

A Four-Year Retrospective Analysis (2021–2024): The Impact of Prior Antibiotic Exposure on CRE Infection Prevalence and Antibigram Profiles in a Tertiary Care Setting

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Abstract

Background.

Carbapenem-resistant Enterobacteriaceae (CRE) are a critical-priority pathogen, and prior antimicrobial exposure is the principal modifiable driver of their emergence through selective pressure. Local antibiogram data are essential for rational empirical prescribing but remain scarce for the Chattogram region of Bangladesh. We examined the prevalence of CRE infection, the relationship between prior antibiotic exposure and resistance phenotype, and the antibiogram profile of isolates.

Methods.

In this retrospective observational study, 15,714 patients observed at a tertiary care centre between January 2021 and December 2024 were screened; 113 with microbiologically confirmed CRE infection formed the analytic cohort. Demographic, comorbidity, prior-exposure and outcome data were abstracted with a standardised questionnaire; prior exposure was defined as documented receipt of an antibiotic class within 30 days. Susceptibility was determined for 19 agents and multidrug resistance (MDR) defined per Magiorakos criteria. Prevalence was estimated with Wilson 95% confidence intervals (CI); associations were tested with the Fisher exact test and the Cochran–Armitage test for trend.

Results.

Period prevalence of CRE infection was 0.72% (95% CI 0.60–0.86%), or 7.19 per 1000 patients observed. Prior antibiotic exposure was near-universal (98/113, 86.7%), most often carbapenem (80.5%) and third-/fourth-generation cephalosporin (77.9%). Every exposure class was significantly associated with an MDR phenotype (all $P < 0.001$), and a clear dose–response gradient was observed: MDR rose from 0.0% among patients exposed to no prior class and 0.0% among those exposed to 1–2 classes, to 22.2% at 3–4 classes and 53.9% among those who had received all five (Cochran–Armitage $z = 4.96$, $P < 0.0001$). Duration of definitive therapy for the index episode was not associated with resistance ($P = 0.143$) or mortality ($P = 0.677$). Antibiogram profiling showed extensive resistance to cephalosporins and fluoroquinolones ($> 84\%$ for most agents) and to meropenem (77.1% of 48 tested), whereas colistin (81.6% susceptible) and tigecycline (88.2% susceptible) retained the greatest in-vitro activity. Overall, 31 of 106 patients with a determinate outcome died (29.2%).

Conclusions.

CRE infection affected approximately 7 per 1000 patients observed. Cumulative prior antibiotic exposure showed a strong, graded association with multidrug resistance, consistent with the selective-pressure hypothesis and providing direct local evidence for carbapenem-sparing empirical strategies. The

antibiogram indicates that colistin and tigecycline remain the principal reserve agents in this setting, and that empirical reliance on cephalosporins or fluoroquinolones is no longer defensible.

1. Introduction

Antimicrobial resistance was linked to an estimated 1.27 million deaths worldwide in 2019, and carbapenem-resistant Enterobacteriaceae (CRE) sit near the top of the World Health Organization's priority list [1, 2]. The reason is straightforward. Carbapenems are often the last agents that still work reliably against serious Gram-negative infection, so once they fail the therapeutic margin all but disappears a loss reflected in delayed appropriate therapy, longer admissions and higher mortality [3, 4].

The burden is disproportionately borne by South and Southeast Asia, where high baseline resistance, unrestricted over-the-counter antibiotic availability and limited microbiological capacity converge [5]. In Bangladesh the reported burden is substantial. A nationwide laboratory-based analysis of 123,933 Enterobacterales isolates from 26 quality-assessed laboratories found 12.3% to be carbapenem-resistant, a proportion that held steady from 2017 to 2020, and a recent systematic review and pooled analysis of Bangladeshi studies estimated a crude CRE prevalence of 11.79% (95% CI 10.64–13.05) among isolates, with substantial between-study heterogeneity [6, 7]. Genomic work at a Dhaka tertiary hospital has characterised the dissemination of carbapenemase determinants in Enterobacterales and their co-selection with multidrug-resistant plasmids [8].

Data specific to Chattogram, Bangladesh's second-largest city and principal port, remain comparatively sparse but are consistent in direction. Clinical observational work across Chattogram hospitals has documented high rates of antibiotic resistance and associated resistance genes in *Klebsiella pneumoniae* isolates [9], subsequent analysis identified extended-spectrum β -lactamase determinants among *Klebsiella* isolates from neonates and adolescents in southern Bangladesh [10], and whole-genome sequencing of clinical *K. pneumoniae* from a Chattogram hospital has confirmed the local circulation of NDM-5, NDM-1 and KPC-2 carbapenemase genes across several international high-risk sequence types [11]. Community-level data reinforce the concern: in the Antibiotic Resistance in Communities and Hospitals (ARCH) study, 37% of hospitalised Bangladeshi participants and 9% of community individuals were colonised with carbapenem-resistant Enterobacterales [12].

Selective pressure offers the mechanistic account. Antibiotics do not manufacture resistance; they clear the susceptible flora and leave the ground to resistant subpopulations that were already present, which then expand to dominate colonisation. What makes this more than a single-drug problem is genetic linkage. Carbapenemase genes frequently travel on mobile elements alongside determinants for aminoglycoside, fluoroquinolone and sulphonamide resistance, so pressure applied through any one class can carry the whole cassette forward [8]. Meta-analytic work on the clinical epidemiology of CRE has repeatedly placed prior carbapenem and cephalosporin use among the strongest risk factors, with pooled odds ratios for carbapenem exposure near 4.7 [13]. The model makes a testable prediction: if co-

selection drives the phenotype, then how many classes a patient has seen should matter, not simply whether they have seen any.

