 Staphylococcus* OR Enterococ* OR (("Gram negative" OR Acinetobacter* OR

695 enterobacteri* OR (enter* W/1 bacteria*)) OR enterobacter* OR Escherichia*

696 OR "e coli" OR Klebsiella* OR Campylobacter* OR Salmonell* OR Shigell*

697 OR Yersinia* OR Neisseria* OR Pseudomonas* OR methicillin* OR MRSA* OR

698 vancomycin* OR VRSA* OR VRE* OR carbapenem* OR Extended-spectrum* OR

699 ESBL* OR colistin*)) AND (resistan* OR coloni* OR ((antibiotic* OR antimicrob*)

700 W/3 sensitivit*) OR susceptib*) AND (hadj* OR hajj* OR pilgrim* OR Makkah

701 OR Mecca OR Mina OR Medina OR Madinah))

702

703 **Google Scholar** "Gram positive"|Streptococcus|Staphylococcus|Enterococcus|"Gram
704 negative"|Acinetobacter|Enterobacteriaceae|Escherichia|Klebsiella|Campylobacter|Sal
705 monella|Shigella|Yersinia|Neisseria|Pseudomonas|methicillin|MRSA|vancomycin|VR
706 SA|VRE|carbapenem|"Extended spectrum"|ESBL|colistin|antibiotic
707 resistance|resistant|colonization|colonisation|susceptibility|Hadj|Hajj|pilgrim|Makkah|
708 Mecca|Mina|Medina|Madinah
709

710 **Table 1.** Prevalence of antibiotic resistance bacteria in 13 studies conducted in pilgrims and Hajj workers
711

Period/Year	Geographical area	Study design	Samples	Country of origin	Microbiological techniques	Number of individuals with positive culture/number of individual tested (%)	Bacteria or gene investigated	Number of individuals with resistant bacteria/ No. of individuals with positive culture (%)	Number of individuals with resistant bacteria/ number of individual tested (%)	References
Hajj 2000 and 2001	Mecca	Cross-sectional survey conducted in 80 ill pilgrims attending the dermatology clinic for pyoderma at King Faisal Hospital	Skin lesion swabs	Saudi Arabia (46.3%), Asia (26.3%), Arabian Peninsula (non-Saudi Arabia) (26.2%), and Europe (1.2%)	Culture and AST	47/80 (58.8)	Methicillin resistant *Staphylococcus aureus* (MRSA)	1/47 (2.1)	1/80 (1.3)	Fatani et al., 2002 [12]
Hajj 2001 and 2002	Mecca	Cross-sectional survey conducted on 428 food handlers	Nasal swabs, throat swabs, nail swabs, stool samples, and wound swabs when available	No data	Culture and AST	45/428 (10.5)	Enterotoxins producer MRSA	0/45 (0)	0/428 (0)	Dablool and Al-Ghamdi, 2011 [13]
Hajj 2004	Mina	Cross-sectional survey conducted on 411 ill pilgrims attending the National Guard Health Affairs facility for medical reason	Nasal, axilla, groin and open wound swabs when available	Saudi Arabia (59.3%), Egypt (17.3%), Pakistan (6.2%), Yemen (3.7%), Sudan (8.7%), India (2.5%), Chad (2.5%), Others (6.2%)	Culture, AST, PCR	85/411 (20.7)	MRSA	6/85 (7.1)	6/411(1.5)	Memish et al., 2006 [14]
Umrah 2009	Mecca	Longitudinal survey conducted on 979 pilgrims before and after the Umrah	Nasal swabs	Turkey (13.2%), Indonesia (13%), Pakistan (10.4%), Syria (10%), Nigeria (10%), Egypt (8%), Iran (7.9%), UK (5.7%), Iraq (5.7%), Malaysia (4%), Libya (2.8%), Sweden (1.4%), US (0.4%), Jordan (0.1%)	Culture and AST	155/979 (15.8) before and 235/979 (24.0) after	MRSA	16/155 (10.3) before and 25/235 (10.6) after	16/979 (1.6) before and 25/979 (2.6)	Johargy et al., 2011 [15]
Hajj 2009	Mecca	Longitudinal survey conducted on 613 pilgrims before and after the Hajj	Nasal swabs	India (26.3%), Nigeria (16.6%), Indonesia (15.5%), Libya (14.7%), Syria (11%), UK (7.5%), Turkey (5.7%), Australia (1.8%), Sweden	Culture and AST	153/613 (25.0) before and128/613 (20.9) after	MRSA	30/153 (19.6) before and 19/128 (14.8) after	30/613 (4.9) before and 19/613 (3.1) after	Johargy et al., 2011 [15]

