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Global Prevalence and Epidemiology of Carbapenem-Resistant Enterobacterales: A Systematic Review

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Abstract

Background: Carbapenem-resistant Enterobacterales (CRE) are now an important part of the global antimicrobial resistance problem. They are particularly relevant in hospital practice because the infections they cause are often difficult to treat and therapeutic choices may be limited. However, reported estimates of CRE burden differ considerably between studies. Much of this variation relates to differences in the populations studied, microbiological definitions, surveillance methods, and the denominators used to report resistance. **Materials and Methods:** We carried out a systematic review of human studies that reported CRE epidemiology using a defined denominator. Studies reporting isolate-based resistance proportions, population- or admission-based incidence, or colonization prevalence were eligible. MEDLINE/PubMed, Embase, Scopus, Web of Science Core Collection, and Global Health were searched from inception to August 13, 2026. Citation searching and targeted surveillance sources were also used. Study selection followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020. Because the studies differed considerably in design and in the epidemiological measures reported, we did not combine the results statistically. Risk of bias was assessed using the Joanna Briggs Institute checklist for prevalence studies, adapted where required for incidence and surveillance studies. **Results:** Fifteen studies were included. CRE burden varied markedly across regions and healthcare settings, with the highest estimates generally reported in intensive-care and tertiary-care populations and lower estimates in community-based and broader national surveillance. In multinational surveillance, meropenem-non-susceptible Enterobacterales accounted for 3.3% of isolates during 2012–2017 and 5.7% during 2018–2019. *Klebsiella pneumoniae* was the predominant CRE species in most datasets. Carbapenemase distribution was geographically heterogeneous, with *Klebsiella pneumoniae* carbapenemases, New Delhi metallo-β-lactamase, and OXA-48-like enzymes predominating in different regions and species. Temporal trends were inconsistent, with increasing resistance in some surveillance systems but declining population-based incidence in the United States. CRE colonization was concentrated among hospitalized and critically ill patients, while direct evidence quantifying progression from colonization to infection was limited. Detailed mortality and other patient-level clinical outcomes were also incompletely reported among the eligible epidemiological studies. The main methodological concerns were representativeness, sampling frame, and surveillance coverage. **Conclusion:** CRE epidemiology is globally heterogeneous and strongly influenced by healthcare setting, organism, resistance mechanism, and surveillance methodology. Isolate-based resistance proportions, incidence measures, and colonization prevalence are epidemiologically distinct and should not be combined into a single global prevalence estimate. More standardized surveillance, particularly in underrepresented regions and high-risk healthcare settings, is needed to improve comparability and better define the clinical and public-health burden of CRE.

Keywords: Antimicrobial resistance, Carbapenemase, Carbapenem-resistant Enterobacterales, Colonization, Epidemiology, Incidence, Prevalence, Systematic review

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Introduction

Global and Clinical Importance of Carbapenem-Resistant Enterobacterales (CRE)

Antimicrobial resistance (AMR) is a significant and growing challenge to global health, reducing the effectiveness of antimicrobial treatment and contributing to the burden of treatable bacterial infections. In 2019, a global analysis estimated that bacterial AMR was associated with around 4.95 million deaths, of which 1.27 million were directly attributable to bacterial AMR.[1] Recent global estimates suggest that the burden will continue to be high in the future, especially in older people and in areas with low diagnostic, therapeutic, and infection prevention capacity.[2]

CRE are a special concern among resistant Gram-negative pathogens. Resistance to carbapenems is a critical threat to the use of these β-lactam agents, which are often reserved for the treatment of multidrug-resistant Enterobacterales, and therefore significantly limits treatment options. Bloodstream, urinary tract, respiratory, intra-abdominal, surgical-site, and other invasive infections are associated with CRE and are more likely to occur in hospitalized, critically ill, immunocompromised, and otherwise medically vulnerable patients.[3] Gastrointestinal colonization may also provide a reservoir for subsequent infection and healthcare-associated transmission.

The public-health importance of CRE is not limited to resistance to any single carbapenem, as they often possess other resistance genes and can spread effectively via clonal expansion and mobile genetic elements.[3,4] CRE are a critical-priority pathogen group

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on the World Health Organization (WHO) 2024 Bacterial Priority Pathogens List due to their clinical significance, spread, and lack of treatment options.[5]

Carbapenemase Mechanisms and Global Dissemination

There are multiple mechanisms by which Enterobacterales can become carbapenem resistant. Epidemiologically, the most significant is the production of carbapenem-hydrolyzing β-lactamases, but resistance can also be due to the production of extended-spectrum β-lactamases or AmpC production and decreased membrane permeability or other mechanisms.[4,6] The carbapenemases found in Enterobacterales are mainly of three Ambler classes: Class A enzymes, such as *Klebsiella pneumoniae* carbapenemases (KPC); Class B metallo-β-lactamases (MBLs), including New Delhi metallo-β-lactamase (NDM), Verona integron-encoded metallo-β-lactamase (VIM), and imipenemase (IMP); and OXA-48-like carbapenemases are Ambler class D beta-lactamase enzymes that hydrolyze penicillins at high levels and carbapenems at low levels.[4,6]

These mechanisms are not evenly distributed around the world and have changed significantly over time. NDM-producing Enterobacterales were more prevalent in the Indian subcontinent and then spread globally, whereas KPC-producing *K. pneumoniae* were established in several healthcare systems and then disseminated internationally.[4,6] OXA-48-like carbapenemases are especially significant in Europe, North Africa, the Middle East, and certain Asian countries, whereas VIM and IMP enzymes are significant in certain countries and bacterial populations.[4,6,7]

Carbapenemase genes can spread horizontally between Enterobacterales species via transferable plasmids, whereas clonal dissemination also contributes to their spread.[4] *K. pneumoniae* has been a major player in the dissemination of CRE in healthcare settings due to the combination of successful high-risk clones and mobile resistance determinants, and *Escherichia coli* and other Enterobacterales increasingly contribute to the spread of NDM, OXA-48-like, and other carbapenemases.[3,4] Thus, modern CRE epidemiology is a dynamic interplay of bacterial species, resistance mechanisms, transmission in healthcare settings, selection pressure from antimicrobial use, and global travel.

Evidence Gap, Rationale, and Review Objective

The global epidemiological burden of CRE is challenging to summarize with a single prevalence estimate, despite the extensive surveillance and the growing literature. Studies differ widely in their sampling frame, patient population, healthcare setting, specimen type, microbiological definition, susceptibility-testing methodology, and surveillance coverage. Importantly, the denominators used to express CRE burden are also heterogeneous. An isolate-based resistance proportion is a fundamentally different epidemiological measure than population-based incidence, cases per hospital admission or discharge, or proportion of screened individuals colonized with CRE.

Geographical coverage and data completeness have improved but are still uneven, with a significant increase in global surveillance. The WHO Global AMR and Use Surveillance System now includes data from over 100 countries, and still shows significant differences in surveillance coverage and data quality between settings.[8] While large multinational laboratory networks offer information on geographic and temporal resistance patterns, they may not be population representative, and many countries are represented primarily by tertiary-care, intensive-care, or single-center studies.

These methodological differences make it difficult to compare the results across regions and can lead to incorrect inferences if epidemiologically different measures are pooled together. A systematic synthesis that clearly separates isolate-based resistance from population- or admission-based incidence and colonization prevalence is therefore required.

Therefore, the aim of this systematic review was to describe the global prevalence and epidemiology of CRE in humans, focusing on proportions of resistance to individual carbapenems, population-based and admission-based incidence, colonization and carriage, distribution of organisms, carbapenemase mechanisms, geographic and healthcare-setting variation, temporal trends, epidemiological risk factors, and clinical outcomes. These measures were not pooled together to create a single global prevalence estimate, because of the anticipated clinical and methodological diversity.

Materials and Methods

Review Design and Reporting

This systematic review evaluated the global prevalence and epidemiology of CRE in human populations. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[9] The final literature search was completed on August 13, 2026. Because substantial heterogeneity was anticipated in study populations, resistance definitions, surveillance methods, and denominator structures, the review was designed for structured narrative synthesis without meta-analysis.

