ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 14, Issue 4, 2021

Online - 2455-3891
Print - 0974-2441

Research Article

GENES CONFERRING ANTIMICROBIAL-RESISTANCE AMONG *KLEBSIELLA PNEUMONIAE* IN THE ARABIAN GULF COUNTRIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Received: 20 January 2021, Revised and Accepted: 22 February 2021

ABSTRACT

Objective: The objective of the study was to look on the prevalence of six AMR genes (CTX-M, TEM, SHV, NDM-1, OXA-48, and VIM genes) in the province of the Arabian Gulf. We performed a systematic review and meta-analysis of the published studies from the Arabian Gulf countries and analyzed the antimicrobial resistance (AMR) genes pattern present in *Klebsiella pneumoniae.*

Methods: The present study used the Meta-analysis Of Observational Studies in Epidemiology as a guideline for reporting findings. An electronic search was conducted in online databases such as PubMed/MEDLINE, EMBASE, Scopus, Google Scholar, Science Direct, and Web of Science from January 2014 to June 2020 following the inclusion and exclusion criteria. Articles published were included in the study resistance pattern among 2036 isolates were analyzed. These isolates conferred the AMR genes including OXA-48 (n=500), CTX-M (n= 1796), SHV (n=1637), TEM (n=1492), NDM-1 (n=500), and VIM (n=302).

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 a mean quality score was 4.2, with an SD of 1.6. The analysis revealed predominant AMR genes wereOXA-48 followed by CTX-M, SHV, TEM, NDM-1, and VIM in the Arabian Gulf region.

Conclusion: The Arabian Gulf countries share a high prevalence of OXA-48, CTX-M followed by SHV, TEM, NDM-1, and VIM genes. Antimicrobial-resistant in *K. pneumoniae is* a threat to public health and this needs strong surveillance to curb this threat.

Keywords: Antimicrobial resistance genes, Arabian Gulf region, *Klebsiella pneumoniae,* Meta-analysis, Systematic review.

 DOI: http://dx.doi.org/10.22159/ajpcr.2021v14i4.40841. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

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 a nosocomial infection [1]. In fact, *Klebsiella* has been reported as the second most common cause of bacteremia 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 cephalosporins and aminoglycosides due to its ability to encode extended-spectrum β-lactamases (ESBLs) and aminoglycoside modifying enzymes [3]. An increase in antimicrobial resistance (AMR) in *Klebsiella pneumonia* isolates is of much concern.

The CDC estimates that within the United States, quite 2 million people are diseased with antibiotic-resistant microorganisms annually. Among them, around 23,000 die every year [5]. Several factors can contribute to the spread of AMR, 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 which are known as ESBLs [7]. The occurrence of ESBL producing Enterobacteriaceae is also reported in human and veterinary medicine [8].

Several studies have addressed increased AMR rates among bacterial organisms in the Arabian Gulf Region. They have reported multiple factors that might be contributing to the increasing AMR rates [9].

The prevalence of AMR genes has severe implications for the future therapy and prevention of infectious diseases in humans. Studies have identified multiple genes to be associated with AMR 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-1, OXA-48, and VIM genes) in the Arabian Gulf region. We conducted a systematic review and meta-analysis of the studies reporting the presence of AMR genes *in K. pneumoniae*, published from the Arabian Gulf region.

METHODS

The present study used the "Meta-analysis Of Observational Studies in Epidemiology (MOOSE)" guidelines for reporting findings [10].

Database searches

We conducted an electronic search in seven online databases PubMed/MEDLINE, EMBASE, Scopus, Google Scholar, Science Direct, and Web of Science for articles published between January 2014 and September 2019. The search strategy included relevant keywords: "*Klebsiella pneumoniae*" OR "*Enterobacteriaceae*" OR "antimicrobial resistance" OR "antibiotic resistance" OR "drug-resistance" OR "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 "Metallobeta-lactamase (MBL)" OR "CTX-M" OR "NDM-1 OR "OXA-48" 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, and 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 January 2014 to June 2020
- Studies that included *K. pneumoniae* clinical isolates
- Studies that reported AMR genes from Arabian Gulf countries.
- Articles reporting resistant genes detection by molecular methods (PCR).

