Review
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Epidemiology of Carbapenem Resistance Enterobacterales in Saudi Arabia: A Systematic Review

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Abstract

The widespread of multidrug-resistant bacteria, particularly carbapenem-resistant Enterobacterales (CRE) bacteria, constitutes a major public health threat worldwide, owing to the limited therapeutic options. This review will describe and uncover the Saudi experience in the challenge against carbapenem resistance (CR). The different carbapenem resistance prevalence and carbapenemase genes detected from various bacterial species were mapped for Saudi regional distribution, based on Saudi published data during a period extended from 2017 to 2021. However, VIM, IMP, and KPC enzymes were usually reported with the predominance of OXA and NDM among Enterobacterales. Although SIM and GIM carbapenemases were uncommonly detected in our country. Collaborative efforts and raising awareness of the threat of carbapenem resistance are required to minimize the spread of multidrug-resistant bacteria.

Keywords: Carbapenem, Enterobacteriaceae, Saudi Arabia, lactamase, resistant, carbapenemase

Introduction

Carbapenem resistance (CR) bacteria is a significant and mounting health concern globally,[1,2] this problem is aggravated by inadequate infection control in developing countries due to poor hygiene, resource and structural constraints, deficient surveillance data, and lack of awareness regarding nosocomial infections.[3,4] It occurs mainly among Gram-negative pathogens such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and may be intrinsic or mediated by transferable carbapenemase-encoding genes,[5,6] the most effective carbapenemases, in terms of carbapenem hydrolysis and globally spread, are KPC, VIM, IMP, NDM and OXA-48 genotypes.[7]

Carbapenem class antibiotics have been a mainstay of treatment for serious infections caused by Enterobacterales, but efficacy has been compromised by the widespread acquisition of resistance genes to these critical drugs.[8] Effective antimicrobial options for Carbapenem-Resistant Enterobacterales (CRE) are often lacking, and treatment typically requires reliance on drugs with a risk of toxicity or other safety concerns.[9] Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is a prominent cause of nosocomial infections associated with high rates of morbidity and mortality, particularly in immune-compromised individuals.[10,11] Carbapenem resistance causes a broad spectrum of diseases including pneumonia, urinary tract infections, bloodstream infections, skin, and soft tissue infections.[12] This resistance is facilitated by complex factors, including the presence of mobile genetic elements, the misuse of antimicrobial drugs, poor infection control practices, and increased international travel.[13]

In healthcare settings, CRE is transmitted from person to person, often via the hands of healthcare personnel or through contaminated medical equipment.[14] Additionally, sink drains and toilets are increasingly recognized as an environmental reservoir and CRE transmission source.[15] Risk factors for CRE colonization and infection have been identified as longer length of hospital stay, prior hospitalization, admission to ICU, renal dysfunction, neurological disorders, tracheostomy, mechanical ventilation, central venous catheter (CVC) use, urinary catheter use, nasogastric tube use, implementation of dialysis, prior use of any antibiotic, and specific use of carbapenems.[16–18]

The aim of this review was to shed light on all studies tackling Carbapenem resistance in Enterobacteriaceae, carbapenem resistance *A. baumannii* (CRAB) and carbapenem resistance *P. aeruginosa* (CRPA) in the Saudi Arabia regions, with an indication for each region, description of studies timeline, the prevalence of carbapenem resistance, and CR-encoding genes detected based on Saudi data published over last 5 years from 2017 to 2021. This study enabled us to gain deep insight into the CR problem in Saudi Arabia, in addition to mapping the regional distribution of carbapenemase enzymes and CR prevalence for each region, which is strongly encouraged by epidemiologists to improve surveillance strategies to minimize the spread of CR gram negative bacteria such as previously described.

Methods

Literature Review

PubMed, ScienceDirect and international Journals Online databases were searched to December 2021. The search key words used were carbapenem resistance in Saudi Arabia, Enterobacteriaceae, CRE, *Escherichia coli,* CREC, *Klebsiella*, CRKP, *Pseudomonas aeruginosa*, CRPA, *Acinetobacter baumannii,* CRAB, carbapenem, -lactam, -lactamase, resistant, carbapenemase, MBL, metallo-b-lactamase, VIM, NDM, OXA, oxacillinase, IMP, KPC to extract articles published only in English in an attempt to include up to date relevant data.

Study Selection Criteria

Only research articles reporting the prevalence or molecular genotyping frequency of carbapenem resistance in clinical pathogens isolated from patients and hospital environment or showed the proportion of carbapenem resistant isolates of all Gram-negative isolates, or clinical data including patient demographics, underlying conditions, and antibiotic treatment in all Saudi Arabia regions. Only Studies elaborating bacteria study population, pathogens identified, phenotypic and genotypic methods used to detect carbapenem resistance were used. Patient populations of all hospital types were included while case reports and review articles were excluded from this systematic review as it has become conventional.[19,20]

Data Extraction

A database was created in which study location, sample collection period, bacterial species isolated, a number of isolates tested for CR, CR isolates, CR prevalence, ESBL & carbapenemase genes, methods used to identify resistant isolates, references, and outcomes were included.

Results

The emergence and rapid spread of carbapenem-resistant Enterobacterales in Saudi Arabia encouraged scientific researchers and epidemiologists to investigate CR hospital associated infection prevalence and the genes involved in resistance to carbapenems. As described in Figure 1A the number of published articles per year was clearly increased and indicated by the highest number recorded in 2021. This is closely related to the dissemination of CRE throughout the country and the increased awareness of the importance of surveillance and control of multidrug-resistant bacteria in order to improve health quality. A high prevalence of carbapenemase producers in Saudi Arabia was mainly identified as *A. baumannii*, followed by *Pseudomonas aeruginosa*, and *Klebsiella pneumonia*.[21–26]

The majority number of published research papers per carbapenemase type was OXA, from all genotyping studies, OXA-48 variant in Enterobacteriaceae and OXA-23 variant in *A. baumannii*, and *P. aeruginosa*, followed by NDM-1 (all the collected studies except two.[27,28] However, low number of published articles (8 studies) has reported the detection of VIM genes.[22,24,28–33] Detection of VIM genes was reported in 5 studies while IMP was reported by El-Badawy, Abdelwahab et al. 2019, Shah, Yasir et al. 2019, Jawhar, AlRashed et al. 2020, Khater, AlFaki et al. 2020, Alqahtani, Tickler et al. 2021)[30,31,28,34,24] and KPC genes was reported in 5 studies[21,24,27,34,35] as described in Figure 1B. Furthermore, until now no studies reported the presence of SIM and GIM genes in the collected bacterial isolates from Saudi Arabia.