Review Question and Eligibility Criteria

The review addressed the question: What is the global burden and epidemiological distribution of CRE among human populations, including isolate-based resistance, infection incidence, and colonization or carriage?

Studies were eligible if they reported original human epidemiological data on CRE and provided a clearly defined denominator permitting calculation or interpretation of at least one pre-specified measure: (1) Isolate-based carbapenem resistance or non-susceptibility proportion, (2) population-, admission-, or discharge-based incidence, or (3) patient-level colonization or carriage prevalence. Studies from all countries, age groups, healthcare settings, and clinical populations were eligible. No geographic or language restriction was applied at the search stage.

Eligible study designs included national and multinational surveillance studies, population-based surveillance, prospective or retrospective cohort studies, cross-sectional prevalence studies, multicenter hospital surveillance, and other observational studies with an appropriate epidemiological denominator. Studies focusing on carbapenemase-producing Enterobacterales (CPE) were eligible where CPE occurrence could be interpreted within an appropriate source population or surveillance denominator.

Studies were excluded if they were restricted to molecular

or genomic characterization of preselected CRE/CPE isolates without a relevant prevalence or incidence denominator; did not permit CRE-specific data to be separated from other organisms or resistance phenotypes; involved exclusively environmental, veterinary, food, wastewater, or other non-human samples; lacked a defensible epidemiological denominator; or were reviews, meta-analyses, editorials, commentaries, or conference abstracts without sufficient methodological information. Where substantially overlapping surveillance populations were reported in more than one publication, duplicate data were not counted independently.

Information Sources and Search Strategy

Five electronic databases were searched from inception to August 13, 2026: MEDLINE/PubMed, Embase, Scopus, Web of Science Core Collection, and Global Health. Database searching was supplemented by citation searching and targeted identification of relevant national, regional, and multinational antimicrobial-resistance surveillance reports.

The search strategy combined controlled vocabulary and free-text terms relating to four principal concepts: Enterobacterales and major constituent species; carbapenem resistance or non-susceptibility; carbapenemase enzymes and genes; and epidemiological measures such as prevalence, incidence, surveillance, colonization, and carriage. Carbapenemase-specific terms included KPC, NDM, OXA-48-like, VIM, and IMP. No geographic filter was applied.

Search syntax was adapted to the indexing and interface requirements of each database. The complete reproducible electronic search strategies are provided.

Study Selection and Data Extraction

All retrieved records were collated and duplicate records eliminated prior to title and abstract screening. Full-text evaluation was performed on potentially eligible reports, using pre-specified inclusion and exclusion criteria. Reasons for exclusion at the full-text stage were documented and included in the PRISMA study-selection flow diagram as per PRISMA 2020.[9] A standardized framework was developed for the review, and data were extracted using this framework. Variables extracted were bibliographic data, country and geographic region, study period, study design, healthcare setting, population characteristics, organism, specimen type, resistance definition, antimicrobial susceptibility testing method, CRE or CPE numerator, epidemiological denominator, prevalence or incidence measure, carbapenemase mechanism, co-resistance (if reported), risk factors, colonization-to-infection progression, clinical outcomes, and temporal trends. Special consideration was paid to the type of denominator, as the interpretation of CRE burden is dependent on the denominator used, whether it is bacterial isolates, screened individuals, hospital admissions or discharges, or a defined population. The complete data-extraction framework is presented in Supplementary Table S2.

Definitions and Outcomes

CRE was defined according to the operational definition used in each included study, provided that carbapenem resistance or non-susceptibility was determined using recognized microbiological criteria or a clearly specified surveillance definition. Definitions varied over time and surveillance systems, so study-specific criteria were kept rather than applying a single resistance threshold retroactively. CPE was used specifically for Enterobacterales in which the production of carbapenemase was phenotypically or molecularly demonstrated. Three main epidemiological indicators were identified. Isolate-based resistance proportion referred to the proportion of Enterobacterales isolates meeting CRE or carbapenem-non-susceptibility criteria within a defined isolate collection. Incidence referred to CRE cases expressed relative to a population, hospital admissions, or hospital discharges over a defined period. Colonization or carriage prevalence referred to the proportion of screened individuals in whom CRE was detected, usually through rectal or stool surveillance. These measures were not considered substitutes for each other. Other outcomes included organism-specific distribution (*K. pneumoniae*, *E. coli*, and *Enterobacter* spp.), distribution of major carbapenemase families (KPC, NDM, OXA-48-like, VIM, and IMP), differences in distribution by healthcare setting and population, temporal trends, epidemiological risk factors for acquisition or infection, progression from colonization to clinical infection, and clinical outcomes such as mortality and length of hospital stay.

Risk-of-Bias Assessment

Methodological quality was assessed primarily using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data,[10] with contextual adaptation for population-based incidence and antimicrobial-resistance surveillance studies. The JBI prevalence checklist contains nine appraisal domains and is intended for critical appraisal of observational epidemiological studies reporting prevalence data.

The appraisal considered appropriateness of the sampling frame, sampling method, sample size, description of participants and setting, coverage of the identified sample, validity of CRE/CPE identification, reliability and consistency of measurement, appropriateness of statistical analysis, and adequacy of response or surveillance coverage. For surveillance studies, domains relating to participant recruitment and response rate were interpreted in relation to laboratory-network participation, site coverage, isolate sampling, and representativeness of the surveillance population.

JBI items were not summed into a numerical quality score. Overall judgments of low, low–moderate, moderate, or moderate–high methodological concern were qualitative review-level interpretations rather than formal JBI categories. Detailed appraisal criteria are provided in Supplementary Table S3.

Data Synthesis and Management of Overlapping Datasets

A narrative synthesis was undertaken because of substantial clinical and methodological heterogeneity across the included studies. No pooled global prevalence estimate or meta-analysis was performed. Results were organized according to epidemiological measure, geographic region, healthcare setting, organism, carbapenemase mechanism, temporal pattern, colonization status, risk factors, and clinical outcomes.

Isolate-based resistance proportions, population- or admission-based incidence, and colonization prevalence were synthesized separately and were not converted into a common metric. Multinational surveillance estimates were interpreted as

proportions within the sampled surveillance network unless the underlying design supported population-level inference.

Where multiple publications used substantially overlapping surveillance populations or study periods, the report providing the most complete, relevant, or methodologically informative dataset was prioritized for the corresponding epidemiological estimate. Non-overlapping periods or complementary outcomes were retained where they contributed distinct information without duplicate counting. This approach was used to minimize double-counting while preserving informative temporal and mechanistic findings.

Results

Study Selection and Characteristics

The literature search was finalized on August 13, 2026, and identified 1158 records, of which 1126 were retrieved from bibliographic databases, and 32 were retrieved from targeted surveillance and citation searching sources. Following the removal of 356 duplicates, 802 records were screened for title and abstract, with 706 records being excluded. Full-text reports were requested for 96 records, four of which were not retrieved, resulting in 92 reports for eligibility assessment. Of these, 77 were excluded, resulting in 15 studies being included in the final narrative synthesis. The entire study-selection process and rationale for full-text exclusion are shown in Figure 1. The 15 studies included were published from 2015 to 2025 and covered multinational surveillance networks, national and population-based surveillance systems, multicenter hospital studies, intensive-care cohorts, and single-center investigations in all major global regions.[11-25] Study populations included general hospital, bloodstream-infection, intensive care unit (ICU), community, and active CRE colonization screening populations. Three main epidemiological indicators were represented: Proportions of isolates resistant or non-susceptible to carbapenems, incidence of resistance or non-susceptibility (per population or per admission), and prevalence of colonization or carriage (per patient). These measures are based on different denominators and were therefore considered separate epidemiological outcomes for the synthesis. The majority of studies employed standardized criteria for antimicrobial susceptibility testing, and some included phenotypic or molecular confirmation of carbapenemase production. The studies included, however, varied in sampling frame, surveillance coverage, definition of resistance, clinical setting, and denominator structure, making it impossible to compare all reported estimates directly. The characteristics of the included studies are detailed in Table 1.

