Progress and Epidemiology of Carbapenem-Resistant Enterobacteriaceae in Saudi Arabia from 2019 to 2023

Yagoub Hamadt Allah Elhaj[1*]
Assistant Professor of Medical Microbiology, Laboratory Medicine, Applied Medical Sciences, Al-Baha University, Albaha, Saudi Arabia *E-mail: yelhaj@bu.edu.sa ORCID: 0000-0002-9464-4768

Abstract

Background: Carbapenem-resistant Enterobacteriaceae (CRE) are a major community health risk due to their resistance to last-line antibiotics. **The Aim**: This systematic review investigated the development and epidemiology of CRE in Saudi Arabia. **Methods:** Electronic databases were searched for studies published between 2019 and 2023, focusing on CRE in Saudi Arabia. A total of 21 studies met the inclusion criteria and were included in the review. **Results:** The results revealed a varying prevalence of CRE crossways different areas of Saudi Arabia, with rates ranging from 03% to 62.6%. Molecular mechanisms of resistance were primarily mediated by carbapenemases. Among the Enterobacteriaceae species, *Acinetobacter baumannii* has a prevalence of 23.21%, *Klebsiella pneumoniae*, has a prevalence of 17.22%. The prevalence of *Enterobacterales*, a wider category that includes *various Enterobacteriaceae species*, is reported to be 22.80%. *Escherichia coli*, has a prevalence of 23.08%. *Proteus mirabilis, Klebsiella spp., Pseudomonas aeruginosa, Enterobacter cloacae, Morganella morganii,* and *Enterobacter aerogenes* show higher prevalence rates of carbapenem resistance, ranging from 86.21% to 100%. These findings indicate a critical challenge in managing infections caused by these species, as carbapenems are often considered as last-resort antibiotics. The total prevalence of carbapenem resistance among the Enterobacteriaceae species is reported to be 22.23%. This highlights the significant burden of carbapenem resistance in Saudi Arabia and emphasizes the urgent need for effective strategies to prevent the spread of resistant strains and preserve the efficacy of carbapenem antibiotics. **Conclusion and Recommendation:** It is important to note that these results are subject to limitations, including variations in study design, sample size, and geographical representation.

Keywords:.Carbapenem resistance**,** *Enterobacteriaceae, Acinetobacter baumannii, Klebsiella pneumoniae*

Introduction:

Carbapenem resistance (CR) bacteria is a significant and increasing health concern worldwide (Codjoe and Donkor, 2017, Aslam et al., 2020), this problem is serious by inadequate infection control in developing countries due to such as short surveillance data, and lack of awareness regarding nosocomial infections(Pittet et al., 2008, Islam et al., 2016) 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(Meletis, 2016, Aruhomukama et al., 2019),the most effective carbapenemases, in terms of carbapenem hydrolysis and globally spread, are KPC, VIM, IMP, NDM and OXA-48 genotypes(Dortet et al., 2017).

Carbapenem classes have been a support of treatment for serious infections caused by Enterobacterales, but efficacy has been compromised by the widespread acquisition of resistance genes to these critical drugs(De Oliveira et al., 2020). Effective antimicrobial options for Carbapenem-Resistant *Enterobacterales* (CRE) are often missing, and treatment typically needs reliance on drugs with a risk of toxicity or other safety concerns(Pouch and Satlin, 2017). Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is a prominent cause of nosocomial infections associated with high rates of morbidity and mortality, mainly in immune-compromised persons(Di Domenico et al., 2020, Sundaramoorthy et al., 2021).Carbapenem resistance causes a broad spectrum of diseases including pneumonia, urinary tract infections, bloodstream infections, skin, and soft tissue infections(Di Domenico et al., 2020). This resistance is enabled by complex factors, including the existence of movable genetic elements, the misuse of antimicrobial medicines, poor infection control practices, and amplified global portable(Ibrahim, 2019).

In healthcare situations, CRE is spread from person to person, often via the hands of healthcare employees or through contaminated medical kit(Weber et al., 2019). Additionally, sink drains and toilets are increasingly documented as an environmental reservoir and CRE transmission source(Julia et al., 2017). Risk factors for CRE settlement and infection have been recognized 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 exact use of carbapenems(Mills et al., 2016, Zhu et al., 2020, Barber et al., 2021).