Exclusion criteria

The following criteria were excluded from the study:

- 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 six AMR genes (CTX-M, NDM-1, OXA-48, TEM, VIM, and SHV) in Klebsiella isolates from patients 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

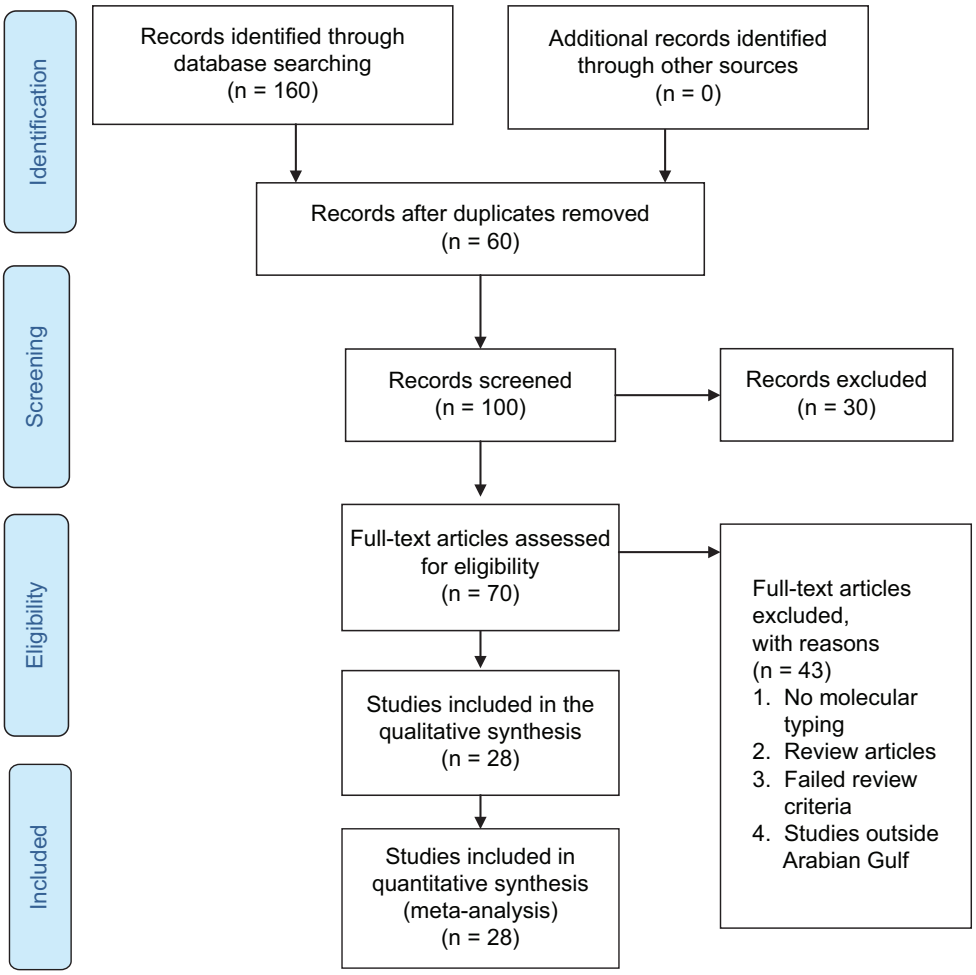

Fig 1. The stages of evaluation and exclusion of the included studies

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 with the principal investigator. We used the Newcastle-Ottawa Scale as a guide for assessing the quality of nonrandomized studies in meta-analysis [11].

Statistical analysis and reporting

We performed a series of single-group analysis based on sample size and event rate. We used Random-effects modeling in the analysis. Using random-effects modeling, 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 a meta-analysis [12-38]; the stages of evaluation and exclusion of the identified studies were as per the inclusion chart is presented in Fig. 1. Study characteristics (e.g., authors, country, year, sample size, patient location, and type of antibiotic-resistant genes) are represented in Table 1.

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-48, followed by CTX-M, SHV, TEM, NDM-1, and VIM. The prevalence of OXA-48 is 61.3% and CTX M is 49.9%, followed by SHV (46.1%), TEM (32.5%), NDM-1 (26.9%), and VIM (6.1%). Detailed results of the point estimate, the 95%CI, and measures of heterogeneity are shown in Table 2. Forest plots of the meta-analysis are presented in Figs. 2-7.

Subgroup analysis

The subgroup analysis of the different AMR genes was conducted by country in which studies were done (Fig. 2-7). As can be seen, by the forest plots, OXA- 48 gene was studied exclusively in Saudi Arabia. Of the eight studies that have studied the OXA-48 gene, six of them reported point prevalence of the gene to be more than 0.5%. The mean point prevalence was 65.1% (Fig 2).

CTX-M gene was studied by two studies from Kuwait, studies from Qatar, 15 studies from Saudi Arabia, and two studies from UAE. The prevalence of the gene was highest in UAE (93.6%), followed by Kuwait (56.4%) and Saudi Arabia (49.1%). Studies from Qatar reported the least prevalence (6.6%) (Fig 3).

SHV gene was also studied by all four countries. Thirteen studies were from Saudi Arabia, while two studies were from each of UAE, Kuwait, and Qatar. The point prevalence of the gene was similar in distribution to the CTX-M gene with maximum prevalence in UAE (85.2%), followed by Kuwait (59.1%), Saudi Arabia (46.8%), and Qatar (7.7%) (Fig. 4).