				(0.5%) and Iran (0.3%)						
Hajj 2013	Mecca, Mina and Medina	Longitudinal survey conducted on 129 pilgrims before and after the Hajj	Rectal samples	France	Culture, AST, PCR screening	0/129 (0.0) before and 5/129 (3.9) after	ESBL and colistin-resistant *Salmonella enterica*	2/5 (40.0) after	2/129 (1.6) after	Olaitan et al., 2015 [16]
Hajj 2013	Mecca and Mina	Longitudinal survey conducted on 1,175 pilgrims before and 1,155 pilgrims after the Hajj	Nasal swabs	12 countries in Africa, Asia, USA, and Europe	Culture and AST, MLST	110/1175 (9.4)	Multidrug-resistant *S. pneumoniae*	25/110 (22.7)	25/1175 (2.1)	Memish et al., 2016 [17]
Hajj 2013	Mecca, Mina and Medina	Longitudinal survey conducted on 129 pilgrims, before and after the Hajj	Rectal samples	France	Culture*, AST, MLST, PCR screening in samples	18/129 (14.0) before and 36/129 (27.9) after	CRO-resistant *E.coli* Ticarcillin-clavulanic-resistant *E. coli* PCR screening of AR gene -CTX-M	5/18 (27.8) before and 18/36 (50.0) after 5/18 (27.8) before and 13/36 (36.1) after 13/129 (10.1) before and 42/129 (32.1) after	5/129 (3.9) before and 18/129 (14.0) after 5/129 (3.9) before and 13/129 (10.1) after 13/129 (10.1) before and 42/129 (32.1) after	Leangapichart et al., 2016 [18]
Hajj 2014	Mecca, Mina and Medina	Longitudinal survey conducted on 129 pilgrims (2013); 98 pilgrims (2014) before, during and after the Hajj	Rectal samples	France	PCR screening in samples	7/89 (7.87) before and 31/89 (34.83) after	PCR screening of AR gene -CTX-M	7/89 (7.87) before and 31/89 (34.83) after	7/89 (7.87) before and 31/89 (34.83) after	Leangapichart et al., 2016 [19]
Hajj 2013 and Hajj 2014	Mecca, Mina and Medina	Longitudinal survey conducted on 129 pilgrims (2013); 98 pilgrims (2014) before, during and after the Hajj	Rectal samples	France	PCR screening of AR gene in samples, culture, AST, and MLST	-	PCR screening of AR gene *-mcr-1* colistin resistance gene	2013: 2/129 (1.6) before and 11/129 (8.53) after, 2014: 1/92 1.0) before and 9/90 (9.2) after	2013: 2/129 (1.6) before and 11/129 (8.53) after, 2014: 1/92 1.0) before and 9/90 (9.2) after	Leangapichart et al., 2016 [20]
Hajj 2014	Mecca, Mina and Medina	Longitudinal survey conducted on 98 pilgrims (98 pilgrims before; 90 pilgrims after the Hajj)	Pharyngeal and rectal swabs collected before and after Hajj	France	Culture, PCR screening in samples, AST, and MLST	*A.baumannii**0/98 before (0) and 43/90 (47.8) after	CRO-resistant *A.baumannii* PCR screening of AR gene -OXA-72 *A.baumannii* -NDM-5 *E.coli*	39/43 (90.6) 1/90 (1.1) 1/90 (1.1)	39/90 (43.3) 1/90 (1.1) 1/90 (1.1)	Leangapichart et al., 2016 [21]
Hajj 2014	Mecca	Cross-sectional survey conducted on 200 male workers from 50 kitchens	Nasal and hand skin swabs	No data	Culture and PCR	165/200 (40.3)	MRSA	33/165 (20.0)	33/200 (16.5)	Ahmed and Mashat, 2014 [22]
Hajj 2014	Mecca	Cross-sectional survey conducted on 226 pilgrims	Sinus secretion swabs under	GULF (58%), Asian (12.4%), South Asia (11.9%), North Africa	Culture and AST	46/226 (20.4)	MRSA IMP-resistant *K.pneumoniae*	13/46 (28.3) 3/14 (21.4)	13/226 (5.8) 3/226 (1.3)	Marglani et al., 2016 [23]

		with acute rhinosinusitis attending Alnoor Specialized Hospital	endoscopic guidance	(11.5%), Africa (3.5%), Europe (2.2%), and American (0.5%)						
January to June 2015	Mecca	Cross-sectional survey conducted on 374 ill pilgrims with community-acquired infections attending Al-Noor Specialist Hospital and Ajyad Emergency Hospital	Urine, blood, sputum	Saudi Arabia (47.3%), Pakistan (8%), Egypt (6.4%), Bangladesh (4%), Yemen (6.7%), Myanmar (5.3%), Nigeria (2.1%), Indonesia (3.5%), Indian (3.5%), and others (13.1%)	Culture and AST	57/374 (15.2)	MRSA ESBLs-*E. coli* Ceftazidime-resistant *A. baumannii* IMP-resistant *E.coli* IMP-resistant *K.pneumoniae* IMP-resistant *A.baumannii* IMP-resistant *P.aeruginosa*	36/57 (63.2) 4/107 (3.7) 16/21 (76.2) 3/107 (2.8) 5/6 (83.3%) 9/10 (90.0) 5/45 (1.1)	36/374 (9.6) 4/374 (1.1) 16/374 (4.3) 3/374 (0.8) 5/374 (1.3) 9/374 (2.4) 5/374 (1.3)	Haseeb et al., 2016 [24]
Hajj 2014 and 2015	Mecca	Cross-sectional survey conducted on 58 *E.coli* isolates from pilgrims suffering urinary tract infection attending two different general hospitals, which tried to be consistent and to present all studies in a similar way	Urine	No data	Culture, AST, PCR, and MLST	58	*E.coli* carrying AR genes -CTX-M -TEM -SHV -OXA-1 -aac6	 27/58 (46.5) 22/58 (37.9) 2/58 (3.2) 28/58 (48.3) 26/58 (44.8)	 27/58 (46.5) 22/58 (37.9) 2/58 (3.4) 28/58 (48.3) 26/58 (44.8)	Alyamani et al., 2017 [25]

