Antimicrobial-resistant genes among Klebsiella pneumoniae in the Arabian Gulf Countries: A systemic review and meta-analysis

Khalid Mubarak Bindayna (bindayna@agu.edu.bh)
Arabian Gulf University https://orcid.org/0000-0002-6222-4128
Ronni Mol Joji
Arabian Gulf University College of Medicine and Medical Science
Hicham Ezzat
Arabian Gulf University College of Medicine and Medical Science
Haitham Ali Jahrami
Salmaniya Medical Complex

Research

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Abstract

Klebsiella is the common pathogen which causes pneumonia, UTI, and bloodstream infections. The vast majority of *Klebsiella* infections are hospital-acquired. Since the recognition of this as bacteria, it has always been a challenge for the clinicians to find effective treatment against their infections. Several studies are addressing increased antimicrobial resistance rates and different antimicrobial genes in various areas of the Arabian Gulf.

Here we aimed to look upon the prevalence of six AMR genes (CTX M, TEM, SHV, NDM, OXA, VIM genes) in this province. We performed a systematic review and meta-analysis of the published studies from the Arabian Gulf countries and analysed the antimicrobial resistance genes pattern present in *Klebsiella pneumoniae.*

Materials and methods

The present study used the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) as a guideline for reporting findings. An electronic search was conducted in online databases such as PubMed/MEDLINE, EMBASE, Scopus, Cochrane, Google Scholar, Science Direct, and Web of Science from December 2017 to February 2019 following the inclusion and exclusion criteria.

Results

Of 160 initially searched studies, 28 entries met the inclusion criteria and were subjected to meta-analysis. Critical appraisal of studies or quality assessment revealed mean quality score was 4.2, with an SD of 1.6. The analysis revealed predominant antimicrobial resistance genes were OXA followed by CTX-M, SHV, TEM, NDM, and VIM in the Arabian Gulf region.

Conclusion

The antibiotic resistance gene prevalences in *Klebsiella pneumoniae* in countries of the Arabian Gulf have been reviewed in this study. These countries share a high prevalence of OXA, CTX-M followed by SHV, TEM, NDM, and VIM genes. Antimicrobial-resistant in *K. pneumoniae is* a threat to public health and this needs strong surveillance to curb this threat.

Introduction:

Klebsiella is one of the common pathogens causing community-acquired bacterial pneumonia, urinary tract infection and septicemia in patients. If untreated, it can lead to a high mortality rate(1, 2). A vast majority of *Klebsiella* infections are hospital-acquired. Individuals with underlying diseases such as diabetes mellitus or chronic pulmonary obstruction or other immunocompromised states can acquire *Klebsiella* as an opportunistic infection(1). In fact *Klebsiella* has been reported as the second most common cause of bacteraemia in patients with burns (3).

It is a challenge to treat *Klebsiella* clinically. Bacteria have developed effective defense mechanisms against most of the antibiotics (4). Multidrug resistance is reported in *Klebsiella* since 1984(3). *Klebsiella* has become resistant to beta-lactam drugs, including extended-spectrum cephalosporin's and aminoglycosides due to its

ability to encode extended-spectrum β-lactamases (ESBLs) and aminoglycoside modifying enzymes(3). An increase in antimicrobial resistance in *K. pneumoniae* isolates is of much concern.

The CDC estimates that in the United States, more than two million people are diseased with antibiotic-resistant microorganisms each year. Among them, around 23,000 die every year(5). Several factors can contribute to the spread of antimicrobial resistance, including inappropriate antibiotic use in the health care sectors and agriculture and lack of new antimicrobial therapeutics(5, 6). Continuous exposure of bacterial strains to multiple β-lactam drugs has induced dynamic and continuous production and mutation of β-lactamases. It has even increased its activity against the newly developed β-lactam antibiotics. These enzymes are known as extended-spectrum β-lactamases (ESBLs)(7). The occurrence of extended-spectrum beta-lactamase (ESBL) producing Enterobacteriaceae is also reported in human and veterinary medicine (8).

Several studies have addressed increased antimicrobial resistance rates among bacterial organisms in the Arabian Gulf Region. They have reported multiple factors that might be contributing to the increasing antimicrobial resistance rates(9). An interplay of antibiotics overuse/misuse in humans and animals, inappropriate infection control measures and continuous mobility of the people due to socio-economic conflicts and multiple war crises has to lead to a dissemination of antimicrobial resistance(10).

Some of the reports from Saudi Arabia have identified CTX-M and SHV genes to be associated with ESBL *K.pneumoniae* (11). Also, given the full diversity of ESBL *K. pneumoniae* isolates, the clonal spread may be playing an insignificant role in the dissemination of these strains(12). Among the carbapenemases, class A carbapenemase group includes SME, IMI, NMC, GES, and KPC families. The class D carbapenemases include OXA-type β-lactamases that are frequently detected in *Acinetobacter baumannii*(13). The Metallo-β-lactamases (IMP, VIM, SPM, GIM, and SIM families) are detected primarily in *Pseudomonas aeruginosa*. Research also shows an increasing rate of this group of β-lactamases in the *Enterobacteriaceae* worldwide (13). In Kuwait, VIM-4, NDM, and OXA-48 carbapenemases were detected in clinical isolates of *K. pneumoniae* strains(14–16). A study from Saudi Arabia reported OXA and NDM carbapenemases (17). Studies from the United Arab Emirates reported NDM, OXA-48, and, to a lesser degree KPC, as the predominant carbapenemases in clinical isolates of *K. pneumoniae*(10). A meta-analysis study in East Africa reported CTX-M, TEM, SHV, and OXA genes predominance among *Enterobacteriaceae* isolates (18).

