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Prevalence of carbapenem-resistant *Enterobacterales* (CRE) in Saudi Arabia: A systematic review and meta-analysis

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ABSTRACT

Antimicrobial resistance is a significant public health issue. In addressing the threat of multidrug resistant bacterial infections, carbapenems have been used. The carbapenem-resistant *Enterobacterales* (CRE) are, however, rapidly expanding worldwide. Since the issue of CRE is also a problem in Saudi Arabia, the current meta-analysis was performed to comprehensively evaluate the resistance rates to the main carbapenem antibiotics and determine the actual prevalence of CRE in the country. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines was followed. Different web databases including PubMed, Scopus, Web of Science, and ScienceDirect were searched for relevant records. Data were extracted, and summary estimates for resistance to carbapenems were calculated using DerSimonian-Laird method of meta-analysis and the random-effects model. From a total of 787 retrieved records, 69 studies were found fully eligible and were included in the final analyses. More than 50 % of all the studies were conducted after 2010, and the most frequently examined members of the *Enterobacterales* were *Escherichia coli* and *Klebsiella pneumoniae*. The pooled prevalence estimate for imipenem resistance was 6.6 % (95 % CI: 4.7–9.2), 9.1 % (95 % CI: 6.7–12.3) for meropenem, and 18.6 % (95 % CI: 11.9–27.9) for ertapenem. High heterogeneity ($I^2 > 97$ %, $p < 0.001$) was observed for all the estimates. Compared to other regions of the country, there was higher resistance rates in the Al-Qassim and Al-Jouf provinces. Additionally, resistance to ertapenem was as high as 34.2 % in the most recent study period (2021–2024). *Proteus spp* was the most prevalent CRE (26.2 %). This review highlights an increasing rate of carbapenem resistance among *Enterobacterales*, emphasizing the need for collaborative efforts to implement strict infection control and prevention measures. Consistent surveillance is indispensable for safeguarding public health, guiding clinical decisions, and strengthening efforts to tackle the challenges of antibiotic resistance.

1. Introduction

Antimicrobial resistance poses a critical threat to global health, undermining the effectiveness of antibiotics and other antimicrobial agents that are essential for treating infections. The growing prevalence of drug-resistant bacteria leads to increased mortality, prolonged illnesses, and rising healthcare costs, as infections become harder to treat (Ahmed et al., 2019; Rabaan et al., 2022a). Initially, many β-lactam antibiotics such as penicillins, cephalosporins, monobactams, and carbapenems were highly effective against Gram-negative bacilli (Carlet et al., 2012). However, over time, Gram-negative bacteria have developed various resistance mechanisms, such as β-lactamase enzyme production and alterations in membrane permeability, allowing them to evade the effects of these drugs (Carlet et al., 2012). This growing resistance has significantly reduced the effectiveness of these once-dependable antibiotics, making the treatment of Gram-negative infections increasingly difficult and highlighting the urgent need for alternative therapies and improved antimicrobial stewardship (Mustafai et al., 2023).

Carbapenem resistance in *Enterobacterales* is an alarming public health issue, as carbapenems are considered last-resort antibiotics for treating severe infections caused by multidrug-resistant bacteria

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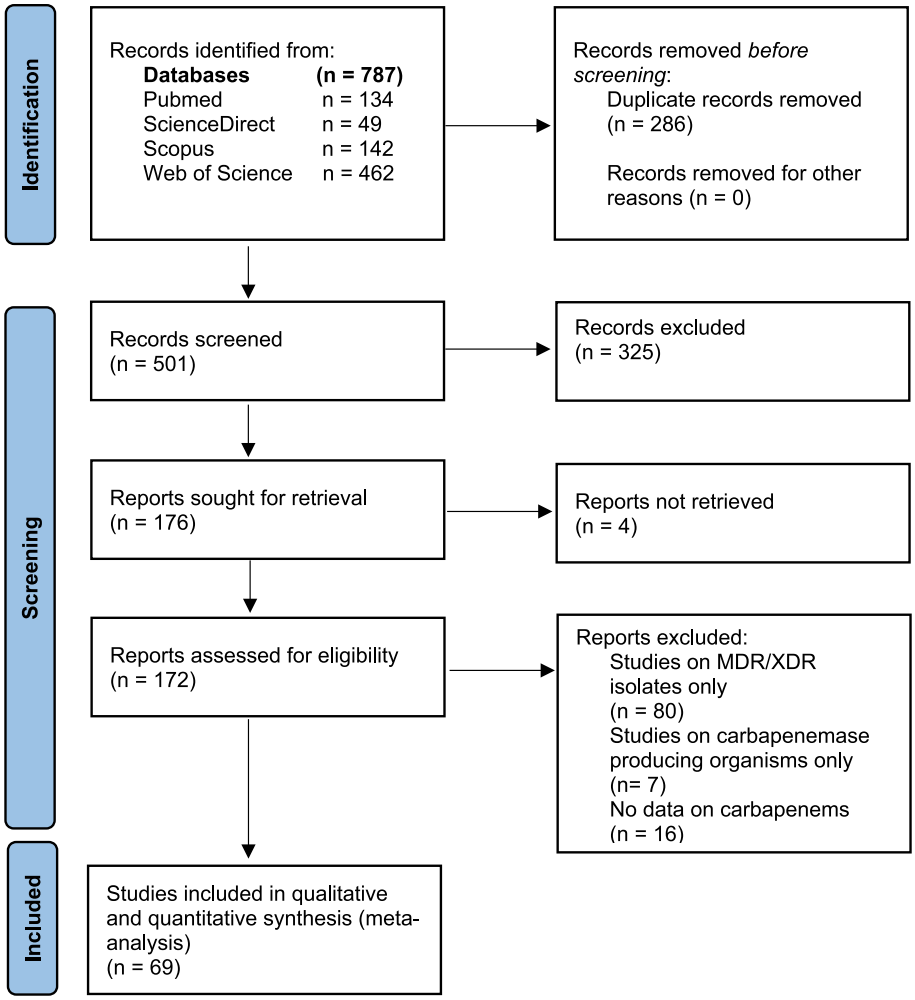

Fig. 1. Process of article search and selection.

(Rabaan et al., 2022b). The rise of carbapenem-resistant *Enterobacterales* (CRE) has led to limited treatment options, higher rates of treatment failure, and increased mortality (Shaikh et al., 2015). Infections caused by CRE are particularly challenging in healthcare settings (Jang et al., 2017; Vila et al., 2016). The emergence of CRE highlights the urgent need for new antibiotics and effective antimicrobial stewardship programs (Ling et al., 2021; Melzer and Petersen, 2007). Carbapenem resistance have been reported among members of the *Enterobacterales*, including *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., *Proteus* spp., *Citrobacter* spp., among others, and the rate of resistance appears to continually increase over the years (Aldrazi et al., 2020; Hansen, 2021; Kotb et al., 2020; Perez and Villegas, 2015).

Carbapenem resistance has risen in Saudi Arabia, likely due to the increased use of antibiotics (Hays et al., 2022; Ibrahim, 2019; Taha et al., 2020). Various studies have indicated a continuous rise in carbapenem resistance within healthcare facilities of Saudi Arabia (Hays et al., 2022; Ibrahim, 2019; Taha et al., 2020). Further, previous studies in Saudi Arabia have reported varying rates of CRE (Aldrazi et al., 2020; Bilal and Gedebou, 2000; Rahim and Mohamed, 2014; Said et al., 2021). This leaves the true prevalence rate unknown. Thus, a comprehensive review of existing data on carbapenem resistance in Saudi Arabia is crucial to accurately assess the prevalence of CRE. Immediate and coordinated action is imperative to combat antimicrobial resistance, including promoting the responsible use of antibiotics, improving infection prevention and control, enhancing public awareness, and investing in the research and development of new treatments and diagnostics. As a result, a thorough investigation was carried out in this study to ascertain the true prevalence of CRE and the resistance rates to the major carbapenem antibiotics in Saudi Arabia. This study, to our knowledge, is the first meta-analysis on CRE in Saudi Arabia. It is hoped that the findings will not only enhance infection control approaches in the country and the world at large but will also promote antibiotic stewardship initiatives.

2. Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009). A study protocol was formulated and registered with PROSPERO (registration number: CRD42022332825) to prevent duplication of existing or ongoing studies.

2.1. Data sources/literature search

We employed a blend of keywords including "*Enterobacteriaceae*," "CRE," "*Enterobacterales*," "*Escherichia*," "*E. coli*," "*Klebsiella*," "*Citrobacter*," "*Salmonella*," "*Shigella*," "*Serratia*," "*Enterobacter*," "Carbapenem," "Imipenem," "Meropenem," "Ertapenem," "Doripenem" and "Saudi Arabia" to search some online databases including Scopus, Pubmed, Web of Science and Science Direct, for studies reporting the prevalence of CRE in Saudi Arabia. The comprehensive strategy employed to access all databases is provided as an accompanying document (File S1). A thorough search was conducted without imposing filters for study design, language, or publication year. The

Table 1
Major characteristics of the included studies.

Study ID	Study period	Location	Study design	Organism tested	Method	Sample type	Total *Enterobacterales*	Reference
A. Aldrazi et al 2019	2016	Dammam	Retrospective	*E. coli, K. pneumoniae, P. mirabilis, M. morganii, Enterobacter* spp., *C. freundii*	Automated systems	Pus, urine, blood, respiratory and cerebrospinal fluid	300	(Aldrazi et al., 2020)
Abalkhail et al 2022	2019–2020	Riyadh	Experimental	*E. coli*	DDT	Urine	510	(Abalkhail et al., 2022)
Abdallah et al 2020	N/A	Taif	NR	*E. coli*	DDT	Urine	50	(Abdallah et al., 2020)
Abdel Azim et al 2019	2016	Riyadh	Cross-sectional	*K. pneumoniae*	DDT	Samples from blood, urine, wound swabs, sputum, tracheal aspirate, eye, groin	23	(Azim et al., 2019)
Abdel-Fattah et al 2005	2004	Taif	NR	*E. coli, K. pneumoniae, Citrobacter* spp., *Proteus* spp., *Enterobacter* spp., *Serratia* spp.	DDT	N/A	592	(Abdel-Fattah, 2005)
Ahmad et al 2009	2004–2007	Al-Kharj	Descriptive	*K. pneumoniae*	NR	Urine, wound swab, blood, aspirate, sputum	328	(Ahmad et al., 2009)
Akbar et al 2000	1998–1999	Jeddah	NR	*Enterobacter* spp.	DDT	Sputum	19	(Akbar et al., 2000)
Al-Agamy et al 2009	2007	Riyadh	Cross-sectional	*K. pneumoniae*	DDT	N/A	220	(Al-Agamy et al., 2009)
Al-Agamy et al 2012	2010	Riyadh	NR	*E. coli*	MIC	Urine	100	(Al-Agamy, 2012)
Al-Agamy et al 2014	2012	Riyadh	NR	*E. coli*	MIC	Urine	250	(Al-Agamy, 2014)
Al-Agamy et al 2016	2014	Riyadh	NR	*E. coli*	MIC	Stool	50	(Al-Agamy et al., 2016)
Al-Garni et al 2018	2017–2018	Taif	Retrospective	*E. coli, K. pneumoniae*	DDT	Urine, blood, sputum, swabs	303	(Al-Garni et al., 2018)
Al-Ghamdi et al 2019	2010–2016	Riyadh	Retrospective	*E. coli, K. pneumoniae*	DDT	Ascitic fluid	52	(Al-Ghamdi et al., 2019)
Al-Harthi et al 2000	1993–1998	Aseer	Retrospective	*K. pneumoniae, S. marcescens*	DDT	Blood, urine, CSF	18	(Al-Harthi et al., 2000)
Al-Jameel et al 2014	2013–2014	Riyadh	Cross-sectional	*K. pneumoniae*	DDT	N/A	250	(Al-Jameel et al., 2014)
Al-Otaibi et al 2016	2013–2015	Riyadh	Retrospective	*E. coli, K. pneumoniae, Enterobacter* spp.	DDT	Blood	36	(Al-Otaibi et al., 2016)
Al-Qahtani et al 2014	2011–2012	Riyadh	Cross-sectional	*K. pneumoniae*	DDT	Urine, sputum, blood	98	(Al-Qahtani et al., 2014)
Al-tawfiq et al 2006	1998–2003	Dhahran	Retrospective	*E. coli*	NR	Blood, urine, wound swab	399	(Al-Tawfiq, 2006)
Al-tawfiq et al 2007	1998–2003	Dhahran	Retrospective	*K. pneumoniae*	NR	Blood, urine, wound swab	422	(Al-Tawfiq and Antony, 2007)
Al-tawfiq et al 2009	2000–2006	Dhahran	Retrospective	*Enterobacter* spp.	Automated systems	N/A	429	(Al-Tawfiq et al., 2009)
Al-Zalabani et al 2020	2014–2018	Madinah	Cross-sectional	*K. pneumoniae*	Automated systems	N/A	27,384	(Al-Zalabani et al., 2020)
Alamri et al 2017	2013–2016	Abha	Retrospective	*E. coli, K. pneumoniae, K. oxytoca, P. mirabilis, E. cloacae, E. faecium, M. morganii, P. Stuartii, C. frundii*	Automated systems	Urine and other UT specimens	34,810	(Alamri et al., 2018)
Alasmary et al 2021	2019–2021	Najran	Retrospective	*E. coli, Enterobacter* spp., *K. oxytoca, K. pneumoniae, P. mirabilis, P. rettgeri, P. stuartii, S. marcescens, Salmonella* spp.	Automated systems	Urine	99	(Alasmary, 2021)
Alavudeen et al 2021	2020–2021	Abha	Retrospective	*E. coli, K. pneumoniae, K. oxytoca*	NR	Urine	78	(Alavudeen et al., 2021)
Alghamdi et al 2023	2019–2022	Al-Baha	Cross-sectional	*E. coli*	Automated systems	Urine	252	(Alghamdi et al., 2023)
Alghoribi et al 2019	2015–2017	Riyadh	NR	*Salmonella* spp.	Automated systems	Blood, wound, abdominal fluid, tissue, urine, stool	200	(Alghoribi et al., 2019)
Alharazi et al 2024	2021–2022	Hail	Retrospective	*E. coli*	Automated systems	Blood, aspirates, CSF, ear swabs, pus, seminal fluid, sputum, urine, and vaginal swabs	112	(Alharazi et al., 2024)
Alhumaid et al 2021	2015–2019	Qassim and Riyadh	Retrospective	*E. coli, Klebsiella* spp., *Proteus* spp., *Enterobacter* spp., *Citrobacter* spp.	Automated systems	Blood, urine, respiratory samples, CSF, cervical fluid, saliva, nasal, rectal	21,437	(Alhumaid et al., 2021)

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Table 1 (*continued*)