- Cefotaxime and Cepacia selective medium
- AST; Antibiotic susceptibility test

717 **Table 2.** Prevalence of antibiotic resistance bacteria in 17 studies conducted in patients hospitalized in Mecca and the Medina area.

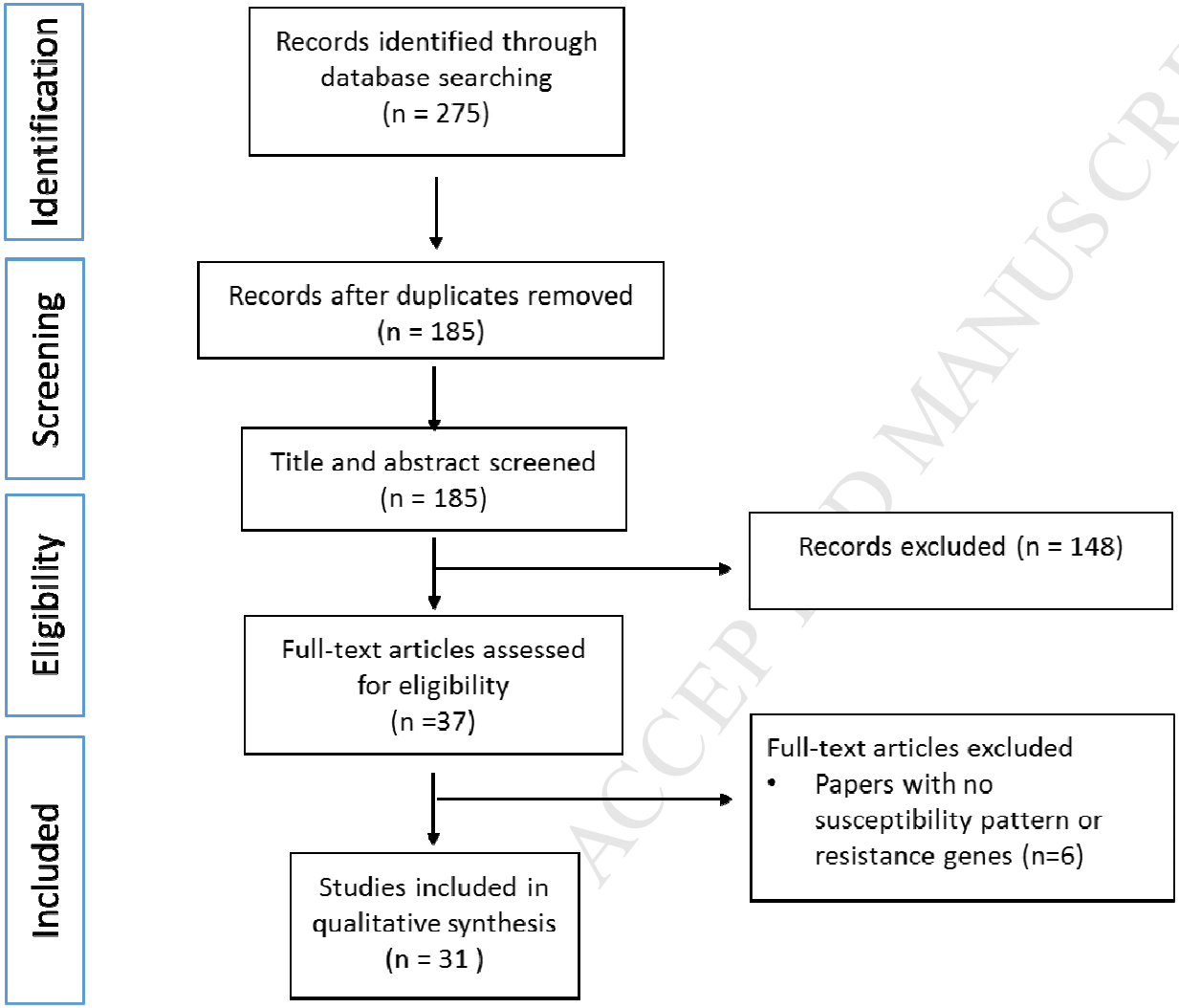
Period/Year	Geographical area	Study design	Samples	Country of origin	Microbiological techniques	Number of individuals with positive culture (or number of positive isolates)/number of individual tested (or total number of isolates) (%)	Bacteria or gene investigated	Number of individuals with resistant bacteria (or number of positive isolates / No. of individuals with positive culture (or total number of isolates) (%)	Number of individuals with resistant bacteria/ number of individual tested (%)	References
April 2003 to March 2004	Mecca	Cross-sectional survey conducted on 512 *S. aureus* clinical isolates from hospitalized patients attending Al-Noor, King Abdul-Aziz, Hera and King Faisal hospitals	Wound swabs, ear swabs, eye swabs, blood, urine, respiratory tract	No data	Culture and AST	512/512 (100.0)	MRSA	199/512 (38.9)	199/512 (38.9)	Asghar and Momenah, 2006 [26]
January 2003 to February 2004	Mecca	Cross-sectional survey conducted on 132 patients with peptic ulcer disease attending Hera General Hospital	Multiple biopsies from gastric antrum and fundus, duodenum	Saudi Arabia (97.7%) others (2.3%)	Culture and AST	132/132 (100.0)	Metronidazole-resistant *Helicobacter pylori* Tetracycline and erythromycin resistant *H. pylori*	41/132 (31.0) 4/132 (3.0)	41/132 (31.0) 4/132 (3.0)	Karima 2006 [27]
April 2004 to March 2005	Mecca	Cross-sectional survey conducted on 1,626 patients with sepsis attending Al-Noor, King Abdul-Aziz, Hera, and King Faisal hospitals	Blood	Saudi Arabia (62.2%) others (37.8%)	Culture and AST	1530/1626 (94.1)	Oxacillin-resistant CoNS MRSA IMP-resistant *E.coli* IMP-resistant *Klebsiella* sp. IMP-resistant *Acinetobacter* sp. IMP-resistant *Pseudomonas* sp.	245/402 (61.0) 161/303 (53.0) 7/148 (5.0) 4/109 (4.0) 18/127 (4.0) 61/142 (43.0)	245/1626 (15.1) 161/1626 (9.9) 7/1626 (0.4) 4/1626 (0.2) 18/1626 (1.1) 61/1626 (3.8)	Asghar 2006 [28]
October 2005 to March 2006	Mecca	Cross-sectional survey conducted on 1,137 clinical isolates from 965 patients attending Al-Noor and Hera hospitals	Different sites of infection; urinary tract infection, respiratory tract infection, wound infection, septicemia, female genital infection, and other infections	No data	Culture and AST	1137/1137 (100.0)	CRO-resistant *E.coli* CRO-resistant *K.pneumoniae* IMP-resistant *E.coli* IMP-resistant *K.pneumoniae*	28/149 (18.8) 11/148 (22.9) 6/74 (8.1) 1/11 (9.1)	28/965 (2.9) 11/965 (1.1) 6/965 (0.6) 1/965 (0.1)	Asghar and Faidah, 2009 [29]
May 2008 to April 2009	Mecca	Cross-sectional survey conducted on 1,087 patients with gram-positive bacterial infection attending Al-Noor, Hera, and King Abdul-Aziz Hospitals	Different sites of infection; urinary tract infection, respiratory tract infection, wound infection, septicemia/blood culture, female genital infection, and ear/eye	22 different countries: Saudi Arabia (81%), Pakistan (4.4%), Yemen (2.0%), Nigeria (1.9%), Egypt (1.7%), others (9%)	Culture and AST	1087/1087 (100.0)	Oxacillin-resistant CoNS MRSA VRSA Ampicillin-resistant *S. pneumoniae* *E. faecalis* VRE *Enterococcus spp.* VRE	85/97 (82.4) 271/688 (39.4) 9/441 (2.0) 4/19 (21.1) 1/149 (2.0) 3/86 (3.5)	85/1087 (7.8) 271/1087 (24.9) 9/1087 (0.8) 4/1087 (0.4) 1/1087 (0.09) 3/1087 (0.3)	Asghar 2011 [30]