The prevalence of antimicrobial resistance genes has severe implications for the future therapy and prevention of infectious diseases in humans. Studies have identified multiple genes to be associated with antimicrobial resistance in the Arabian Gulf region. However, there are no comprehensive reviews of these studies. This article aims to review the occurrence of six AMR genes (CTX M, TEM, SHV, NDM, OXA, VIM genes) in the gulf region. We conducted a systematic review and meta-analysis of the studies reporting the presence of antimicrobial resistance genes *in Klebsiella pneumoniae*, published from the Arabian Gulf region.

Materials And Methods:

The present study used the “Meta-analysis Of Observational Studies in Epidemiology (MOOSE)” guidelines for reporting findings (19).

Database Searches

We conducted an electronic search in the online databases PubMed/MEDLINE, EMBASE, Scopus, Cochrane, Google Scholar, Science Direct, and Web of Science for articles published between December 2017 and February 2019. The search strategy included relevant keywords: "*Klebsiella pneumoniae*" OR "*Enterobacteriaceae*" OR antimicrobial resistance" OR "antibiotic resistance" OR "drug-resistance" AND "Eastern Mediterranean" OR "The Middle East" OR "antimicrobial resistance" OR "antibiotic resistance" OR "drug-resistance" OR "Gulf Co-operation Council (GCC)" OR "Saudi Arabia (KSA)" OR "Bahrain" OR "Kuwait" OR "Oman" OR "United Arab Emirates (UAE)" OR "Qatar"OR "resistant genes" AND "Extended-Spectrum Beta-Lactamase (ESBL)" OR "Metallo beta-lactamase (MBL)" OR "CTX M" OR "NDM" OR "OXA" OR "TEM" OR "VIM" OR "SHV."

Two authors independently reviewed the titles and abstracts and chose those fitting the selection criteria for full-text evaluation and excluded irrelevant publications. Any discrepancies regarding study eligibility were discussed with other authors to reach a consensus. To standardize data extraction, the reviewers collected data for study characteristics (e.g., type of bacterial isolates, country, year, sample size, type of antibiotic-resistant genes). Extracted data were entered into Microsoft Excel Sheet for analysis.

Inclusion Criteria:

We included observational studies and intervention studies reporting the presence of any of the selected six AMR genes in clinical strains of *K.pneumoniae.*

- Inclusion criteria for study selection were:
- All original research articles published in the English language.
- Publication date between December 2017 to the end of February 2019.
- Studies that included *K.pneumoniae* clinical isolates.
- Studies that reported antimicrobial resistance genes (AMR) from Arabian Gulf countries.
- Articles reporting resistant genes detection by molecular methods (PCR).

Exclusion Criteria:

- Studies conducted on *K.pneumoniae* strains from environmental resources such as food, water, and air.
- Studies reporting secondary data.
- Studies on other AMR genes that are not included in the selection criteria.
- Studies reporting resistance genes by phenotypic methods.
- Case reports, short communications, abstracts, review articles, editorials, and non-English-language articles.
- Unpublished, non-peer-reviewed data, all of which were excluded from the quantitative and qualitative analysis.

If more than one article is published from a single study, the results are combined, and the studies are considered only once for analysis. The flow diagram of study selection is shown in Fig. 1.

Primary Outcome:

The primary outcome of this review is the prevalence of the selected six AMR genes in the Arabian Gulf region.

Critical Appraisal Of Studies (quality Assessment)

Two reviewers independently assessed the methodological quality of studies using a standardized checklist consisting of six items. The items included sample size, sampling technique, standardization of data collection, appropriateness of statistical analyses, quality of reporting results, and generalizability. The appraisal scores range between zero and six were given. A score of 0–2 corresponds to low quality, 3–4 to medium quality, and 5–6 to high quality. If there was a discrepancy, the quality score was assigned for each study by consensus of all authors after discussion.

Statistical Analysis And Reporting:

We performed a series of sub-group analysis based on sample size and event rate. We used Random-effects modeling in the analysis. By using random-effects modelling, we, therefore, assume that there is not only one true effect size, instead, a distribution of true effect sizes. We, therefore, sought to estimate the mean of the distribution of true effect sizes. Moderator analysis was performed on the variable country and was performed using subgroup analyses. All statistical analyses were performed using the Comprehensive Meta-Analysis version 3.0.

Results:

Of 160 initially searched studies, 28 entries met the inclusion criteria and were subjected to meta-analysis(12, 14, 16, 20–44); the stages of evaluation and exclusion of the identified studies were as per inclusion chart is presented in Fig. 1. Study characteristics (e.g., authors, country, year, sample size, type of antibiotic-resistant genes) are represented in Table 1.

Table 1
Study characteristics

Authors	Country	Sample size	OXA	CTX - M	SHV	TEM	NDM	VIM
Al-Qahtani et al (2014) (12)	Saudi Arabia	98		32	34	20		
Jamal et al (2013)(14)	Kuwait	9		4	7	5	3	6
Jamal et al (2016)(16)	Kuwait	14		9	6		14	
Al-zahrani et al (2018) (20)	Saudi Arabia	54	44				4	1
Altamimi et al (2017) (21)	Saudi Arabia	34	18				4	1
Shibl et al (2013)(22)	Saudi Arabia	60	47	37	39	17	12	1
Sonnevend et al (2015)(23)	Arabian Peninsula	145	43				78	6
Eltai et al (2018)(24)	Qatar	13		0	0	0		
Elhassan et al (2016) (25)	Saudi Arabia	359		6	9	8		
Alsultan et al (2013) (26)	Saudi Arabia	37		0	29	16		
Ahmed et al (2016) (27)	Qatar	629		42	49	30		
Alfaresi et al (2018) (28)	UAE	5		5	4	5		
Alzahrania et al (2016) (29)	Saudi Arabia	3		3		2		
Hassan et al (2013) (30)	Saudi Arabia	90		82	77	43		
Leangapichart et al (2016)(31)	Saudi Arabia	1				1		