Study ID	Study period	Location	Study design	Organism tested	Method	Sample type	Total *Enterobacterales*	Reference
						swab, lavage, wound, semen, tissue biopsies		
Ali et al 2018	2016–2017	Rafha	Retrospective	*E. coli, Klebsiella* spp.	DDT	Urine	270	(Ali, 2018)
Aloraifi et al 2023	2016–2020	Riyadh, Al-Ahsa, Dammam, and Madinah	Retrospective	*E. coli, K. pneumoniae*	DDT	Blood	1740	(Aloraifi et al., 2023)
Alqasim et al 2018	2018	Riyadh	Cross-sectional	*E. coli*	DDT	Urine	100	(Alqasim et al., 2018)
Alqasim et al 2019	2018	Riyadh	Cross-sectional	*E. coli*	DDT	Blood	31	(Alqasim et al., 2020)
Alrefeai et al 1998	1998	Madinah	NR	*E. coli, K. pneumoniae, Enterobacter* spp., *M. morganii, P. mirabilis, S. typhi, S. paratyphi, K. oxytoca*	DDT	N/A	179	(Al-Refeai et al., 1998)
Alsaadi et al 2024	2015–2022	Riyadh	Retrospective	*M. morganii*	Automated systems	Blood	17	(Alsaadi et al., 2024)
Alsanie et al 2020	N/A	Taif	Cross-sectional	*K. pneumoniae*	Automated systems	N/A	23	(Alsanie, 2020)
Alshehri et al 2021	N/A	Jeddah	Cross-sectional	*E. coli, K. pneumoniae, E. cloacae*	DDT	Stool	193	(Alshehri and Moussa, 2021)
Alsubaie et al 2023	2019–2021	Jeddah	Retrospective	*E. coli, K. pneumoniae, Enterobacter* spp., *Citrobacter* spp., *M. morganii, P. mirabilis, Serratia* spp., *K. oxytoca, Providencia* spp., *P. vulgaris*	DDT	Urine	421	(Alsubaie et al., 2023)
Altamimi et al 2023	2019–2020	Riyadh	Retrospective	*E. coli, Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp. *Proteus* spp., *Serratia* spp.	DDT	Urine	949	(Altamimi et al., 2023)
Alyamani et al 2017	2014–2015	Makkah	Cross-sectional	*E. coli*	Automated systems	Urine	58	(Alyamani et al., 2017)
Alzahrani et al 2016	2015	Taif	Cross-sectional	*E. coli, K. pneumoniae*	Automated systems	Urine, wound swabs	43	(Alzahrani et al., 2016)
Alzahrani et al 2021	2017–2018	Al-Baha	Retrospective	*E. coli, K. pneumoniae*	Automated systems	Urine	48	(Alzahrani et al., 2016)
Alzahrani et al 2022	2017–2018	Al-Baha	Retrospective	*E. coli, K. pneumoniae, Enterobacter* spp., *P. mirabilis*	NR	Urine	910	(Alzahrani et al., 2022)
Amashah et al 2023	2023	Taif	NR	*E. coli, K. pneumoniae*	Automated systems	N/A	566	(Amashah et al., 2023)
Arafa et al 2022	2020	Makkah	Cross-sectional	*E. coli*	Automated systems	Urine	50	(Arafa et al., 2022)
Badger-Emeka et al 2020	N/A	Al-Hafouf	Cross-sectional	*E. coli, K. pneumoniae*	Automated systems	Blood	24	(Badger-Emeka et al., 2020)
Badger-Emeka et al 2021	N/A	Al-Hafouf	Cross-sectional	*K. pneumoniae*	Automated systems	N/A	78	(Badger-Emeka et al., 2021)
Badger-Emeka et al 2021	2017–2019	Al-Ahsa	Retrospective	*E. coli*	Automated systems	N/A	170	(Badger-Emeka et al., 2022)
Banawas et al 2023	2020	Riyadh	NR	*K. pneumoniae, E. coli, E. cloacae, S. marcescens*	Automated systems	Blood	325	(Banawas et al., 2023)
Bandy et al 2020	2019	Al-Jouf	Cross-sectional	*E. coli, K. pneumoniae*	Automated systems	Blood	86	(Bandy and Almaeen, 2020)
Bandy et al 2021	2019	Al-Jouf	Retrospective	*E. coli, K. pneumoniae, P. mirabilis*	Automated systems	N/A	349	(Bandy and Tantry, 2021)
Bandy et al 2022	2019	Al-Jouf	Retrospective	*E. coli, K. pneumoniae*	DDT	Wound swabs	88	(Bandy et al., 2022)
Bazaid et al 2021	2015–2019	Hail	Retrospective	*E. coli, K. pneumoniae, P. mirabilis*	Automated systems	Urine	220	(Bazaid et al., 2021)
Bilal et al 2000	1997–1999	Abha	Retrospective	*K. pneumoniae*	DDT	HVS, urine, blood, sputum, aspirates, wound swabs, body fluids	860	(Bilal and Gedebou, 2000)
Bshabshe et al 2020	2018–2019	Aseer	Observational	*K. pneumoniae*	Automated systems	Respiratory tract samples	107	(Al Bshabshe et al., 2020)
El-Karsh et al 1995	N/A	Riyadh	NR	*E. coli, E. cloacae, K. pneumoniae, C. freundii*	Automated systems	CSF, blood, sputum/ wound swabs	70	(ElKarsh et al., 1995)

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Table 1 (*continued*)

Study ID	Study period	Location	Study design	Organism tested	Method	Sample type	Total *Enterobacterales*	Reference
El-Tahawi et al 2000	1997–1999	Jeddah	Cross-sectional	*E. coli, K. pneumoniae, P. mirabilis*	DDT	Aspirates/swabs of diabetic foot	31	(El-Tahawy, 2000)
Elbehiry et al 2024	2020	Riyadh	Cross-sectional	*E. cloacae*	DDT	Urine	82	(Elbehiry et al., 2024)
Eltahawy et al 1997	1995–1996	Jeddah	NR	*E. coli, K. pneumoniae, Enterobacter* spp.	Automated systems	Samples from respiratory tract, wounds, urinary tract, blood	47	(Eltahawy, 1997)
Hafiz et al 2023	2019–2020	Riyadh	Retrospective	*K. pneumoniae*	DDT	Blood	152	(Hafiz et al., 2023)
Ibrahim et al 2018	2016–2018	Bisha	Retrospective	*K. pneumoniae, E. coli, P. mirabilis*	Automated systems	Blood, urine, sputum, tracheal aspirate, wound swab, eye swab, throat swab, umbilical discharge, ear swab, and high vaginal swab.	115	(Ibrahim, 2018)
Jalal et al 2023	2011–2021	Makkah	Retrospective	*K. pneumoniae*	Automated systems	Sputum, blood, wound, urine, tip and catheter	7229	(Jalal et al., 2023)
Khanfar et al 2009	2004–2005	Dhahran	NR	*E. coli, K. pneumoniae, K. oxytoca*	DDT	Urine	6750	(Khanfar et al., 2009)
Marzouk et al 2024	2021–2022	Al-Qassim	NR	*K. pneumoniae*	Automated systems	Urine, wound, blood, samples from respiratory tract	190	(Marzouk et al., 2024)
Moustafa et al 2023	2021	Riyadh	Retrospective	*K. pneumoniae*	DDT	Blood, urine, endotracheal aspirate, sputum, wound sample	229	(Moustafa et al., 2023)
Orfali et al 2024	2023	Riyadh	Prospective	*S. marcescens, E. coli, P. mirabilis, E. aerogenes, C. koseri, Morganella* spp., *P. penneri*	Automated systems	Diabetic foot ulcer swab	32	(Orfali et al., 2024)
Rahim et al 2014	2012–2013	Hafr al-Batin	NR	*K. pneumoniae*	DDT	Urine, suction tip, pus, blood specimens	130	(Rahim and Mohamed, 2014)
Said et al 2021	2020	Hail	NR	*E. coli, K. pneumoniae, P. mirabilis, P. stuartii, M. morganii, Citrobacter* spp., *Shigella* spp., *Salmonella* spp.	NR	Respiratory samples, blood, sputum, urine, and wound specimens	431	(Said et al., 2021)
Said et al 2022	N/A	Hail	Retrospective	*E. coli, K. pneumoniae*	Automated systems	Urine, sputum, blood, wound/pus, others	72	(Said et al., 2022)
Taha et al 2018	N/A	Jizan	NR	*E. coli*	Automated systems	Wound, urine, stool, blood	95	(Tahai et al., 2018)

N/A, not applicable; NR, not reported; DDT, disk diffusion technique; MIC, minimum inhibitory concentration

comprehensive search covering all records up to August 28, 2024, resulted in a total of 787 entries. All retrieved records from the databases were exported to EndNote X8 software for the removal of duplicates and initial screening.