There is a practical reason why local antibiogram data matter. Empirical regimens must be chosen before susceptibility results return, and resistance patterns vary enough between regions that guidance developed elsewhere can send initial therapy in the wrong direction. Bangladesh has been named specifically as lacking the data on carbapenem use and resistance needed to make those decisions well [14]. We therefore set out to establish the four-year prevalence of CRE infection among patients seen at a tertiary care centre, to examine how prior antibiotic exposure both by class and by cumulative intensity relates to the multidrug-resistant phenotype, and to map the antimicrobial resistance of the isolates recovered.

2. Materials and Methods

2.1 Study design and setting

This retrospective observational study was conducted at a tertiary care hospital in Chattogram, Bangladesh, and covered the four-year period from January 2021 to December 2024. Over this interval 15,714 patients were observed and screened for eligibility.

2.2 Case definition and participants

A case was defined as a patient of any age from whom a clinical specimen yielded a carbapenem-resistant Enterobacterales isolate, together with a clinical syndrome compatible with infection at the corresponding site. Patients with isolates judged to represent colonisation without a compatible syndrome were not eligible. Each patient contributed a single index isolate; where multiple isolates were recovered from the same patient, only the first was retained. A total of 113 patients met the case definition and constituted the final analytic cohort (Fig. 1).

2.3 Data collection

Data were abstracted onto a standardised, pre-piloted questionnaire covering demographic details, ward of admission, infection onset category, comorbid conditions, prior healthcare and antimicrobial exposure, specimen type, organism, antimicrobial susceptibility results, treatment and discharge outcome. Prior antibiotic exposure was defined as documented receipt of the relevant class within the 30 days preceding isolation and was recorded separately for carbapenems, third-/fourth-generation cephalosporins, fluoroquinolones, piperacillin–tazobactam and polymyxins. Cumulative exposure intensity was operationalised as the number of distinct classes received, counting only the five specific classes recorded (range 0–5); the separate any-antibiotic field was treated as a summary indicator rather than an additional class. Infection onset was classified as community-acquired, healthcare-associated or hospital-acquired using standard temporal criteria. Separately, the duration of definitive antibiotic therapy administered for the index CRE episode was recorded in three categories (≤ 7 days, 7–14 days, ≥ 14 days); this field captures treatment duration for the index infection and not the duration of

prior antibiotic exposure, which was not collected. Direct patient identifiers were removed before analysis.

Two data-quality observations are recorded for transparency. The supportive-care field contained a single out-of-range entry (a value of 11 where the field is binary), which was treated as missing rather than imputed. One isolate was recorded as *Enterococcus* species, which is not a member of Enterobacteriaceae; it was retained in the cohort denominator but flagged as a probable coding error and excluded from Enterobacteriaceae-specific interpretation.

2.4 Antibiotic Susceptibility testing

Clinical specimens were processed by routine diagnostic methods, with isolates identified to species level by standard biochemical testing. Antimicrobial susceptibility was determined and reported categorically as susceptible, intermediate or resistant according to contemporaneous Clinical and Laboratory Standards Institute breakpoints. Nineteen agents spanning cephalosporins, β -lactam/ β -lactamase inhibitor combinations, carbapenems, aminoglycosides, fluoroquinolones, folate-pathway inhibitors, tetracyclines and polymyxins were tested. Testing was performed selectively according to specimen type and clinical context rather than as a fixed panel, so the denominator differs by agent and is reported for each. Carbapenem resistance was confirmed by phenotypic susceptibility testing, minimum inhibitory concentration determination or molecular assay. A multidrug-resistant phenotype was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories [15].

2.5 Outcomes

The outcome of interest was in-hospital disposition, analysed among patients with a determinate outcome (death or discharge alive). Patients transferred to another facility ($n = 5$) or discharged against medical advice ($n = 2$) had vital status at discharge that could not be ascertained and were excluded from outcome analysis, leaving $n = 106$. Recovery was defined as discharge alive; a graded clinical-response measure was specified on the questionnaire but was not recorded for this cohort (see Limitations).

2.6 Statistical analysis

Categorical variables are presented as counts and percentages, and continuous variables as median (interquartile range, IQR) or mean $\pm$ standard deviation. Period prevalence was calculated as confirmed cases divided by patients observed, with Wilson score 95% confidence intervals (CI). Associations between prior exposure and the MDR phenotype, and between exposure and outcome, were assessed with the Fisher exact test; odds ratios (OR) with 95% CIs were computed using the Haldane–Anscombe correction where a zero cell was present. Dose–response across ordered exposure-intensity strata and temporal trends across the four years were tested with the Cochran–Armitage test for trend. Continuous distributions were compared with the Mann–Whitney U test and across years with the Kruskal–Wallis

test. Two-sided $P < 0.05$ was considered statistically significant. Analyses were performed in Python 3 (pandas, SciPy, statsmodels).

3. Results

3.1 Study population and four-year prevalence

Of 15,714 patients observed between January 2021 and December 2024, 113 met the case definition for confirmed CRE infection, giving a period prevalence of 0.72% (95% CI 0.60–0.86%), equivalent to 7.19 cases per 1000 patients observed (95% CI 5.99–8.64). The study selection process is summarised in Fig. 1. Year-specific denominators were not available; the annual figures reported below therefore describe the distribution of confirmed cases across the study period rather than annual prevalence rates.