Leangapichart et al (2016)(32)	Saudi Arabia	5		5	4	4	
Soliman et al (2018) (33)	Saudi Arabia	33		13	12	0	
Somily et al (2015)(34)	Saudi Arabia	27		23	16	1	
Sonnevend et al (2017)(35)	UAE	9		9	8	8	
Uz Zaman et al (2014) (36)	Saudi Arabia	23	23	23	23	22	
Alsheikh et al (2014) (37)	Saudi Arabia	92		9	0	44	
Al-agamy et al (2013) (38)	Saudi Arabia	9	7	8	9		2
Zowawi et al (2014) (39)	Saudi Arabia	147	34	48			10
Alotaibi et al (2017) (40)	Saudi Arabia	5	1				3
Al-agamy et al (2018) (41)	Saudi Arabia	21	14	19			7
Ahn et al (2015)(42)	UAE	2	2				0
Shahid M (2014)(43)	Bahrain	5		5			
Hassan H (2014)(44)	Saudi Arabia	107		9	3		

Critical appraisal of studies or quality assessment revealed mean quality score was 4.2, with an S.D. of 1.6; indicating that studies were generally of medium quality.

The most common resistance genes reported are OXA, followed by CTX M, SHV, TEM, NDM, and VIM. The prevalence of antimicrobial resistance gene is shown in Table 2.

Table 2
Prevalence of antimicrobial resistance genes

Parameters	OXA	CTX M	SHV	TEM	NDM	VIM
Number of studies (K)	10	22	19	16	11	5
Number of isolates (N)	500	1796	1637	1492	500	302
Proportion (95% CI)	61.3% (41%-78.4%)	49.9% (31.1%-68.8%)	46.1% (25.6%-68%)	32.5% (17.2%-52.8%)	26.9% (13.5% – 46.5%)	6.1% (1.1%-28.2%)
Q-value	102.938	416.089	418.179	265.348	93.550	28.150
Df (Q)	9	21	18	15	10	4
P value	0.000	0.000	0.000	0.000	0.000	0.000
I^2	91.257	94.953	95.696	94.347	89.311	85.790
Tau^2	1.330	2.869	3.475	2.318	1.627	3.475

Subgroup analysis by country of publication:

The Figs. 2 to 7 present the subgroup analysis conducted based on the country of published studies. In Saudi Arabia the prevalence of OXA gene is 65.1% (Fig. 2). CTX-M gene is 93.6% in UAE, 56.4% in Kuwait, 49.1% in Saudi Arabia and 6.6% in Qatar (Fig. 3).SHV gene analysis showed its prevalence in UAE (85.2%), Kuwait (59.1%), Saudi Arabia (46.8%) and Qatar (7.7%)(Fig. 4). The prevalence of TEM gene is 89.9% in UAE, 30.5% in Saudi Arabia and 4.7% in Qatar (Fig. 5).NDM gene prevalence is 75.8% in Kuwait and 17% in Saudi Arabia as shown in Fig. 6. VIM prevalence is 2.1% in Saudi Arabia which is shown in Fig. 7.

Discussion:

Klebsiella pneumoniae is a pathogen known for its resistance to most of the antibiotics used. The increasing trends in the isolation of antimicrobial-resistant *K. pneumoniae* are of much concern(6). *K. pneumoniae* have acquired carbapenemases, which are capable of breaking down most β-lactams, including carbapenems, and confer resistance to these drugs. Reports indicate that carbapenemase-producing *Enterobacteriaceae* isolates are increasing in number in the last few years (45).

In this study, the OXA (61.3%) is seen to be the most predominant antimicrobial gene in the Arabian Gulf Region. OXAKp isolates are detected worldwide. The first description of isolates with OXA 48 like genes was reported in 2013 in the United States(46). A study from China has reported 14.98% of the clinical isolates of K. pneumoniae with OXAKp(47). In a study from India, significantly, 80% of their isolates were $bla_{OXA-232}$ producers. (48) A study from Turkey reported 86% of their isolates harbored the OXA 48 gene (49).

CTX-M enzymes are class A extended-spectrum β-lactamases (ESBLs) that are spreading rapidly among *Enterobacteriaceae* worldwide(50). In our study analysis, the CTX-M gene(49.9%) was the next predominant gene persistent in clinical isolates. No CTX-M was detected in the U.S. before 2000 among ESBL-producing *K. pneumoniae* isolates, with all CTX-M–producing *K. pneumoniae* isolates recovered from U.S. patients in or after 2004(51). The emergence and spread of CTX-M in *K. pneumoniae* have evolved recently in the mid to late 2000s in the United States. To date, CTX-M–producing *K. pneumoniae* has been recognized in several U.S. states, including Texas, Nebraska, Pennsylvania, California, Massachusetts, Michigan, New Jersey, New York, Washington, and Wisconsin(52). Jemima and Verghese reported the presence of CTX-M genes in 40% of Klebsiella spp (53). Another study in India by Sekar et al. reported the prevalence of the CTX-M gene in 35.89% of Gram-negative isolates(54).