Saudi Arabia is divided into 13 administrative regions, and geographically these regions are distributed in five major areas of the country (central, eastern, northern, southern and western areas). Most of the studies about CRE were conducted in the central, and western areas and small data came from the eastern, southern, and northern areas. The results according to the literature search and study selection indicate that a total of 24 studies met the inclusion criteria and were included for final review, of these 3 (12.5%) reported extended studies for more than three regions or shared with other countries, 8 (33.3%) reported from the central area, 7 (29%) reported from the western area, 2 (8.3%) reported from the eastern area, 3 (12.5%) reported from the south area, and one (4.2%) reported from north area (Figure 1C). There was no data reported from Najran, Tabuk and North border regions. Also, 18 studies (75%) reported genotype including carbapenemase or β-lactamase genes distribution and 16 studies (66.7%) reported clinical CR surveillance data. Two studies reported systematic reviews of CR from Saudi Arabia[13,36] and three studies reported CR cases[37–39] (excluded from this study). The regional distribution of the different carbapenemases gene prevalence were mapped in Saudi Arabia from five years up to date (Figure 2), and regional distribution CR prevalence in Enterobacterales over several Saudi regions were mapped (Figure 3).

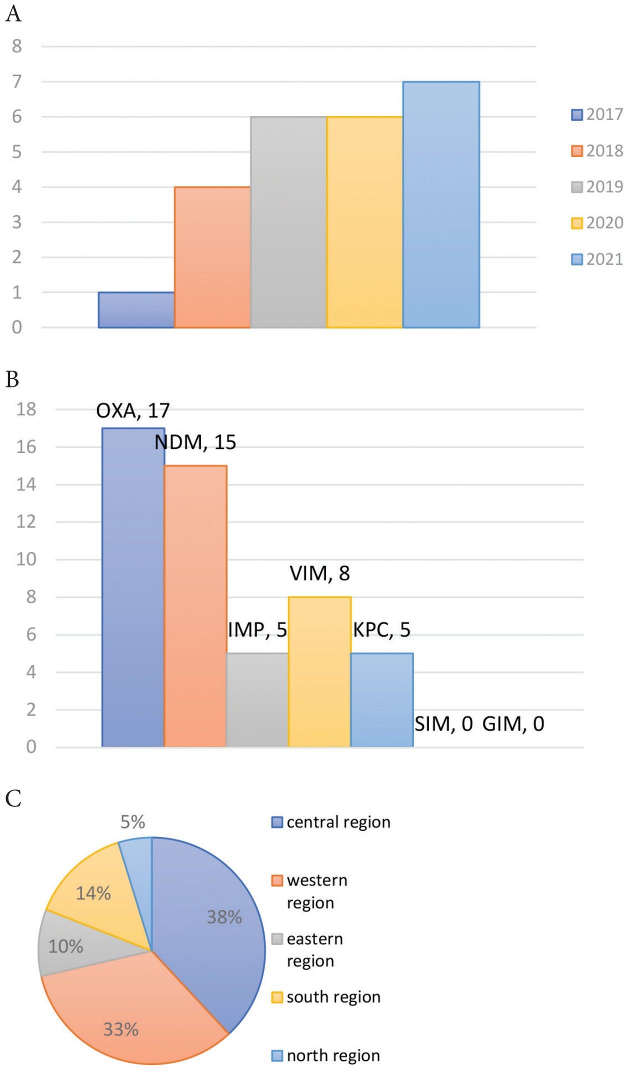

Fig. 1 **(A) Number of published papers reporting CRE bacteria in Saudi Arabia from 2017 to 2021, (B) Number of published papers per carbapenemase genes in Saudi Arabia from 2017 to 2021, and (C) Number of published papers per Saudi regions from 2017 to 2021.**

Extended Studies from All Saudi Arabia

There is a wide modern study to determine the prevalence of carbapenem resistance gram-negative genes in Gulf Cooperation Council hospitals including Saudi Arabia (Table 1).[24] The results indicate the rates of carbapenem resistance genes varied across the GCC hospitals and even among hospitals in the same country and this result was confirmed by the study of Al-Abdely et al. (2021)[40] which explained the circulating strain causing outbreaks in this specific region. In