Confirmed cases were distributed unevenly across the study period: 28 in 2021, 12 in 2022, 32 in 2023 and 41 in 2024. The cohort had a median age of 41 years (IQR 32–56) and was predominantly male (72 (63.7)). Patients became significantly younger across the period (Kruskal–Wallis $H = 20.41$, $P < 0.001$). Most infections were community-acquired (89 (78.8)), with fewer healthcare-associated (19 (16.8)) or hospital-acquired (5 (4.4)) cases. *Klebsiella pneumoniae* predominated (52 (46.0)), followed by *Enterobacter* spp. (35 (31.0)) and *Escherichia coli* (25 (22.1)); a single *Enterococcus* spp. isolate was recorded. An MDR phenotype was present in 43 (38.1) of isolates overall, declining from 53.6% in 2021 to 29.3% in 2024 (Cochran–Armitage $z = -1.92$, $P = 0.055$). Full characteristics by year are given in Table 1.

Table 1
Demographic and clinical characteristics of patients with confirmed CRE infection, by year of isolation, 2021–2024.

Characteristic	2021	2022	2023	2024	Overall (N = 113)
Patients, n	28	12	32	41	113
Share of all cases, %	24.8	10.6	28.3	36.3	100.0
Age, years, median (IQR)	56 (40–69)	56 (39–67)	34 (28–44)	34 (32–48)	41 (32–56)
Male sex, n (%)	23 (82.1)	9 (75.0)	18 (56.2)	22 (53.7)	72 (63.7)
Infection onset, n (%)					
Community-acquired	28 (100.0)	12 (100.0)	23 (71.9)	26 (63.4)	89 (78.8)
Healthcare-associated	0 (0.0)	0 (0.0)	8 (25.0)	11 (26.8)	19 (16.8)
Hospital-acquired	0 (0.0)	0 (0.0)	1 (3.1)	4 (9.8)	5 (4.4)
Organism, n (%)					
<i>Klebsiella pneumoniae</i>	11 (39.3)	5 (41.7)	11 (34.4)	25 (61.0)	52 (46.0)
<i>Enterobacter spp.</i>	8 (28.6)	4 (33.3)	13 (40.6)	10 (24.4)	35 (31.0)
<i>Escherichia coli</i>	8 (28.6)	3 (25.0)	8 (25.0)	6 (14.6)	25 (22.1)
<i>Enterococcus spp.</i>	1 (3.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
Prior antibiotic exposure, n (%)	28 (100.0)	10 (83.3)	25 (78.1)	35 (85.4)	98 (86.7)
Multidrug-resistant, n (%)	15 (53.6)	4 (33.3)	12 (37.5)	12 (29.3)	43 (38.1)
In-hospital mortality, n/N (%)	6/28 (21.4)	2/10 (20.0)	13/31 (41.9)	10/37 (27.0)	31/106 (29.2)

IQR, interquartile range. Period prevalence of CRE infection across the full study window was 0.72% (95% CI 0.60–0.86%) of 15,714 patients observed; year-specific denominators were not available, so annual counts represent the distribution of cases rather than annual prevalence. Mortality denominators exclude 5 patients transferred and 2 discharged against medical advice.

3.2 Prior antibiotic exposure and resistance phenotype

Prior antibiotic exposure was near-universal in this cohort: 98 of 113 patients (86.7%) had documented receipt of at least one antibiotic class within the preceding 30 days. Carbapenem exposure was recorded in 80.5%, third-/fourth-generation cephalosporin in 77.9%, fluoroquinolone in 76.1%, piperacillin–tazobactam in 70.8% and polymyxin in 74.3%. The median number of classes received was 5 (IQR 3–5).

Every recorded exposure class was significantly associated with an MDR phenotype (Table 2). Among patients exposed to any prior antibiotic, 43.9% carried an MDR isolate compared with 0.0% of unexposed patients (OR 24.3, 95% CI 1.41–417.6, $P < 0.001$); the corresponding figures for prior carbapenem exposure were 46.2% versus 4.5% (OR 18.0, $P < 0.001$). Point estimates are large but imprecise, reflecting small unexposed reference groups; the consistency of direction and significance across all six exposures is the more robust observation. Patients with an MDR isolate had received more antibiotic classes than those without (mean 4.93 ± 0.34 versus 3.1 ± 2.12 ; Mann–Whitney $U = 2217.0$, $P < 0.001$).

Table 2

Association between prior antibiotic exposure by class and the multidrug-resistant phenotype among patients with confirmed CRE infection (N = 113).

Prior exposure (≤ 30 days)	Exposed, n (%)	MDR if exposed, n (%)	MDR if unexposed, n (%)	OR (95% CI)	P
Any prior antibiotic	98 (86.7)	43/98 (43.9)	0/15 (0.0)	24.30 (1.41–417.6)	< 0.001
Carbapenem	91 (80.5)	42/91 (46.2)	1/22 (4.5)	18.00 (2.32–139.5)	< 0.001
3rd/4th-generation cephalosporin	88 (77.9)	43/88 (48.9)	0/25 (0.0)	48.76 (2.88–825.9)	< 0.001
Fluoroquinolone	86 (76.1)	43/86 (50.0)	0/27 (0.0)	55.00 (3.25–930.5)	< 0.001
Piperacillin–tazobactam	80 (70.8)	42/80 (52.5)	1/33 (3.0)	35.37 (4.61–271.5)	< 0.001
Polymyxin	84 (74.3)	42/84 (50.0)	1/29 (3.4)	28.00 (3.64–215.3)	< 0.001

MDR, multidrug-resistant; OR, odds ratio; CI, confidence interval. P values from the Fisher exact test. Odds ratios incorporate the Haldane–Anscombe correction where a zero cell was present; wide intervals reflect the small number of unexposed patients. Because every patient in this cohort had confirmed CRE, these estimates describe the association between exposure and resistance phenotype among cases and do not represent the risk of acquiring CRE relative to CRE-negative patients.