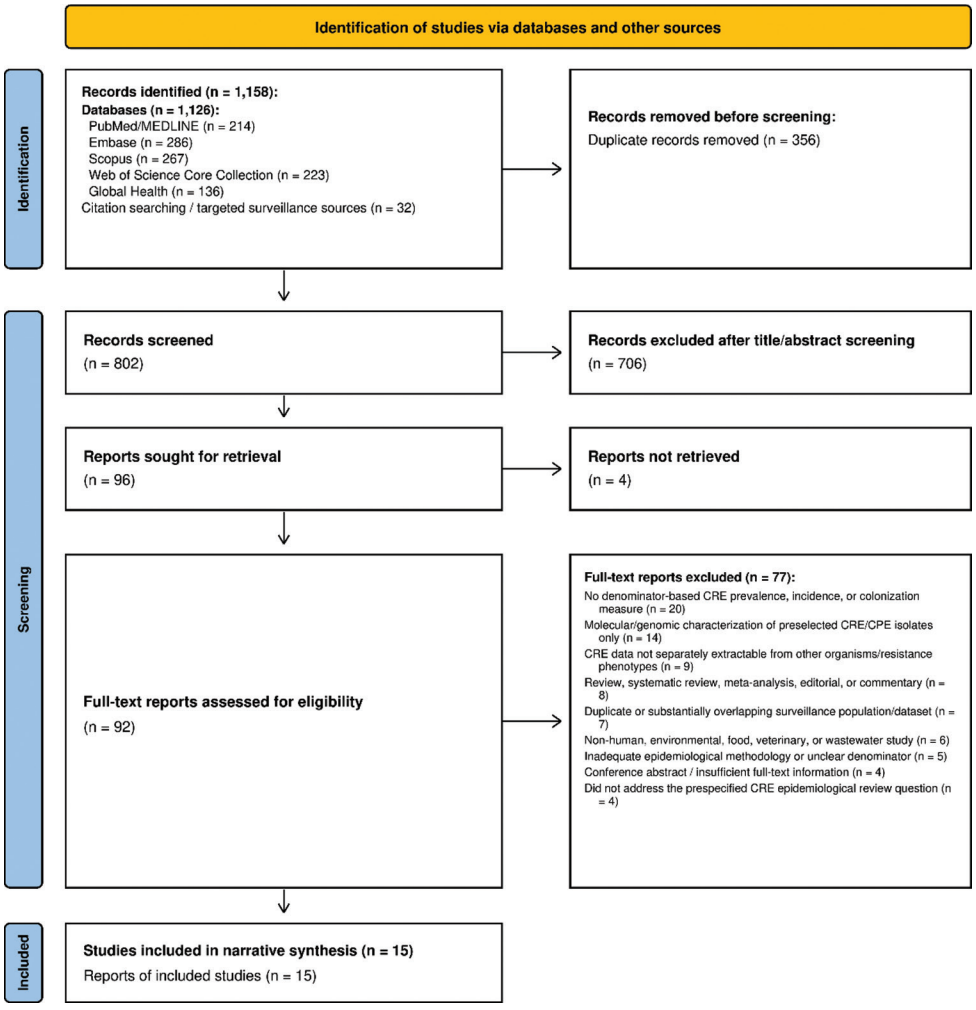

Figure 1: PRISMA 2020 flow diagram of study selection

Table 1: Characteristics of included studies

Study	*Country/ Region*	*Study period*	*Study design/ Surveillance type*	*Population/Setting*	*Epidemiological measure/Denominator*	*CRE/CPE definition or laboratory approach*	*Principal epidemiological contribution*
Kazmierczak *et al.*, 2021[11]	Global; 39 countries	2012–2017	Multinational antimicrobial-resistance surveillance (ATLAS)	Clinical Enterobacterales isolates from participating hospitals/laboratories	Isolate-based meropenem non-susceptibility; 81,781 Enterobacterales isolates	Meropenem MIC≥2 µg/mL; molecular characterization of resistance determinants among non-susceptible isolates	2666/81,781 (3.3%) meropenem-non-susceptible; major global source for organism and carbapenemase distribution
Estabrook *et al.*, 2023[12]	Global; 55 countries	2018–2019	Multinational antimicrobial-resistance surveillance	Clinical Enterobacterales isolates	Isolate-based meropenem non-susceptibility; 39,368 isolates	Meropenem non-susceptibility with molecular characterization of carbapenemase determinants	2228/39,368 (5.7%) meropenem-non-susceptible; demonstrates changing global carbapenemase distribution
Grundmann *et al.*, 2017[13]	Europe; 36 countries	Nov 2013–Apr 2014	Prospective multinational sentinel surveillance (EuSCAPE)	455 sentinel hospitals; clinical *K. pneumoniae* and *E. coli* isolates	Admission-based CPE occurrence plus organism-specific surveillance denominators	Standardized phenotypic screening and molecular confirmation of carbapenemases	CPE occurrence approximately 1.3 patients/10,000 hospital admissions; detailed KPC/ OXA-48-like/NDM/VIM epidemiology
Wielders *et al.*, 2022[14]	Netherlands	2017–2019	National laboratory surveillance	Clinical *E. coli* and *K. pneumoniae* isolates submitted through national surveillance	Species-specific isolate-based carbapenem resistance	National surveillance criteria with confirmatory characterization of suspected carbapenemase producers	Carbapenem resistance remained very low: *E. coli* 0.02%, *K. pneumoniae* 0.18%
Guh *et al.*, 2015[15]	United States; 7 surveillance communities	2012–2013	Population-based active surveillance	Residents of defined Emerging Infections Program catchment areas	Population-based CRE incidence	Standardized surveillance case definition using clinical laboratory susceptibility results	599 CRE cases in 481 persons; 2.93/100,000 population/year
Duffy *et al.*, 2023[16]	United States; 7 EIP sites	2016–2020	Population-based surveillance	Defined population catchments	Population-based annual CRE incidence	Standardized EIP surveillance definition	4996 incident CRE cases; incidence declined from 7.51 to 6.08/100,000
Zhang *et al.*, 2018[17]	China; 14 provinces	2015	Prospective multicenter surveillance	25 tertiary hospitals; patients with CRE infection	CRE infection incidence per hospital discharges	Clinical and microbiological CRE definitions with centralized epidemiological characterization	Approximately 4 CRE infections/10,000 hospital discharges
Wu *et al.*, 2023[18]	China	Prospective study period reported by authors	Prospective multicenter ICU study	1133 patients across 24 ICUs	Patient-level CRE colonization/infection prevalence and ICU acquisition	Active screening and clinical microbiological identification of CRE	5.9% positive at ICU admission; additional 8.5% acquired CRE during ICU stay
DebBarma *et al.*, 2025[19]	Bihar, India	Jul 2021–Jul 2023	Prospective tertiary-care laboratory study	Inpatient and outpatient clinical Enterobacterales isolates	Isolate-based CRE proportion; 3421 isolates	Phenotypic antimicrobial susceptibility and carbapenem resistance characterization	1128/3421 (32.97%) CRE; inpatient burden 47.74% vs outpatient 14.48%
Rajni *et al.*, 2025[20]	Western India	Prospective study period reported by authors	Prospective observational tertiary-care study	Consecutive non-duplicate Enterobacterales/CRE isolates	Isolate-based CRE proportion; 213 Enterobacterales isolates	Phenotypic carbapenem resistance and molecular carbapenemase detection	91/213 (43%) CRE; 91% carbapenemase producers; OXA-48 prominent
Wangchinda *et al.*, 2022[21]	Thailand	2018–2021	Prospective active-surveillance cohort	528 hospitalized patients at a university hospital	Patient-level intestinal CRE colonization prevalence	Active rectal/stool surveillance with microbiological identification	15.5% colonized with CRE at hospital admission

(*Contd...*)

Table 1: (*Continued*)