In the present analysis, the SHV gene was present in 46.1%, TEM in 32.5%, NDM in 26.9%, and VIM in 6.1% of the total studies. Globally, Greece has the highest rate of reported carbapenem resistance (68%) followed by India and eastern Mediterranean regions with 54% resistance. USA (11%), China (11%), and Africa (4%) have the lowest resistance rates, respectively(46). Dehshiri et al. demonstrated the presence of the genes TEM (16.1%), and SHV (85.5%) among the *K. pneumoniae* isolates from urine samples(55). While in India, amongst the ESBLs, SHV, TEM, and CTX-M have been commonly reported by Veeraraghavan et al(56). In China, Zhang et al. reported eight *K. pneumoniae* isolates producing NDM-1 in the neonatal ward of a teaching hospital (57). Liu et al. reported four diverse types (NDM-1, KPC-2, VIM-2, and IMP-4) of carbapenemase of K. pneumoniae clones in a single hospital in China (58).

The VIM gene is extensively distributed worldwide, with VIM-2 the most widespread variant. VIM enzymes endemicity has been reported in Greece, Taiwan, and Japan, and outbreaks and single strains of VIM producers have been stated in many other countries including México, Argentina, Colombia and Venezuela(59).VIM-1-producing *Enterobacteriaceae* have been associated with single cases, small outbreaks or polyclonal spread affecting different species of bacteria in Spain (60).

The increasing use of antibiotics through prescriptions or non-prescriptions or self medications is related to the spread of multidrug-resistant organisms (MDROs)(10). In the Arabian Gulf countries, studies have reported a high prevalence of self medications (S.M.), (32 to 42%) Lebanon, (32 to 62%) Jordan, (98%) Palestine, (85%) Syria. In the Arabian Gulf countries, the rates are as high as 89.2% in the United Arab Emirates(UAE), 48% in Saudi Arabia (KSA), and 60% in Yemen(61). Even, inappropriate use of antibiotics is also another added reason for the dissemination of MDROs in the Arabian Gulf countries. (10)

Conclusion:

The antibiotic resistance gene prevalences of *Klebsiella pneumoniae* in countries of the Arabian Gulf, namely, Saudi Arabia, Bahrain, Kuwait, United Arab Emirates, Oman, and Qatar, have been critically reviewed in this study. These countries share a high prevalence of OXA, CTX-M followed by SHV, TEM, NDM, and VIM genes. Antimicrobial-resistant in *K. pneumoniae* is a threat to public health, and this needs robust surveillance to curb this menace. Healthcare sectors need to monitor and report changes in antimicrobial-resistant isolates. A multifactorial approach, including standard guidelines, and appropriate infection control measures are necessary to curb this threat.