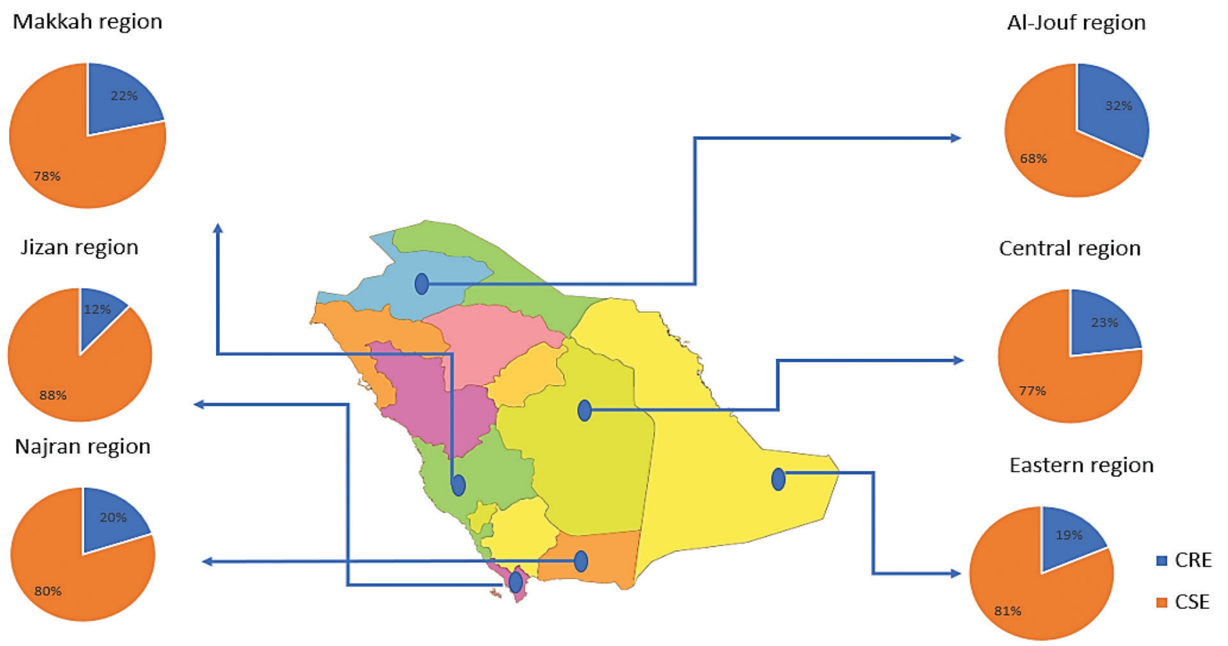

Fig. 2 **Percentage of epidemiology of carbapenem resistance Enterobacterales in Saudi Arabia regions.**[21,23–26] **CRE, carbapenem resistance Enterobacterales; CSE, carbapenem sensitive Enterobacterales.**

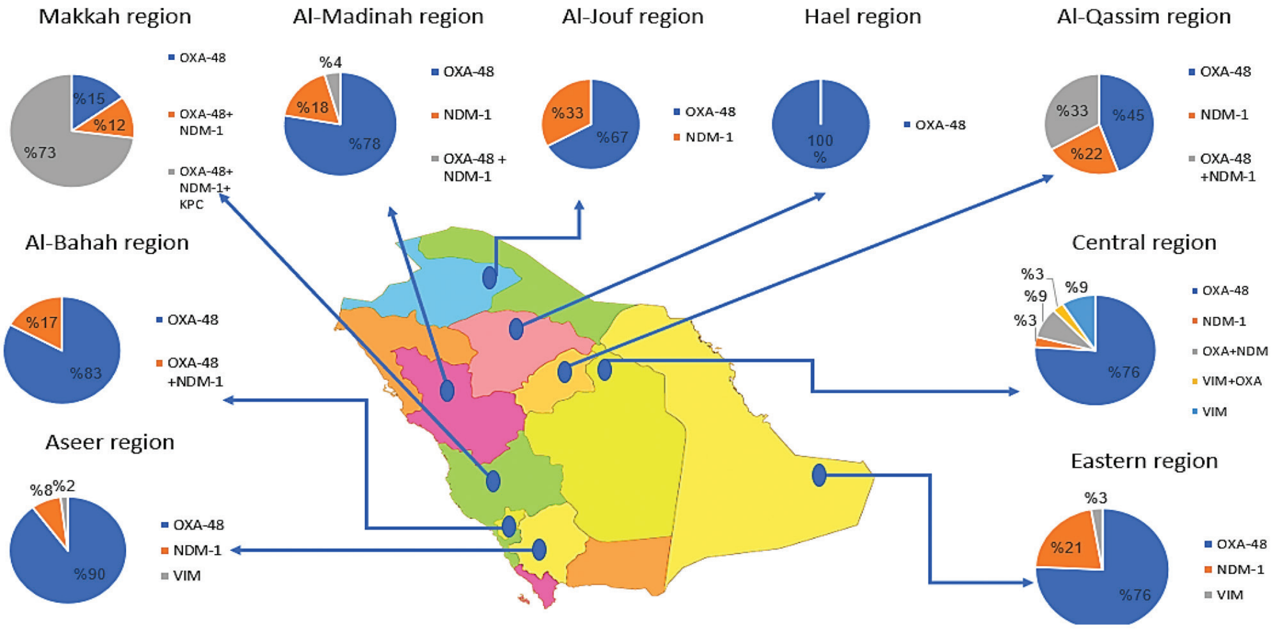

Fig. 3 **Molecular classification of carbapenem resistance *K. pneumoniae* genes distribution over Saudi Arabia regions.**[21,24,29,32,40]

Table 1. **Participating cities, CR prevalence and molecular classification of CR isolates in (Alqahtani, Tickler et al. 2021)**[24] **study**

City	Number of isolates	CR isolates	CR prevalence (%)	Carbapenemase genes detected
Dammam	266	49	18.4%	OXA-48 (14.3%), NDM (4.1%)
Khamis Mushait	250	50	20.0%	OXA-48 (14.0%), NDM; OXA-48 (6.0%)
Riyadh	73	49	67.3%	OXA-48 (51.0%), NDM (2.0%) NDM; OXA-48 (6.1%) VIM; OXA-48 (2.0%), VIM (6.1%)

addition to the other two studies, Table 2 illustrated the presence of carbapenem resistance genes in Enterobacteriaceae and *P. aeruginosa* isolates in more than 3 regions in Saudi Arabia (Table 3).[22,40]

Epidemiology of Central Area

In the last five years, there are eight published studies related to clinical CR infection from a central area (Table 4), six of them detect the carbapenemase genes distribution among specific hospitals,[28,34,35,41–43] other three studies give a prevalence rated to CR dissemination,[34,35,44] two studies focus on CRKP,[34,43] and one study detect CRG in *P. aeruginosa* and *A. baumannii.*[28]

Epidemiology of Western Area

The western area includes the Makkah region that had two largest cities (Makkah and Jeddah) with the highest population outside the central region. Millions of Muslims from across the globe arrive annually in Makkah to perform pilgrimage and Umrah. These mass gatherings could be a good environment for spreading multi-drug resistant organisms around the world.[13,45] There were seven studies published in the last five years from the western region of Saudi Arabia, three of them from Makkah city,[21,33,46] two studies from Jeddah city,[27,31] one study from Taif[30] and one study from Al-Madinah.[47] Five of these studies detect the carbapenemase genes dissemination ratios and four studies give a CR surveillances,[47] and one study focus on CRKP[33] while two studies detect the CRG genes in *P. aeruginosa* CRPA. Other studies focus on CRAB[30,31] while carbapenem resistance *Klebsiella quasipneumoniae* in Jeddah was described by Hala et al. (2019).[27]