Study	*Country/ Region*	*Study period*	*Study design/ Surveillance type*	*Population/Setting*	*Epidemiological measure/Denominator*	*CRE/CPE definition or laboratory approach*	*Principal epidemiological contribution*
Mannathoko *et al.*, 2022[22]	Botswana	Study period reported by authors	Cross-sectional/ active carriage surveillance (ARCH)	Hospital, clinic, community adults, and community children; 2469 participants	Patient-level CRE carriage prevalence	Active screening for intestinal CRE carriage	42/2469 (1.7%) overall; hospital 6.8%, clinic 0.7%, community substantially lower
Kotb *et al.*, 2020[23]	Egypt	National surveillance period reported by authors	National ICU healthcare-associated infection surveillance	ICU patients with Enterobacteriaceae healthcare-associated infections	CRE proportion among Enterobacteriaceae HAI cases; 1598 cases	National surveillance definitions and antimicrobial susceptibility testing	871/1598 (54.1%) were carbapenem resistant
Thomsen *et al.*, 2023[24]	United Arab Emirates	2010–2021	Retrospective national AMR surveillance	317 surveillance sites; clinical Enterobacterales isolates	National isolate-based CRE proportion; 381,535 Enterobacterales isolates	Routine national microbiological surveillance with CRE classification	14,593/381535 (3.8%) CRE; provides long-term national temporal trends
Bell *et al.*, 2025[25]	Australia	2023	National bloodstream-isolate surveillance (AGAR GnSOP)	57 hospitals; 9503 Enterobacterales bloodstream isolates	Species-specific meropenem resistance among bloodstream isolates	Standardized national antimicrobial susceptibility surveillance with carbapenemase characterization where indicated	Meropenem resistance 0.2% in *E. coli* and 0.4% in *K. pneumoniae* complex; overall carbapenem resistance remained uncommon

AGAR: Australian Group on Antimicrobial Resistance, AMR: Antimicrobial resistance, CPE: Carbapenemase-producing Enterobacterales, CRE: Carbapenem-resistant Enterobacterales, EIP: Emerging infections program, HAI: Healthcare-associated infection, ICU: Intensive care unit, MIC: Minimum inhibitory concentration, NS: Non-susceptible. The included studies reported heterogeneous epidemiological measures. Isolate-based resistance proportions, population- or admission-based incidence, and patient-level colonization prevalence were therefore treated as distinct outcomes and were not directly pooled. Multinational surveillance proportions reflect the participating surveillance network and should not be interpreted as population prevalence unless the underlying study design supports such inference

Global and Regional CRE Burden

The burden of CRE varied markedly across geographic regions, healthcare settings, and denominator types. Because isolate-based resistance proportions, population- or admission-based incidence, and colonization prevalence represent distinct epidemiological measures, they were interpreted separately rather than combined into a single global prevalence estimate.

In multinational surveillance, meropenem-non-susceptibleEnterobacterales accounted for 2666 of 81,781 isolates (3.3%) collected across 39 countries during 2012–2017[11] and 2228 of 39,368 isolates (5.7%) collected across 55 countries during 2018–2019.[12] These estimates represent resistance proportions within structured surveillance collections rather than population prevalence. In Europe, EuSCAPE reported carbapenemase-producing *Klebsiella pneumoniae* or *E. coli* from clinical specimens in approximately 1.3 patients/10,000 hospital admissions across 455 sentinel hospitals in 36 countries,[13] whereas national surveillance from the Netherlands demonstrated very low carbapenem resistance among *E. coli* (0.02%) and *K. pneumoniae* (0.18%).[14]

Population-based surveillance in the United States reported an overall CRE incidence of 2.93/100,000 population per year during 2012–2013.[15] Subsequent surveillance across the same Emerging Infections Program network demonstrated a decline in crude incidence from 7.51/100,000 population in 2016 to 6.08/100,000 in 2020, with an adjusted overall reduction of approximately 24%.[16] In China, the China CRE Network reported approximately 4.0 CRE infections per 10,000 hospital discharges across tertiary-care hospitals.[17]

Substantially higher isolate-based resistance proportions were reported in several hospital-based Asian studies. In Bihar, India, 1128 of 3421 Enterobacterales isolates (32.97%) were carbapenem resistant,[19] whereas a tertiary-care study from western India reported CRE in 91 of 213 isolates (43%).[20] In Egypt, national ICU healthcare-associated infection surveillance identified carbapenem resistance in 871 of 1598 Enterobacteriaceae HAI cases (54.1%).[23] By contrast, national surveillance in the United Arab Emirates identified 14,593 CRE among 381,535 non-repetitive Enterobacterales isolates (3.8%) during 2010–2021.[24] Australian bloodstream-isolate surveillance likewise showed low meropenem resistance, at 0.2% among *E. coli* and 0.4% among *K. pneumoniae* complex isolates, although elevated meropenem resistance was observed in 0.4% and 0.8%, respectively.[25]

Colonization studies demonstrated a pronounced healthcare-associated gradient. In a prospective multicenter ICU study, 5.9% of patients had CRE colonization or infection at ICU admission, and a further 8.5% acquired CRE during ICU stay.[18] In Thailand, active surveillance identified CRE colonization in 15.5% of hospitalized patients at admission,[21] whereas the Botswana ARCH study reported an overall carriage prevalence of 1.7%, rising to 6.8% among hospital participants compared with substantially lower prevalence in clinic and community populations.[22]

Overall, CRE burden was consistently influenced by both geography and intensity of healthcare exposure. The highest estimates generally arose from tertiary-care and ICU populations, whereas national surveillance and community-based studies tended to report lower burdens. Detailed resistance, incidence, and colonization measures are summarized in Table 2, whereas healthcare-setting and population-specific comparisons are presented in Table 3.

Organisms, Carbapenemases, and Temporal Trends

K. pneumoniae was the predominant CRE species in most multinational and hospital-based surveillance datasets. In the 2012–2017 ATLAS program, *K. pneumoniae* accounted for 2046 of 2666 meropenem-non-susceptible Enterobacterales isolates (76.7%), substantially exceeding *Enterobacter cloacae* complex (6.6%) and *E. coli* (5.1%).[11] This pattern persisted during 2018–2019, when *K. pneumoniae* represented 1592 of 2228 resistant isolates (71.5%), compared with 8.7% for *E. cloacae* complex and 6.6% for *E. coli*.[12] EuSCAPE similarly demonstrated a greater burden of carbapenemase production among carbapenem-non-susceptible *K. pneumoniae* than *E. coli*: 850 of 1203 non-susceptible *K. pneumoniae* and 77 of 194 non-susceptible *E. coli* were confirmed as carbapenemase producers.[13] National surveillance from the United Arab Emirates also showed *K. pneumoniae* as the largest contributor to CRE, accounting for approximately 48.1% of resistant Enterobacterales, followed by *E. coli* (25.1%).[24] Organism-specific findings are summarized in Table 4.

Carbapenemase distributions differed substantially by geographic region, species, and surveillance period. During 2012–2017, KPC was the predominant carbapenemase group in the ATLAS surveillance collection, accounting for approximately 47.4% of meropenem-nonsusceptible isolates, whereas MBLs accounted for 20.6% and OXA-48-like enzymes for approximately one-fifth.[11] By 2018–2019, MBLs had become the most frequently detected group, occurring in 818 of 2228 isolates (36.7%), compared with 568 (25.5%) carrying KPC and 538 (24.1%) carrying OXA-48-like enzymes.[12] NDM predominated among MBLs, representing 723 of 818 (88.4%), whereas VIM and IMP were much less common. Two carbapenemases were detected in approximately 7.9% of resistant isolates.[12]

European data showed a distinct but similarly heterogeneous molecular profile. Among 927 confirmed CPE isolates in EuSCAPE, KPC accounted for approximately 42%, OXA-48-like enzymes 38%, NDM 12%, and VIM 7%.[13] Species-specific differences were evident: KPC predominated among carbapenemase-producing *K. pneumoniae*, whereas OXA-48-like enzymes were the most frequent mechanism among carbapenemase-producing *E. coli*. In western India, blaOXA-48 was detected in 61.4% of carbapenemase-producing isolates, and 35% carried more than one carbapenemase gene, indicating considerable local molecular complexity.[20] Overall, KPC, NDM, and OXA-48-like enzymes constituted the dominant carbapenemase families, although their relative importance varied substantially across regions and organisms [Table 5].