Table 1: Study characteristics

Authors	Country	Patient location	Sample size	OXA-48	CTX -M	SHV	TEM	NDM-1	VIM
Al-Qahtani *et al*. (2014) [19]	Saudi Arabia	Hospital	98		32	34	20		
Jamal *et al*. (2013) [16]	Kuwait	Medical and surgical ward, ICU	9		4	7	5	3	6
Jamal *et al*. (2016) [31]	Kuwait	Public hospitals	14		9	6		14	
Al-Zahrani *et al*. (2018) [12]	Saudi Arabia	Province hospitals	54	44				4	1
AlTamimi *et al*. (2017) [13]	Saudi Arabia	Inpatients and outpatients	34	18				4	1
Shibl *et al*. (2013) [14]	Saudi Arabia	Inpatients	60	47	37	39	17	12	1
Sonnevend *et al*. (2015) [15]	Arabian Peninsula	Inpatients	145	43				78	6
Eltai *et al*. (2018) [17]	Qatar	Pediatric patients	13		0	0	0		
Elhassan *et al*. (2016) [18]	Saudi Arabia	Inpatients and outpatients	359		6	9	8		
Alsultan *et al*. (2013) [20]	Saudi Arabia	Inpatients and outpatients	37		0	29	16		
Ahmed *et al*. (2016) [21]	Qatar	ICU	629		42	49	30		
Alfaresi *et al*. (2018) [22]	United Arab Emirates	General Hospital	5		5	4	5		
Alzahrania *et al*. (2017) [23]	Saudi Arabia	Inpatients	3		3		2		
Hassan *et al*. (2013) [24]	Saudi Arabia	Inpatients and outpatients	90		82	77	43		
Leangapichart *et al*. (2016) [25]	Saudi Arabia	Adults	1				1		
Leangapichart *et al*. (2016) [25]	Saudi Arabia	Adults	5		5	4	4		
Soliman *et al*. (2018) [26]	Saudi Arabia	Inpatients and outpatients	33		13	12	0		
Somily *et al*. (2015) [27]	Saudi Arabia	Inpatients and outpatients	27		23	16	1		
Sonnevend *et al*. (2017) [28]	United Arab Emirates	Adult	9		9	8	8		
Uz Zaman *et al*. (2014) [29]	Saudi Arabia	Patients	23	23	23	23	22		
Alsheikh *et al*. (2014) [30]	Saudi Arabia	Patients	92		9	0	44		
Al-agamy *et al*. (2013) [32]	Saudi Arabia	Patients	9	7	8	9		2	
Zowawi *et al*. (2014) [33]	Saudi Arabia	Hospital	147	34	48			10	
Alotaibi *et al*. (2017) [34]	Saudi Arabia	Inpatients	5	1				3	
Al-Agamy *et al*. (2018) [35]	Saudi Arabia	Hospitals	21	14	19			7	
Ahn *et al*. (2015) [36]	United Arab Emirates	ICU	2	2				0	
Shahid (2014) [37]	Bahrain	Adult patients	5		5				
Hassan (2014) [38]	Saudi Arabia	Hospital	107		9	3			

