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REVIEW ARTICLE

HIGH PREVALENCE OF CARBAPENEM RESISTANT ENTEROBACTERIACEAE IN BANGLADESH: A SYSTEMATIC REVIEW AND POOLED ANALYSIS

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Abstract:

Background: *Carbapenem-resistant* Enterobacteriaceae *(CRE) poses a public-health threat due to limited treatment options thus leading to substantial morbidity and mortality. We aimed to systematically review the prevalence of CRE in Bangladesh from previously published literatures with organism distribution and associated resistance genes.* **Methods:** *Following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines, we searched PubMed, Google Scholar, and the Directory of Open Access Journals (DOAJ) to identify cross-sectional studies from Bangladesh. After screening and eligibility assessment, we identified seven studies that met the inclusion criteria.* **Results:** *The crude prevalence of CRE was 11.79% (95% CI, 10.64–13.05). The pooled prevalence was 15.46% (95% CI, 6.85–31.27; I^2 = 93.1%), indicating high between-study heterogeneity. Predominant species were* Escherichia coli *(40.57%),* Klebsiella pneumoniae *(25.47%), and* Enterobacter cloacae *(3.77%);* Enterobacter spp. *(15.09%) and* Klebsiellaspp. *(4.72%) were also frequent.Among resistance genes, the NDM family predominated: blaNDM-5 was detected in 30 isolates and blaNDM-1 in 29. Other reported genes included blaOXA-1 (n = 17) and blaCTX-M-1 (n = 10).***Conclusion:** *It's urgent to strengthen the national antimicrobial resistance surveillance and establishment of antimicrobial-stewardship programs. Further research should investigate the transmission dynamics and genetic contexts of resistance determinants within these bacterial lineages.*

Keywords:*Carbapenem-resistance,* Enterobacteriaceae*, Prevalence, Resistance genes.*

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Introduction

Enterobacteriaceae are gram-negative bacteria found in the guts of humans, birds, animals and environment.[1,2] They cause a variety of diseases including pneumonia, urinary tractinfections, gastroenteritis, and bloodstream infections. In recent years, there has been an increasing prevalence of *Enterobacteriaceae* that are resistant to several antibiotics. Thus, it is growing global health crisis due to infections with limited or untreatable options.[1,3-5]

In Bangladesh, antimicrobial resistance (AMR) is an alarming public health threat with decreased antibiotic effectiveness observed during the last decade. Common *Enterobacteriaceae such as Escherichia coli, Klebsiella pneumoniae*and other *Klebsiella spp.* show high levels of resistance to commonly available antibiotics. Poor knowledge about antibiotic use, misuse, lack of regulation, extensive use in poultry and animal farming leading to increasing threats.[6-8]

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Carbapenem-resistant *Enterobacteriaceae* (CRE) shows resistance to carbapenem, which is the last-line treatments options for many serious infections. CREis now commonly found in the environment, hospitals, nursing homes, human and livestock samples and several other healthcare facilities[9,10]. The emergence of CRE in these various settings has raised concerns about the widespread dissemination of these multidrug-resistant pathogens. Previous researchers have identified variety of carbapenem resistance gene in *Enterobacteriaceae* organisms, categorized into three classes of â-lactamases: Ambler class-A (KPC, SME, IMI,NMC, GES types), class-B metallo-ß-lactamases (VIM, IMP, GIM, SMP, and NDM types), and class-D â-lactamases (primarily OXA-48). Additionally, there are also rare chromosome-encoded enzymes (class C).[9,11,12]

Several genes, including blaOXA-48, blaOXA-23,blaOXA-58,bla*VIM-2, and* blaVIM-4, were identified to play role in carbapenem resistance[13,14]. The presence of CRE in livestock raises concerns about the potential transmission of antibiotic-resistant bacteria to humans. If these bacteria can move from animals to humans, it creates a significant risk to public health by reducing the effectiveness of treatment for severe infections[15,16]. Therefore, it is essential to identify these sources and enforce necessary control measures.