Temporal trends were likewise non-uniform. Within ATLAS, meropenem non-susceptibility increased from approximately 2.7% during 2012–2014 to 3.8% during 2015–2017,[11] and subsequently from 4.9% in 2018 to 6.4% in 2019.[12] This increase coincided with a changing carbapenemase profile, characterized by a lower relative contribution of KPC and increasing representation of MBLs, particularly NDM.[11,12] National surveillance in the United Arab Emirates showed CRE increasing from approximately 0.2% in 2010 to 3.7% by 2014, followed by a comparatively stable level of approximately 3.4–4.2% during subsequent years.[24] In contrast, population-based surveillance in the United States demonstrated a decline in CRE incidence from 7.51/100,000 population in 2016 to 6.08/100,000 in 2020, corresponding to an adjusted reduction of approximately 24%.[16]

Table 2: Global and regional epidemiological burden of Carbapenem-resistant Enterobacterales

Study	*Region/ Country*	*Epidemiological measure*	*Population/ denominator*	*CRE/CPE estimate*	*Key interpretation*
Kazmierczak *et al*., 2021[11]	Global; 39 countries	Isolate-based meropenem non-susceptibility	81,781 Enterobacterales isolates	2666/81,781 (3.3%)	Multinational surveillance proportion; not population prevalence.
Estabrook *et al*., 2023[12]	Global; 55 countries	Isolate-based meropenem non-susceptibility	39,368 Enterobacterales isolates	2228/39,368 (5.7%)	Higher surveillance proportion than in the earlier ATLAS period.
Wielders *et al*., 2022[14]	Netherlands	Isolate-based carbapenem resistance	National *Escherichia coli* and *Klebsiella pneumoniae* surveillance	*E. coli* 0.02%; *K. pneumoniae* 0.18%	Very low national resistance burden.
DebBarma *et al*., 2025[19]	India	Isolate-based CRE proportion	3421 Enterobacterales isolates	1128/3421 (32.97%)	High tertiary-care burden.
Rajni *et al*., 2025[20]	India	Isolate-based CRE proportion	213 Enterobacterales isolates	91/213 (43%)	High single-center tertiary-care burden.
Kotb *et al*., 2020[23]	Egypt	CRE among Enterobacteriaceae HAI cases	1598 ICU HAI cases	871/1598 (54.1%)	Very high burden in a selected national ICU HAI population.
Thomsen *et al*., 2023[24]	United Arab Emirates	National isolate-based CRE proportion	381,535 Enterobacterales isolates	14,593/381,535 (3.8%)	Broad national surveillance estimate.
Bell *et al*., 2025[25]	Australia	Bloodstream-isolate meropenem resistance	9503 Enterobacterales bloodstream isolates	*E. coli* 0.2%; *K. pneumoniae* complex 0.4% resistant	Elevated meropenem MICs occurred in 0.4% and 0.8%, respectively; resistance and elevated MIC should not be conflated.
Grundmann *et al*., 2017[13]	Europe; 36 countries	Admission-based CPE occurrence	455 sentinel hospitals	1.3 patients/10,000 admissions	Admission-based occurrence, not isolate prevalence.
Guh *et al*., 2015[15]	United States	Population-based CRE incidence	Seven surveillance communities	2.93/100,000 population/year	Population-based active surveillance.
Duffy *et al*., 2023[16]	United States	Population-based CRE incidence	Seven EIP sites	7.51/100,000 in 2016→6.08/100,000 in 2020	Adjusted overall incidence declined approximately 24%.
Zhang *et al*., 2018[17]	China	Admission/ discharge-based infection incidence	25 tertiary hospitals	4.0/10,000 discharges	Patient-based CRE infection burden.
Wu *et al*., 2023[18]	China	ICU colonization/ infection prevalence and acquisition	1133 ICU patients	5.9% at admission; 8.5% acquired	Demonstrates ongoing ICU acquisition.
Wangchinda *et al*., 2022[21]	Thailand	CRE colonization prevalence	528 hospitalized patients	15.5% at admission	Active intestinal carriage surveillance.
Mannathoko *et al*., 2022[22]	Botswana	CRE colonization prevalence	2469 participants	42/2469 (1.7%)	Overall carriage low but strongly setting dependent.

CPE: Carbapenemase-producing Enterobacterales, CRE: Carbapenem-resistant Enterobacterales, EIP: Emerging infections program, HAI: Healthcare-associated infection, ICU: Intensive care unit, MIC: Minimum inhibitory concentration. Isolate-based resistance proportions, population- or admission-based incidence, and patient-level colonization prevalence have different denominators and should not be directly compared or quantitatively pooled

Taken together, these data demonstrate that CRE evolution is characterized by both organism-specific dominance and changing resistance mechanisms, rather than a uniform global trajectory. *K. pneumoniae* remains the principal CRE species in most surveillance systems, while the balance between KPC, NDM, and OXA-48-like carbapenemases varies substantially by geography and time. Organism-specific epidemiology, carbapenemase distributions, and temporal trends are presented in Tables 4-6.

Colonization, Risk Factors, and Progression to Infection

CRE colonization was concentrated predominantly in hospitalized and critically ill populations, with the available studies consistently indicating a strong association between healthcare exposure and carriage. In the prospective multicenter ICU study by Wu *et al*.[18] 5.9% of patients had CRE colonization or infection at ICU admission and a further 8.5% acquired CRE during the ICU stay, demonstrating both importation of CRE into critical-care settings and ongoing healthcare-associated acquisition. In Thailand, Wangchinda *et al*.[21] identified CRE intestinal colonization in 15.5% of hospitalized patients at admission, whereas the Botswana ARCH study reported a substantially higher carriage prevalence among hospitalized participants (6.8%) than among clinic attendees (0.7%) or community participants.[22] These findings support a clear gradient of increasing CRE carriage with greater intensity of healthcare exposure.

Across the included studies, risk was most consistently associated with factors that characterize high-acuity healthcare

Table 3: CRE epidemiology by healthcare setting and population

Study	*Country/Region*	*Setting/population comparison*	*Main finding*	*Epidemiological interpretation*
DebBarma *et al*., 2025[19]	India	Inpatient versus outpatient isolates	47.74% inpatient versus 14.48% outpatient	Markedly greater CRE burden among inpatient isolates.
Wu *et al*., 2023[18]	China	ICU admission versus acquisition during ICU stay	5.9% positive at admission; 8.5% subsequently acquired	Demonstrates both imported and healthcare-acquired CRE burden in ICUs.
Wangchinda *et al*., 2022[21]	Thailand	Hospital admission screening	15.5% colonized at admission	Substantial carriage among hospitalized patients entering care.
Mannathoko *et al*., 2022[22]	Botswana	Hospital, clinic, and community	Overall 1.7%; hospital 6.8%, clinic 0.7%, community substantially lower	Clear gradient with increasing healthcare exposure.
Kotb *et al*., 2020[23]	Egypt	National ICU HAI surveillance	54.1% of Enterobacteriaceae HAI cases were carbapenem resistant	Represents a highly selected critical-care population rather than general population prevalence.
Guh *et al*., 2015[15]	United States	Population-based surveillance	2.93 CRE cases/100,000 population/year	Provides population-level context for predominantly healthcare-associated CRE.
Duffy *et al*., 2023[16]	United States	Population-based surveillance over time	7.51→6.08/100,000 from 2016 to 2020	Demonstrates declining population incidence despite continuing healthcare-associated burden.
Zhang *et al*., 2018[17]	China	Tertiary hospitals	4.0 CRE infections/10,000 discharges	Illustrates patient-based burden in tertiary-care settings.
Grundmann *et al*., 2017[13]	Europe	455 sentinel hospitals	1.3 CPE-positive patients/10,000 admissions	Hospital-admission denominator permits comparison of CPE occurrence across participating countries.
Thomsen *et al*., 2023[24]	UAE	National hospitals and outpatient/clinic surveillance	3.8% overall CRE	Broad multisite surveillance captures a wider patient spectrum than single-center hospital studies.
Bell *et al*., 2025[25]	Australia	Bloodstream infections from 57 hospitals	Meropenem resistance 0.2% in *Escherichia coli* and 0.4% in *Klebsiella pneumoniae* complex	Low carbapenem resistance within national bloodstream surveillance.