			infections							
September 2009 to March 2010	Mecca	Cross-sectional survey conducted on 509 clinical isolates from 313 ICU patients attending Al-Noor, Hera, and King Abdul-Aziz Hospitals	Urine, wound swabs, and other sample types	Saudi Arabia (50.9%), Pakistan (8.8%), India (5.9%), Egypt (5.7%) and Yemen (5.1%)	Culture, AST, PCR	509/509 (100.0)	*E.coli* carrying AR genes -CTX-M -TEM -SHV *K.pneumoniae* carrying AR genes -CTX-M -TEM -SHV *P.aeruginosa* carrying AR genes -VIM -IMP -VIM&IMP *A.baumannii* carrying AR genes -VIM -IMP -VIM&IMP	 10/54 (18.5) 10/54 (18.5) 4/54 (7.4) 35/116 (30.1) 22/116 (19.0) 20/116 (17.2) 6/148 (4.1) 7/148 (4.7) 2/148 (1.4) 22/191 (11.5) 26/191 (13.6) 6/191 (3.1)	 10/313 (3.2) 10/313 (3.2) 4/313 (1.3) 35/313 (11.1) 22/313 (7.0) 20/313 (6.4) 6/313 (1.9) 7/313 (2.2) 2/313 (0.6) 22/313 (7.0) 26/313 (8.3) 6/313 (1.9)	Asghar 2012 [31]
September 2009 to March 2010	Mecca	Cross-sectional survey conducted on 478 clinical isolates from 365 ICU patients attending Al-Noor, Hera, and King Abdul-Aziz hospitals	Sputum, wound swabs, and urine	Saudi Arabia (64%), Pakistan (7.1%), Egypt (5.0%), Yemen (3.3%), India (3.1%), and Nigeria (1.9%)	Culture, AST, PCR	478/478 (100.0)	MBL-producing *P. aeruginosa* carrying AR genes -IMP -VIM -IMP&VIM	33/76 (43.4) 16/76 (21.0) 14/76 (18.4) 3/76 (3.9)	33/365 (9.0) 16/365 (4.4) 14/365 (3.8) 3/365 (0.8)	Asghar 2012 [32]
February-April 2011	Mecca	Cross-sectional survey conducted on 43 hospitalized patients attending Al-Noor, Hera, Maternity and Children, King Abdul Aziz, and King Faisal hospitals	Sputum, endotracheal tube secretion, tracheal aspiration, wound swabs, urine, and blood	No data	Culture and AST	43/43 (100.0)	IMP-resistant *A.baumannii* CTX-resistant *A. baumannii*	26/43 (60.5) 28/43 (65.1)	26/43 (60.5) 28/43 (65.1)	Khan et al., 2012 [33]
June 2011 to June 2012	Mecca	Cross-sectional survey conducted on 138 diabetic patients attending Umm Al-Qura University	Foot infection and urinary tract infection samples	No data	Culture and AST	129/138 (93.5)	CTX-resistant *E.coli* MRSA	15/27 (55.6) 15/26 (57.7)	15/138 (10.9) 15/138 (10.9)	Johargy 2016 [34]
March to September 2012	Mecca	Cross-sectional survey conducted on 206 *S. aureus* isolates collected from five major tertiary-care hospitals	No data	No data	Culture and PCR	206/206 (100.0)	MRSA carrying AR genes mecA PVL	 100/206 (48.5) 19/100 (19.0)	 100/206 (48.5) 19/206 (9.2)	Asghar 2014 [35]
January 2012 to October 2013	Mecca	Cross-sectional survey conducted on 190 Coagulase-negative Staphylococci (CoNS) isolates from neonatal septicemia patients	Blood	No data	Culture and AST	190/190 (100.0)	Oxacillin-resistant CoNS	178/190 (93.6)	178/190 (93.6)	Khan et al., 2014 [36]