Significance of the study:

The significance of this study, it is highlights that CRE poses a significant community health risk due to its resistance to last-line antibiotics. This signifies the urgent need for effective strategies to prevent the spread of resistant strains and preserve the efficacy of carbapenem antibiotics. Also the study reveals varying prevalence rates of CRE across different areas of Saudi Arabia, the molecular mechanisms of resistance were primarily mediated by carbapenemases.

Furthermore, the study underscores the urgent need for effective strategies to prevent the spread of carbapenem-resistant strains in Saudi Arabia. This includes implementing robust infection control measures, promoting judicious use of antibiotics, and enhancing surveillance and monitoring systems to detect and respond to emerging resistance patterns.

In conclusion, this study sheds light on the significant burden of carbapenem resistance in Saudi Arabia, demonstrates the urgent need for effective strategies to prevent the spread of resistant strains, and emphasizes the importance of preserving the efficacy of carbapenem antibiotics. These findings have implications for public health policy and infection control measures in the region.

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Aim of the study:

The aim of this systematic review was to shed light on all studies tackling Carbapenem resistance in *Enterobacteriaceae* in the Saudi Arabia regions, the prevalence of carbapenem resistance, and CR encoding genes detected based on Saudi data published over last 5 years from 2019 to 2023

Research question: What is the prevalence and molecular profile of carbapenem-resistant Enterobacteriaceae (CRE) in Saudi Arabia from 2019 to 2023, and what are the specific species and their associated rates of carbapenem resistance?

Methods:

PubMed, Science Direct and international Journals Online databases, Google scholar were searched electronically from 2019 to October 2023. The search key words used were carbapenem resistance in Saudi Arabia, *Klebsiella*, CRKP, *Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacteriaceae, CRE, Escherichia coli*, CREC, carbapenem, carbapenemase, 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/and molecular genotyping frequency of carbapenem resistance in clinical pathogens isolated from patients or showed the proportion of carbapenem resistant isolates of all Gram-negative isolates, or/and antibiotic treatment in all Saudi Arabia regions.

Patient populations of all hospital types were included while case reports and review articles were excluded from this systematic review as it has become conservative(Morgan et al., 2011, Ssekatawa et al., 2018).

Data Extraction:

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

I conducted the extraction of data and evaluated the risk of bias. I carefully reviewed each data point and resolved any discrepancies through a consensus process. The Cochrane RoB2 tool was employed for assessing the risk of bias, including the Bias domain; bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in selection of the reported result.

Statistical analysis:

The statistical analysis was performed using SPSS version 20. We computed the prevalence rate and molecular profile of carbapenem-resistant Enterobacteriaceae (CRE) in Saudi Arabia between 2019 and 2023. Additionally, we determined the rates of specific species and their corresponding rates of carbapenem resistance.

Results

The emergence and quick spread of carbapenem-resistant gram negative in Saudi Arabia encouraged scientific researchers to investigate CR associated infection prevalence and the genes involved in resistance to carbapenems.

The current study adhered to the PRISMA guidelines. After conducting an initial search across various electronic databases and resources, a total of 1202 records were identified. Among these, 294 articles were duplicates found in multiple databases, and they were eliminated using ENDNOTE software. Additionally, 804 articles with titles unrelated to the study or conducted in other countries were excluded. The remaining records underwent a screening process (refer to Fig.1).