ICU: Intensive care unit, CRE: Carbapenem-resistant Enterobacterales

Table 4: Organism-specific epidemiology of Carbapenem-resistant Enterobacterales

Study	*Setting*	*Resistant/CPE denominator*	*K. pneumoniae*	*E. coli*	*Other important Enterobacterales*	*Main finding*
Kazmierczak *et al*., 2021[11]	Global, 2012–2017	2666 meropenem-NS isolates	2046 (76.7%)	136 (5.1%)	*E. cloacae* complex 177 (6.6%); others 307 (11.5%)	*K. pneumoniae* overwhelmingly predominated among resistant isolates.
Estabrook *et al*., 2023[12]	Global, 2018–2019	2228 meropenem- NS isolates	1592 (71.5%)	148 (6.6%)	*E. cloacae* complex 193 (8.7%); others 13.2%	Persistent predominance of *K. pneumoniae*.
Grundmann *et al*., 2017[13]	Europe	1203 carbapenem-NS *Klebsiella pneumoniae*; 194 carbapenem-NS *Escherichia coli*	850/1203 confirmed CPE	77/194 confirmed CPE	—	Carbapenemase production was more frequent among non-susceptible *K. pneumoniae*.
Wielders *et al*., 2022[14]	Netherlands	National surveillance	0.18% carbapenem resistant	0.02% carbapenem resistant	—	Very low national resistance, but higher in *K. pneumoniae* than *E. coli*.
Thomsen *et al*., 2023[24]	United Arab Emirates	14,593 CRE	7023 (48.1%)	3668 (25.1%)	Other Enterobacterales 3902 (26.8%)	*K. pneumoniae* was the largest contributor to national CRE burden.
Bell *et al*., 2025[25]	Australia	National bloodstream surveillance	0.4% meropenem resistant	0.2% meropenem resistant	Other Enterobacterales represented within the 9503-isolate collection	Carbapenem resistance remained uncommon in national bloodstream surveillance.

CPE: Carbapenemase-producing Enterobacterales, CRE: Carbapenem-resistant Enterobacterales, NS: Non-susceptible. Percentages in the ATLAS rows describe the species composition of meropenem-non-susceptible isolates, not species-specific prevalence in the entire surveillance population

Table 5: Distribution of major carbapenemase mechanisms among eligible studies

Study/organism	*Relevant denominator*	*KPC (%)*	*NDM/MBL (%)*	*OXA-48-like (%)*	*VIM (%)*	*IMP*	*Multiple carbapenemases/other findings*
Kazmierczak *et al.*, 2021[11]	2666 meropenem-non-susceptible Enterobacterales	1263 (47.4)	MBL: 548 (20.6); among MBLs, NDM 61	506 (19.0)	Within MBL group; approximately 30% of MBL-positive isolates	Within MBL group; approximately 9% of MBL-positive isolates	Dual-carbapenemase combinations included MBL+OXA-48-like, MBL+KPC, and MBL+GES; no carbapenemase detected in 413 (15.5%) isolates
Estabrook *et al.*, 2023[12]	2228 meropenem- non-susceptibleEnterobacterales	568 (25.5)	MBL: 818 (36.7); NDM: 723/818 (88.4)	538 (24.1)	91/818 MBLs (11.1)	4/818 MBLs (0.5%)	173/2228 (7.8%; reported as 7.9% after rounding) carried two carbapenemases; NDM+OXA-48-like was the dominant combination
Grundmann *et al.*, 2017,[13] overall EuSCAPE	927 confirmed CPE	393 (42)	NDM 113 (12)	353 (38)	68 (7)	NR	Carbapenemase distribution differed substantially by species and country
— *K. pneumoniae*	850 confirmed CPE	379 (45)	NDM 93 (11)	310 (37)	68 (8)	NR	KPC was the predominant carbapenemase family
— *E. coli*	77 confirmed CPE	14 (18)	NDM 20 (26)	43 (56)	0	NR	OXA-48-like enzymes predominated
Rajni *et al.*, 2025[20]	Carbapenemase-producing CRE from tertiary-care study	NR	NR	blaOXA-48 detected in 61.4	NR	NR	35% carried >1 carbapenemase gene

CPE: Carbapenemase-producing Enterobacterales, IMP: Imipenemase, KPC: *Klebsiella pneumonia* carbapenemase, MBL: Metallo-β-lactamase, NDM: New Delhi metallo-β-lactamase, OXA: Oxacillinase, VIM: Verona integron-encoded metallo-β-lactamase. Denominators differ between studies. Gene-family percentages should therefore be interpreted within each study rather than compared as population prevalence. Rounded EuSCAPE percentages may not total exactly 100%

environments, including ICU admission, prolonged hospitalization, prior healthcare contact, antimicrobial exposure, and use of invasive devices. Although the included epidemiological studies were not uniformly designed for formal risk-factor modeling, the distribution of CRE across inpatient, outpatient, ICU, and community populations consistently indicated that healthcare exposure was a major determinant of acquisition. This pattern was also reflected in the markedly higher CRE proportion among inpatient than outpatient isolates in the Bihar tertiary-care study[19] and in the high burden observed in Egyptian ICU healthcare-associated infection surveillance.[23]

Direct evidence quantifying progression from colonization to subsequent clinical infection was limited among the 15 included studies. Nevertheless, the occurrence of CRE carriage at admission together with additional acquisition during hospitalization indicates that colonized patients constitute an important reservoir within healthcare settings and may remain at risk for subsequent infection. Because studies differed in screening methods, follow-up duration, definitions of colonization and infection, and patient populations, no pooled estimate of colonization-to-infection progression was calculated.

Overall, the included evidence supports a continuum in which increasing healthcare exposure is associated with CRE acquisition and intestinal carriage, particularly in ICU and other high-risk hospital populations. However, the proportion of colonized patients who subsequently develop clinical infection remains insufficiently characterized within the eligible epidemiological literature. Colonization prevalence and setting-specific burden are summarized in Table 2, whereas study-specific risk-factor and progression findings are summarized in Table 7.

Clinical Outcomes and Mortality

The 15 studies that fulfilled the denominator-based epidemiological eligibility criteria for the review had relatively limited clinical outcome reporting. The majority of studies included were primarily aimed at estimating the prevalence, incidence, colonization, or surveillance burden of CRE, but not at detailed evaluation of mortality or other patient-level outcomes. Therefore, outcome data were not sufficiently standardized for comparative synthesis or quantitative pooling.

When clinical outcomes were reported, the results generally indicated that CRE occurred predominantly in high-risk groups of hospitalized patients with significant healthcare exposure, especially in intensive-care and tertiary-care units.[17-23] These populations also showed higher rates of CRE acquisition, colonization, and infection, indicating a clinically relevant burden in addition to microbiological resistance. The studies included, however, differed in case definition, site of infection, length of follow-up, and reporting of outcomes, so a reliable pooled estimate of mortality or length of stay could not be obtained.

The evidence available therefore suggests an association between CRE and clinically vulnerable populations, but detailed estimates of mortality, treatment failure, and progression from colonization to invasive disease were incompletely characterized in the included epidemiological studies. Where reported, these outcomes are summarized in Table 7. More detailed evidence on mortality and prognostic factors from dedicated clinical outcome cohorts is included in the Discussion as contextual literature and not as part of the primary systematic-review Results.

Table 6: Temporal trends in CRE epidemiology

Study	*Setting/Period*	*Temporal finding*	*Interpretation*
Kazmierczak *et al*., 2021[11]	Global ATLAS, 2012–2017	Meropenem non-susceptibility increased from approximately 2.7% in 2012–2014 to 3.8% in 2015–2017	Increasing resistance within the multinational surveillance collection.
Estabrook *et al*., 2023[12]	Global ATLAS, 2018–2019	Meropenem non-susceptibility increased from approximately 4.9% in 2018 to 6.4% in 2019	Continued increase, accompanied by greater representation of MBLs/NDM.
Duffy *et al*., 2023[16]	United States, 2016–2020	Incidence declined from 7.51 to 6.08/100,000 population; adjusted decline approximately 24%	Population-level CRE incidence decreased over the surveillance period.
Thomsen *et al*., 2023[24]	UAE, 2010–2021	CRE increased from approximately 0.2% in 2010 to 3.7% by 2014, then remained broadly around 3.4–4.2%	Rapid early emergence followed by relative stabilization.