2.2. Study eligibility criteria

Included in this work were studies that investigated CRE in humans in Saudi Arabia. Studies were considered for inclusion provided they contained relevant CRE data. We excluded (1) reviews, letters, case reports, editorials, book chapters and opinions; (2) studies whose CRE data originated from countries other than Saudi Arabia; (3) studies that assessed CRE from sample sources other than humans; (4) articles whose full texts were not available; (5) investigations involving already known cases of CRE which does not represent prevalence among a sampled population.

All authors established and agreed upon the criteria for screening, selecting, and assessing articles. Independently, the two authors conducted the initial screening of articles based on their titles and abstracts. Subsequently, the full texts of the screened articles were thoroughly assessed. In cases of discrepancies, discussion between the authors was employed to reach a resolution.

2.3. Data extraction and quality assessment

For data extraction, a pre-established Excel spreadsheet was employed. Independently, the authors gathered the following information from the studies that were included: Study ID, study period, study location, study design, members of the *Enterobacterales* tested, method of resistance determination, sample type, number of resistant organisms, and the total number of *Enterobacterales* assessed.

To evaluate the methodological quality of the included studies, the Joanna Briggs Institute (JBI) critical appraisal checklist for prevalence data (Ahmed et al., 2021; AL-Mhanna et al., 2022) was employed, and the assessment tool is available in the supplementary file (File S2). The authors independently conducted the appraisal, assigning a total quality score ranging from 0 to 9. Studies were deemed of satisfactory quality if they achieved a score of 7 or higher (Irekeola et al., 2021; Yusof et al., 2021).

2.4. Statistical analysis and data synthesis

The collected data underwent a thorough examination to identify and address any potential duplicate entries before being subjected to analysis. OpenMeta Analyst software and Comprehensive Meta-Analysis 3.0 (CMA 3.0) software were employed for the data analysis process. Summary estimates for resistance to each of the carbapenems (imipenem, meropenem, and ertapenem) were calculated. The DerSimonian-Laird method of *meta*-analysis and the random-effects model were utilized to derive pooled estimates. To evaluate potential publication bias, a funnel plot was generated. Egger's regression test was applied to assess the symmetry of the plot. Cochran's Q test was employed to evaluate

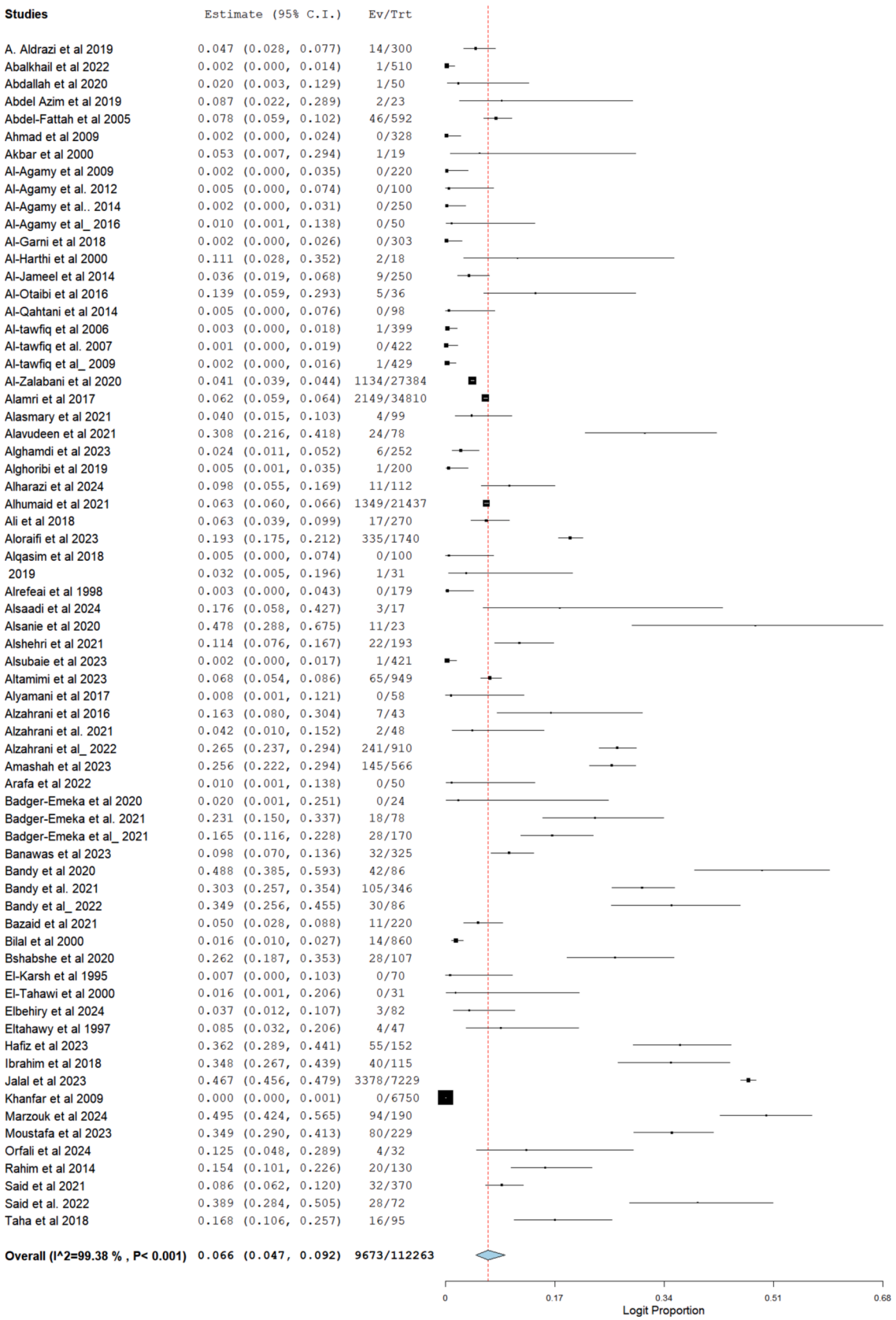

Fig. 2. Forest plot of the pool prevalence of imipenem resistance in CRE. Estimates were derived using the random effects model.