There are number of studies from Bangladesh have reported CRE across diverse clinical and environmental samples. However, a consolidated national estimate with a synthesis of species distribution and resistance gene profileshas been lacking. Our systematic review addresses that gap by estimating the prevalence of CRE and summarizing organism and gene distributions in Bangladeshi settings.

Methods

Study design:

This was systematic review focusing CRE in Bangladesh with article published between January 2010 to December 2024. The review was conducted in accordance with the PRISMA 2020 guidelines[17].

Eligibility criteria:

We have selected cross-sectional laboratory or surveillance studies that: (i) were conducted in Bangladesh using human, animal, or environmental specimens; (ii) evaluated Enterobacteriaceae/ Enterobacterales (e.g., *Escherichia coli, Klebsiella spp., Enterobacter spp., Citrobacter spp., Serratia spp., Proteus spp.*, etc.); and (iii) defined carbapenem resistance using CLSI or EUCAST breakpoints assessed by disk diffusion or MIC[18,19]. We considered only peer-reviewed articles published in English. We have also excluded case reports/series, reviews, editorials, outbreak investigations, studies lacking extractable numerators/denominators for prevalence, and studies conducted outside Bangladesh.

Information sources and search strategy:

We searched PubMed, Google Scholar, and the Directory of Open Access Journals (DOAJ) for English-language records published 1 January 2010–31 December 2024. Searches combined three concept blocks with Boolean operators: (a) Microorganisms: *Enterobacteriaceae*, *Enterobacterales*, *Escherichia coli*,*Klebsiella*, *Enterobacter*,*Citrobacter*,*Serratia*, *Proteus*, *Morganella*, *Providencia*, *Pantoea*, *Shigella*, *Salmonella.*(b)Resistance: "carbapenem-resistant", carbapenemase, CRE, CPE, and carbapenemcombined with resistant / non-susceptible. (c) Setting: Bangladesh / Bangladeshi.In PubMed, we used MeSH terms ("Enterobacteriaceae," "Enterobacterales," "Carbapenems," "Carbapenemases," "Drug Resistance, Bacterial") combined with Title/Abstract terms; in Google Scholar and DOAJ, and restricted results to 2010–2024. We applied no study-design or specimen filters at the search stage; these were handled during screening (Figure 1).

Records from all sources (n=6260) were imported into a reference manager (n=695 removed) due to duplication. Two reviewers (KB, MMA) independently screened titles (n=5,665). We sought 921 reports and excluded another 843 after verifying implementation country/abstract and assessed 78 full texts for eligibility. Seventy-one full-text reports were excluded for: resistance definition missing/other than CLSI/ EUCAST (n=28), outcome out of scope (n=31), and no prevalence design/no extractable numerator–denominator (n=12). Seven studies met inclusion criteria and were carried forward to synthesis (Figure 1).

Data extraction

Using a piloted extraction form, two reviewers independently collected bibliographic details (author, year), study period, setting (hospital, community, environmental, animal), and sample sources and testing methods; organism counts (by species and overall Enterobacteriaceae tested); and denominators for CRE prevalence; and carbapenemase gene data (gene type/variant, number tested, number positive). When reporting was unclear, we recorded data as presented. If both species-level and overall totals were available, overall totals were used for the primary prevalence analysis, with species-level data summarized as secondary outcomes.

Outcomes

The primary outcome was the prevalence of CRE, calculated as the number of CRE isolates divided by the total number of Enterobacteriaceae isolates tested. Secondary outcomes included (i) distribution of species among Enterobacteriaceae isolates and (ii) prevalence of specific carbapenemase genes among isolates tested for those genes.