*Empty field: Not reported, ICU: Intensive care unit

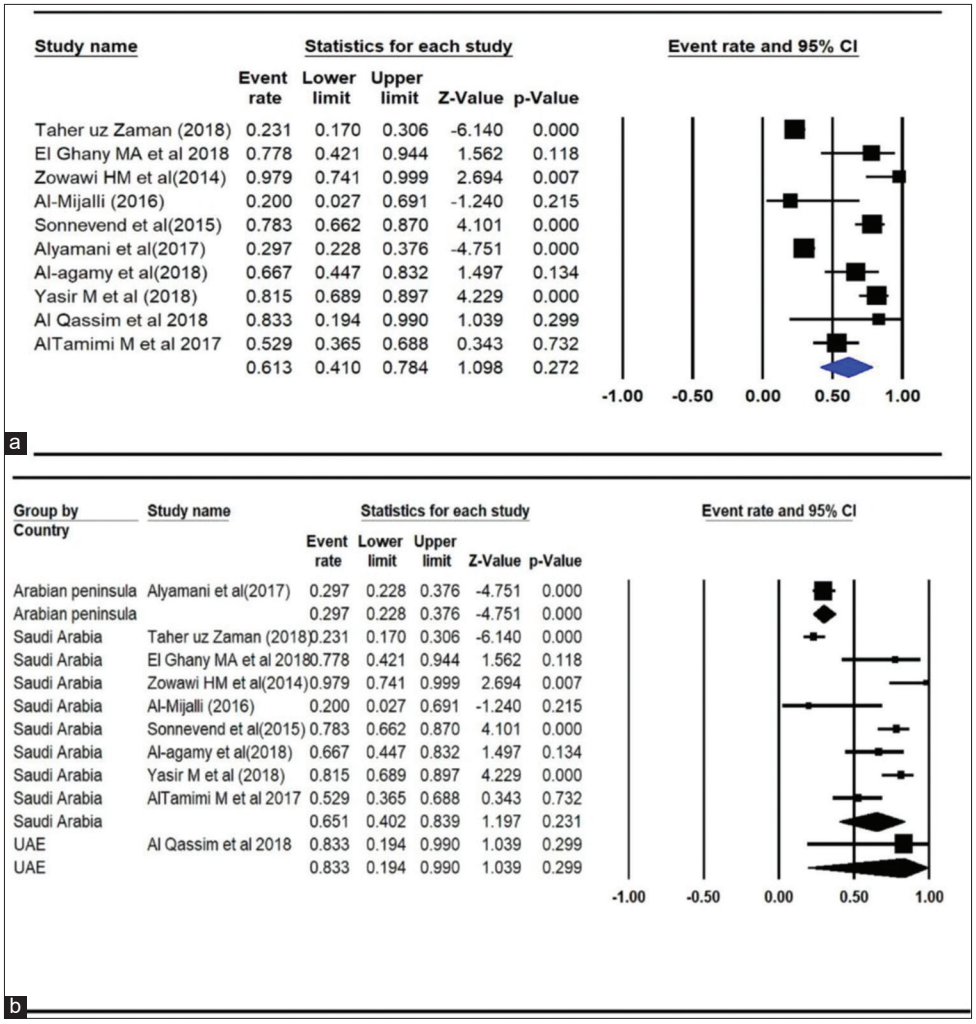

Fig. 2: Klebsiella OXA-48 gene. (a) Meta-analysis results. (b) Subgroup (by country) meta-analysis results

Table 2: Prevalence of antimicrobial resistance genes

Parameters	OXA-48	CTX-M	SHV	TEM	NDM-1	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	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

CI: Confidence interval, Q-value: Cochran's Q, Df: A degree of freedom, I^2: A measure of variability between studies, P: P value, Tau^2: Variance of the two effect sizes

There were no studies on the TEM gene from Kuwait. There were two studies from each of Qatar and UAE while 11 studies were from Saudi Arabia. The prevalence of the gene was highest in the UAE (89.9%), while it was 30.5% in Saudi Arabia and 4.7% in Qatar (Fig. 5).

Two studies from Kuwait and seven studies from Saudi Arabia studied the NDM-1 gene. The point prevalence of the gene was 75.5% in Kuwait. However, the studies differed significantly in their estimation of the prevalence, and the mean confidence interval was broad. Studies from Saudi Arabia reported a prevalence of 4.7% (Fig. 6).

VIM gene was studied exclusively in Saudi Arabia. Only three studies reported studying the VIM gene. The mean point prevalence of the gene was 2.1% (Fig. 7).