Epidemiology of Eastern Area

There were two genotypic studies published recently from the western region of Saudi Arabia.[32,48] The first one aimed to assess different genotypic and phenotypic methods to detect carbapenemases; however, each has a limitation, Talal (2019)[32] study evaluated the performance of modified Carbapenem Inactivation Method (mCIM) test in Enterobacteriaceae in

Table 2. **Participating hospitals, carbapenem resistance prevalence and molecular classification of 456 isolates of *K. pneumoniae* in (Al-Abdely, AlHababi et al. 2021)[40] study**

Saudi Hospital name	CRKP prevalence	Carbapenemase genes detected
1. King Salman Bin Abdulaziz Hospital, Riyadh	96%	NDM-1 (11%), OXA48 (89%)
2. King Khalid Hospital and Prince Sultan Center for Health Service, Al Kharj	53%	NDM-1 (33%), OXA48 (67%)
3. King Fahd Specialist Hospital, Buraydah	90%	NDM-1 (22%), OXA48 (44%), NDM-1 +OXA48 (33%)
4. Regional Laboratory and Blood Bank, Microbiology Department, Dammam	100%	OXA48 (100%)
5. Gurayat General Hospital	96%	NDM-1 (32%), OXA48 (50%), NDM-1 +OXA48 (18%)
6. Hael General Hospital	83%	OXA48 (100%)
7. Arar Central Hospital	100%	NDM-1 (33%), OXA48 (67%)
8. Asir Hospital	93%	NDM-1 (25%), OXA48 (71%), NDM-1 +OXA48 (4%)
9. King Fahd Hospital, Al Baha	100%	OXA48 (83%), NDM-1 +OXA48 (17%)
10. King Faisal Medical Complex, Taif	80%	NDM-1 (17%), OXA48 (67%), NDM-1 +OXA48 (17%)
11. King Abdulaziz Specialist Hospital, Taif	100%	NDM-1 (13%), OXA48 (88%)
12. King Fahad Hospital, Madina Munawara	84%	NDM-1 (16%), OXA48 (70%), NDM-1 +OXA48 (4%)
13. Hera General Hospital, Jeddah	80%	NDM-1 (25%), OXA48 (35%), NDM-1 +OXA48 (50%)

Table 3. **Review of carbapenem resistance studies which include more than 3 regions in Saudi Arabia**

Regions	Number of isolates	CR prevalence (%)	Carbapenemase genes detected	Organism	Methods used	Refs.
Gulf Cooperation Council	529 of rectal swabs	26.1%	One gene; OXA-48 (59.4%), NDM (13.8%), VIM (6.5%) & IMP (0.7%) Two genes; OXA-48 & NDM (8.7%), OXA-48 & VIM (6.5%), NDM & KPC (1.5%) & OXA-48 & KPC (0.7%)	–	XpertCarba-R Assay	Alqahtani et al. (2021)[24]
Five regions include Central, North, East, South & West	519 of Enterobacterales	84.7%	OXA-48 (71.2%), NDM-1 (20.7%) & NDM+OXA-48 (8%).	*K. pneumoniae* (90%), *K. oxytoca* (0.5%), *E. coli* (4%), *E. cloacae* (2.5%) & Others	E-test XpertCarba-R Assay	Al-Abdely et al. (2021)[40]
Five hospitals in the east, west and center regions	635 of *P. aeruginosa*	28.2% for imipenem 23.0% for meropenem 18.7% for meropenem & imipenem	Carbapenemase genes; GES (9%), VIM (3.4%), NDM (6%) & OXA48 (0.5%) ESBL genes; PER (1.1%) & VEB (1.1%) Carbapenemase and ESBL genes; VIM + PER (1.1%), VIM + VEB (0.5%)	*P. aeruginosa*	VITEK-II PCR	Al Hassinah et al. (2020)[22]

Table 4. **Review of carbapenem resistance studies in Central, Western, Eastern, Northern and Southern areas of Saudi Arabia**

Area (city)	Number of isolates	CR prevalence (%)	Carbapenemase genes	Organism	Methods used	Refs.
1. Riyadh & Qassim	162,665	23.2%	–	*Enterobacterales* (14%), *E. coli* (6.4%), *K. pneumoniae* (9.6%), *A. baumanii* (19.5%) & *P. aeruginosa* (19.2%)	VITEK-II BD Phoenix MicroScan plus	Mutair et al. (2021)[44]
2. Riyadh	1,864	7.6%	ESBL (53.3%), KPC (11.5%), OXA-48 (1.3%) & NDM (0.67%)	–	VITEK-II XpertCarba- R assay	Aleidan et al. (2021)[35]
3. Riyadh	–	–	*P. aeruginosa*; OXA-23 (55%), OXA 40 (5%), OXA 10 (7.5%), OXA 48 (3.75%), IMP (1.25%), VIM (46%), OXA-1 (22%) & GIM (15%) *A. baumannii*; OXA-23 (85.7%), OXA 40 (17%), VIM (11.4%), IMP (17%), GIM (2.8%), OXA-1(2.8%) & OXA-48 (2.8%)	*P. aeruginosa* (80 isolates) *A. baumannii* (35 isolates)	E-test VITEK-II PCR	Jawhar et al. (2020)[28]
4. Al-Quwayiyah	541 All samples 78 of *K. pneumoniae*	6.7% for all samples 46.2% for *K. pneumoniae*	OXA-48 (77.8%), NDM (13.9%), KPC (5.6%), IMP (2.8%), & OXA-48 & NDM (13.9%)	*K. pneumoniae*	VITEK-II D70C MHT PCR	Khater et al. (2020)[34]
5. Riyadh	–	–	–	*K. pneumonia* (47%), *E. coli* (31%), *Enterobacter sp.* (5.3%), *Citrobacter sp.* (5.3%), *KluyveraAscorbata* (5.3%), & *Proteus* (5.3%)	–	Alzomor et al. (2019)[50]
6. Riyadh	–	–	Chromosomal; CTX-M-15 (90%), NDM-1 (20%), NDM-5 (40%), & OXA-181 (40%) Plasmid; CTX-M-15 (100%), NDM-1 (20%), NDM-5 (30%), CTX-M-17 (10%), TEM-18 (90%), OXA-1 (40%), OXA-181 (40%), & CMV-42 (80%)	*E. coli*	Microbroth dilution method PCR WGS	Abd El Ghany et al. (2018)[41]
7. Riyadh	–	–	OXA-48 (58.1%) NDM (41.9%) CTX-M-1 (77.4%) CTX-M-9 (9.6%) TEM-1 (74.2%) OXA-1 (54.8%) SHV-1 (4.4%)	*K. pneumoniae* (21 isolates), & *E. coli* (10 isolates)	E-test Imipenem + EDTA strip MHT PCR	Al-Agamy et al. (2018)[42]
8. Riyadh	–	–	OXA-48 (67.6%), NDM-1 (12.7%), CTX-M-15 (66.2%), & CTX-M-14 (21%)	*K. pneumoniae*	E-test VITEK-II PCR	(uz Zaman, Alrodayyan et al. 2018)[43]
9. Makkah	–	–	VIM (31%), & GES (8.6%)	*Pseudomonas aeruginosa*	PCR MLST	(Al-Zahrani, Ibrahim et al. 2021)[33]
10. Medina	15,708	38.4% for Imipenem 46.1% for Meropenem	–	*K. pneumoniae*	VITEK-II	Al-Zalabani et al. (2020)[47]