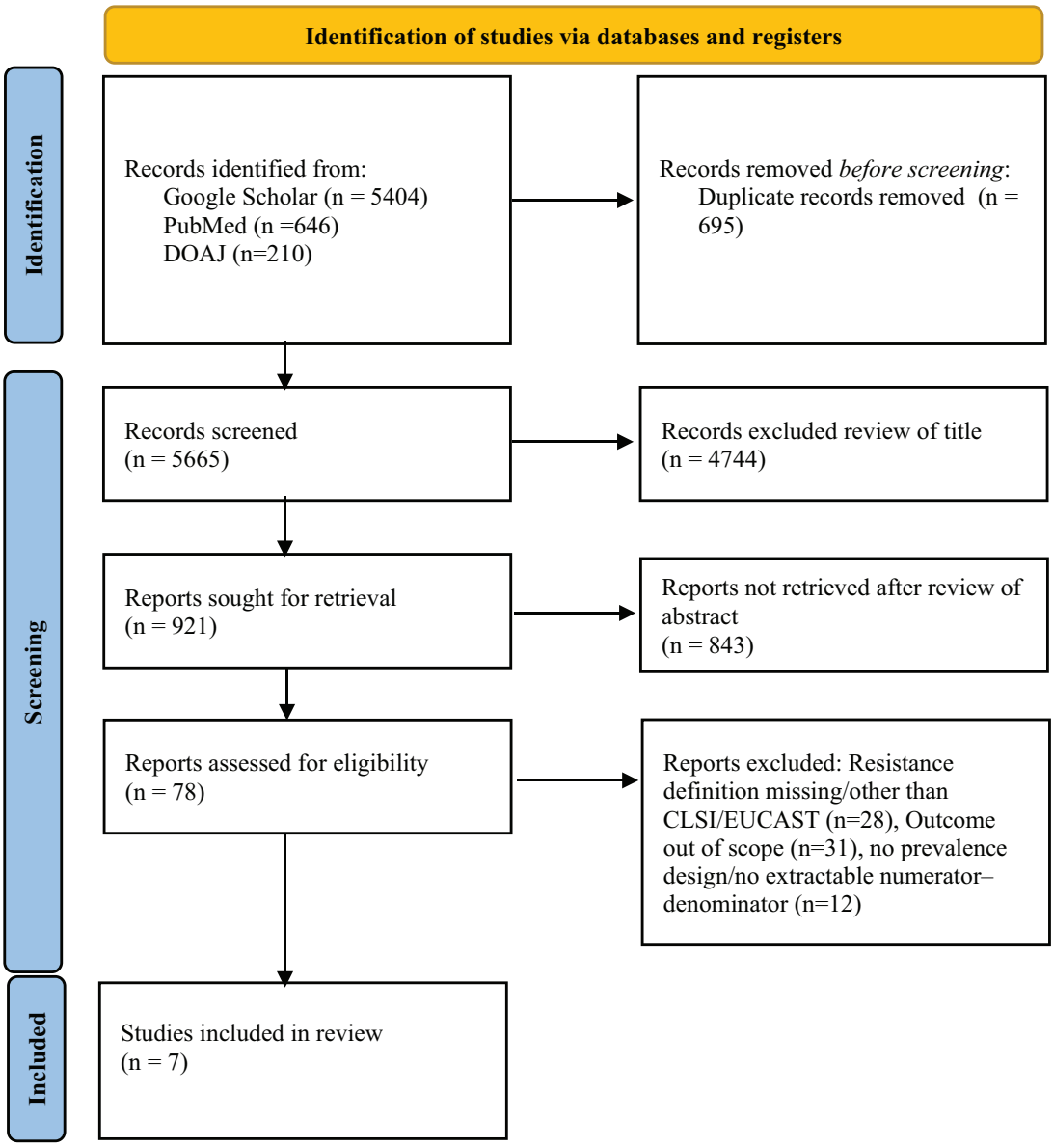

Figure 1. *PRISMA 2020 flow diagram for selection of the studies.*

Statistical analysis:

We summarized crude prevalence with 95% confidence intervals (CIs). For analysis of proportions, we used a random-effects model given anticipated heterogeneity. To stabilize variances, we applied a variance-stabilizing transformation for proportions, and back-transformed pooled estimates for interpretability. Between-study heterogeneity was quantified using $\mathbf{I^2}$ and $\hat{\mathbf{o}}^2$ (restricted maximum likelihood). We report pooled prevalence with 95% CIs and provide the $\mathbf{I^2}$ statistic to indicate heterogeneity. Where applicable, we calculated a 95% prediction interval to reflect the expected range of prevalence in new settings.