DISCUSSION

K. 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-

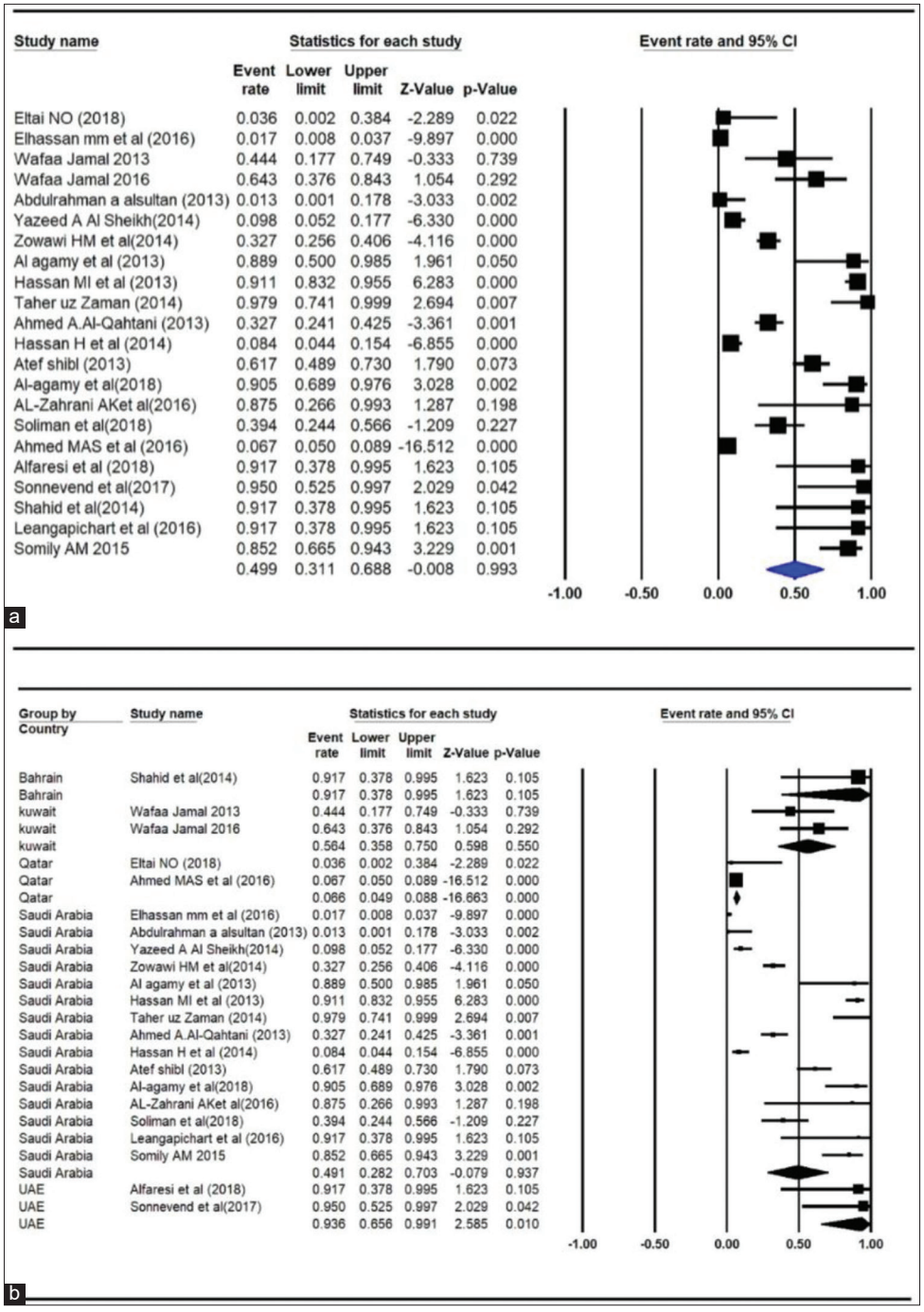

Fig. 3: Klebsiella CTX-M gene. (a) Meta-analysis results. (b) Subgroup (by country) meta-analysis results

producing *Enterobacteriaceae* isolates are increasing in number in the last few years [39].

In this study, the OXA-48 (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 [40]. A study from China has reported 14.9% of the clinical isolates of *K. pneumoniae* with OXAKp [41]. In a study from India, significantly, 80% of their isolates were blaOXA-232 producers [42]. A study from Turkey reported 86% of their isolates harbored the OXA-48 gene [43]. The high prevalence of OXA-48 in the Arabian Gulf reflects the extensive flow between the countries of the Middle East and endemic countries including Turkey, India, and Pakistan[12].

CTX-M enzymes are Class A ESBLs that are spreading rapidly among Enterobacteriaceae worldwide [44]. 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 [45]. The emergence and spread of CTX-Min 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,