		attending Maternity and Children Hospital								
2014 (4 month-period)	Medina	Cross-sectional survey conducted on 48 patients attending out-patients clinic at King Fahd Hospital	Wound swabs, sputum, urine, blood	No data	AST and PCR	48/48 (100.0)	*A.baumannii* carrying VIM-1	13/48 (27.1)	13/48 (27.1)	El-Ageery and Al-Hazmi, 2014 [37]
2012 to 2014	Mecca	Cross-sectional survey conducted on 107 clinical isolates from ICU patients attending local general hospitals	Blood, and skin wound infection	No data	Culture, AST, PCR, MLST	107/107 (100.0)	ESBLs-*A. baumannii* *A. baumannii* carrying AR genes -CTX-M -TEM -SHV -OXA-51 -OXA-23	100/107 (94.0) 87/107 (81.0) 73/107 (71.0) 0/107 (0.0) 100/107 (94.0) 97/107 (91.0)	100/107 (94.0) 87/107 (81.0) 73/107 (71.0) 0/107 (0.0) 100/107 (94.0) 97/107 (91.0)	Alyamani et al., 2015 [38]
August 2013 to January 2014	Mecca	Cross-sectional survey conducted on 64 *P. aeruginosa* clinical isolates from patients at Al-Noor and Maternity and Children hospitals	Respiratory surgical, genital samples, urine, blood, ear swabs, eye swabs, burn swabs	No data	Culture and AST	64/64 (100.0)	IMP-resistant *P.aeruginosa*	14/64 (21.9)	14/64 (21.9)	Khan and Faiz, 2016 [39]
No data	Mecca	Cross-sectional survey conducted on 50 *S. aureus* clinical isolates from clinical laboratories	Blood cultures, wound swabs, urine, nasal swabs, and sputum	No data	Culture, AST, PCR	50/50 (100.0)	MRSA carrying AR genes mecA fnBPA PVL van gene	 11/50 (22.0) 4/50 (8.0) 0/50 (0.0) 0/50 (0.0)	 11/50 (22.0) 4/50 (8.0) 0/50 (0.0) 0/50 (0.0)	Abulreesh et al., 2016 [40]
January to July 2015	Mecca	Cross-sectional survey conducted on 260 *K. pneumoniae* clinical isolates from patients at Al-Noor, King Faisal, King Abdul Aziz, Hera, and Maternity and Children hospitals	No data	No data	Culture and AST	260/260 (100.0)	CRO-resistant *K. pneumoniae* IMP-resistant *K. pneumoniae*	111/260 (42.7) 31/260 (11.9)	111/260 (42.7) 31/260 (11.9)	Khan and Faiz, 2016 [41]
June and August 2015	Medina	Cross-sectional survey conducted on 134 patients suffering from diarrhea attending Ouhud Hospital	Stool samples	No data	Culture and AST	30/134 (22.4)	Shiga toxin-producing *E.coli* resistant to Trimethoprim/Sulfamethoxazole	21/30 (70.0	21/134 (15.7)	Sharaf and Shabana, 2016 [42]

718
719
- AST; Antibiotic susceptibility test

720 **Figure 1 Study selection.** Flow diagram of identification and selection process included in systematic review.