Temporal trends were derived using the epidemiological measures reported by each surveillance system. Changes in isolate-based resistance proportions should not be interpreted as equivalent to changes in population incidence. CRE: Carbapenem-resistant Enterobacterales, MBLs: Metallo-β-lactamases, NDM: New Delhi metallo-β-lactamase

Table 7: Epidemiological risk factors and clinical outcomes associated with CRE acquisition, colonization, and infection

Study	*Population/Setting*	*Epidemiological domain*	*Main finding*	*Interpretation*
Guh *et al*., 2015[15]	Seven US population-based surveillance communities	Healthcare exposure/CRE infection	CRE cases occurred predominantly in patients with substantial recent or ongoing healthcare exposure	Supports the predominantly healthcare-associated epidemiology of CRE despite population-based case ascertainment
Duffy *et al*., 2023[16]	Seven US Emerging Infections Program sites	Healthcare-associated CRE epidemiology	Healthcare-associated community-onset and hospital-onset disease remained important components of incident CRE during 2016–2020	Healthcare exposure remained epidemiologically important despite declining overall population incidence
Zhang *et al*., 2018[17]	25 tertiary hospitals in China	Hospital-associated CRE infection	Approximately 4 CRE infections per 10,000 discharges were identified	Demonstrates clinically important CRE burden within tertiary-care populations
Wu *et al*., 2023[18]	1133 patients across 24 ICUs	Colonization/ acquisition during ICU stay	5.9% had CRE colonization or infection at ICU admission; an additional 8.5% acquired CRE during ICU stay	Demonstrates both importation and ongoing acquisition of CRE within critical-care environments
DebBarma *et al*., 2025[19]	Tertiary-care center, India	Healthcare setting as epidemiological risk marker	CRE occurred in 47.74% of inpatient isolates compared with 14.48% of outpatient isolates	Strong inpatient–outpatient gradient supports greater CRE burden with healthcare exposure
Rajni *et al*., 2025[20]	Tertiary-care hospital, western India	High-risk hospital population	CRE represented approximately 43% of Enterobacterales isolates; most CRE were carbapenemase producers	Indicates substantial CRE burden in a selected tertiary-care population, although formal patient-level risk modeling was limited
Wangchinda *et al*., 2022[21]	528 hospitalized patients, Thailand	Admission colonization/clinical follow-up	CRE intestinal colonization was detected in 15.5% of patients at hospital admission	Identifies a substantial reservoir of asymptomatic carriage among hospitalized patients
Mannathoko *et al*., 2022[22]	Hospital, clinic, and community populations in Botswana	Healthcare exposure/ colonization	Overall carriage was 1.7%; prevalence was 6.8% in hospital participants, 0.7% in clinic attendees, and substantially lower in community groups	Provides one of the clearest healthcare-exposure gradients for CRE colonization
Kotb *et al*., 2020[23]	National ICU healthcare-associated infection surveillance, Egypt	Critical-care setting/ infection burden	871/1,598 (54.1%) Enterobacteriaceae HAI cases were carbapenem resistant	Very high burden in a selected ICU HAI population; illustrates concentration of CRE in critically ill patients
Thomsen *et al*., 2023[24]	National UAE surveillance network	Healthcare setting/ national CRE distribution	14,593/381,535 (3.8%) Enterobacterales isolates were CRE across a broad national network	Provides broader healthcare-system context and demonstrates a lower overall burden than many single-center tertiary-care studies
Grundmann *et al*., 2017[13]	455 sentinel hospitals in 36 European countries	Hospital exposure/ CPE occurrence	CPE occurred at approximately 1.3 patients per 10,000 hospital admissions	Demonstrates measurable hospital-associated CPE burden across Europe using an admission-based denominator

CPE: Carbapenemase-producing Enterobacterales, CRE: Carbapenem-resistant Enterobacterales, HAI: Healthcare-associated infection, ICU: Intensive care unit. The included studies were heterogeneous in design and were not uniformly constructed for formal patient-level risk-factor or outcome modeling. Accordingly, setting-based associations such as ICU exposure, hospitalization, and inpatient status should be interpreted as epidemiological indicators of increased CRE burden rather than necessarily independent causal risk factors. Direct quantification of progression from colonization to subsequent infection and detailed mortality analyses was limited among the studies meeting the review's denominator-based eligibility criteria

Table 8: Risk of bias and methodological quality of included studies

Study	*Q1 Appropriate sampling frame*	*Q2 Appropriate sampling*	*Q3 Adequate sample size*	*Q4 Subjects/ setting adequately described*	*Q5 Sufficient sample coverage*	*Q6 Valid CRE/CPE identification*	*Q7 Standard/ reliable measurement*	*Q8 Appropriate statistical analysis*	*Q9 Adequate response/ surveillance coverage*	*Overall methodological concern*
Kazmierczak *et al*., 2021[11]	N	N	Y	Y	U	Y	Y	Y	NA	Moderate–high
Estabrook *et al*., 2023[12]	N	N	Y	Y	U	Y	Y	Y	NA	Moderate–high
Grundmann *et al*., 2017[13]	Y	Y	Y	Y	Y	Y	Y	Y	U	Low–moderate
Wielders *et al*., 2022[14]	Y	Y	Y	Y	Y	Y	Y	Y	NA	Low
Guh *et al*., 2015[15]	Y	Y	Y	Y	Y	Y	Y	Y	NA	Low
Duffy *et al*., 2023[16]	Y	Y	Y	Y	Y	Y	Y	Y	NA	Low
Zhang *et al*., 2018[17]	N	U	Y	Y	Y	Y	Y	Y	NA	Moderate
Wu *et al*., 2023[18]	Y	U	Y	Y	Y	Y	Y	Y	Y	Low–moderate
DebBarma *et al*., 2025[19]	N	U	Y	Y	U	Y	Y	Y	NA	Moderate–high
Rajni *et al*., 2025[20]	N	U	Y	Y	U	Y	Y	Y	NA	Moderate–high
Wangchinda *et al*., 2022[21]	Y	U	Y	Y	Y	Y	Y	Y	Y	Low–moderate
Mannathoko *et al*., 2022[22]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Low
Kotb *et al*., 2020[23]	N	N	Y	Y	Y	Y	Y	Y	NA	Moderate
Thomsen *et al*., 2023[24]	Y	U	Y	Y	U	Y	U	Y	NA	Moderate
Bell *et al*., 2025[25]	Y	Y	Y	Y	Y	Y	Y	Y	NA	Low

JBI domain definitions

Domain	*Appraisal question*
Q1	Was the sample frame appropriate to address the target population?
Q2	Were study participants or isolates sampled in an appropriate way?
Q3	Was the sample size adequate?
Q4	Were the study subjects and setting described in sufficient detail?
Q5	Was data analysis conducted with sufficient coverage of the identified sample?
Q6	Were valid methods used for identification of CRE/CPE?
Q7	Was resistance or carbapenemase status measured in a standard and reliable way for all observations?
Q8	Was the statistical analysis appropriate?
Q9	Was the response rate, participation rate, or surveillance coverage adequate or appropriately addressed?

Summary of overall methodological judgments

Overall methodological concern	*Number of studies*	*Interpretation*
Low	5	Broad population or national surveillance coverage with standardized ascertainment and well-defined denominators
Low–moderate	3	In general robust methodology with minor limitations in representativeness or sampling
Moderate	3	Important limitations related mainly to sampling frame, surveillance representativeness, or longitudinal coverage
Moderate–high	4	Restricted or non-population-based sampling substantially limits prevalence inference despite generally strong microbiological methods
High	0	No included study had methodological limitations severe enough to render its epidemiological findings uninterpretable

Ratings: Y: Yes, N: No, U: Unclear, NA: Not applicable. CPE: Carbapenemase-producing Enterobacterales, CRE: Carbapenem-resistant Enterobacterales, JBI: Joanna Briggs Institute, NA: Not applicable. The overall categories of low, low–moderate, moderate, and moderate–high methodological concern are review-level qualitative judgments and are not official JBI scoring categories. JBI item responses were not summed into a numerical score. For multinational and national surveillance studies, sampling frame, response rate, and coverage were interpreted in relation to surveillance-network participation, laboratory coverage, and representativeness rather than conventional participant recruitment

Risk of Bias and Overall Synthesis

Methodological quality varied across the included studies, largely because of differences in sampling frame, surveillance design, population coverage, and denominator structure. The strongest studies were population-based or national surveillance systems with clearly defined populations, standardized CRE ascertainment, and consistent laboratory methods. In contrast, several tertiary-care, ICU, and commercial surveillance studies had greater concerns regarding representativeness and external validity, despite generally robust microbiological identification.