Results

The crude prevalence of CRE was 11.79% (95% confidence interval [CI] 10.64 – 13.05). Across seven included studies, the pooled prevalence of carbapenem resistance among bacterial isolates was 15.46% (95% CI 6.85 – 31.27%) using a random-effects (DerSimonian–Laird) meta-analysis of logit-transformed proportions with a 0.5 continuity correction; between-study heterogeneity was substantial (I^2 = 93.1%, Q = 86.96), supporting the use of random-effects. For comparison, the fixed-effect model estimated 16.50% (95% CI 13.64 – 19.82).

Table I

Summary of Included Studies: Sample Sources, Carbapenem-Resistant Organisms, and Associated Resistance Genes

SN	Author	Year	Sample type	Sample source	Isolate Sample	Carbapenem resistance	Organism	Isolate number	Genes blaNDM-1	blaNDM-5	blaIMP	blaKPC	blaOXA-1	blaVIM-2	blaVIM-5	blaCTX-M-1	blaTEM	blaSHV	blaCMY	blaOXA48	blaIMI1
1	Islam MA	2012	Clinical	Throat, urine, pus, and wound	403	13	*Klebsiella pneumoniae*	8	7				5			7	7	6			
							Escherichia coli	3	2				1			2			1		
							Citrobacter freundii	1	1				0			1			1		
							Providencia rettgeri	1	1				0	1		0			1		
2	Nandi SP	2013	Poultry	Cloacal	18	11	*Escherichia coli*	1													
							Shigella Flexnari	1													
							Pantoea agglomerns	1													
							Enterobacter hormachei	2													
							Enterobacter aerogenes	1													
							Enterobacter cancerogenes	1													
							Enterobacter cloacae	4													
3	Begum N	2016	Clinical	NM	138	19	*Escherichia coli*	13	7			2	3	5	2						
							Klebsiella spp	5	4			0	1	2	1						
							Citrobacter spp	1	1			0	0	1	0						
4	Rakhi NN	2019	Clinical	Wound, pus, urine, blood, vaginal swab	71	2	*Klebsiella pneumoniae*	1	2	4											6
							Citrobacter sedlakii	1	1				1								1
5	Munny NN	2023	Clinical	Urine, wound swab and pus, blood, ETA	28	9	*Enterobacter spp.*	9													
6	Nisa TT	2023	Environmental	Meat, fish, vegetab	136	38	*Escherichia coli*	26	1	24			2								
							Klebsiella pneumoniae	4	2	1		1									

Table II

Frequency and Prevalence of carbapenem Resistance Genes

Gene	Family	Count (n)	Prevalence (%)
blaNDM-5	NDM	30	3.48
blaNDM-1	NDM	29	3.36
blaOXA-1	OXA (other)	17	1.97
blaCTX-M-1	CTX-M	10	1.16
blaTEM	TEM	7	0.81
blaOXA-48	OXA-48	7	0.81
blaSHV	SHV	6	0.7
blaKPC	KPC	5	0.58
blaVIM-2	VIM	4	0.46
blaCMY	CMY	3	0.35
blaIMP	IMP	2	0.23
blaIMI-1	IMI	2	0.23
blaVIM-5	VIM	0	0