(Continued)

Table 4. **Review of carbapenem resistance studies in Central, Western, Eastern, Northern and Southern areas of Saudi Arabia**

Area (city)	Number of isolates	CR prevalence (%)	Carbapenemase genes	Organism	Methods used	Refs.
11. Jeddah	286 of *Klebsiella spp*	–	KPC-2	*Klebsiella spp.*	VITEK-II Broth Microdilution PCR WGS	Hala et al. (2019)[27]
12. Taif	45 of *Acinetobacter spp.*	71%	OXA-51 (100%), IMP (87.5%), NDM (62.5%), OXA-23 (59.4%), VIM (9.3%), & OXA-40 (3.1%)	*A. baumannii*	VITEK-II Disk diffusion ERIC-PCR	El-Badawy et al. (2019)[30]
13. Jeddah	135 of *A. baumannii*	55.6%	OXA-51 (100%), OXA-23 (92%), IMP (84%), NDM-1 (1.3%), OXA-24/40 (5.3%), VIM (92%), TEM (84%), & SHV (10.7%)	*A. baumannii*	VITEK-II PCR	Shah et al. (2019)[31]
14. Makkah	864 All samples 120 of Enterobacteriaceae	21.7%	OXA-48 (100%), NDM-1 (84.7%), & KPC (73.1%)	*K. pneumoniae* (80.7%) *E. cloacae* (7.7%) *E. coli* (7.7%) *P. mirabilis* (3.8%)	VITEK-II Disk PCR	Khan et al. (2019)[21]
15. Makkah	4,803 of Gram negative bacilli	58.23%	-	*A. baumannii* (99.13%) *P. aeruginosa* (62.4%) *K. pneumonia* (38%) *E. coli* (5.59%)	VITEK-II	Faidah et al. (2017)[46]
16. Makkah	–	–	VIM (31%), & GES (8.6%)	*Pseudomonas aeruginosa*	Multiplex PCR MLST	Al-Zahrani et al. (2021)[33]
17. Al- Qatif	753 of patients 208 of Clinical Surfaces	2.8% of patients 36% of Clinical Surfaces	OXA-66/OXA-23 /armA (37%), OXA-69/OXA-23/ GES-11 (4.2%), OXA-94/NDM-1 (2.1%), OXA-66/OXA-23 (9.5%), & OXA-51/OXA-23 (1%)	*A. baumannii*	BD Phoenix PCR WGS	Al-Hamad et al. (2020)[48]
18. Dammam	–	–	OXA-48 (Dominant), NDM (second CRE gene dissemination), & VIM (low prevalence)	–	mCIM PCR	Talal (2019)[32]
19. Al-Jouf	617 of *Enterobacterales*	32%	–	*K. pneumoniae* (63%), *P. mirabilis* (29%), & *E. coli* (8%)	BD Phoenix	Bandy and Tantry (2021)[25]
20. Jizan	50	10% for imipenem 12% for meropenem	CTX-M (70%), SHV (16%), TEM (12%), & NDM-1 (0%).	*E. coli* (50%), *K. pneumoniae* (40%), *A. baumanii* (4%), *P. aeruginosa* (4%), & *E. cloacae* (2%)	CDT VITEK-II PCR	Sobia et al. (2021)[26]
21. Abha	276 of *K. pneumoniae*	61.7% for Meropenem 44.5% for Imipenem	–	*K. pneumoniae*	VITEK-II	Al Bshabshe et al. (2020)[49]
22. Abha	54 of *K. pneumoniae*	63% for Imipenem 57.4% for Meropenem	OXA-48 (81.5%), NDM (7.4%), & VIM (1.8%)	*K. pneumoniae*	VITEK-II E-test PCR	Al-Zahrani and Alasiri (2018)[29]

D70C,Carbapenemase Detection Set; MHT, Modified Hodge test; UTI, Urinary Tract Infection; MLST, Multi Locus Sequencing Types; WGS, Whole Genome Sequencing; mCIM, modified Carbapenem Inactivation Method.

reference to molecular methods. Their obtained results confirm that mCIM test is a simple tool for the reliable confirmation of carbapenemase activity with 97.3% sensitivity in Enterobacteriaceae, especially in clinical microbiological laboratories with limited resources.[32] The second study isolated environmental and clinical CRAB to assess the potential environmental contamination by this pathogen from frequent-hand-touch surfaces of intensive care unit (ICU), medical, and surgical units were randomly sampled for a month-long period, and the CRAB identified were compared to clinical isolates of the same period.[48]

Epidemiology of Northern Area

Data regarding the CR patterns of Enterobacterales in the northern regions are scarce, there was one surveillance non-genotypic report from Al-Jouf. Bandy and Tantry (2021) analyzed the antibiograms of Enterobacterales identified from January 2019 to December 2019.[25] In total, 617 Enterobacterales were identified. *K. pneumoniae* exhibited 62.5%, 62%, and 58.3% resistance towards ertapenem, imipenem, and meropenem, respectively. In *E. coli* and *K. pneumoniae*, seasonal variation in the antimicrobial resistance rate was observed for imipenem and meropenem and the resistance were significantly higher in winter. Furthermore, the *K. pneumoniae* meropenem resistance rate was significantly higher in samples received from intensive care units than from other units.[25]