721 **Figure 2** Antibiotic susceptibility patterns of gram-positive bacteria from in-Hajj and out-Hajj periods. Blue highlights indicate the study was
722 conducted during Hajj seasons. Prevalence of bacteria resistant to a given antibiotic were calculated from the number of AR bacteria divided by
723 the total number of isolates tested, red, ≥ 67%; orange, < 67% and ≥ 33%; green, <33% are highlighted. Different numbers of isolates tested for
724 resistance are marked with asterisk.

Study	Total number of isolates screened for resistance	Aminoglycosides				Tetracyclines	Glycylcyclines	Macrolides		Lincosamides	Streptogramins	Steroidal	Phenicols	Oxazolidinones	Pseudomonic acid	Penicillins							Penicillins/Beta-lactamase inhibitors		Cephalosporins										Monobactam	Carbapenems	Glycopeptides		Lipopeptides	Phosphonic	Polymyxins	Pyrimidines/Sulfonamides	Quinolones/ Fluoroquinolones						Rifamycin	Nitrofurans
		Amikacin	Gentamicin	Neomycin	Tobramycin	Tetracycline/ Oxytetracycline	Tigecycline	Erythromycin	Azithromycin	Clindamycin	Quinupristin/dalfopristin	Fusidic acid	Chloramphenicol	Linezolid	Mupirocin	Ampicillin	Ampicillin/sulbactam	Benzylpenicillin	Methicillin	Oxacillin	Penicillin/ Penicillin G	Piperacillin	Amoxicillin/clavulanic acid	Piperacillin/Tazobactam	Cefalotin	Cefazolin	Cefalexin	Cefoxitin	Cefuroxime	Cefotaxime	Ceftriaxone	Ceftazidime	Ceftizoxime	Cefepime	Aztreonam	Imipenem	Teicoplanin	Vancomycin	Daptomycin	Fosfomycin	Polymyxin B	Trimethoprim/ sulfamethoxazole	Nalidixic acid	Ciprofloxacin	Gatifloxacin	Levofloxacin	Moxifloxacin	Norfloxacin	Norfloxacin/Ciprofloxacin	Rifampicin	
Staphylococcus aureus																																																		
Fatani et al., 2002 [12]	47		6			13		4		4										2	81			2														4												
Dablool and Al-Ghamdi, 2011 [13]	45		0			4		2		0										0	100			4														7												
Asghar and Momenah, 2006 (MRSA) [26]	199		85			90		85								100				100	100			100													0				80								
Asghar and Momenah, 2006 (MSSA) [26]	313		10			19		14								83				0	96			5													0				9								
Memish et al., 2006 [14]	85																		7								7																						
Asghar, 2006 [28]	303		44					56		48						79				53	92		38		49			42									0				58								
Asghar, 2011 [30]	1-688*	60	36	0		50		42		34	8		32	5		92	63			39	93		42			64	31	30	24	25	51	22	60		33	23		2			38	26	100	46	6	36			27	17	21
Johargy et al., 2011 (Umrah) [15]	235		3		4	19	0	11		10		11		0	1			88	11								11									0	0		11		3			4	3			0	2
Johargy et al., 2011 (Makkah) [15]	128		9		10	49	0	25		22		20		0	0			79		15							15									0	0		22		12				20	10			0	
Johargy, 2016 [34]	26	54	54			54				58										58	100	77	50		54				62		100										58								
Abulreesh et al., 2016 [40]	50		6			16		10	12	10		18		0		100				22	100		16					22								18		0	0	0			0		0	0			0	
Marglani et al., 2016 (MRSA) [23]	13		46			39		77	92	31						100							100	100				100			100	100		100		100	0			54		62		69				
Marglani et al., 2016 (MSSA) [23]	33		3			18		18	21	9						39							21	0				0			0	3		0		15	0			0		12		12				
Haseeb et al., 2016 (MRSA) [24]	5-24*		42													78					91		75		87	84		30	80	60	67	50		60	72	50					63		0	42				
Haseeb et al., 2016 (MSSA) [24]	7-17*															91				24	89		29		0	0		0	0	0					0	43					40		0	40	0				
Coagulase-negative staphylococci																																																	
Asghar, 2006 [28]	402		26					72		50						72				61	91		34		49			26									0				75								
Asghar, 2011 [30]	1-86*	91	63	100		36		83		63	0		50			87	95			82	90		60			92	56	67	71	71	89	80	50		100	50		3			0	47	50	80	11	60			64	27	0
Khan et al., 2014 [36]	190		82					78	78	60	2			0		99				94	100		93					0									0	2											
Enterococcus spp.																																																	
Asghar, 2006 [28]	78		95					83		98						23				96	84		11		98			95									0				98								
Asghar, 2011 [30]	1-99*	2	48	0		78		44		60	50		0	14		15	0			9	12		79			0	64	50	50	67	60	33	33		50	20		4			0	93	50	38	100	33			71	33	4
Asghar, 2011 (*E.faecalis*) [30]	1-56*	0	83	0		94		65		83	75		0	0		27	50			0	33		25			0	0	67	0	100	50	0	0		0	100		2			0	86	67	56	0	61			50	50	0
Streptococcus spp.																																																	
Fatani et al., 2002 (*Streptococcus pyrogenes*) [12]	24																			0	0																													
Asghar, 2006 (*Streptococcus spp*) [28]	70		89					26		24						13				27	26		1		23			33									0				79								
Asghar, 2006 (*Streptococcus pneumoniae*) [28]	44		89					16		9						7				16	7		5		14			18									0				68								
Asghar, 2011 (*Streptococcus pneumoniae*) [30]	1-19*	100	70	0		33		17		39	100		0	0		21	100			67	20		7			100	25	8	13	17	8	13	100		0	0		20			0	70	0	100	50	67			0	100	100
Asghar, 2011 (*Streptococcus pyrogenes*) [30]	1-12*		56			60				17																	13			33	14	50									78								
Memish et al., 2016 [17]	110					56		25		13			6								8		0					0									0				48				1	1				
Haseeb et al., 2016 (*Streptococcus spp*) [24]	3-15*	0																			20		0		36			75			0				0											100			