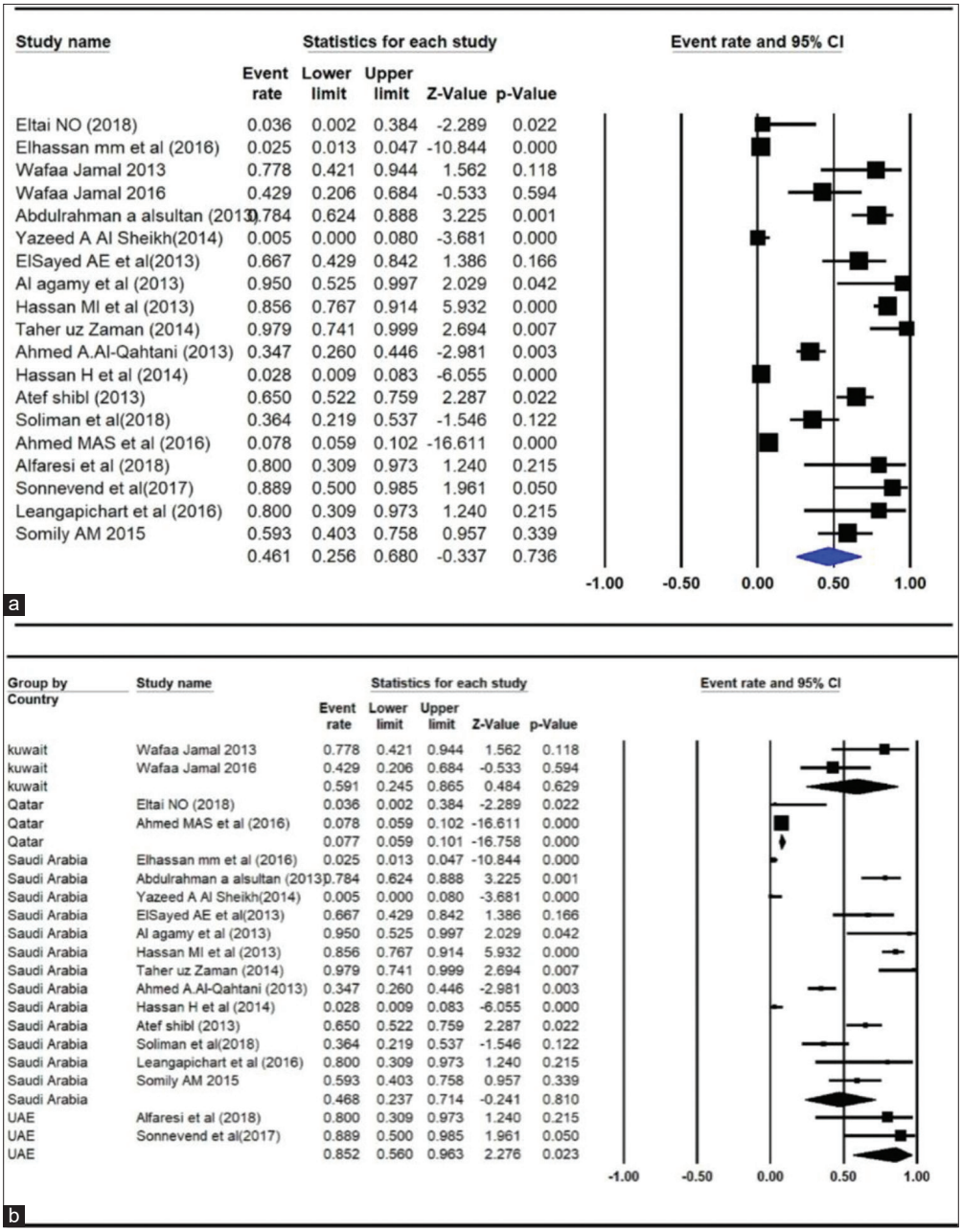

Fig 4: Klebsiella SHV gene. (a) Meta-analysis results. (b) Subgroup (by country) meta-analysis results

Pennsylvania, California, Massachusetts, Michigan, New Jersey, New York, Washington, and Wisconsin [46]. Jemima and Verghese reported the presence of CTX-M genes in 40% of *Klebsiella* spp. [47]. Another study in India by Sekar *et al.* reported the prevalence of the CTX-M gene in 35.89% of Gram-negative isolates [48]. The presence of the CTX-M gene is worrisome as the plasmids carrying this determinant has also the ability to seize other resistance determinants, including carbapenemases genes [49], and thus spread multidrug resistance.

In the present analysis, the SHV gene was present in 46.1%, TEM in 32.5%, and the carbapenem-resistant genes – NDM-1 in 26.9% and VIM in 6.1% of the total studies. Al-Qahtani *et al.* in Saudi Arabia reported the presence of SHV-12 (29.73%) and SHV-5 (5.4%) and TEM (54.05%). A study in Kuwait observed a high prevalence of VIM-4 (66.6%), followed by NDM-1 (33.3%) and SHV-11 (55.5%), SHV-31 (11.1%), and SHV-26 (11.1%). Interestingly, they also reported OKP type in *K. pneumoniae* which is a variant of naturally occurring SHV-type enzymes. This suggests wide dissemination of the genes throughout Arabian countries [16]. Some studies have reported the co-existence of MBLs and ESBLs in the enterobacterial isolates [16,50]. Treatment of patients infected with these multi-resistant infectious agents is challenging.

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 [40]. Dehshiri *et al*. in Iran demonstrated the presence of the genes TEM (16.1%), and SHV (85.5%) among the K. pneumoniae isolates from urine samples [51], while in India, among the ESBLs, SHV, TEM, and CTX-M have been commonly reported by Veeraraghavan *et al*. [52]. In China,