Declarations

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Figures

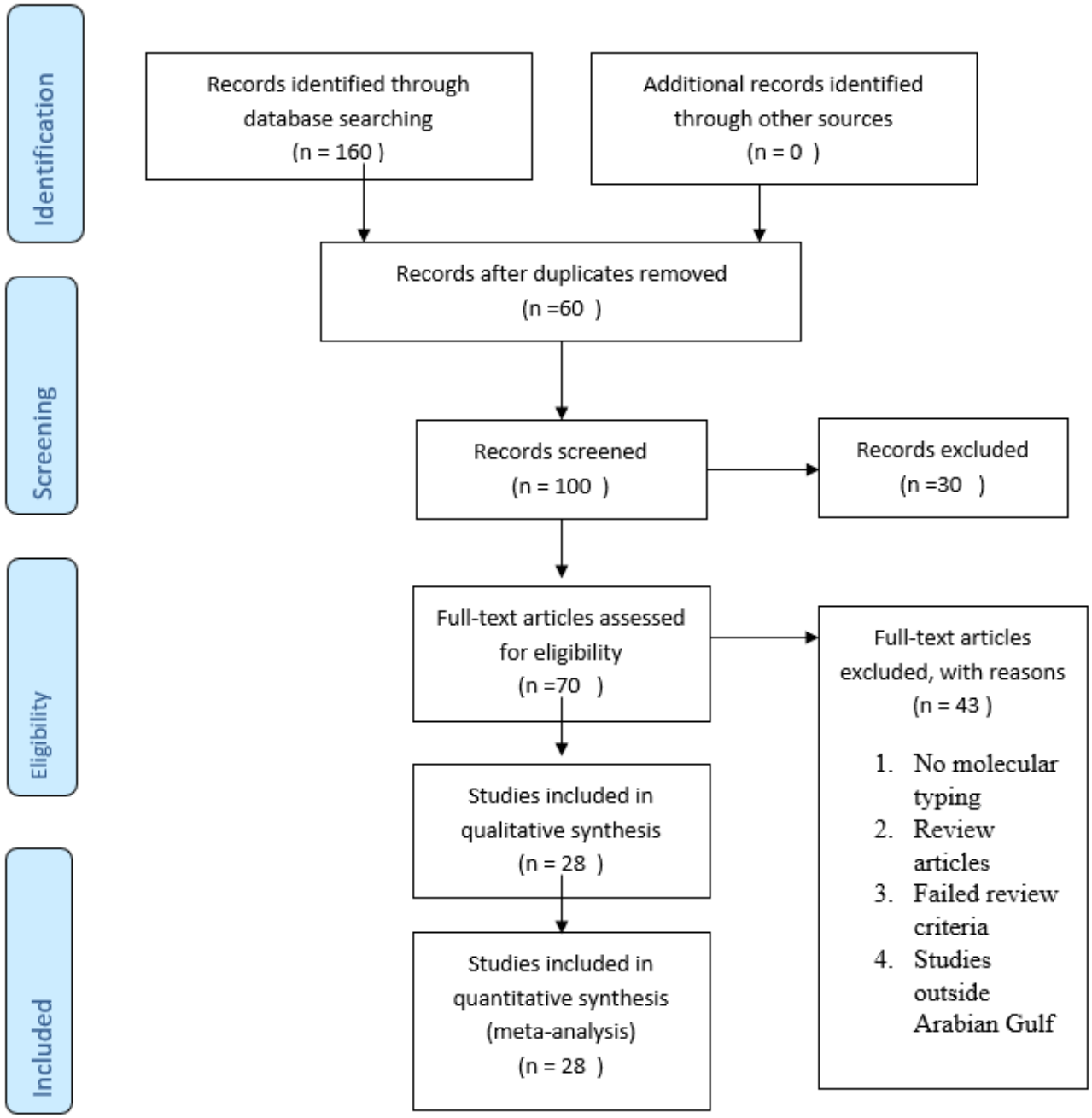

Figure 1

The stages of evaluation and