3.3 Antibiotic duration, cumulative exposure intensity and resistance

Duration of definitive antibiotic therapy for the CRE episode was ≤ 7 days in 41 patients (36.3%), 7–14 days in 68 (60.2%) and ≥ 14 days in 4 (3.5%). Treatment duration was not significantly associated with

the MDR phenotype (29.3%, 42.6% and 50.0% across increasing duration strata; Cochran–Armitage $z = 1.47$, $P = 0.143$) nor with in-hospital mortality (34.2%, 25.0% and 50.0%; $z = -0.42$, $P = 0.677$). The ≥ 14 -day stratum contained only 4 patients, so these comparisons are underpowered at the upper end of the range (Table 3, panel A).

By contrast, stratification by the number of prior antibiotic classes received revealed a marked dose–response relationship (Table 3, panel B; Fig. 2). No patient exposed to fewer than three classes carried an MDR isolate: the MDR proportion was 0.0% among the 15 patients with no prior exposure and 0.0% among the 13 exposed to one or two classes. This rose to 22.2% among the 9 patients exposed to three or four classes and to 53.9% among the 76 who had received all five (Cochran–Armitage $z = 4.96$, $P < 0.0001$). The gradient is monotonic across all four strata. Taken together, these two panels indicate that it is the breadth of prior antimicrobial exposure, rather than the duration of therapy given for the index episode, that tracks with the resistance phenotype in this cohort.

Table 3
Duration of definitive antibiotic therapy (panel A) and cumulative prior antibiotic exposure intensity (panel B) in relation to multidrug resistance and in-hospital outcome.

Stratum	Patients, n (%)	MDR phenotype, n (%)	In-hospital mortality, n/N (%)
Panel A – Duration of definitive antibiotic therapy for the index episode			
≤ 7 days	41 (36.3)	12/41 (29.3)	13/38 (34.2)
7–14 days	68 (60.2)	29/68 (42.6)	16/64 (25.0)
≥ 14 days	4 (3.5)	2/4 (50.0)	2/4 (50.0)
Panel B – Number of prior antibiotic classes received (≤ 30 days before isolation)			
0 classes	15 (13.3)	0/15 (0.0)	8/13 (61.5)
1–2 classes	13 (11.5)	0/13 (0.0)	2/13 (15.4)
3–4 classes	9 (8.0)	2/9 (22.2)	3/9 (33.3)
5 classes	76 (67.3)	41/76 (53.9)	18/71 (25.4)

MDR, multidrug-resistant. Panel A, Cochran–Armitage test for trend: MDR $z = 1.47$, $P = 0.143$; mortality $z = -0.42$, $P = 0.677$ – neither significant, and the ≥ 14 -day stratum contains only 4 patients. Panel B, MDR $z = 4.96$, $P < 0.0001$; mortality $z = -1.83$, $P = 0.067$. The recorded duration field refers to therapy administered for the index CRE episode, not to the duration of prior antibiotic exposure; duration of prior exposure was not captured (see Limitations). Mortality denominators exclude patients with indeterminate disposition.

3.4 Antibiotic resistance pattern

Resistance to first- and second-line agents was extensive (Table 4). Among cephalosporins, resistance exceeded 77% for every agent tested, including ceftriaxone (90.7% of 54 isolates). Fluoroquinolone resistance was similarly high (ciprofloxacin 90.0% of 50). Meropenem resistance was confirmed in 77.1% of 48 isolates tested, consistent with the cohort case definition. Aminoglycoside activity was limited (amikacin 23.8% susceptible). By contrast, colistin and tigecycline retained substantial in-vitro activity, with 81.6% and 88.2% of tested isolates susceptible respectively, positioning them as the principal reserve agents in this setting. Ceftazidime–avibactam was tested in only 11 isolates, of which 27.3% were susceptible; this denominator is too small to support firm conclusions. Organism-stratified resistance patterns are presented in detail in Table 5 and summarised in Fig. 3, which together highlight a clinically important divergence for colistin: resistance was low in *K. pneumoniae* and *E. coli* but substantially higher in *Enterobacter spp.*, consistent with the variable intrinsic susceptibility recognised in that genus.

Among agents tested in at least 20 isolates, only trimethoprim–sulfamethoxazole showed a statistically significant change in resistance across the study period, rising from 7.1% in 2021 to 76.9% in 2024 (Cochran–Armitage $P < 0.001$). Resistance to meropenem, ceftazidime, ciprofloxacin and amikacin fluctuated without significant directional trend (all $P > 0.19$).

Table 4

Antibiogram profile of CRE isolates: susceptibility, intermediate susceptibility and resistance by agent.