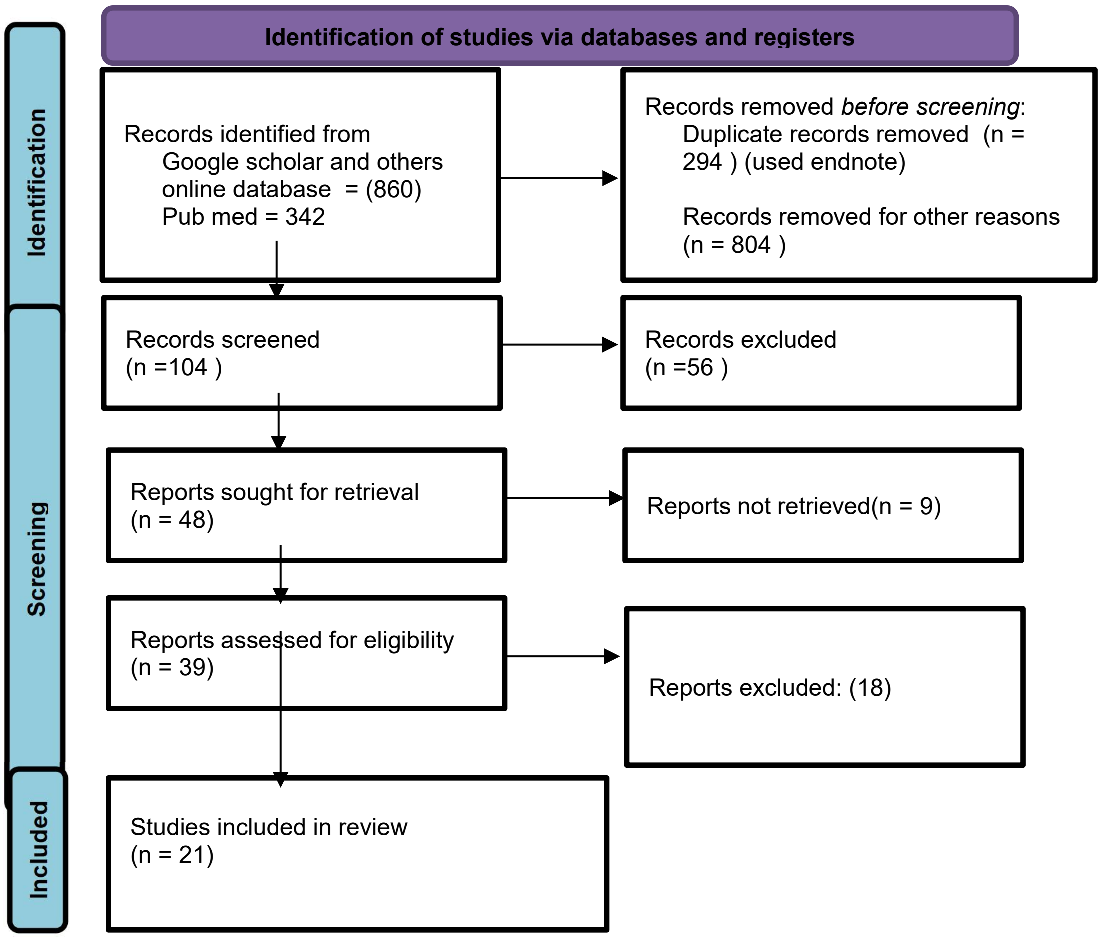

Figure 1 PRISMA flow diagram for search results

Table1: Participating cities, CR prevalence and molecular classification of CR isolates in Saudi Arabia

City	Number of isolates	CR isolates	CR %	Carbapenemase genes detected
Riyadh and Qassum	164681	37936	23%	ESBL (53.3%), KPC (11.5%), OXA-48 (1.3%) & NDM (0.67%)
Makkah	295	84	28.5%	blaOXA blaVIM blaNDM1 blaOXA VIM (31%), & GES (8.6% OXA-48 (100%), NDM-1 (84.7%), & KPC (73.1%)
Medina	15,708	8561	54.5%	
Jeddah	226	201	88.9%	blaOXA-48 blaNDM blaVIM blaKPC OXA-51 (100%), OXA-23 (92%), IMP (84%), NDM-1 (1.3%), OXA-24/40 (5.3%), VIM (92%), TEM (84%), & SHV (10.7%)
Taif	45	32	71%	OXA-51 (100%), IMP (87.5%), NDM (62.5%), OXA-23 (59.4%), VIM (9.3%), & OXA-40 (3.1%)
Al-Quwayiyah	78	36	46.2%	OXA-48 (77.8%), NDM (13.9%), KPC (5.6%), IMP (2.8%), & OXA-48 & NDM (13.9%
Al- Qatif	74	3	4.1%	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%)
Dammam	45	9	20%	GES - OXA-48
Al-Jouf	617	198	32%	
Jizan	100	44	44%	blaCTX-MGp1 and blaCTX-MGp26 CTX-M (70%), SHV (16%), TEM (12%), & NDM-1 (0%).
Abha	330	161	48.8	OXA-48 (81.5%), NDM (7.4%), & VIM (1.8%)
Bisha	311	120	38.6	ESBL