exclusion of the included studie

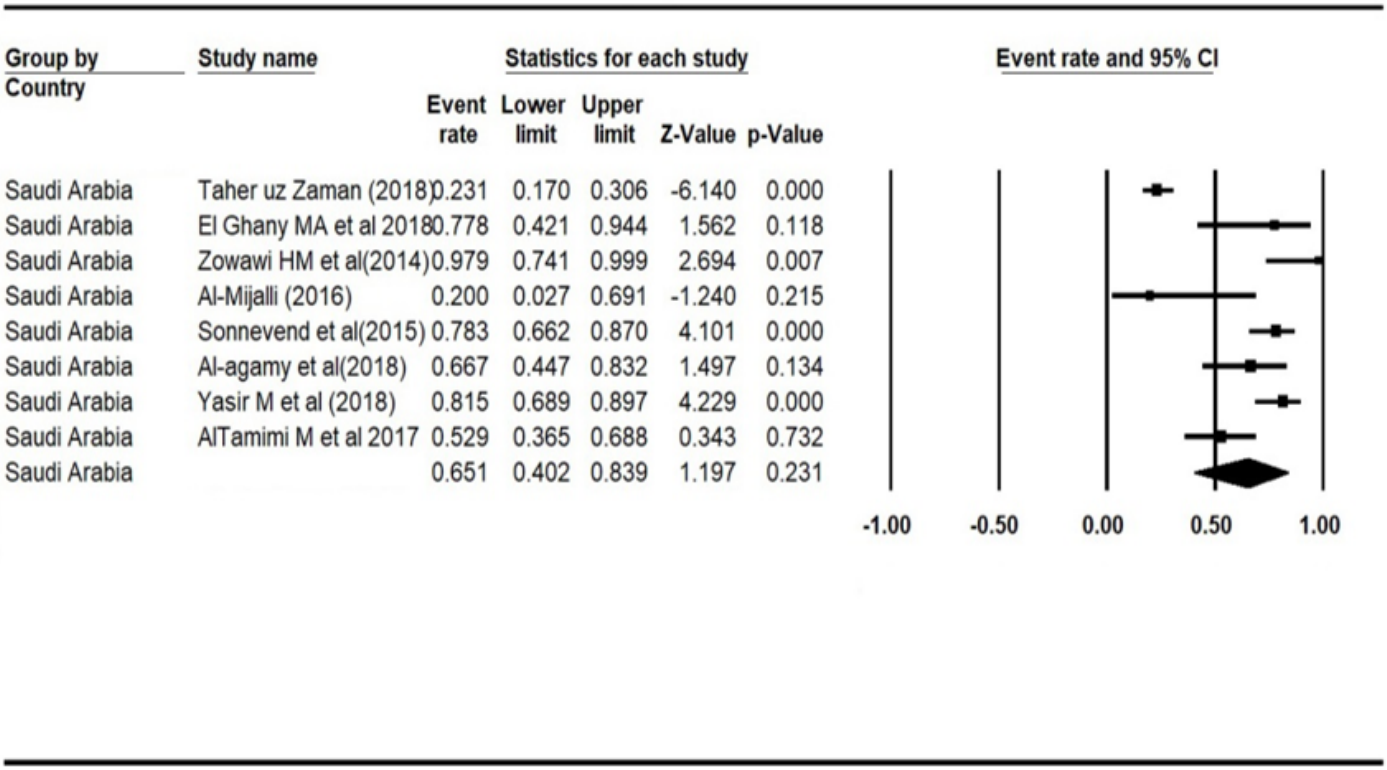

Figure 2

Klebsiella OXA gene

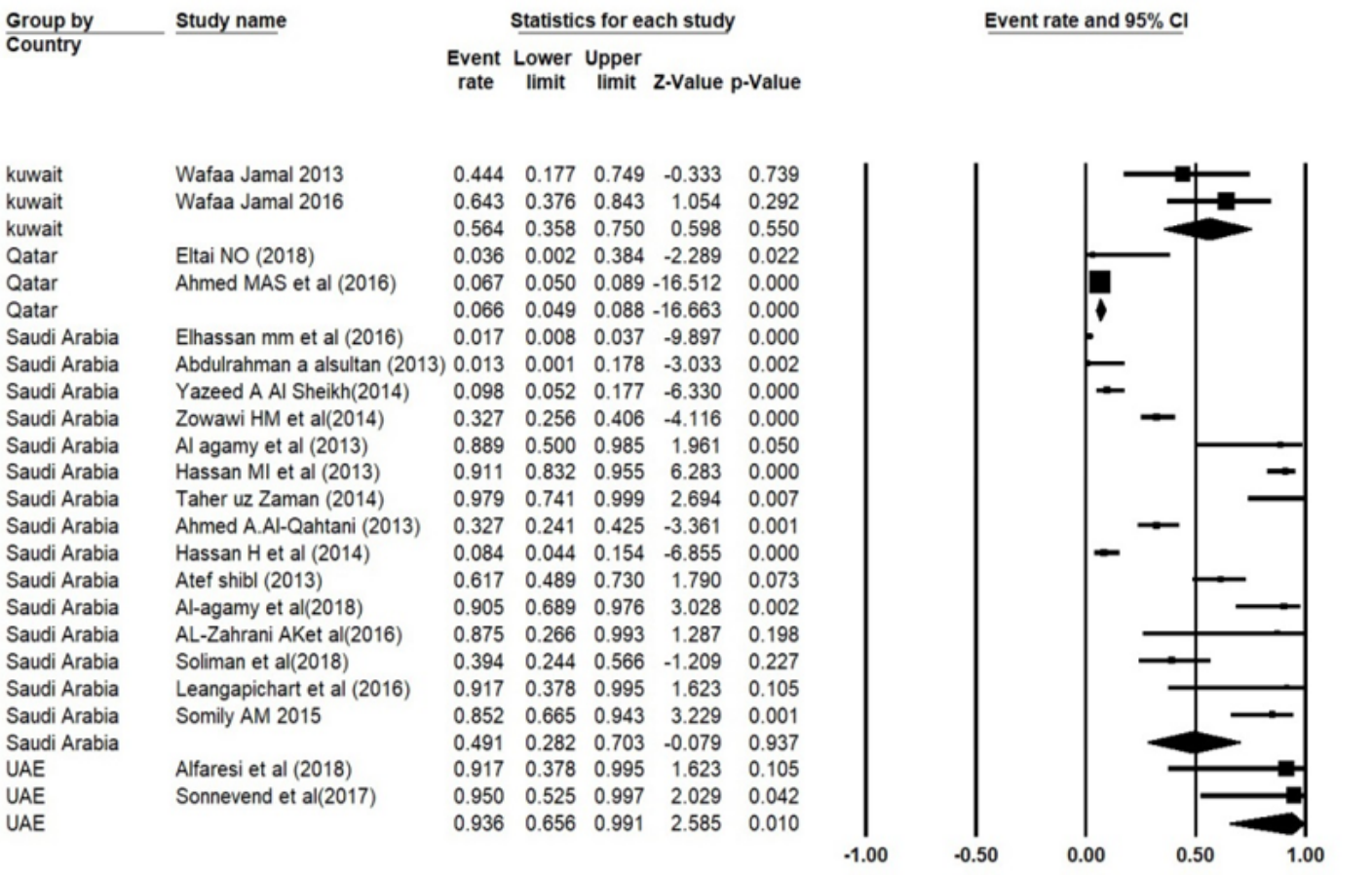

Figure 3