Antimicrobial agent	Isolates tested, n	Susceptible, %	Intermediate, %	Resistant, %	Trend P†
Cefixime	55	7.3	0.0	92.7	0.083
Ceftriaxone	54	9.3	0.0	90.7	0.368
Cefuroxime	45	11.1	0.0	88.9	0.410
Ceftazidime	106	22.6	0.0	77.4	0.195
Cefepime	57	21.1	1.8	77.2	0.686
Amoxicillin–clavulanate	53	11.3	0.0	88.7	0.521
Piperacillin–tazobactam	47	19.1	0.0	80.9	0.708
Meropenem	48	22.9	0.0	77.1	0.420
Ceftazidime–avibactam	11	27.3	0.0	72.7	—
Amikacin	63	23.8	6.3	69.8	0.224
Gentamicin	49	28.6	0.0	71.4	0.276
Ciprofloxacin	50	8.0	2.0	90.0	0.702
Levofloxacin	52	15.4	0.0	84.6	0.653
Trimethoprim–sulfamethoxazole	45	48.9	0.0	51.1	0.000
Nitrofurantoin	24	41.7	0.0	58.3	0.487
Chloramphenicol	20	15.0	0.0	85.0	—
Tetracycline	23	78.3	0.0	21.7	0.229
Tigecycline	17	88.2	0.0	11.8	—
Colistin	49	81.6	4.1	14.3	0.536

Percentages are calculated on the number of isolates tested against each agent; testing was performed selectively by specimen type and clinical context, so denominators differ by agent. †Cochran–Armitage test for trend in resistance across 2021–2024, reported for agents tested in ≥ 20 isolates; — indicates insufficient isolates for trend testing. Ceftazidime–avibactam results are based on 11 tested isolates and should be interpreted with caution.

Table 5
Resistance pattern of different antibiotics among carbapenem-resistant Enterobacterales, stratified by organism.

Name of antibiotics	<i>K. pneumoniae</i> (n = 52)	<i>Enterobacter</i> spp. (n = 35)	<i>E. coli</i> (n = 25)	All CRE (N = 113)
Cefixime	28/29 (96.6%)	7/7 (100.0%)	15/18 (83.3%)	51/55 (92.7%)
Ceftriaxone	27/28 (96.4%)	6/7 (85.7%)	15/18 (83.3%)	49/54 (90.7%)
Cefuroxime	25/26 (96.2%)	4/5 (80.0%)	11/14 (78.6%)	40/45 (88.9%)
Ceftazidime	33/47 (70.2%)	31/34 (91.2%)	17/24 (70.8%)	82/106 (77.4%)
Cefepime	27/29 (93.1%)	3/8 (37.5%)	13/19 (68.4%)	44/57 (77.2%)
Amoxicillin–clavulanate	26/27 (96.3%)	5/7 (71.4%)	15/18 (83.3%)	47/53 (88.7%)
Piperacillin–tazobactam	26/27 (96.3%)	3/4 (75.0%)	8/15 (53.3%)	38/47 (80.9%)
Ceftazidime–avibactam	2/2 (100.0%)	4/5 (80.0%)	2/4 (50.0%)	8/11 (72.7%)
Meropenem	23/26 (88.5%)	4/6 (66.7%)	9/15 (60.0%)	37/48 (77.1%)
Amikacin	27/32 (84.4%)	5/10 (50.0%)	11/20 (55.0%)	44/63 (69.8%)
Gentamicin	23/26 (88.5%)	4/6 (66.7%)	8/17 (47.1%)	35/49 (71.4%)
Ciprofloxacin	27/27 (100.0%)	5/6 (83.3%)	13/17 (76.5%)	45/50 (90.0%)
Levofloxacin	25/27 (92.6%)	5/6 (83.3%)	13/18 (72.2%)	44/52 (84.6%)
Trimethoprim–sulfamethoxazole	15/25 (60.0%)	1/4 (25.0%)	7/16 (43.8%)	23/45 (51.1%)
Nitrofurantoin	10/12 (83.3%)	3/4 (75.0%)	1/8 (12.5%)	14/24 (58.3%)
Chloramphenicol	7/8 (87.5%)	4/5 (80.0%)	6/7 (85.7%)	17/20 (85.0%)
Tetracycline	4/13 (30.8%)	0/3 (0.0%)	1/6 (16.7%)	5/23 (21.7%)

Name of antibiotics	<i>K. pneumoniae</i> (n = 52)	<i>Enterobacter</i> spp. (n = 35)	<i>E. coli</i> (n = 25)	All CRE (N = 113)
Tigecycline	1/7 (14.3%)	0/4 (0.0%)	1/6 (16.7%)	2/17 (11.8%)
Colistin	1/27 (3.7%)	4/6 (66.7%)	2/15 (13.3%)	7/49 (14.3%)

Values are the number of resistant isolates / number tested (percentage resistant). Susceptibility was interpreted per CLSI criteria; testing was performed selectively by specimen type and clinical context, so the number tested varies by organism and agent and is shown explicitly in each cell. –, not tested for that organism–agent combination. Fewer than 10 isolates tested for that organism–agent combination; the corresponding percentage should be interpreted with caution (CLSI M39). The single *Enterococcus* spp. isolate is not a member of the *Enterobacterales* and is excluded from the organism columns, being retained only in the overall count.

3.5 Clinical characteristics

Uncomplicated urinary tract infection was the commonest clinical syndrome (37, 32.7%), followed by pneumonia (27, 23.9%); bloodstream infection accounted for 10 cases. Urine (54, 47.8%) and blood (41, 36.3%) were the predominant specimen types. Comorbidity was present in 73 patients (64.6%), most frequently hypertension (56.6%) and diabetes mellitus (40.7%), with a median of 2 comorbid conditions per patient (IQR 0–4). Sepsis was documented in 34 patients (30.1%) and septic shock in 15 (13.3%). Full details are presented in Table 6.

Table 6
Clinical characteristics of the cohort: site of infection, specimen type and comorbid conditions (N = 113).