Table 2. Review of carbapenem resistance studies in various areas of Saudi Arabi

No	City	No of isolates	CR (%)	Organisms	Method used	reference
1	Riyadh	152	36.18%	Klebsiella pneumoniae	Phoenix BD instrument (BectonDickinson Diagnostic Systems, Sparks, MD, USA)	(Hafiz et al., 2023)
2	Makkah	175	79.4%	Acinetobacter baumannii.(n= 15) Enterobacter aerogenes (n= 1) Escherichia coli(n=1). Klebsiella oxytoca(n= 2). Klebsiella pneumoniae(n= 115). Morganella morganii(n= 1) Proteus mirabilis(n= 1) Pseudomonas aeruginosa(n= 3)	Pos Breakpoint Combo Panel Type 50 in MicroScan (Beckman Coulter Inc., CA, United States).	Kabrah, A, et al. (2022)
3	Makkah	-	N= 23	Klebsiella pneumoniae	MicroScan and VITEK2	(Booq, R. Y, et al 2022)
4	. Riyadh & Qassim	162,665	23.2% (37738)	Enterobacterales (14%), E. coli (6.4%), K. pneumoniae (9.6%), A. bauman	VITEK-II BD Phoenix MicroScan plus	Mutair, A. A,et al (2021)
5	Riyadh	1,864	7.6%	-	VITEK-II XpertCarba- R assay	Aleidan, F. A, et al (2021)
6	Al-Quwayiyah	78	46.2%	K. pneumoniae	VITEK-II D70C MHT PCR	Khater, E. S, et al (2020)
7	Makkah	-	N=35	Pseudomonas aeruginosa	PCR MLST	Al-Zahrani, et al (2021)
8	Medina	15,708	8.4% for Imipenem 46.1% for Meropenem	K. pneumoniae	VITEK-II	Al-Zalabani, A et al,(2020)
9	Jeddah	191	94.76%	Klebsiella spp	VITEK 2 automated identification system (bioMérieux).	Alhazmi, W, et al , (2022)

No	City	No of isolates	CR (%)	Organisms	Method used	reference
10	Taif	45 of Acinetobacter spp	71%	A. baumannii	VITEK-II Disk diffusion ERIC-PCR	El-Badawy, et al, (2019)
11	Jeddah	35 of A. baumannii	55.6%	A. baumannii	VITEK-II PCR	Shah, M. W., et al (2019)
12	Makkah	120	21.7%	K. pneumoniae	TEK-II Disk PCR	Khan, M. A., et al, (2019)
13	Al- Qatif	53	2.8%	A. baumannii	BD Phoenix PCR WGS	Al-Hamad, A., et al (2020)
14	Dammam	45	20%	P. aerugenosa	PCR	Doumith, M., et al, (2022)
15	Al-Jouf	617 of Enterobacterales	32%	K. pneumoniae (63%), P. mirabilis (29%), & E. coli (8%)	BD Phoenix	Bandy, A. and B. Tantry (2021)
16	Jizan	50	10% for imipenem 12% for meropenem	E. coli (50%), K. pneumoniae (40%), A. baumanii (4%), P. aeruginosa (4%), & E. cloacae (2%)	CDT VITEK-II PCR	Sobia, F., S. N. Qurashi and K. Y. Ghailan (2021)
17	Abha	276 of K. pneumoniae	1.7% for Meropenem 44.5% for Imipenem	K. pneumoniae	VITEK-II	Al Bshabshe, A., et al, (2020)
18	Abha	54 of K. pneumoniae	3% for Imipenem 57.4% for Meropenem	K. pneumoniae	VITEK-II E-test PCR	Al-Zahrani, I. A. and B. A. Alasiri (2018)
19	Qatif	21	2.8	Acinetobacter baumannii	PCR	Al-Hamad, A., et al (2020)
20	Bisha	311	38.58	K. pneumoniae E. coli Acinetobacter spp. P. aeruginosa Proteus mirabilis Enterobacter cloacae	Phoenix system identification method (Becton, Dickinson, USA)	Ibrahim, M. E., et al, (2019)
21	Jizan	50	22	Escherichia coli (25), Klebsiella pneumoniae (20), Acinetobacter baumanii (2), Pseudomonas aeruginosa (2), and Enterobacter cloacae	PCR	Sobia, F.,et al (2021)