Klebsiella CTX-M gene

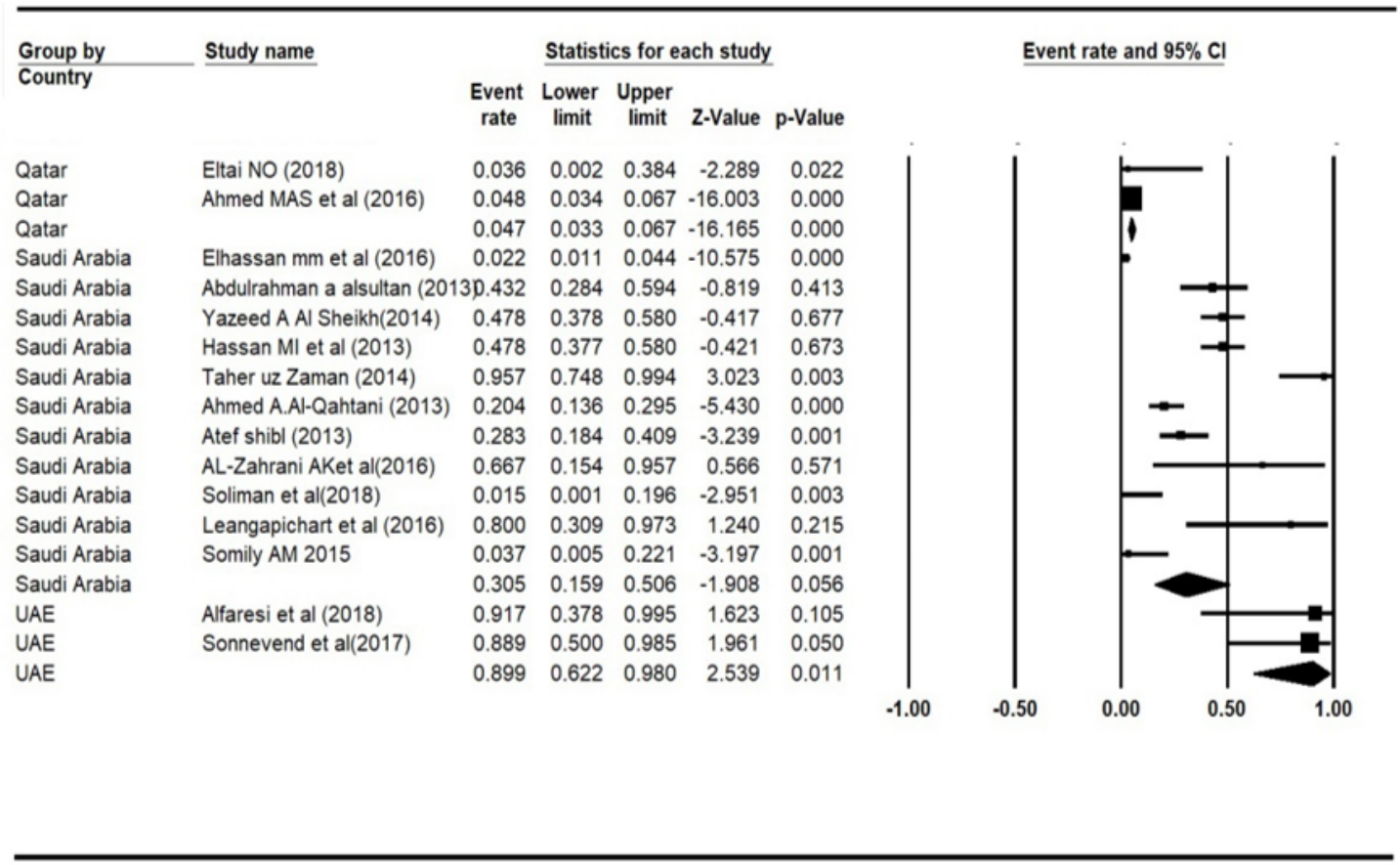

Figure 4

Klebsiella SHV gene

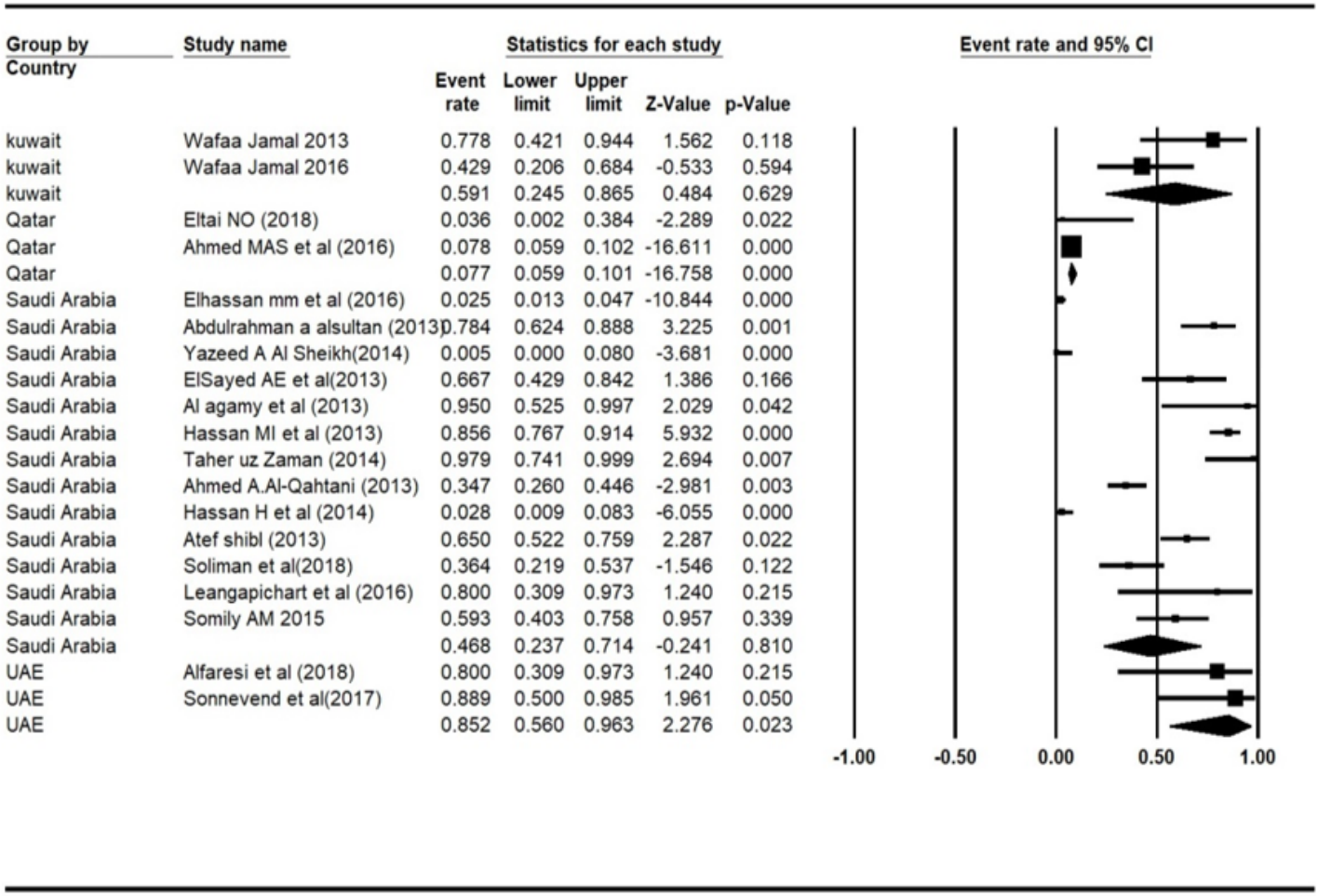

Figure 5