Epidemiology of Southern Area

In the last five years, there were just three studies from southern regions, Saudi Arabia. Two of them from Abha city.[29,49] The earlier study aims to identify the prevalence of CRKP and the most common types of cabapenemases between late April and September in 2015.[29] The results of this study indicate that increasing age and intensive care unit admission were associated with CRKP isolation, the major type of carbapenemases in the southern region was OXA-48 with 81.5% and it seems to reach an endemic level, NDM was the second most frequent carbapenemase by 7.4% of isolates, this study refers OXA-48 and NDM carbapenem resistance strains dissemination in Saudi Arabia to receives large numbers of visitors and migrant workers from OXA-48 and NDM endemic countries such as Turkey, India, and Pakistan every year.[29] The Third studies aimed to examine *K. pneumoniae* infections in the ICU of Aseer Central Hospital and to determine their antimicrobial susceptibility and their relationship to patients' clinical outcomes from patients with various infections.[49]

Conclusion

Carbapenem-resistant Enterobacterials (CRE) is a growing threat and serious health concern spreading in Saudi Arabia and worldwide. This dilemma has been documented in many parts of the country and may challenge local health authorities. However, data is still scarce in certain local areas as well as in the Eastern, Northern border, Tabuk, and Najran regions. OXA-48 β-lactamase and NDM-1 β-lactamase are a prevalent gene responsible in CR strains in Saudi Arabia. The high rates of resistant Enterobacterials in Saudi Arabia call for comprehensive surveillance programs to understand the origins and extent of the CR problem in depth as a major step to controlling the menace, developing a local antibiogram database coupled with nationwide antimicrobial stewardship and an infection prevention program might help in improving the knowledge of CR patterns.

Multiple complex risk factors associated with CR infection to the hospital environment, patient comorbidities, duration of hospital admission, ICU complexity, intercurrent illness and the usage of antimicrobial agents contribute to the spread of CR infection. The findings of risk factors associated with CR infection may help clinicians and hospital epidemiologists estimate the likelihood of CR infection in different situations, and thereby initiate timely, targeted treatment and prevention measures.

Colistin, tigecycline, and a combination of carbapenem-containing regimens are the mainstay of the current treatment options. However, new antimicrobials such as avibactam, plazomicin, or siderophore cephalosporins are promising and the research efforts should be focused on the molecular basis of CR and discovering new therapies.

References

1. Codjoe, F. S. and E. S. Donkor (2018). "Carbapenem resistance: a review." Medical Sciences 6(1): 1.
2. Aslam, B., M. Rasool, S. Muzammil, A. B. Siddique, Z. Nawaz, M. Shafique, M. A. Zahoor, R. Binyamin, M. Waseem and M. Khurshid (2020). "Carbapenem resistance: Mechanisms and drivers of global menace." Pathog. Bact.
3. Pittet, D., B. Allegranzi, J. Storr, S. B. Nejad, G. Dziekan, A. Leotsakos and L. Donaldson (2008). "Infection control as a major World Health Organization priority for developing countries." Journal of Hospital Infection 68(4): 285–292.
4. Islam, T. A. B., S. Shamsuzzaman, N. Nehar and J. Fardows (2016). "Prevalence and Antibiogram of Microbial Agents Causing Nosocomial Urinary Tract Infection in Surgical Ward of Dhaka Medical College Hospital." Journal of Enam Medical College 6(2): 75–79.
5. Meletis, G. (2016). "Carbapenem resistance: overview of the problem and future perspectives." Therapeutic advances in infectious disease 3(1):15–21.
6. Aruhomukama, D., C. F. Najjuka, H. Kajumbula, M. Okee, G. Mboowa, I. Sserwadda, R. Mayanja, M. L. Joloba and D. P. Kateete (2019). "Bla VIM- and bla OXA-mediated carbapenem resistance among Acinetobacter baumannii and Pseudomonas aeruginosa isolates from the Mulago hospital intensive care unit in Kampala, Uganda." BMC Infectious Diseases 19(1):1–8.
7. Dortet, L., G. Cuzon, V. Ponties and P. Nordmann (2017). "Trends in carbapenemase-producing Enterobacteriaceae, France, 2012 to 2014." Eurosurveillance 22(6): 30461.
8. De Oliveira, D. M., B. M. Forde, T. J. Kidd, P. N. Harris, M. A. Schembri, S. A. Beatson, D. L. Paterson and M. J. Walker (2020). "Antimicrobial resistance in ESKAPE pathogens." Clinical Microbiology Reviews 33(3):e00181-00119.
9. Pouch, S. M. and M. J. Satlin (2017). "Carbapenem-resistant Enterobacteriaceae in special populations: solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies." Virulence 8(4): 391–402.
10. Di Domenico, E. G., I. Cavallo, F. Sivori, F. Marchesi, G. Prignano, F. Pimpinelli, I. Sperduti, L. Pelagalli, F. Di Salvo and I. Celesti (2020). "Biofilm Production by Carbapenem-Resistant Klebsiella pneumoniae significantly increases the risk of death in oncological patients." Frontiers in cellular and infection microbiology 10.
11. Sundaramoorthy, N. S., S. Thothathri, M. Bhaskaran, A. GaneshPrasad and S. Nagarajan (2021). "Phages from Ganges River curtail in vitro biofilms and planktonic growth of drug resistant Klebsiella pneumoniae in a zebrafish infection model." AMB Express 11(1):1–11.
12. Di Domenico, E. G., I. Cavallo, F. Sivori, F. Marchesi, G. Prignano, F. Pimpinelli, I. Sperduti, L. Pelagalli, F. Di Salvo and I. Celesti (2021). "Biofilm Production

by Carbapenem." Enterobacteriaceae Antimicrobial Agents and Resistance: Relationship with the Therapeutic Approach.