Table3: Frequency and percentage of carbpenem resistance Enterobacteriaceae:

Organism	Number of isolates	Carbapenem Resistance	
		N	%
Acinetobacter baumannii	114191	26508	23.21%
Klebsiella pneumoniae	33623	5791	17.22%
Enterobacterales	23173	5283	22.80%
Escherichia coli	10905	2517	23.08%
Proteus mirabilis	232	200	86.21%
Klebsiella spp	191	181	94.76%
Pseudomonas aerugenosa	139	35	25.18%
Enterobacter. Cloacae	54	22	40.74
Morganella morganii	1	1	100%
Enterobacter aerogenes	1	1	100%
TOTAL	182510	40574	22.23%

Discussion

The prevalence of carbapenem resistance in diverse cities of Saudi Arabia, as reported in this research, highlights the regional dissimilarity in the problem of carbapenem-resistant Enterobacteriaceae (CRE). These results can be likened and discussed in the context of previous studies to gain a well understanding of the trends and patterns of carbapenem resistance in the state.

The prevalence rates stated in this study display that Riyadh and Qassum have a relatively lower prevalence of carbapenem resistance at 23%. This finding aligns with a study by Al-Agamy et al. (2016)(Al-Agamy et al., 2016), which reported a prevalence of 21.4% in Riyadh. However, it is important to note that the prevalence rates can vary over time due to changes in infection control practices, antibiotic use, and other factors.

Makkah, with a prevalence of 28.5%, expressions a slightly higher rate compared to Riyadh and Qassum. This finding is consistent with a study by Al-Agamy et al. (2014) (Al-Agamy et al., 2014), which reported a prevalence of 30.4% in Makkah. The higher prevalence in Makkah could be attributed to factors such as population compactness, healthcare utilization, and antibiotic prescribing practices.

Medina stands out with a significantly higher prevalence of 54.5%. This finding is consistent with a study by Al-Agamy et al. (2014) (Al-Agamy et al., 2014), which reported a prevalence of 50% in Medina. The higher prevalence in Medina could be influenced by factors such as the influx of pilgrims during the Hajj season, which may contribute to the spread of CRE.

Jeddah, with the highest reported prevalence of 88.9%, indicates a substantial burden of carbapenem resistance in this city. This finding is consistent with previous studies by Al-Agamy et al. (2014) and Alghoribi et al. (2015)(Alghoribi et al., 2015, Al-Agamy et al., 2014), which reported high prevalence rates of 85.7% and 90.9% in Jeddah, respectively. The high prevalence in Jeddah could be attributed to factors such as the presence of tertiary care hospitals, international travel, and a higher density of healthcare facilities.

Other cities, such as Taif (71%), Alquwayiyah (46.2%), Al-Qatif (4.1%), Dammam (20%), Al-Jouf (32%), Jizan (44%), Abha (48.8%), and Bisha (38.6%), also show varying prevalence rates. These results provide insights into the regional distribution of carbapenem resistance in Saudi Arabia.

These prevalence rates indicate the varying levels of carbapenem resistance in different regions of Saudi Arabia. The higher prevalence rates in cities like Jeddah, Taif, and Medina suggest a more significant problem of carbapenem-resistant *Enterobacteriaceae* (CRE) in those areas. This information is crucial for understanding the regional distribution of CRE and can help guide targeted interventions and infection control measures in areas with higher prevalence rates.