Figure 3 Antibiotic susceptibility patterns of Enterobacteriaceae from in-Hajj and out-Hajj periods. Blue highlights indicate the study was conducted during Hajj seasons. Prevalence of bacteria resistant to a given antibiotic were calculated from the number of AR bacteria divided by the total number of isolates tested, red, ≥ 67%; orange, < 67% and ≥ 33%; green, <33% are highlighted. Different numbers of isolates tested for resistance are marked with asterisk.

Study	Total number of isolates screened for resistance	Aminoglycosides					Tetracyclines	Macrolides	Phenicols	Penicillins				Penicillin/ Beta-lactamase inhibitors			Cephalosporins									Monobactam	Carbapenems			Phosphonic	Polymyxins	Quinolones/ Fluoroquinolones							Pyrimidines/ Sulfonamides		Nitrofurans
		Amikacin	Gentamicin	Kanamycin	Streptomycin	Tobramycin	Tetracycline	Erythromycin	Chloramphenicol	Amoxicillin	Ampicillin	Mezlocillin	Piperacillin	Amoxicillin/clavulanic acid	Piperacillin/Tazobactam	Ticarcillin/clavulanic acid	Cephalothin	Cefazolin	Cefoxitin	Cefuroxime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime	Aztreonam	Imipenem	Meropenem	Ertapenem	Fosfomycin	Colistin	Nalidixic acid	Ciprofloxacin	Norfloxacin	Norfloxacin/Ciprofloxacin	Ofloxacin	Levofloxacin	Moxifloxacin	Trimethoprim/sulfamethoxazole	Sulfamethoxazole	Nitrofurantoin
Escherichia coli																																							
Asghar, 2006 [28]	148	17	43								89		55	70	9		76		38			43		20	45	5						35						65		
Asghar and Faidah, 2009 [29]	40-316*	11	26			22	56				84		59	52	9		58		12	36	15	25	19		30	8	1				49	46	32	39		53		59		12
Asghar, 2012 [31]	22-52*		47				70				83		91	67	47		91		28	56	54	53	46	55	52	6	4					58	44					72		32
Johargy, 2016 [34]	9-27*	0	30			50		100	11				78	59			67				56	50									100		67					56	6
Sharaf and Shabana, 2016 [42]	30		13	57	47		77		33		23																					17				70		
Marglani et al., 2016 [23]	8		0								75			0	0				0			0	0	0		0					0				0		13		
Leangapichart et al., 2016 (a) (ESBL) [18]	18		28												0	72							100			0				0									
Leangapichart et al., 2016 (b) (*mcr-1*) [20]	10		40							100				100									40	10	20				20	100	30	10					60		
Haseeb et al., 2016 [24]	3-100*	7	28			57					84	100		59			97	40	24	45	31	34		41	49	3					75	60	44			100	63			
Haseeb et al., 2016 (ESBL) [24]	4	75	75																0							0	0	0				75								
Alyamani et al., 2017 [25]	58										97								5		76	81		75	90	0	0					80								
K. pneumoniae																																							
Asghar, 2006 (*Klebsiella sp* .) [28]	109	42	54								96		68	62	8		76		32			61		18	60	4						26						67		
Asghar and Faidah, 2009 (*Klebsiella sp* .) [29]	2-65*	21	32			36	67				99		44	44	7		37		19	60	33	32	42		37	9					47	34	56	57		50		52		32
Asghar and Faidah, 2009 [29]	4-85*	10	25			20	86				95		54	29	10		38		16	38	23	32	23		34	9					42	32	39	33		50		37		27
Asghar, 2012 [31]	30-106*		51				61				100		84	71	47		78		44	62	63	64	56	60	73	13	17					53	43					64		75
Khan and Faiz., 2016 [41]	260																					29	43	31		12	12													
Leangapichart et al., 2016 (ESBL) [18]	5		40												0	60						100				0				0									
Leangapichart et al., 2016 (*mcr-1*) [20]	1									100				100																							100		
Marglani et al., 2016 [23]	14		0								100			40	40				0			0	0	0		20					0				0		0		
Haseeb et al., 2016 [24]	6-63*	5	38			46					94			52	17		67	43	20	35	23	24	0	27	23	82	10	13				41	0			44	55			
Enterobacter spp.																																							
Asghar, 2006 [28]	19	5	16								84		26	89	11		95		84			26		0	26	0						0						32		
Asghar and Faidah, 2009 [29]	1-19*	8	39			67					95		50	100	20		100		90	100		46	56		47						57	9	33	67				24		29
Haseeb et al., 2016 (*E.clocae*) [24]	4-9*		50			0					75			84	0		100		100	0	0		0				0	0			0	45	0						
Salmonella enterica																																							
Asghar, 2006 (*Salmonella spp* .) [28]	11	0	9								55		36	36	0		27		0			0		0	0	0						0						64		
Olaitan et al., 2015 [16]	5	0	40	0		0				60				40								40	40		40	0				40		0			0		0		
Haseeb et al., 2016 [24]	4													0						0	0	0		0		0	0	0				0				0	0		
Proteus spp.																																							
Asghar, 2006 [28]	12	25	17								83		42	58	0		75		67			8		0	17	8						25						33		
Asghar and Faidah, 2009 [29]	3-36*	27	43			86					53		19	32	33		33		16	29	33	7			12	6					80	17	4			50		67		
Haseeb et al., 2016 (*P. mirabilis*) [24]	6-16*	34	75								88			50			100		23			70		58								60								