Of the 15 included studies, five were judged to have low methodological concern, three low–moderate concern, three moderate concern, and four moderate–high concern; none were considered to have a great concern. The principal strength across the evidence base was reliable microbiological ascertainment, whereas the most frequent limitation was restricted or non-population-based sampling. Large multinational surveillance programs therefore provided valuable information on resistance patterns and geographic distribution but were interpreted as surveillance proportions rather than direct estimates of population prevalence. Detailed domain-level appraisal is presented in Table 8.

Appraisal framework

Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data, adapted where necessary for surveillance and incidence studies.[10]

Discussion

Principal Findings

The results of this systematic review show that the epidemiology of CRE is very variable by geographic region, healthcare setting, bacterial species, resistance mechanism, and surveillance system. In the 15 studies included, CRE burden was consistently highest in intensive-care units, tertiary-care hospitals, and other groups with high healthcare exposure, while more general national and community-based surveillance yielded lower estimates.[11-25] The differences between multinational isolate-based surveillance, population-based incidence, hospital admission-based occurrence, and patient-level colonization further support the idea that a single pooled "global prevalence" would mask rather than reveal the epidemiological picture.

In most multinational and hospital-based datasets, *K. pneumoniae* was the predominant CRE species, with *E. coli* and other Enterobacterales species contributing to the data in varying amounts, depending on region and setting.[11-13,24] The distribution of carbapenemase was also not even. KPC was still well represented in a number of global and European databases, whereas NDM and OXA-48-like enzymes were especially significant in Asian and other non-KPC-dominant environments.[11-13,20] Temporal patterns were also divergent, with increasing meropenem nonsusceptibility observed in multinational surveillance,[11,12] and decreasing incidence observed in the US population-based surveillance during 2016–2020.[16] These results support the general conclusion that CRE are not a single entity, but a group of resistance phenotypes influenced by local antimicrobial pressure, circulating clones and plasmids, healthcare transmission, and surveillance methodology.[3,4]

Interpreting Global, Regional and Molecular Patterns

The differences found between studies should not be taken as a reflection of only geographical differences in resistance. Much of the apparent difference is due to denominator and setting. Very high proportions were reported in Indian tertiary-care and Egyptian ICU populations,[19,20,23] which are not directly comparable with national bloodstream surveillance in Australia,[25] national laboratory surveillance in the Netherlands,[14] or population-based incidence estimates from the United States.[15,16] This distinction is especially relevant in international AMR studies, as countries with strong national surveillance might seem to have lower resistance burdens than those represented predominantly by referral hospitals or ICUs. WHO surveillance similarly continues to document substantial differences in AMR burden and surveillance coverage between countries.[8]

The high proportion of *K. pneumoniae* in this review is in line with its known status as a significant healthcare-associated reservoir of carbapenem resistance.[3,4] The species is well adapted to the convergence of successful hospital clones and transferable carbapenemase plasmids. A helpful external comparison is provided by molecular surveillance from China: Han *et al*. analyzed 935 CRE isolates from 36 hospitals and found that *K. pneumoniae* accounted for 709 isolates, with KPC-2 predominating among *K. pneumoniae* and NDM predominating among *E. coli*.[26] This is very similar to the species–mechanism relationships observed in the present review, with KPC being the most common enzyme among *K. pneumoniae* in Europe, and NDM and OXA-48-like enzymes making a greater relative contribution among *E. coli* and some Asian populations.[11-13,20]

The increase in metallo-β-lactamase representation in the later ATLAS period[12] is also of epidemiological significance. NDM-producing Enterobacterales have spread beyond their initial geographic focus, whereas OXA-48-like enzymes continue to spread throughout Europe, the Middle East, North Africa and Asia.[4,6,7] The increasing convergence of hypervirulence and carbapenem resistance in *K. pneumoniae* is also a growing concern. The international emergence of carbapenem-resistant hypervirulent *K. pneumoniae*, especially in Asia, with the potential for simultaneous high-level resistance, enhanced virulence, and healthcare transmission, has been described recently.[27] Therefore, future surveillance should shift from simple resistant/susceptible classification to species-, clone-, and carbapenemase-specific reporting.

Colonization, Clinical Outcomes, and Healthcare Implications

The colonization studies reviewed here demonstrated a clear healthcare-associated gradient, with CRE carriage concentrated among hospitalized and critically ill patients.[18,21,22] This pattern is biologically and epidemiologically plausible because subsequent infection or transmission can occur from a reservoir of intestinal colonization. While there was limited evidence of direct quantification of the progression from colonization to infection in the 15 eligible studies, broader evidence supports this relationship. In a systematic review and meta-analysis of 14 ICU studies published in 2024, involving 37,305 patients, acquisition of multidrug-resistant organisms during ICU admission was common and increased with the duration of ICU stay.[27] This contextual evidence reinforces the interpretation of the ICU acquisition patterns found in the present review.[18]

The clinical significance of CRE is not limited to colonization. We had relatively limited mortality data due to our strict epidemiological eligibility criteria, but dedicated outcome cohorts consistently show poor prognosis in invasive CRE infection. Wilson *et al*. highlighted the significant mortality associated with CRE bloodstream infection and ongoing uncertainty regarding the best treatment approach in a cohort of 393 patients with CRE bacteremia from the US Veterans Affairs system.[28] Previous comparative studies and meta-analyses have also linked carbapenem resistance to significantly higher mortality rates than susceptibility in Enterobacterales infections. Although mortality was not a primary outcome in most studies in this review, these data support the interpretation that the high CRE burden observed in ICUs and tertiary-care settings is clinically significant.

The practical implication is that surveillance, infection prevention, and antimicrobial stewardship cannot be considered separately. In certain high-risk groups, admission screening may be beneficial, but screening programs should be accompanied by effective contact precautions, antimicrobial stewardship, rapid laboratory identification, and local knowledge of circulating carbapenemases. A recent systematic review and meta-analysis assessed active screening cultures for CRE and provides an example of the increasing interest in whether surveillance itself can translate into improved clinical outcomes.[29]

Research and Surveillance Priorities

Future CRE surveillance would benefit from greater standardization of case definitions, susceptibility breakpoints, denominator reporting, and distinction between carbapenem resistance and confirmed carbapenemase production. Population-based surveillance remains particularly limited in many low- and middle-income settings, where available evidence is often derived from tertiary referral hospitals. Linking microbiological surveillance with patient-level clinical data would permit better estimation of colonization-to-infection progression, attributable mortality, and healthcare burden.

Greater integration of genomic surveillance is also needed. Monitoring high-risk clones, plasmid-mediated dissemination, co-carriage of multiple carbapenemases, and emerging carbapenem-resistant hypervirulent *K. pneumoniae* may provide earlier warning of epidemiological shifts than phenotypic resistance surveillance alone.[26,30]

Conclusion

CRE represent a heterogeneous and predominantly healthcare-associated global AMR threat. CRE burden varies substantially by region, healthcare setting, organism, resistance mechanism, and surveillance methodology, with *K. pneumoniae* and the KPC, NDM, and OXA-48-like carbapenemases playing major epidemiological roles. Because isolate-based resistance proportions, incidence measures, and colonization prevalence use fundamentally different denominators, they should not be combined into a single global prevalence estimate. Continued standardized surveillance, improved molecular characterization, and stronger linkage between microbiological and clinical data are essential to monitor emerging CRE patterns and guide prevention, infection-control, and antimicrobial-stewardship strategies.

AI Declaration

No generative AI was used for conceptualization, analysis, or content generation. AI use was limited to language refinement, and the authors remain fully responsible for the accuracy, originality, validity, and integrity of the manuscript's content.

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