Characteristic	n	%
Site of infection, n (%)		
Uncomplicated UTI	37	32.7
Pneumonia	27	23.9
Intra-abdominal infection	12	10.6
Soft tissue infection	12	10.6
Other	12	10.6
Bloodstream Infection	10	8.8
Complicated UTI	3	2.7
Specimen type, n (%)		
Urine	54	47.8
Blood	41	36.3
Sputum	11	9.7
Wound Swab	7	6.2
Comorbid conditions, n (%)		
Any comorbidity	73	64.6
Hypertension	64	56.6
Diabetes mellitus	46	40.7
Cardiovascular disease	39	34.5
Chronic lung disease	24	21.2
HIV infection	21	18.6
Chronic kidney disease	19	16.8
Malignancy	5	4.4
Chronic liver disease	2	1.8
Severity at presentation, n (%)		
Sepsis	34	30.1

Characteristic	n	%
Site of infection, n (%)		
Septic shock	15	13.3

Percentages are calculated on the full cohort. Comorbid categories are not mutually exclusive.

3.6 Outcomes by prior antibiotic history

Among the 106 patients with a determinate disposition, 31 died in hospital (29.2%) and 75 were discharged alive. Stratification by prior antibiotic history produced a counter-intuitive pattern (Table 7): mortality was lower among exposed than unexposed patients for every class examined. Among patients with any prior antibiotic exposure, 24.7% died compared with 61.5% of unexposed patients (OR 0.21, 95% CI 0.06–0.69, $P = 0.018$); the pattern was similar for prior carbapenem exposure (24.4% versus 50.0%, OR 0.32, $P = 0.031$). An MDR phenotype was likewise not associated with increased mortality (22.5% versus 33.3%, OR 0.58, $P = 0.276$).

These associations should not be interpreted causally. Prior antibiotic exposure is a marker of prior healthcare contact, and patients with such contact were systematically different from those without: they presented earlier in the course of illness, were already under medical supervision, and were more likely to receive prompt microbiological sampling and directed therapy. The apparent protective direction is therefore most plausibly explained by confounding by healthcare access and indication rather than by any biological benefit of prior exposure. This interpretation is developed further in the Discussion.

Table 7

In-hospital outcome stratified by prior antibiotic exposure history (n = 106 patients with determinate disposition).

Prior exposure	Recovery, exposed	Death, exposed	Recovery, unexposed	Death, unexposed	OR (95% CI)‡	P
Any prior antibiotic	70/93 (75.3)	23/93 (24.7)	5/13 (38.5)	8/13 (61.5)	0.21 (0.06–0.69)	0.018
Carbapenem	65/86 (75.6)	21/86 (24.4)	10/20 (50.0)	10/20 (50.0)	0.32 (0.12–0.88)	0.031
3rd/4th-generation cephalosporin	62/83 (74.7)	21/83 (25.3)	13/23 (56.5)	10/23 (43.5)	0.44 (0.17–1.15)	0.120
Fluoroquinolone	58/81 (71.6)	23/81 (28.4)	17/25 (68.0)	8/25 (32.0)	0.84 (0.32–2.22)	0.803
Piperacillin–tazobactam	55/75 (73.3)	20/75 (26.7)	20/31 (64.5)	11/31 (35.5)	0.66 (0.27–1.62)	0.482
Polymyxin	60/79 (75.9)	19/79 (24.1)	15/27 (55.6)	12/27 (44.4)	0.40 (0.16–0.99)	0.053

Recovery is defined as discharge alive. OR, odds ratio; CI, confidence interval; P values from the Fisher exact test. ‡Odds ratios are for in-hospital death in exposed relative to unexposed patients; values below 1.0 indicate lower observed mortality among exposed patients. These estimates are unadjusted and are considered to reflect confounding by healthcare access and indication rather than a protective effect of prior antibiotic exposure (see Discussion).

4. Discussion

Across four years and 15,714 patients seen at a tertiary centre in Chattogram, 113 had confirmed CRE infection — a period prevalence of 0.72% (95% CI 0.60–0.86%). Three results stand out. Prior antibiotic exposure was almost universal among cases, and the more classes a patient had received, the more likely the isolate was multidrug-resistant. The antibiogram showed conventional first- and second-line agents to be close to exhausted, leaving colistin and tigecycline as the working reserve. And the crude association between prior exposure and death pointed the wrong way, which we attribute to confounding rather than to any benefit of exposure.

4.1 Prevalence in context

Direct comparison of our prevalence estimate with published Bangladeshi figures requires care because the denominators differ fundamentally. The nationwide laboratory analysis reporting 12.3% CRE and the pooled systematic review estimate of 11.79% both use Enterobacteriales isolates as the denominator, whereas our estimate of 0.72% is expressed per patient observed [6, 7]. These quantities answer different questions: the former describes the resistance proportion among organisms recovered, the latter the clinical burden of CRE infection across a patient population. Our figure is therefore not evidence of a lower resistance burden in Chattogram, and should not be read as such; it quantifies how frequently clinicians in this setting encounter a confirmed CRE infection. Establishing a directly comparable isolate-level proportion would require the denominator of total Enterobacteriaceae isolates recovered over the same period, which was not available.

4.2 Selective pressure and the exposure gradient

The exposure gradient is the strongest signal in the data. Not one patient who had received fewer than three antibiotic classes carried a multidrug-resistant isolate; among those who had received all five, 53.9% did (Cochran–Armitage $P < 0.0001$). This is what selective pressure predicts. Each additional class removes another slice of susceptible flora, and because resistance determinants so often sit together on mobile elements, it simultaneously selects for the genes linked to them [8]. The same relationship appears on a continuous scale: patients with MDR isolates had received a mean of 4.93 classes, against 3.1 in those without.