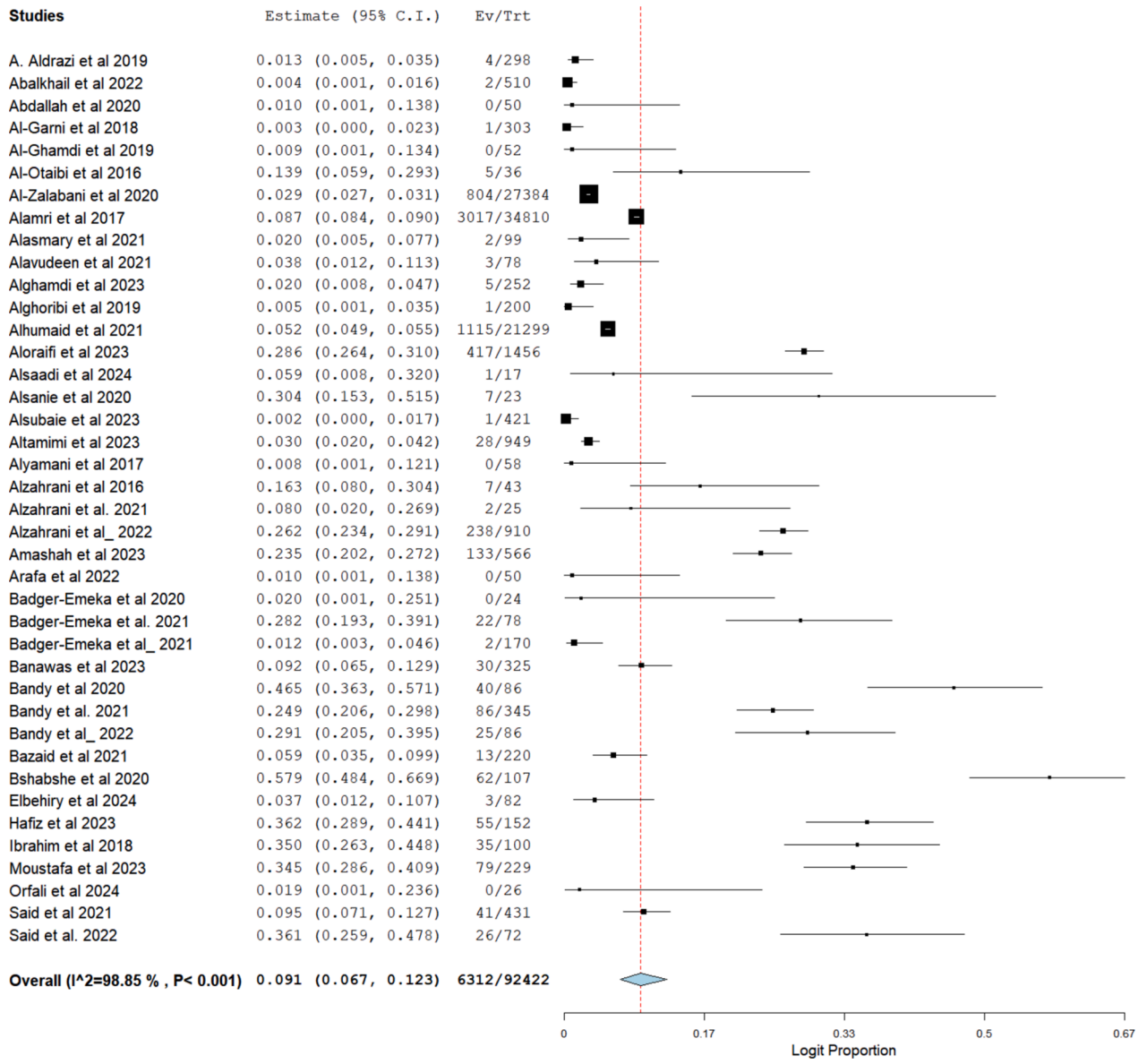

Fig. 3. Forest plot of the pool prevalence of meropenem resistance in CRE. Estimates were derived using the random effects model.

heterogeneities in the study-level estimates, with I^2 statistics used for quantification. I^2 values of 25 %, 50 %, and 75 %, respectively, were considered indicative of low, moderate, and high heterogeneity (Higgins and Thompson, 2002; Irekeola et al., 2022; Yusof et al., 2022). The analysis of heterogeneity sources was conducted through subgroup *meta*-analysis based on the available subgroup data from the included studies (i.e., studies without the relevant subgroup information were excluded from the analysis). In all statistical tests, a p-value of < 0.001 was considered statistically significant.

3. Results

3.1. Study selection

This study's process of article identification and selection is summarized in Fig. 1. From our exploration of four electronic databases, a total of 787 records were obtained. Following the removal of duplicates and the exclusion of studies not meeting the predefined inclusion criteria, the full texts of 172 studies underwent evaluation for eligibility. Sixty-nine studies were deemed fully eligible and were consequently incorporated into the qualitative and quantitative synthesis.

3.2. Characteristics of the included studies

The research included in this study were conducted at different locations within Saudi Arabia, with virtually all the country's province represented. However, majority of the reports were from the Riyadh province. More than 50 % of all the studies were conducted after 2010. Sample types from which the *Enterobacterales* were assessed were quite diverse, including but not limited to urine, blood, sputum, stool, cerebrospinal fluid, wound swab and rectal swab. Assessment of carbapenem resistance was done on a variety of *Enterobacterales* with *E. coli* and *K. pneumoniae* being the most tested. The testing methods included the use of disk diffusion techniques, minimum inhibitory concentration (MIC), as well as the use of automated systems. Features of the included studies are detailed in Table 1.

3.3. Pooled prevalence

Of the 69 studies included in this meta-analysis, resistance data for

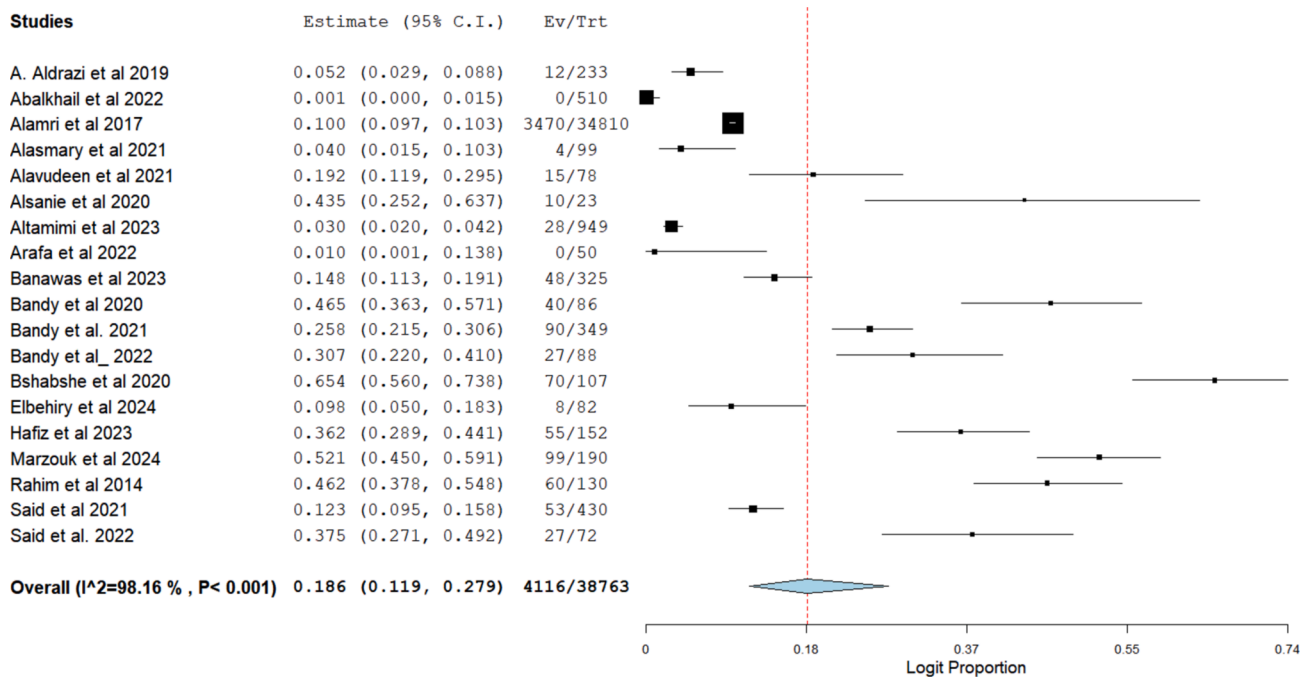

Fig. 4. Forest plot of the pool prevalence of ertapenem resistance in CRE. Estimates were derived using the random effects model.

imipenem, meropenem, and ertapenem were available in 68, 40, and 15 studies, respectively, with the total number of tested *Enterobacterales* being 112263, 92422, and 38763, respectively. Upon calculating summary estimate using the random-effect model, the pooled prevalence estimate for imipenem resistance among CRE was 6.6 % (95 % CI: 4.7–9.2). An estimate of 9.1 % (95 % CI: 6.7–12.3) was derived for meropenem, and 18.6 % (95 % CI: 11.9–27.9) for ertapenem (Figs. 2-4). High heterogeneity (I^2 > 97 %, p < 0.001) was observed for all the estimates.

3.4. Prevalence of CRE in different subgroups

The resistance rates of the tested *Enterobacterales* to imipenem, meropenem and ertapenem antibiotics were further evaluated based on variables including the period of study, region, method, and study design. This was done to provide a robust overview of the resistance rate and probe the heterogeneity observed.