13. Ibrahim, M. E. (2019). "Prevalence of Acinetobacter baumannii in Saudi Arabia: risk factors, antimicrobial resistance patterns and mechanisms of carbapenem resistance." Annals of clinical microbiology and antimicrobials 18(1):1–12.
14. Weber, D. J., E. E. Sickbert-Bennett, H. Kanamori and W. A. Rutala (2019). "New and emerging infectious diseases (Ebola, Middle Eastern respiratory syndrome coronavirus, carbapenem-resistant Enterobacteriaceae, Candida auris): Focus on environmental survival and germicide susceptibility." American journal of infection control 47:A29–A38.
15. Julia, L., K. Vilankar, H. Kang, D. E. Brown, A. Mathers and L. E. Barnes (2017). Environmental reservoirs of nosocomial infection: imputation methods for linking clinical and environmental microbiological data to understand infection transmission. AMIA Annual Symposium Proceedings, American Medical Informatics Association.
16. Mills, J. P., N. J. Talati, K. Alby and J. H. Han (2016). "The epidemiology of carbapenem-resistant Klebsiella pneumoniae colonization and infection among long-term acute care hospital residents." infection control & hospital epidemiology 37(1):55–60.
17. Zhu, W., Z. Yuan and H.-y. Zhou (2020). "Risk factors for carbapenem-resistant Klebsiella pneumoniae infection relative to two types of control patients: a systematic review and meta-analysis." Antimicrobial Resistance & Infection Control 9(1):1–13.
18. Barber, K. E., J. L. Wagner, R. C. Larry and K. R. Stover (2021). "Frequency of and risk factors for carbapenem-resistant Enterobacteriaceae." Journal of Medical Microbiology 70(2).
19. Morgan, D. J., I. N. Okeke, R. Laxminarayan, E. N. Perencevich and S. Weisenberg (2011). "Non-prescription antimicrobial use worldwide: a systematic review." The Lancet Infectious Diseases 11(9):692–701.
20. Ssekatawa, K., D. K. Byarugaba, E. Wampande and F. Ejobi (2018). "A systematic review: the current status of carbapenem resistance in East Africa." BMC Research Notes 11(1):1–9.
21. Khan, M. A., A. M. Mohamed, A. Faiz and J. Ahmad (2019). "Enterobacterial infection in Saudi Arabia: First record of Klebsiella pneumoniae with triple carbapenemase genes resistance." The Journal of Infection in Developing Countries 13(04):334–341.
22. Al Hassinah, S., M. Alzayer, L. Okdah, M. Doumith, S. Al Johani, R. Alarfaj, E. Alrashidi, N. Alhuseinan, B. A. Alwan and B. Bakhashween (2020). "Prevalence of Molecular Mechanisms of Carbapenem Resistance in Pseudomonas aeruginosa clinical isolates from Saudi Arabia." Journal of Infection and Public Health 13(2):329.
23. Al Mutair, A., S. Alhumaid, Z. Al Alawi, A. R. Z. Zaidi, A. J. Alzahrani, J. A. Al-Tawfiq, H. Al-Shammari, A. A. Rabaan, O. Khojah and A. Al-Omari (2021). "Five-year resistance trends in pathogens causing healthcare-associated infections at a multi-hospital healthcare system in Saudi Arabia, 2015–2019." Journal of global antimicrobial resistance 25:142–150.
24. Alqahtani, M., I. Tickler, Z. Al Deesi, W. AlFouzan, A. Al Jabri, R. Al Jindan, S. Al Johani, S. Alkahtani, A. Al Kharusi and E. Mokaddas (2021). "Molecular detection of carbapenem resistance genes in rectal swabs from patients in Gulf Cooperation Council hospitals." Journal of Hospital Infection 112:96–103.
25. Bandy, A. and B. Tantry (2021). "ESBL Activity, MDR, and Carbapenem Resistance among Predominant Enterobacterales Isolated in 2019." Antibiotics 10(6):744.
26. Sobia, F., S. N. Qurashi and K. Y. Ghailan (2021). "Occurrence of blaCTX-MGp1 and blaCTX-MGp26 in third generation cephalosporin-resistant and carbapenem-resistant bacterial isolates from southwest region of Saudi Arabia-a preliminary study." Saudi Journal of Biological Sciences 28(9): 5408–5413.
27. Hala, S., C. P. Antony, M. Alshehri, A. O. Althaqafi, A. Alsaedi, A. Mufti, M. Kaaki, B. T. Alhaj-Hussein, H. M. Zowawi and A. Al-Amri (2019). "First report of Klebsiella quasipneumoniae harboring bla KPC-2 in Saudi Arabia." Antimicrobial Resistance & Infection Control 8(1):1–8.
28. Jawhar, W. N. B., M. M. AlRashed, A. M. Somily and A. M. AlBarrag (2020). "Molecular characterization of carbapenem-resistance genes among Pseudomonas aeruginosa and acinetobacter baumannii clinical isolates in Riyadh." Pharmacophore 11(6).
29. Al-Zahrani, I. A. and B. A. Alasiri (2018). "The emergence of carbapenem-resistant Klebsiella pneumoniae isolates producing OXA-48 and NDM in the Southern (Asir) province, Saudi Arabia." Saudi medical journal 39(1):23.
30. El-Badawy, M. F., S. F. Abdelwahab, S. A. Alghamdi and M. M. Shohayeb (2019). "Characterization of phenotypic and genotypic traits of carbapenem-resistant Acinetobacter baumannii clinical isolates recovered from a tertiary care hospital in Taif, Saudi Arabia." Infection and drug resistance 12:3113.
31. Shah, M. W., M. Yasir, M. Farman, A. A. Jiman-Fatani, S. B. Almasaudi, M. Alawi, D. El-Hossary and E. I. Azhar (2019). "Antimicrobial susceptibility and molecular characterization of clinical strains of Acinetobacter baumannii in Western Saudi Arabia." Microbial Drug Resistance 25(9):1297–1305.
32. Talal, L. (2019). "Phenotypic and genotypic characterization of carbapenem-resistant Enterobacteriaceae in Bahrain and Saudi Arabia." Journal of Infection and Public Health 12(2):299.