These findings align directionally with the international literature. The systematic review and meta-analysis by van Loon and colleagues identified prior carbapenem exposure as among the most consistently reported CRE risk factors, with a pooled odds ratio near 4.7 [13]. Our point estimates are considerably larger, but this reflects a structural difference in design rather than a stronger effect: because every patient in our cohort had CRE, our comparison is between exposed and unexposed cases with respect to resistance breadth, not between cases and controls with respect to CRE acquisition. Our estimates should therefore be read as characterising the intensity of the resistance phenotype rather than the risk of acquiring CRE, and the wide confidence intervals arising from small unexposed strata reinforce that caution.

4.3 Antibigram implications for empirical therapy

The antibiogram carries immediate prescribing consequences. With cephalosporin resistance above 77% and fluoroquinolone resistance above 84%, neither class can be regarded as a defensible empirical choice for suspected Gram-negative sepsis in patients with prior healthcare exposure in this setting. Aminoglycoside activity was also limited. Colistin (81.6% susceptible) and tigecycline (88.2% susceptible) remain the principal reserve options, a finding consistent with genomic evidence from Chattogram documenting local circulation of NDM-5, NDM-1 and KPC-2 determinants across multiple high-risk *K. pneumoniae* sequence types [11]. The organism-specific divergence in colistin activity, with markedly higher resistance among *Enterobacter* spp., argues for organism-directed rather than uniform reserve prescribing. The significant rise in trimethoprim–sulfamethoxazole resistance over the study

period is a further signal meriting surveillance. Ceftazidime–avibactam was tested too infrequently to guide policy, and expanding access to this and other newer agents, alongside routine testing, is a priority.

4.4 The paradoxical outcome association

Prior exposure was associated with lower crude mortality, and this needs saying plainly because a literal reading would be dangerous: nothing here suggests antibiotics taken beforehand protect anyone. Confounding is the likelier account. Prior exposure is really a marker of prior contact with the health system. Patients arriving without it tend, in this setting, to arrive late and from the community, having had no medical attention at all, and are correspondingly sicker on presentation. The pattern is not unique to us. A genomic-epidemiological study at a Dhaka tertiary hospital reported several prior-exposure variables with protective-direction odds ratios and no mortality difference by carbapenem resistance, which the authors put down to ward-level confounding and thin clinical data [8]. Ours behaves the same way, and neither the MDR phenotype nor the severity markers predicted death either – which suggests the recorded outcome is poorly aligned with infection severity in this dataset. Until severity is captured properly and deaths are adjudicated as CRE-attributable, no prognostic claim about prior exposure can be supported.

4.5 Comparison with limitations reported in previous studies

Several limitations we encountered are recurrent in this literature rather than unique to our cohort. The Bangladeshi pooled analysis reported very high between-study heterogeneity, reflecting inconsistent case definitions and laboratory methods across sites [7]. The nationwide laboratory study was constrained to susceptibility data without linked clinical or exposure variables [6]. The Dhaka genomic study, though methodologically strong, reported limited clinical information and ward-level confounding as explicit constraints on causal interpretation [8]. Colonisation surveys such as ARCH capture carriage rather than infection and cannot speak to clinical outcome [12]. Our study shares the constraints of retrospective single-centre design but adds linked exposure, phenotype and outcome data at the patient level, which most prior Bangladeshi work has lacked.

4.6 Limitations

Several limitations should temper interpretation. First, the retrospective design means exposure data were abstracted from existing records and, where documentation relied on patient or attendant report, are subject to recall bias; unrecorded over-the-counter antibiotic use is common in Bangladesh and would bias exposure classification toward the null. Second, although duration of therapy was recorded, the available field captures treatment duration for the index CRE episode rather than the duration of prior antibiotic exposure; the latter was not collected, so the pre-planned analysis of prior-exposure duration could not be performed and cumulative class count serves as the available measure of exposure burden, capturing breadth but not intensity or timing. The ≥ 14 -day treatment stratum moreover contained only four patients, leaving that comparison underpowered. Third, the study is single-centre, and referral patterns to a tertiary facility in Chattogram limit generalisability. Fourth, year-specific denominators were

unavailable, precluding analysis of annual prevalence trends. Fifth, because all participants had CRE, no CRE-negative comparison group was available, so the association between exposure and CRE acquisition itself could not be estimated; the near-universal exposure additionally produced a ceiling effect that widened confidence intervals. Sixth, susceptibility testing was selective rather than a fixed panel, so antibiogram denominators vary by agent and some agents were tested too rarely for reliable estimation. Seventh, a graded clinical-response measure and length-of-stay data were not recorded, restricting outcome assessment to in-hospital mortality. Finally, one isolate was recorded as *Enterococcus* spp., which is not a member of the Enterobacteriaceae; it was retained in the cohort denominator but flagged as a probable coding error and excluded from Enterobacteriaceae-specific interpretation.

5. Conclusion

CRE infection affected 0.72% of patients observed at this tertiary centre over four years, approximately 7.19 per 1000. Prior antibiotic exposure was near-universal among cases and showed a strong, monotonic dose–response relationship with multidrug resistance, providing direct local evidence for the selective pressure hypothesis. The accompanying antibiogram demonstrates that conventional first- and second-line agents are no longer dependable for empirical therapy in this population.