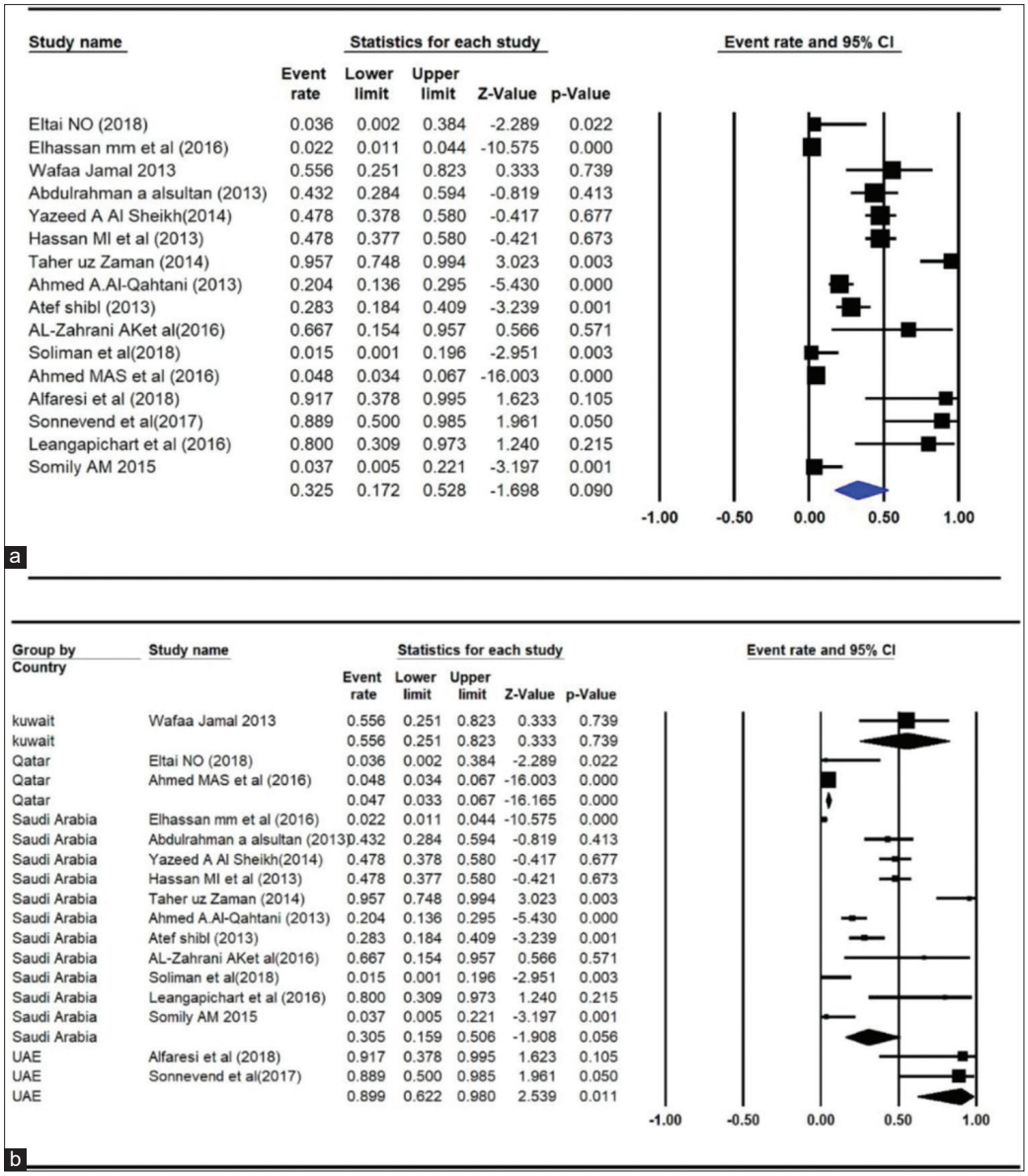

Fig. 5: Klebsiella TEM gene. (a) Meta-analysis results. (b) Subgroup (by country) meta-analysis results

Zhang *et al*. reported NDM-1 producing *K. pneumoniae* isolates in the neonatal ward of a teaching hospital [53]. 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 [54]. The VIM gene is extensively distributed worldwide, with VIM-2 the most widespread variant. VIM enzyme 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 [55]. VIM-1-producing *Enterobacteriaceae* have been associated with single cases, small outbreaks, or polyclonal spread affecting different species of bacteria in Spain [11].

As can be seen from the subgroup analysis, the maximum number of studies was conducted in Saudi Arabia, while the other three countries had near equal representation. Some genes (OXA-48 & VIM) were studied exclusively in Saudi Arabia. One of the reasons for the same can be the country size and the drive for research. The population of Saudi Arabia is nearly 16 times that of Qatar, more than 8 times Kuwait, and more than 3 times the population of the UAE. Furthermore, Saudi Arabia is a forerunner in the research front and has an active and zealous research community. This might have manifested in maximum representation from the country.

However, all four countries are in geographic continuity and share similar demography, environment, disease epidemiology, and even cultural practices. The differences observed in the prevalence of different AMR genes might be due to the differences in the number of studies and the sample sizes than true prevalence. For the same reason, the results of the study can be generalized to other gulf countries.

Overall, Arabian Gulf Countries are more susceptible to multidrug infections including carbapenem-resistant genes. This is mainly due to the high resident expatriate population (average 48%), extensive international links, lack of clear guidelines on antimicrobial use, and deficiency of policies for containing and reviewing antimicrobial prescriptions [15].