Klebsiella TEM gene

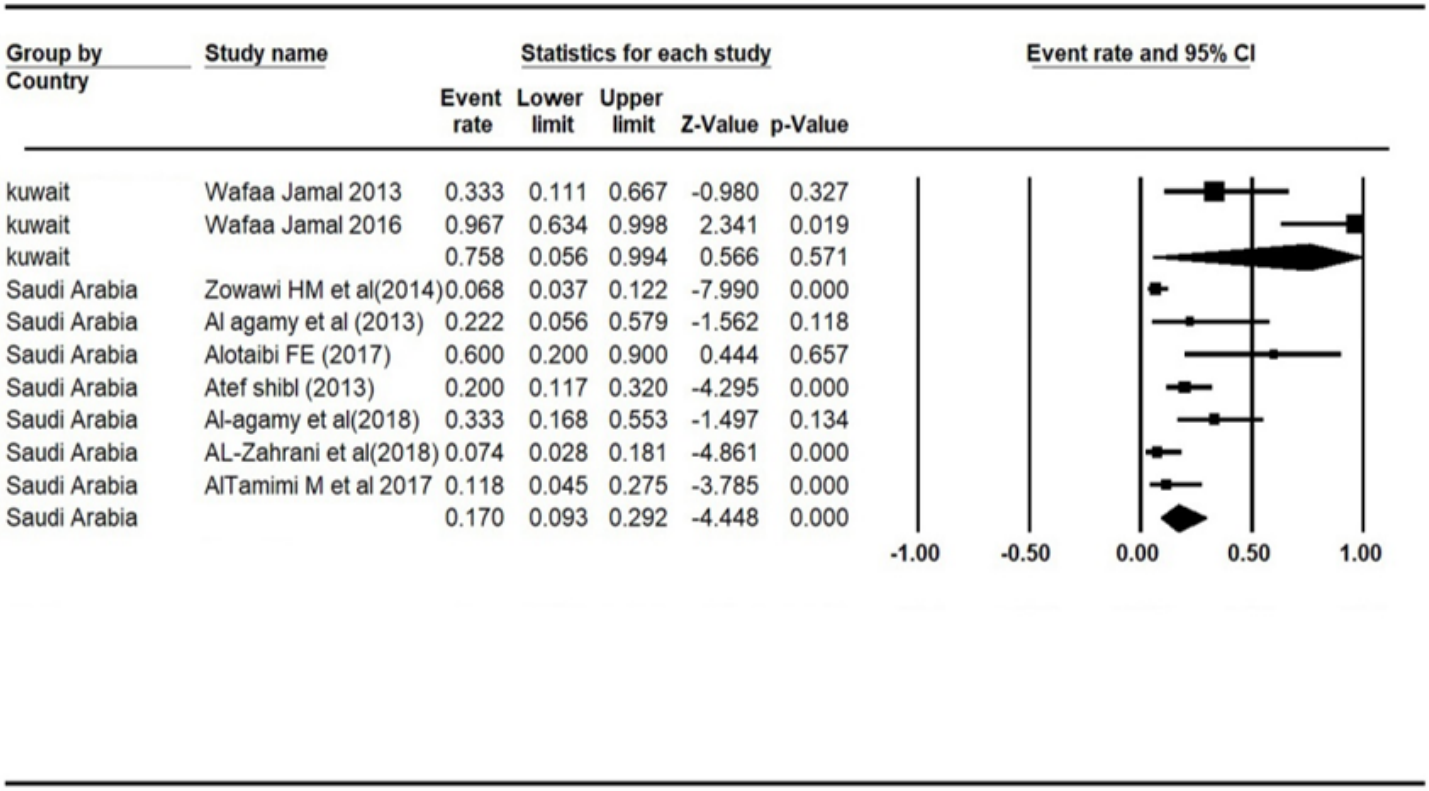

Figure 6

Klebsiella NDM gene

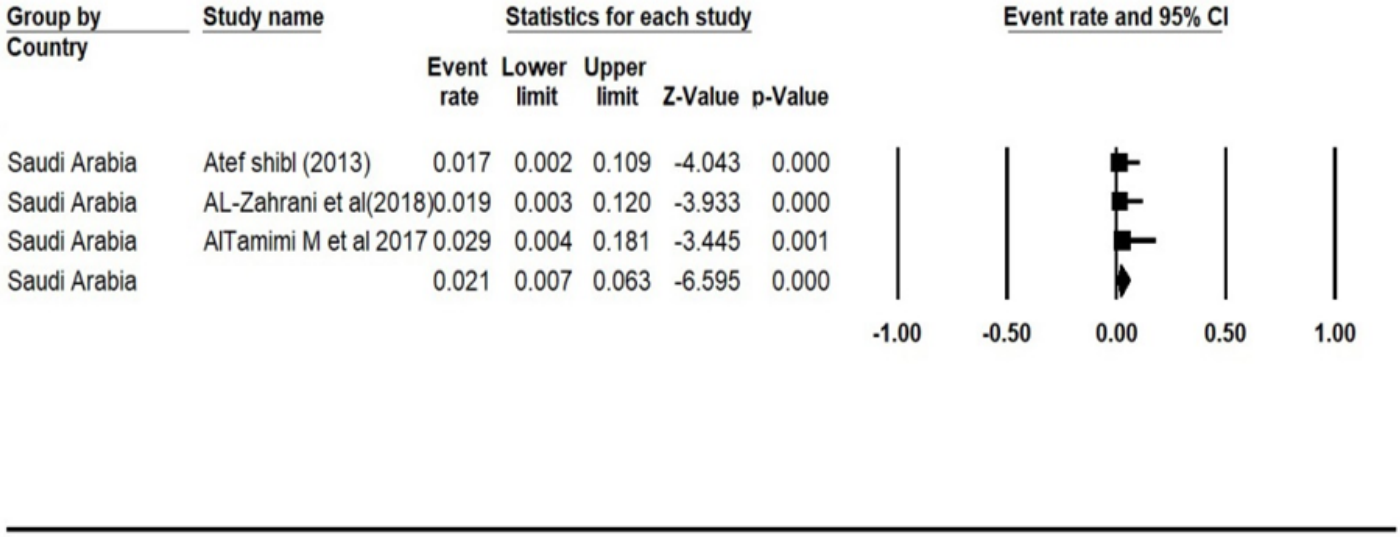

Figure 7

Klebsiella VIM gene