33. Al-Zahrani, Ibrahim, Al-Ahmadi and Bashaer (2021). "Dissemination of VIM-producing Pseudomonas aeruginosa associated with high-risk clone ST654 in a tertiary and quaternary hospital in Makkah, Saudi Arabia." Journal of Chemotherapy 33(1):12–20.
34. Khater, E. S., A. A. AlFaki and S. S. Abd Elmoaty (2020). "Carbapenem-Resistant Klebsiella pneumonia Isolated from Patients Admitted in Tertiary Care Hospital in Saudi Arabia." Journal of Advances in Microbiology:76–85.
35. Aleidan, F. A., H. Alkhelaifi, A. Alsenaid, H. Alromaizan, F. Alsalham, A. Almutairi, K. Alsulaiman and A. G. Abdel Gadir (2021). "Incidence and risk factors of carbapenem-resistant Enterobacteriaceae infection in intensive care units: a matched case–control study." Expert Review of Anti-infective Therapy 19(3):393–398.
36. Alotaibi, F. (2019). "Carbapenem-resistant Enterobacteriaceae: an update narrative review from Saudi Arabia." Journal of Infection and Public Health 12(4):465–471.
37. Alotaibi, F. E., E. E. Bukhari, M. M. Al-Mohizea, T. Hafiz, E. B. Essa and Y. I. AlTokhais (2017). "Emergence of carbapenem-resistant Enterobacteriaceae isolated from patients in a university hospital in Saudi Arabia. Epidemiology, clinical profiles and outcomes." Journal of Infection and Public Health 10(5):667–673.
38. Abdallah, M., R. Alhababi, N. Alqudah, B. Aldyyat and A. Alharthy (2018). "First report of carbapenem-resistant Providencia stuartii in Saudi Arabia." New Microbes and New Infections 26:107–109.
39. Alghoribi, M. F., K. Binkhamis, A. A. Alswaji, A. Alhijji, A. Alsharidi, H. H. Balkhy, M. Doumith and A. Somily (2020). "Genomic analysis of the first KPC-producing Klebsiella pneumoniae isolated from a patient in Riyadh: A new public health concern in Saudi Arabia." Journal of Infection and Public Health 13(4):647–650.
40. Al-Abdely, H., R. AlHababi, H. M. Dada, H. Roushdy, M. M. Alanazi, A. A. Alessa, N. M. Gad, A. M. Alasmari, E. E. Radwan and H. Al-Dughmani (2021). "Molecular characterization of carbapenem-resistant Enterobacterales in thirteen tertiary care hospitals in Saudi Arabia." Annals of Saudi Medicine 41(2): 63–70.
41. Abd El Ghany, M., H. Sharaf, M. H. Al-Agamy, A. Shibl, G. A. Hill-Cawthorne and P.-Y. Hong (2018). "Genomic characterization of NDM-1 and 5, and OXA-181 carbapenemases in uropathogenic Escherichia coli isolates from Riyadh, Saudi Arabia." PloS one 13(8): e0201613.
42. Al-Agamy, M. H., A. Aljallal, H. H. Radwan and A. M. Shibl (2018). "Characterization of carbapenemases, ESBLs, and plasmid-mediated quinolone determinants in carbapenem-insensitive Escherichia coli and Klebsiella pneumoniae in Riyadh hospitals." Journal of Infection and Public Health 11(1):64–68.
43. uz Zaman, T., M. Alrodayyan, M. Albladi, M. Aldrees, M. I. Siddique, S. Aljohani and H. H. Balkhy (2018). "Clonal diversity and genetic profiling of antibiotic resistance among multidrug/carbapenem-resistant Klebsiella pneumoniae isolates from a tertiary care hospital in Saudi Arabia." BMC Infectious Diseases 18(1):1–11.
44. Mutair, A. A., S. Alhumaid, Z. A. Alawi, A. R. Z. Zaidi, A. J. Alzahrani, J. Al-Tawfiq, H. Al-Shammari, A. Rabaan, O. Khojah and A. Al-Omari (2021). "Five-year resistance trends in pathogens causing healthcare-associated infections at a multi-hospital healthcare system in Saudi Arabia, 2015-2019." Journal of Global Antimicrobial Resistance.
45. Leangapichart, T., P. Gautret, K. Griffiths, K. Belhouchat, Z. Memish, D. Raoult and J.-M. Rolain (2016). "Acquisition of a high diversity of bacteria during the Hajj pilgrimage, including *Acinetobacter baumannii* with *bla* $_{\text{OXA-72}}$ and *Escherichia coli* with *bla* $_{\text{NDM-5}}$ carbapenemase genes." Antimicrobial agents and chemotherapy 60(10):5942–5948.
46. Faidah, H. S., A. M. Momenah, H. M. El-Said, A. A. Barhameen, S. S. Ashgar, A. Johargy, A. Elsawy, W. Almalki and S. Al Qurashi (2017). "Trends in the annual incidence of carbapenem resistant among gram negative bacilli in a large teaching hospital in Makah City, Saudi Arabia." Journal of Tuberculosis Research 5(04):229.
47. Al-Zalabani, A., O. A. AlThobyane, A. H. Alshehri, A. O. Alrehaili, M. O. Namankani and O. H. Aljafri (2020). "Prevalence of Klebsiella pneumoniae Antibiotic Resistance in Medina, Saudi Arabia, 2014-2018." Cureus 12(8).

48. Al-Hamad, A., T. Pal, H. Leskafi, H. Abbas, H. Hejles, F. Alsubikhy, D. Darwish, A. Ghazawi and A. Sonnevend (2020). "Molecular characterization of clinical and environmental carbapenem resistant Acinetobacter baumannii isolates in a hospital of the Eastern Region of Saudi Arabia." Journal of Infection and Public Health 13(4):632–636.
49. Al Bshabshe, A., A. Al-Hakami, B. Alshehri, K. A. Al-Shahrani, A. A. Alshehri, M. B. Al Shahrani, I. Assiry, M. R. Joseph, A. Alkahtani and M. E. Hamid (2020). "Rising Klebsiella pneumoniae infections and its expanding drug resistance in the intensive care unit of a tertiary Healthcare Hospital, Saudi Arabia." Cureus 12(8).
50. Alzomor, O. A., T. S. Alfawaz, A. Abu-Shaheen, M. A. Alshehri and D. Al Shahrani (2019). "A matched case-control study to assess the carbapenem-resistant Enterobacteriaceae infections among hospitalized children at King Fahad Medical City, Riyadh, Saudi Arabia." Saudi Medical Journal 40(11):1105.