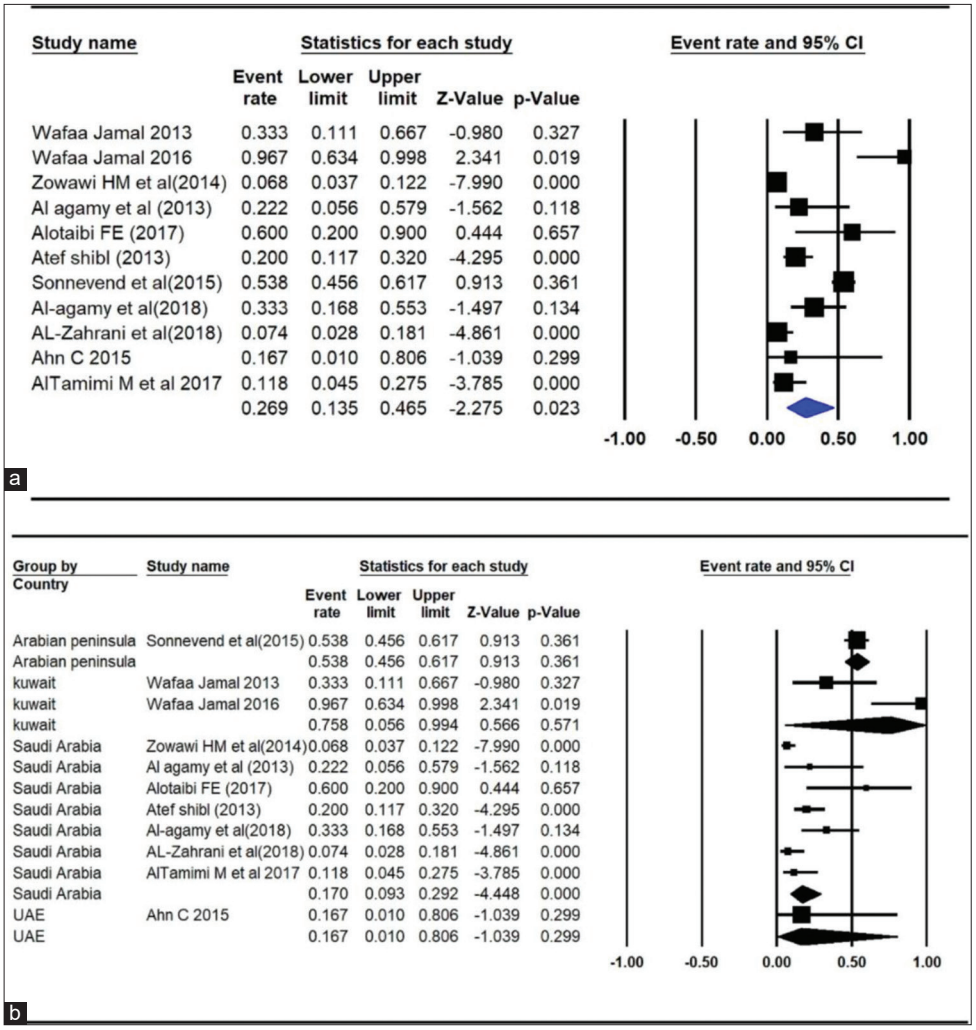

Fig. 6: Klebsiella NDM-1 gene. (a) Meta-analysis results. (b) Subgroup (by country) meta-analysis results

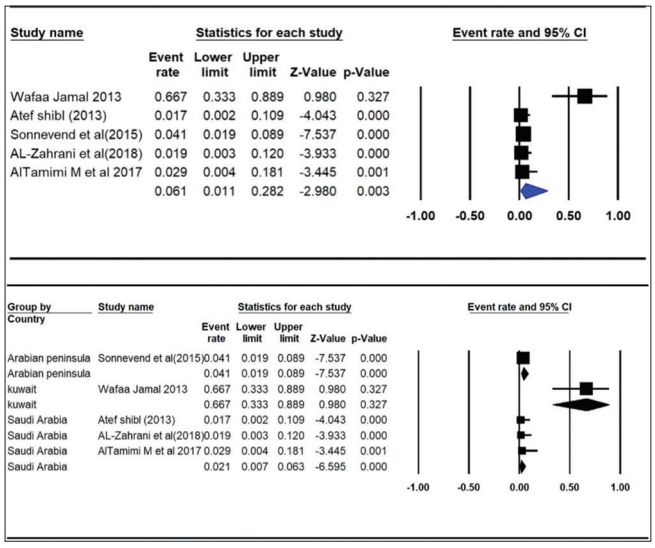

Fig. 7: Klebsiella VIM gene. (a) Meta-analysis results. (b) Subgroup (by country) meta-analysis results

CONCLUSION

The antibiotic resistance gene prevalence's of *K. 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. Health-care sectors need to monitor and report changes in antimicrobial-resistant isolates. A multifactorial approach, including standard guidelines, and appropriate infection control measures is necessary to curb this threat.

AUTHORS CONTRIBUTION

Khalid Bindayna designed the study. Ronni Joji, Khalid Bindayna coordinated data search, data entry, and data cleaning. Haitham performed the statistical analysis. Ronni Joji wrote the first draft and Khalid Bindayna, Hicham Ezzat provided intellectual contributions to strengthening the manuscript. All authors provided critical revisions of the manuscript and approved the final version.

CONFLICT OF INTEREST

Nil.

AUTHORS FUNDING

None.

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