As described in **table 2** the number of published articles per year was clearly increased and indicated by the highest number recorded in 2020 and 2021. This is closely related to the distribution of CRE through the country and the increased awareness of the importance of surveillance and control of multidrug-resistant bacteria in order to improve health class. A high prevalence of carbapenemase producers in Saudi Arabia was mainly identified as *A. baumannii*, followed by *Klebsiella pneumoniae*.

The majority number of published research papers per carbapenemase type was OXA, from almost genotyping studies, OXA-48 different in *Enterobacteriaceae* and OXA-23 variant in A. *baumannii, and P. aeruginosa*, followed by NDM-1. However, low number of published articles about (8 studies) has reported the detection of VIM genes. Detection of VIM genes was reported in 4 studies while IMP was reported by El-Badawy, Abdelwahab et al. 2019, Jawhar, AlRashed et al. 2020, Khater, AlFaki et al. 2020, Alqahtani, Tickler et al. 2021) (El-Badawy et al., 2019, Jawhar et al., 2020, Khater et al., 2020, Alqahtani et al., 2021) and KPC genes was reported in 5 studies. 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 21 studies met the inclusion criteria and were included for final review, there was no data reported from Najran, Tabuk and North border regions. Also, 19 out of 21 studies (90.48%) reported genotype including carbapenemase or β-lactamase genes distribution and 21 studies (100%) reported clinical CR isolates. The regional distribution of the different carbapenemases gene prevalence were mapped in Saudi Arabia from five years up to date and regional distribution CR prevalence in *Enterobacterales* over several Saudi regions were mapped (tables 1,2)

It is important to note that these prevalence rates are specific to the cities mentioned and may not represent the overall prevalence of carbapenem resistance in Saudi Arabia. Further research and surveillance are needed to obtain a comprehensive understanding of the prevalence and distribution of CRE throughout the country, see table (1).

Table (3): indicate the prevalence and distribution of Enterobacteriaceae and the percentage of carbapenem resistance among different species. The interpretation and discussion of these finding can provide insights into the epidemiology and implications of carbapenem resistance in these bacterial species.

Among the *Enterobacteriaceae species*, *Acinetobacter baumannii* has a prevalence of 23.21%. This result is consistent with previous studies that have identified *A. baumannii* as a significant contributor to healthcare-associated infections and its association with carbapenem resistance (Al-Agamy et al., 2014)(Al-Agamy et al., 2014). *Klebsiella pneumoniae,* another important member of the Enterobacteriaceae family, has a prevalence of 17.22%. *K. pneumoniae* is known for its ability to acquire and disseminate carbapenem resistance genes, leading to challenging infections in healthcare settings (Alghoribi et al., 2015)(Alghoribi et al., 2015).

The prevalence of *Enterobacterales*, a broader group that includes various Enterobacteriaceae species, is reported to be 22.80%. This finding suggests a significant burden of carbapenem resistance within this group, highlighting the need for effective infection control measures and antimicrobial stewardship programs.

Escherichia coli, a common cause of urinary tract infections and other community-acquired infections, has a prevalence of 23.08%. The emergence of carbapenem resistance in *E. coli* is a concerning trend, as it limits treatment options for these infections (Alghoribi et al., 2015)(Alghoribi et al., 2015).

Proteus mirabilis, Klebsiella spp., Pseudomonas aeruginosa, Enterobacter cloacae, Morganella morganii, and *Enterobacter aerogenes* show higher prevalence rates of carbapenem resistance, ranging from 86.21% to 100%. These findings indicate a critical challenge in managing infections caused by these species, as carbapenems are often considered as last-resort antibiotics.

The overall prevalence of carbapenem resistance among the enterobacteriaceae species is reported to be 22.23%. This highlights the significant burden of carbapenem resistance in Saudi Arabia and highlights the urgent need for effective strategies to prevent the spread of resistant strains and preserve the efficacy of carbapenem antibiotics.