Table 2 summarizes the prevalence of imipenem resistance in CRE according to the analyzed variables. Based on the period of study, majority of the studies (n = 39) were conducted in the year 2011–2020, with the highest pooled prevalence (20.0 %, 95 % CI: 11.9–31.6) occurring in the 2021–2024 study period. Studies contributing to subgroup analysis of imipenem resistance were from 13 provinces with Riyadh being the most represented (n = 21). Although supported by only one study, the highest prevalence (49.5 %, 95 % CI: 42.4–56.5) was from Al-Qassim province, and the least from Madinah province (1.6 %, 95 % CI: 0.1–17.4). Based on the method of assessing imipenem resistance, automated systems were the most used (n = 32). In addition, the highest pooled resistance rate (10.9 %, 95 % CI: 6.8–17.0) occurred in this group. Lastly, based on study design, retrospective studies were the most predominant (n = 29). A high prevalence rate of 26.2 % (95 % CI: 18.7–35.3) was observed for observational studies. However, the estimate was from only one study. Further, heterogeneity was generally high.

Table 3 provides information on the rates of meropenem resistance in CRE according to the analyzed variables. Based on the period of study, studies conducted in the year 2011–2020 were the most numerous (n = 30). Further, the highest pooled resistant rate to meropenem antibiotics (10.0 %, 95 % CI: 4.3–21.3) was in the year 2021–2024. Studies contributing to subgroup analysis of meropenem resistance were from 10 provinces, with Riyadh being the most represented (n = 11). The highest pooled resistance rate was from Al-Jouf province (32.6 %, 95 % CI: 21.2–46.5). Automated system was the most widely employed method (n = 25) for the assessment of meropenem resistance. The resistance rate in the automated systems subgroup was higher (10.4 %, 95 % CI: 7.5–14.3) than that in disk diffusion technique (6.4 %, 95 % CI: 3.2–12.3). Based on design, retrospective studies were the most common (n = 22). A high meropenem resistance rate of 57.9 % (95 % CI: 48.4–66.9) was estimated for observational study design. However, the estimate was derived from only one study. Except for studies conducted in Hail province, heterogeneity was high (>85 %) in all the variables assessed for meropenem resistance.

Table 4 summarizes the prevalence of ertapenem resistance in CRE according to the analyzed variables. There were more studies in the 2011–2020 study period than the 2021–2014 period. However, a higher pooled resistant rate (34.2 %, 95 % CI: 10.5–69.7) was observed in 2021–2024 period compared to 2011–2020 (15.2 %, 95 % CI: 9.3–23.8). Most of the studies included in the ertapenem subgroup analysis were from Riyadh province (n = 5). However, the highest pooled resistance rate was estimated for the Al-Qassim province (52.1 %, 95 % CI: 45.0–59.1). Analysis based on method revealed the use of automated system as the most common, accounting for the highest ertapenem resistant rate (22.2 %, 95 % CI: 11.9–37.6). Based on design, retrospective studies were the most dominant. A high prevalence was estimated for the observational study subgroup (65.4 %, 95 % CI: 56.0–73.8). However, the estimate was from a single study. Heterogeneity was generally high (>85 %) in all the variables assessed for ertapenem resistance. Forest plots for subgroup analyses are provided as a supplementary file (File S4).

3.5. Prevalence of carbapenem resistant organisms

The prevalence of specific CRE genera resistant to at least one carbapenem antibiotic was also assessed. The analysis identified *Proteus spp* as the most resistant, with a prevalence of 26.2 % (95 % CI: 15.7–40.4), followed by *Providencia spp* at 22.1 % (95 % CI: 20.7–23.7). In contrast,

Table 2
Prevalence of imipenem resistance in CRE in different subgroups.

Subgroup	Number of studies	Prevalence (%)	95 % CI	Heterogeneity test	
				I^2 (%)	*p*-value
Year					
2021–2024	7	20.0	11.9 – 31.6	94.6	<0.001
2011–2020	39	7.4	4.8 – 11.3	99.63	<0.001
2001–2010	6	0.3	0.0 – 3.4	90.53	<0.001
1991–2000	8	1.8	0.7 – 5.1	73.11	<0.001
Overall	60	6.0	4.2 – 8.5	99.45	<0.001
Region/ Province					
Eastern province	9	2.4	0.9 – 6.2	92.05	<0.001
Riyadh	21	3.7	2.0 – 6.9	93.05	<0.001
Makkah	11	6.6	3.0 – 13.9	97.86	<0.001
Taif	3	10.0	1.3 – 48.9	90.76	0.046
Aseer	6	13.1	5.0 – 30.3	98.04	<0.001
Madinah	2	1.6	0.1 – 17.4	73.3	0.002
Najran	1	4.0	1.5 – 10.3	NA	NA
Al-Baha	3	7.1	0.9 – 37.5	95.91	0.015
Hail	4	12.1	4.5 – 28.5	94.47	<0.001
Northern borders province	1	6.3	3.9 – 9.9	NA	NA
Al-Jouf	3	37.2	27.0 – 48.7	80.45	0.030
Al-Qassim	1	49.5	42.4 – 56.5	NA	NA
Jazan	1	16.8	10.6 – 25.7	NA	NA
Overall	66	6.1	4.2 – 8.8	99.34	<0.001
Method					
Automated systems	32	10.9	6.8 – 17.0	99.69	<0.001
DDT	27	5.0	3.2 – 7.8	94.52	<0.001
MIC	3	0.5	0.1 – 2.2	0	<0.001
Overall	62	6.8	4.8 – 9.7	99.42	<0.001
Study design					
Retrospective	29	9.2	5.6 – 14.7	99.67	<0.001
Experimental	1	0.2	0.0 – 1.4	NA	NA
Cross-sectional	18	5.5	2.7 – 10.9	95.13	<0.001
Descriptive	1	0.2	0.0 – 2.4	NA	NA
Observational	1	26.2	18.7 – 35.3	NA	NA
Prospective	1	12.5	4.8 – 28.9	NA	NA
Overall	51	7.4	5.0 – 10.7	99.52	<0.001

Table 3
Prevalence of meropenem resistance in CRE in different subgroups.

Subgroup	Number of studies	Prevalence (%)	95 % CI	Heterogeneity test	
				I^2 (%)	*p*-value
Year					
2021–2024	5	10.0	4.3 – 21.3	94.01	<0.001
2011–2020	30	8.1	5.8 – 11.4	99.02	<0.001
Overall	35	8.3	6.0 – 11.3	98.97	<0.001
Region/ Province					
Eastern province	4	3.5	0.4 – 26.5	94.23	0.005
Riyadh	11	5.3	2.1 – 12.6	96.1	<0.001
Makkah	5	1.6	0.1 – 17.9	90.16	0.002
Taif	3	7.7	1.1 – 37.6	89.87	0.014
Madinah	1	2.9	2.7 – 3.1	NA	NA
Aseer	4	19.4	4.8 – 53.6	98.82	0.075
Najran	1	2.0	0.5 – 7.7	NA	NA
Al-Baha	3	8.1	1.1 – 40.9	95.27	0.021
Al-Jouf	3	32.6	21.2 – 46.5	86.58	0.015
Hail	2	7.9	5.0 – 12.3	59.04	<0.001
Overall	37	8.0	5.6 – 11.3	98.51	<0.001
Method					
Automated systems	25	10.4	7.5 – 14.3	98.71	<0.001
DDT	12	6.4	3.2 – 12.3	96.34	<0.001
Overall	37	9.0	6.5 – 12.2	98.82	<0.001
Study design					
Retrospective	22	10.0	6.9 – 14.2	98.85	<0.001
Experimental	1	0.4	0.1 – 1.6	NA	NA
Cross-sectional	10	7.3	2.2 – 21.2	97.64	<0.001
Observational	1	57.9	48.4 – 66.9	NA	NA
Prospective	1	1.9	0.1 – 23.6	NA	NA
Overall	35	9.4	6.8 – 12.9	98.95	<0.001

Escherichia coli showed the lowest resistance (3.9 %, 95 % CI: 2.8–5.5) among the CRE evaluated (Fig. 5).