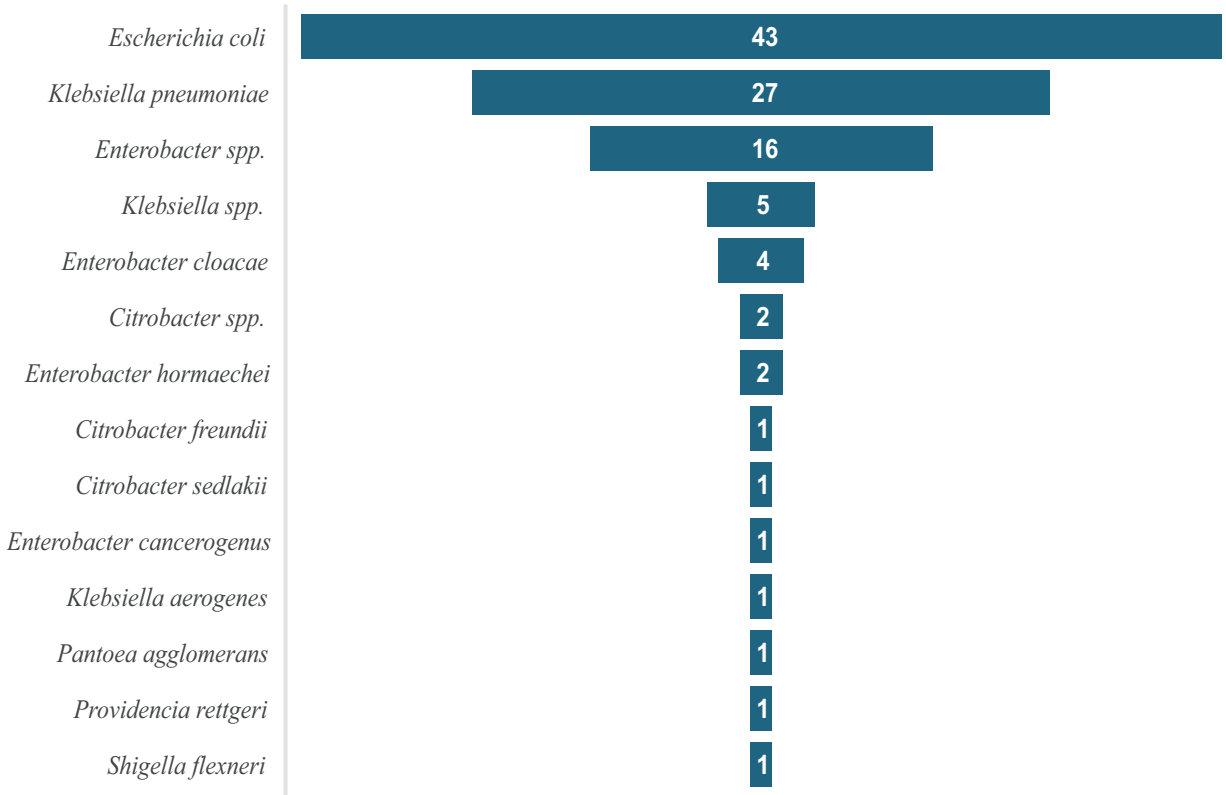

Figure 2. *Distribution of carbapenem-resistant Enterobacteriaceae species across included studies in Bangladesh (n = 106 isolates).*

*Escherichia coli*was most common (43/106; 40.57%), followed by *Klebsiella pneumoniae* (27/106; 25.47%) and *Enterobacter cloacae* (3.77%). Enterobacter spp. (16/106; 15.09%) and *Klebsiella spp.* (4.72%) were also frequent taxa. Single isolatewas detected (0.94% each) for*Citrobacter freundii, Citrobacter sedlakii, Citrobacter spp., Enterobactercancerogenus, Klebsiella aerogenes, Pantoeaagglomerns, Providencia rettgeri, and Shigella flexneri.* Together, *E. coli* and *K. pneumoniae* comprised ~66% of all isolates (Figure 2).

Among resistance genes, NDM variants predominated—blaNDM-5 (n=30) and blaNDM-1 (n=29)—for a combined NDM frequency of 59. Other detections included blaOXA-1 (n=17), blaCTX-M-1 (n=10), blaTEM and blaOXA-48 (n=7 each), blaSHV (n=6), blaKPC (n=5), blaVIM-2 (n=4), and blaCMY (n=3), with blaIMI-1 and blaIMP (n=2) and blaVIM-5 not detected. Overall, carbapenemases were driven mainly by NDM, while OXA-48, KPC, and VIM were present at lower levels; ESBL-associated genes (CTX-M-1, TEM, SHV) were also observed at modest frequencies.