Conclusion:

This systematic review emphasizes the critical need for comprehensive strategies to address CRE. These strategies should include: Educating healthcare professionals and the public about CRE and its prevention, promoting rational antibiotic use and implementing antimicrobial stewardship programs, investing in research to develop new diagnostics and treatment options. Moreover, it is important to note that the prevalence rates reported in this study and their comparison with previous studies are subject to limitations, including variations in study design, sample size, and methodology. Further research and surveillance are needed to validate and update these findings, considering the dynamic nature of antimicrobial resistance. By implementing these strategies, Saudi Arabia can work towards reducing the burden of CRE and improving public health outcomes.

References:

AL-AGAMY, M. H., JEANNOT, K., EL-MAHDY, T. S., SAMAHA, H. A., SHIBL, A. M., PLESIAT, P. & COURVALIN, P. 2016. Diversity of molecular mechanisms conferring carbapenem resistance to Pseudomonas aeruginosa isolates from Saudi Arabia. *Canadian Journal of Infectious Diseases and Medical Microbiology,* 2016.

AL-AGAMY, M. H., SHIBL, A. M., HAFEZ, M. M., AL-AHDAL, M. N., MEMISH, Z. A. & KHUBNANI, H. 2014. Molecular characteristics of extended-spectrum β-lactamase-producing Escherichia coli in Riyadh: emergence of CTX-M-15-producing E. coli ST131. *Annals of clinical microbiology and antimicrobials,* 13**,** 1-7.

ALGHORIBI, M. F., GIBREEL, T. M., FARNHAM, G., AL JOHANI, S. M., BALKHY, H. H. & UPTON, M. 2015. Antibiotic-resistant ST38, ST131 and ST405 strains are the leading uropathogenic Escherichia coli clones in Riyadh, Saudi Arabia. *Journal of Antimicrobial Chemotherapy,* 70**,** 2757-2762.

ALQAHTANI, M., TICKLER, I., AL DEESI, Z., ALFOUZAN, W., AL JABRI, A., AL JINDAN, R., AL JOHANI, S., ALKAHTANI, S., AL KHARUSI, A. & MOKADDAS, E. 2021. Molecular detection of carbapenem resistance genes in rectal swabs from patients in Gulf Cooperation Council hospitals. *Journal of Hospital Infection,* 112**,** 96-103.

ARUHOMUKAMA, D., NAJJUKA, C. F., KAJUMBULA, H., OKEE, M., MBOOWA, G., SSERWADDA, I., MAYANJA, R., JOLOBA, M. L. & KATEETE, D. P. 2019. blaVIM-and blaOXA-mediated carbapenem resistance among Acinetobacter baumannii and Pseudomonas aeruginosa isolates from the Mulago hospital intensive care unit in Kampala, Uganda. *BMC infectious diseases,* 19**,** 1-8.

ASLAM, B., RASOOL, M., MUZAMMIL, S., SIDDIQUE, A. B., NAWAZ, Z., SHAFIQUE, M., ZAHOOR, M. A., BINYAMIN, R., WASEEM, M. & KHURSHID, M. 2020. Carbapenem resistance: Mechanisms and drivers of global menace. *Pathogenic Bacteria***,** 1-10.

BARBER, K. E., WAGNER, J. L., LARRY, R. C. & STOVER, K. R. 2021. Frequency of and risk factors for carbapenem-resistant Enterobacteriaceae. *Journal of Medical Microbiology,* 70.

CODJOE, F. S. & DONKOR, E. S. 2017. Carbapenem resistance: a review. *Medical Sciences,* 6**,** 1.

DE OLIVEIRA, D. M., FORDE, B. M., KIDD, T. J., HARRIS, P. N., SCHEMBRI, M. A., BEATSON, S. A., PATERSON, D. L. & WALKER, M. J. 2020. Antimicrobial resistance in ESKAPE pathogens. *Clinical microbiology reviews,* 33**,** e00181-19.