3.6. Study quality and publication bias assessment

Assessment of methodological quality using the JBI tool showed that the included studies were of good quality (File S3). Funnel plots were created to evaluate potential publication bias. The plots, as depicted in Fig. 6, exhibited asymmetry, suggesting the presence of potential publication bias. Further exploration of funnel plot asymmetry was conducted through Egger's regression test. Nevertheless, the test yielded a non-significant *p*-value for studies contributing to the imipenem (p =

Table 4
Prevalence of ertapenem resistance in CRE in different subgroups.

Subgroup	Number of studies	Prevalence (%)	95 % CI	Heterogeneity test	
				I^2 (%)	*p*-value
Year					
2021–2024	2	34.2	10.5 – 69.7	95.51	0.388
2011–2020	15	15.2	9.3 – 23.8	97.97	<0.001
Overall	17	16.7	10.3 – 25.9	98.26	<0.001
Region/ Province					
Eastern province	2	17.9	1.4 – 76.5	98.44	0.269
Riyadh	5	7.3	2.2 – 21.8	97.25	<0.001
Aseer	3	26.8	5.2 – 70.9	99.0	0.299
Najran	1	4.0	1.5 – 10.3	NA	NA
Taif	1	43.5	25.2 – 63.7	NA	NA
Makkah	1	1.0	0.1 – 13.8	NA	NA
Al-Jouf	3	33.5	22.4 – 46.7	85.34	0.015
Al-Qassim	1	52.1	45.0 – 59.1	NA	NA
Hail	2	22.3	6.5 – 54.3	96.16	0.085
Overall	19	18.6	11.9 – 27.9	98.16	<0.001
Method					
Automated systems	11	22.2	11.9 – 37.6	98.52	0.001
DDT	6	12.1	3.7 – 33.0	97.71	0.002
Overall	17	18.8	11.3 – 29.6	98.36	<0.001
Study design					
Retrospective	9	14.6	8.4 – 24.2	97.5	<0.001
Experimental	1	0.1	0.0 – 1.5	NA	NA
Cross-sectional	4	20.3	6.2 – 49.5	90.65	0.047
Observational	1	65.4	56.0 – 73.8	NA	NA
Overall	15	16.2	9.5 – 26.3	97.77	<0.001

0.8005), meropenem ($p = 0.2176$) and ertapenem ($p = 0.0229$) resistance estimates.

4. Discussion

The global rise and spread of CRE is alarming, highlighting the critical need for immediate actions to combat this growing threat (Hansen, 2021). Carbapenem antibiotics, which are considered drugs of last resort in many hospitals, have been faced with the problem of antimicrobial resistance (Hansen, 2021). Thus, epidemiological data are crucial to help keep track of the trend in carbapenem resistance. Varying resistance rates to carbapenem antibiotics have been reported in the past in Saudi Arabia, and the true prevalence in yet unknown (Aldrazi et al., 2020; Bilal and Gedebou, 2000; Rahim and Mohamed, 2014; Said et al., 2021). The current study and analyses were performed based on data

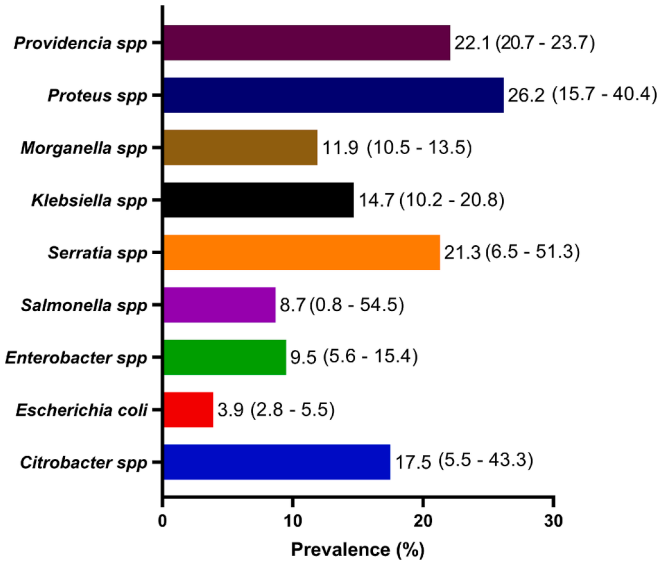

Fig. 5. Prevalence of specific CRE genera. The 95% confidence intervals are provided in parentheses.

available from 69 published records retrieved from different databases to evaluate the prevalence of CRE throughout Saudi Arabia. We aimed to investigate the resistance rates of imipenem, meropenem, and ertapenem, three common carbapenem antibiotics, and to accurately estimate the prevalence of CRE in Saudi Arabia.

The studies included in this work encompassed the last three decades, highlighting the robustness of our data. Additionally, most of the studies were conducted in the most recent decade, indicating increased interest in CRE, which is probably due to the escalating carbapenem resistance reports. Although CRE reports originated from virtually all regions, the reports were predominantly from the Riyadh province. The most frequently examined members of the *Enterobacterales* were *E. coli* and *K. pneumoniae*. The decision to regularly screen *E. coli* and *K. pneumoniae* for carbapenem resistance could be influenced by their capacity to induce severe infections and their tendency to develop resistance, thereby restricting available treatment options (Chang et al., 2021; Jalil and Al Atbee, 2022). It is important to emphasize that concentrating on these pathogens does not reduce the significance of monitoring other members of the *Enterobacterales* for carbapenem resistance, as resistance can manifest in different species within this bacterial group. Moreover, other members were also tested in the studies included in this work.

This study revealed highest resistance rate to ertapenem antibiotics (18.6 %) among CRE compared to imipenem (6.6 %) and meropenem (9.1 %). These observed rates are in line with reports from Malaysia where carbapenem resistance rate of 5.4 % was reported (Zaidah et al., 2017). While the resistance rate is higher than those reported in Lebanon (3 %) (Moghnieh et al., 2019), Afghanistan (3.4 %) (Mende et al., 2017), and Belgium (3.5 %) (Huang et al., 2013), carbapenem resistance rate of over 40 % have been reported in some other parts of the world (Hammour et al., 2023; Kotb et al., 2020). Antimicrobial resistance is being increasingly recognized as a global health security threat that requires integrated action across government sectors and society as a whole (Salam et al., 2023). Different studies show global data about CRE infections. For instance, earlier investigations documented incidences of CRE in the United States and European countries, registering at 2.93 per 100,000 populations and 1.3 per 10,000 hospital admissions, respectively (Zhang et al., 2018).

Our analysis showed that different regions of Saudi Arabia had different carbapenem resistance rates. However, for all the carbapenem antibiotics analyzed, there was consistently higher prevalence in the Al-Qassim and Al-Jouf province compared to other regions. These