728 **Figure 4** Antibiotic susceptibility patterns of *Acinetobacter sp.* and *Pseudomonas aeruginosa* from in-Hajj and out-Hajj periods. Blue highlights
729 indicate the study was conducted during Hajj seasons. Prevalence of bacteria resistant to a given antibiotic were calculated from the number of
730 AR bacteria divided by the total number of isolates tested, red, ≥ 67%; orange, < 67% and ≥ 33%; green, <33% are highlighted. Different
731 numbers of isolates tested for resistance are marked with asterisk.

Study	Total number of isolates screened for resistance	Aminoglycosides				Tetracyclines	Penicillins					Penicillins / Beta-lactamase inhibitors			Cephalosporins							Monobactams	Carbapenems			Polymyxins	Quinolones/ Fluoroquinolones							Pyrimidines/ Sulfonamides	Rifamycins	Nitrofurans
		Amikacin	Gentamicin	Neomycin	Tobramycin	Tetracycline	Amoxicillin	Ampicillin	Mezlocillin	Piperacillin	Ticarcillin	Amoxicillin/clavulanic acid	Piperacillin/Tazobactam	Ticarcillin/clavulanic acid	Cephalothin	Cefoxitin	Cefuroxime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime	Aztreonam	Imipenem	Meropenem	Ertapenem	Colistin	Nalidixic acid	Ciprofloxacin	Norfloxacin	Norfloxacin/Ciprofloxacin	Ofloxacin	Levofloxacin	Moxifloxacin	Trimethoprim/sulfamethoxazole	Rifampicin	Nitrofurantoin
Acinetobacter baumannii																																			
Asghar, 2006 (*Acinetobacter sp.*) [28]	127	75	72					97		73		87	8		98	92			79		45	90	14					77						76		
Asghar and Faidah, 2009 [29]	1-106*	84	76		57			97				93	43		100	98	100	83	87	97		95	46	28			33		71			64		75		83
Asghar, 2012 [31]	107-183*	93	81							99			95						97		93		87	93				96								
Khan et al., 2012 [33]	43	54	44			65		65		95	74							65	58		58	72	61					61						63		
El-Ageery and Al-Hazmi, 2014 [37]	48	90	81	100				100		71		94			100	100			100			96	100					100								
Leangapichart et al., 2016 [21]	43	0	2		2		37					74		40		100		49		91		93	2			0		5			7		5	0	
Haseeb et al., 2016 [24]	3-24*	67	46		50			100	100				0					100	77		77		90	64	0			83				67				
Pseudomonas aeruginosa																																			
Fatani et al., 2002 [12]	5	0	0		0					0									0				0					0								
Asghar, 2006 [28]	142	42	61					89		34		82	10		87	76			44		22	56	43					24						73		
Asghar and Faidah, 2009 [29]	16-339*	48	50		54	73		70		49		77	34		76	73			53	83		58	39	20			96	51	58	44		75		77		96
Asghar, 2012 [31]	62-139*	47	55							44			57						63		69		44	53				60								
Asghar, 2012 [32]	90-464*	32	42			32		97		47		94	41		97	94	94	78	51	70	52	50	29	36				43						92		
Khan and Faiz, 2016 [39]	64	20	27							28	30		8						20		11	23	22	42				22				27				
Haseeb et al., 2016 [24]	3-45*	12	21		0			75	100		59		33			0		95	36		34		11	17				49	0			0	100			