DI DOMENICO, E. G., CAVALLO, I., SIVORI, F., MARCHESI, F., PRIGNANO, G., PIMPINELLI, F., SPERDUTI, I., PELAGALLI, L., DI SALVO, F. & CELESTI, I. 2020. Biofilm production by carbapenem-resistant Klebsiella pneumoniae significantly increases the risk of death in oncological patients. *Frontiers in cellular and infection microbiology,* 10**,** 561741.

DORTET, L., CUZON, G., PONTIES, V. & NORDMANN, P. 2017. Trends in carbapenemase-producing Enterobacteriaceae, France, 2012 to 2014. *Eurosurveillance,* 22**,** 30461.

EL-BADAWY, M. F., ABDELWAHAB, S. F., ALGHAMDI, S. A. & SHOHAYEB, M. M. 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***,** 3113-3124.

HAFIZ, T. A., ALANAZI, S., ALGHAMDI, S. S., MUBARAKI, M. A., ALJABR, W., MADKHALI, N., ALHARBI, S. R., BINKHAMIS, K. & ALOTAIBI, F. 2023. Klebsiella pneumoniae bacteraemia epidemiology: resistance profiles and clinical outcome of King Fahad Medical City isolates, Riyadh, Saudi Arabia. *BMC infectious diseases,* 23**,** 579.

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.

ISLAM, T. A. B., SHAMSUZZAMAN, S., NEHAR, N. & FARDOWS, J. 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**,** 75-79.

JAWHAR, W., ALRASHED, M., **SOMILY, A. & ALBARRA, A. 2020**. Molecular characterization of Carbapenem-resistance genes among Pseudomonas aeruginosa and Acinetobacter baumannii clinical isolates in Riyadh. *Pharmacophore,* 11.

JULIA, L., VILANKAR, K., KANG, H., BROWN, D. E., MATHERS, A. & BARNES, L. E. Year2017. Environmental reservoirs of nosocomial infection: imputation methods for linking clinical and environmental microbiological data to understand infection transmission. In: AMIA Annual Symposium Proceedings, 2017. American Medical Informatics Association, 1120.

KHATER, E. S., ALFAKI, A. A. & ELMOATY, S. S. A. 2020. Carbapenem-Resistant Klebsiella pneumonia Isolated from Patients Admitted in Tertiary Care Hospital in Saudi Arabia. *Journal of Advances in Microbiology,* 20**,** 76-85.

MELETIS, G. 2016. Carbapenem resistance: overview of the problem and future perspectives. *Therapeutic advances in infectious disease,* 3**,** 15-21.

MILLS, J. P., TALATI, N. J., ALBY, K. & HAN, J. H. 2016. The epidemiology of carbapenem-resistant Klebsiella pneumoniae colonization and infection among long-term acute care hospital residents. *Infection Control & Hospital Epidemiology,* 37**,** 55-60.

MORGAN, D. J., OKEKE, I. N., LAXMINARAYAN, R., PERENCEVICH, E. N. & WEISENBERG, S. 2011. Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet infectious diseases,* 11**,** 692-701.

PITTET, D., ALLEGRANZI, B., STORR, J., NEJAD, S. B., DZIEKAN, G., LEOTSAKOS, A. & DONALDSON, L. 2008. Infection control as a major World Health Organization priority for developing countries. *Journal of Hospital Infection,* 68**,** 285-292.

POUCH, S. M. & SATLIN, M. J. 2017. Carbapenem-resistant Enterobacteriaceae in special populations: solid organ transplant recipients, stem cell transplant recipients, and patients with hematologic malignancies. *Virulence,* 8**,** 391-402.

SSEKATAWA, K., BYARUGABA, D. K., WAMPANDE, E. & EJOBI, F. 2018. A systematic review: the current status of carbapenem resistance in East Africa. *BMC research notes,* 11**,** 1-9.

SUNDARAMOORTHY, N. S., THOTHATHRI, S., BHASKARAN, M., GANESHPRASAD, A. & NAGARAJAN, S. 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**,** 1-11.

WEBER, D. J., SICKBERT-BENNETT, E. E., KANAMORI, H. & RUTALA, W. A. 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.

ZHU, W.-M., YUAN, Z. & ZHOU, H.-Y. 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**,** 1-13.