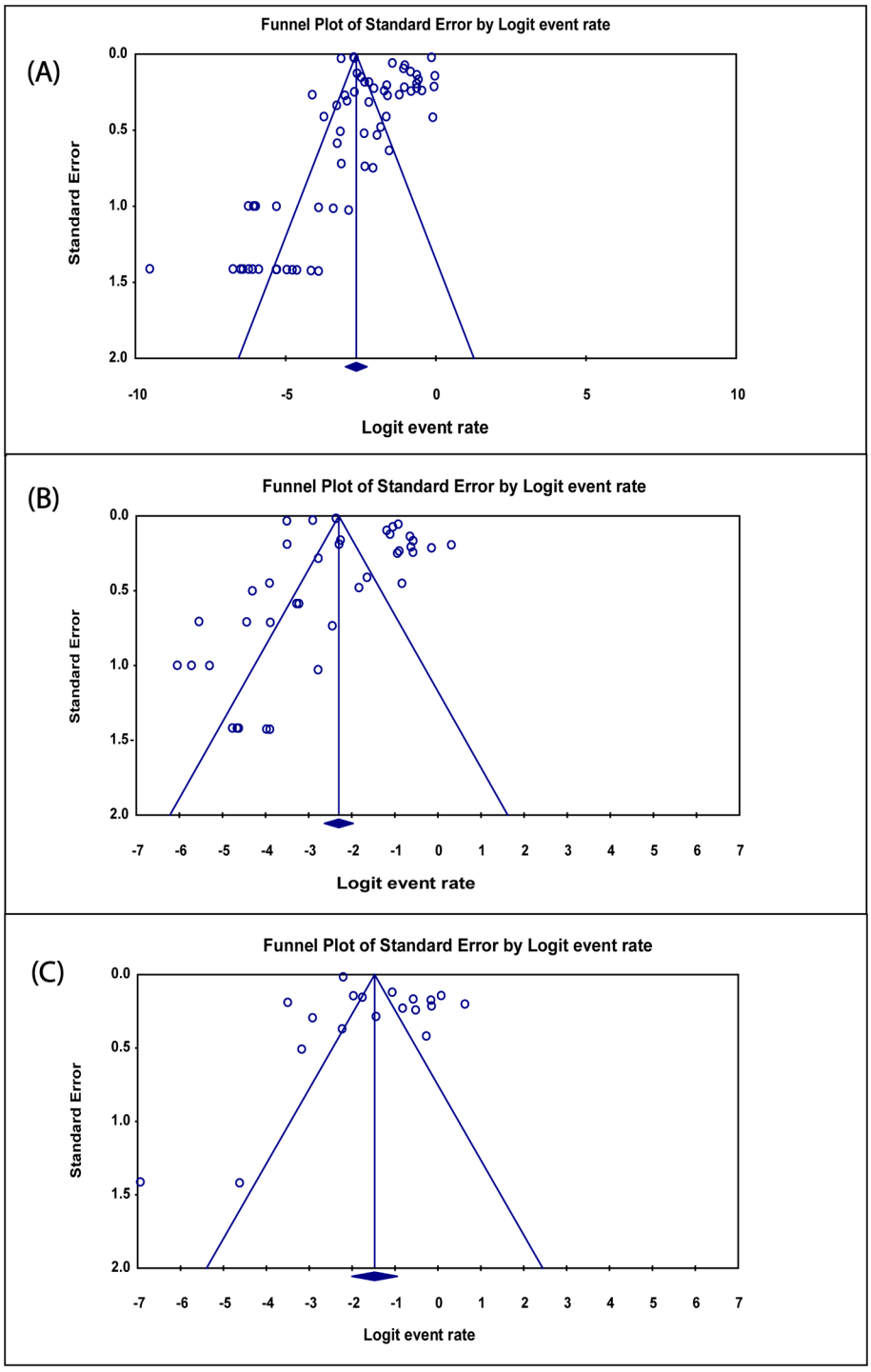

Fig. 6. Funnel plot illustrating the assessment of publication bias for (A) imipenem [Egger's test, $p = 0.8005$] (B) meropenem [Egger's test, $p = 0.2176$] and (C) ertapenem [Egger's test, $p = 0.0229$] resistance estimates.

observations could be linked to the location of the regions. For instance, Al-Jouf is partially bordered by Jordan to the west. A previous report from Jordan documented a 41.2 % prevalence of carbapenem resistance Gram-negative isolates (Hammour et al., 2023). The proximity of Al-Jouf to Jordan and the intra-city activities may have facilitated the spread of CRE. In contrast, the noticeably lower resistance rates (below 3 %) observed for imipenem (in the Eastern province and Madinah), meropenem (in Makkah, Madinah, and Najran), and for ertapenem (in Makkah) seem unaffected by neighboring countries such as Oman, Yemen, the United Arab Emirates, and Kuwait, where higher resistance rates have been documented (Al Mamari et al., 2022; Humaid et al., 2024; Jamal et al., 2022; Thomsen et al., 2023). The low resistance rates may, however, be attributed to increased awareness about antibiotic misuse and the dangers of antimicrobial resistance (Almutairi et al., 2023; Alnasser et al., 2021).

Further, we found carbapenem resistance as a problem in the recent years in Saudi Arabia, as distinctly higher resistance rates were documented for the carbapenem antibiotics. Moreover, a recent study conducted in Western Saudi Arabia also suggested increase in CRE prevalence (Taha et al., 2023). These revelations further underscore the

importance of surveillance, as it will help in safeguarding public health, guiding clinical decision-making, and supporting efforts to address the challenges posed by antibiotic resistance. Thus, a multifaceted and coordinated response among all relevant stakeholders is essential.

In this study, while the *Proteus* species was not one of the most tested *Enterobacterales,* it was found to be the most prevalent CRE among the *Enterobacterales* examined, with a prevalence of 26.2 %. This rate is higher than the estimates derived for carbapenem resistant *Proteus* species in studies conducted in Iran (14.5 %) and Jordan (3.3 %) (Hammour et al., 2023; Vaez et al., 2022). *Proteus* species is commonly present in soil and water and is recognized for causing urinary tract infections and food poisoning in humans (Lv et al., 2022). Moreover, a previous study documented a prevalence of 71.7 % in animals, suggesting potential risk to humans (Lv et al., 2022). These findings highlight the importance of addressing the high prevalence rates observed in this study.

Healthcare professionals play a pivotal role in curbing the problem of CRE by implementing stringent infection control measures, such as hand hygiene, isolation protocols, and antimicrobial stewardship programs to minimize the misuse and overuse of antibiotics (Bankar et al., 2022; Shelke et al., 2023). Their vigilance in early detection and effective management of CRE cases is crucial to curbing its spread within healthcare settings. Further, policymakers are essential in shaping the legislative and regulatory frameworks that support these efforts. By enacting policies that promote the prudent use of antibiotics, fund research initiatives, and ensure the availability of resources for infection control, they create an environment conducive to combating antimicrobial resistance (Gyssens, 2011; Wasan et al., 2023). Researchers, on the other hand, contribute by advancing our understanding of CRE through studies that elucidate mechanisms of resistance, identify novel therapeutic targets, and develop new antibiotics or alternative treatments. Lastly, public engagement is equally important. Awareness campaigns can educate the community about the risks associated with antibiotic misuse and the importance of adhering to prescribed treatments (Burstein et al., 2019; West and Cordina, 2019). Public cooperation in following hygiene practices and vaccination schedules can significantly reduce the incidence of infections that may otherwise necessitate antibiotic use. Collectively, these efforts form a robust defense against the spread of CRE, emphasizing the need for a united approach to safeguard public health and ensure the efficacy of existing antibiotics for future generations.

This study possesses both strengths and limitations. Notably, it represents the first meta-analysis examining the prevalence of CRE in Saudi Arabia. By including all published data regardless of study or publication year, our report provides a comprehensive and unbiased analysis. However, the limited availability of studies from certain regions constrained the scope of our analyses.

5. Conclusion

Carbapenem resistance among *Enterobacterales* is a significant global health threat, and its prevalence is increasing in Saudi Arabia. CRE have been detected nationwide in Saudi Arabia, posing a potential threat to regional healthcare facilities. While this study found carbapenem resistance rates hovering between 6.6 % and 18.6 %, Al-Qassim and Al-Jouf regions particularly had higher resistance rates compared to other regions of Saudi Arabia. Additionally, the *Proteus* species was the most resistant CRE identified in this study. A comprehensive and coordinated effort involving healthcare professionals, policymakers, researchers, and the public is crucial to prevent and reduce the prevalence of CRE. A sustained commitment to these recommendations can contribute to the containment of CRE within and beyond Saudi Arabia, preserving the effectiveness of antibiotics and safeguarding public health.

CRediT authorship contribution statement

Ahmad A. Alshehri: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Ahmad Adebayo Irekeola:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2024.102186.

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