Discussion

We have identified some important finding from this systematic review into the CRE prevalence and types of microorganism from Bangladesh across diverse clinical and environmental samples, along with a synthesis of species distribution and resistance gene profiles.*Enterobacteriaceae* causes a wide range of infections which can be particularly serious in young children, the elderly, and people with weakened immune systems[20]. The findings from this systematic review would have important implications in the public health sector of Bangladesh to control AMR burden.

The crude prevalence of CRE was 11.79% and the pooled prevalence was estimated at 15.46%. Our findings are consistent with the other reports of various parts of the world indicating high prevalence of CRE infections, representing the growing challenge of AMR in various settings[21,22]. Though many studies also got significantly higher prevalence than Bangladesh, the observed pooled prevalence of our study also indicates an alarming high prevalence of CRE, suggesting immediate actions at the national level[23,24].We have also observed a wide 95% confidence interval (6.85 – 31.27%), between-study heterogeneity was substantial (I^2 = 93.1%, Q = 86.96).These indicates a high variability in CRE prevalence across different sample source of Bangladesh. The previously conducted studies also identified a substantial variability not only among various samples but also various regions of the world. There might be several factors behind theheterogeneity including inappropriate use, differencesin healthcare practices, infection control, healthcare settings, environment, etc. [21,25].

CRE is concerning as it is considered as the last line of defense against many severe infections caused by Enterobacteriaceae and some other Gram-negative bacteria. Itshigh prevalence also signifies the need for effective interventions to control resistant strains and preserve the efficacy of available antibiotics[26,27]. Some previous studies suggestedsupport through the one health approach. Our findings may support health policies, develop AMR control programs, andinfection control strategiesin Bangladesh. Judicious use of antibiotics andinfection control programs may also play an important role[28-31].

E. coli was most common (40.57%), followed by *K. pneumoniae* (25.47%) and *E. cloacae* (3.77%). Together, *E. coli* and *K. pneumoniae* comprised ~66% of all isolates.However, most studies conducted worldwide found*K. pneumoniae*is predominant, thus need to identify the reason of this difference.This might be due to the abundant collection of data from clinical studies. A high prevalence Enterobacteriaceae in our studies particularly environment sources indicate the high prevalence in animal and human feces, suggesting implementation of one health approach[28–30]. More research should be conducted to see the factors driving the predominance of these species and to identify specific interventions to control their AMR.

The spread of carbapenem- resistant strains by Enterobacteriaceae infections is a highly concerning issue. Both *E. coli* and *K. pneumoniae* have a notably high occurrence of carbapenemase resistance genes. Among resistance genes, NDM variants predominated, blaNDM-5 (n=30) and blaNDM-1 (n=29), for a combined NDM frequency of 59. Other detections also included blaOXA-1, blaCTX-M-1, blaTEM, blaOXA-48, blaSHV, blaKPC, blaVIM-2, and blaCMY, and blaIMP. These diversity of genes highlight the complexity of antimicrobial resistance within the *Enterobacteriaceae* family. This shows the urgent need for national level infection control measures for Bangladesh with one health approach to control AMR infection. The prevention and control measures should include hand hygiene, proper cleaning and

disinfection of surfaces, and the use of antibiotics only when necessary[32-34]. The findings of this study highlight the importance of national level surveillance and continued research into the genetic determinants of CRE and the factors influencing resistance genes.

As there is a high variability among studies on CRE and due to limited evidence base, Bangladesh would benefit from larger, representative, multicenter studies that include human, animal, and environmental reservoirs, use uniform laboratory methods, and incorporate molecular epidemiology (e.g., WGS) and plasmid context to track transmission.[35-37]. These future studies should prioritizethe expansion of laboratory capacity in Bangladesh and quality assurance. These studies should also focus on implementing carbapenem-sparing treatment pathways guided by rapid diagnosticsand integrating a One Health approach to control spread.

Conclusion

CRE in Bangladesh constitutes a pressing public-health threat. This burden is concentrated in *Escherichia coli* and *Klebsiella pneumoniae*, and resistance is predominantly mediated by NDM carbapenemases. These findings underscore an immediate need to strengthen national AMR surveillance, standardize susceptibility testing and reporting, and scale up infection prevention and control and antimicrobial-stewardship programs across clinical and community settings.

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