On the basis of these findings we offer the following evidence-based recommendations for antimicrobial stewardship in comparable settings:

1. Restrict empirical carbapenem use through formal pre-authorisation and enforce 48–72 hour de-escalation review against culture results, since cumulative exposure breadth—not any single agent—tracked most strongly with multidrug resistance.
2. Treat the number of antibiotic classes a patient has recently received as an actionable bedside risk indicator: in this cohort, exposure to three or more classes marked the threshold above which multidrug resistance emerged.
3. Abandon empirical cephalosporin and fluoroquinolone monotherapy for suspected Gram-negative sepsis in patients with recent healthcare or antibiotic exposure, given resistance exceeding 77% and 84% respectively.
4. Reserve colistin and tigecycline through a stewardship-gated pathway, and prescribe them organism-directed rather than uniformly, given the substantially higher colistin resistance observed among *Enterobacter* spp.
5. Expand routine susceptibility testing for ceftazidime–avibactam and other newer agents, which were tested too infrequently here to inform policy.
6. Strengthen community-level stewardship and restrict over-the-counter antibiotic dispensing, since most infections in this cohort were community-onset yet followed extensive prior exposure.
7. Institute prospective capture of exposure duration, severity scores and CRE-attributable outcomes so that future analyses can move from association to adjusted causal inference.

Declarations

Ethical Consent: This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Apollo Imperial Hospitals (Ref: AIHL/IRB/202608-17), with a waiver of informed consent.

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Dr. Ayesha Ahmed Khan, Dr. Zaved Mehedi Hasan and Prof. Dr. Md. Akram Hossain conceived and designed the study. **Dr. Ayesha Ahmed Khan** collected the data and managed the literature search. **Nayeem Uddin** performed the formal data analysis and interpretation. **Dr. Nayeem Uddin and Dr.**

Showrov Sen Emu wrote the main manuscript text, and all authors critically revised and approved the final manuscript for publication.

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Figures

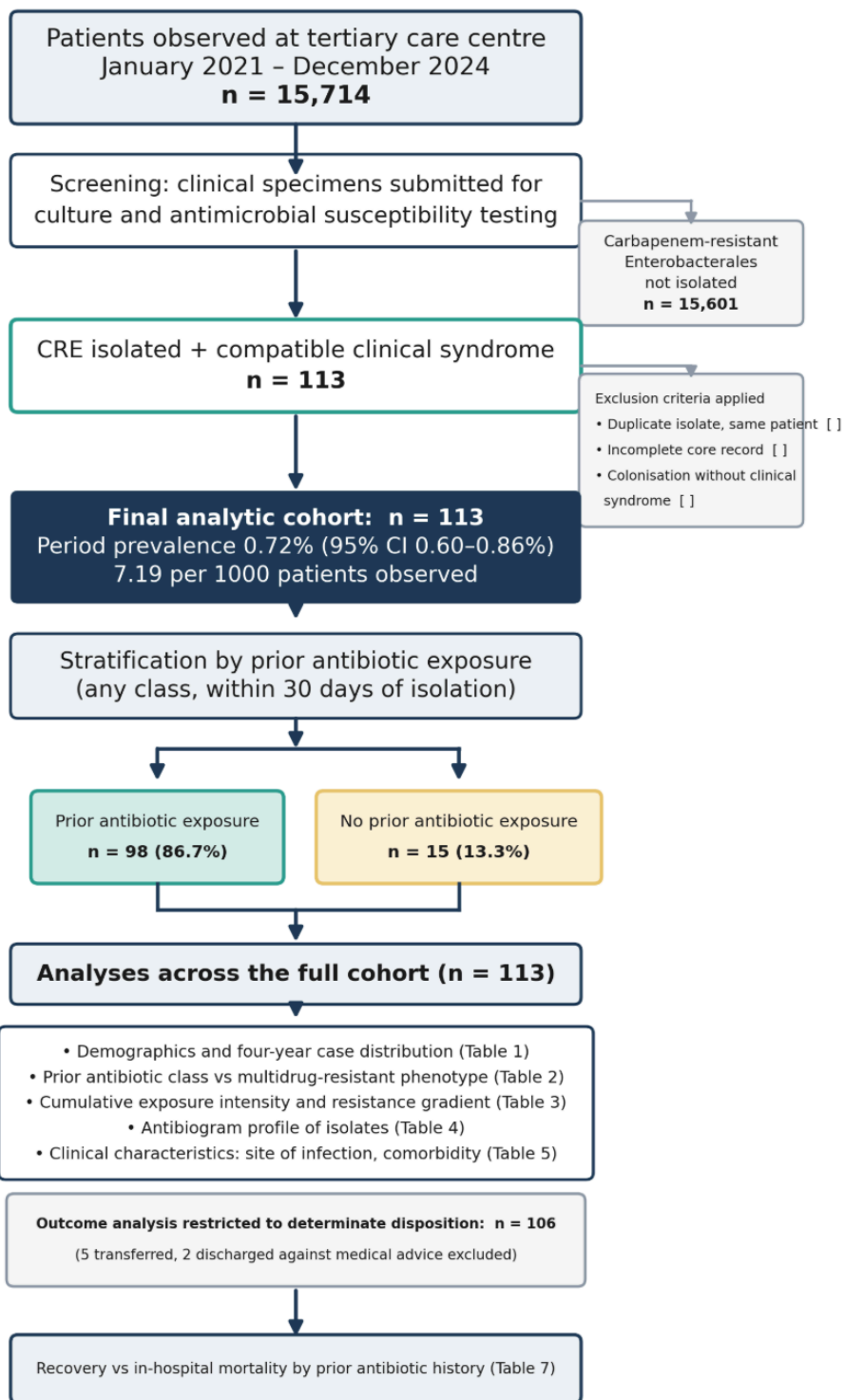


Figure 1

Study selection flowchart. Screening, application of exclusion criteria, derivation of the final analytic cohort, stratification by prior antibiotic exposure, and the analyses performed. Bracketed counts in the exclusion box are to be completed from the screening log.

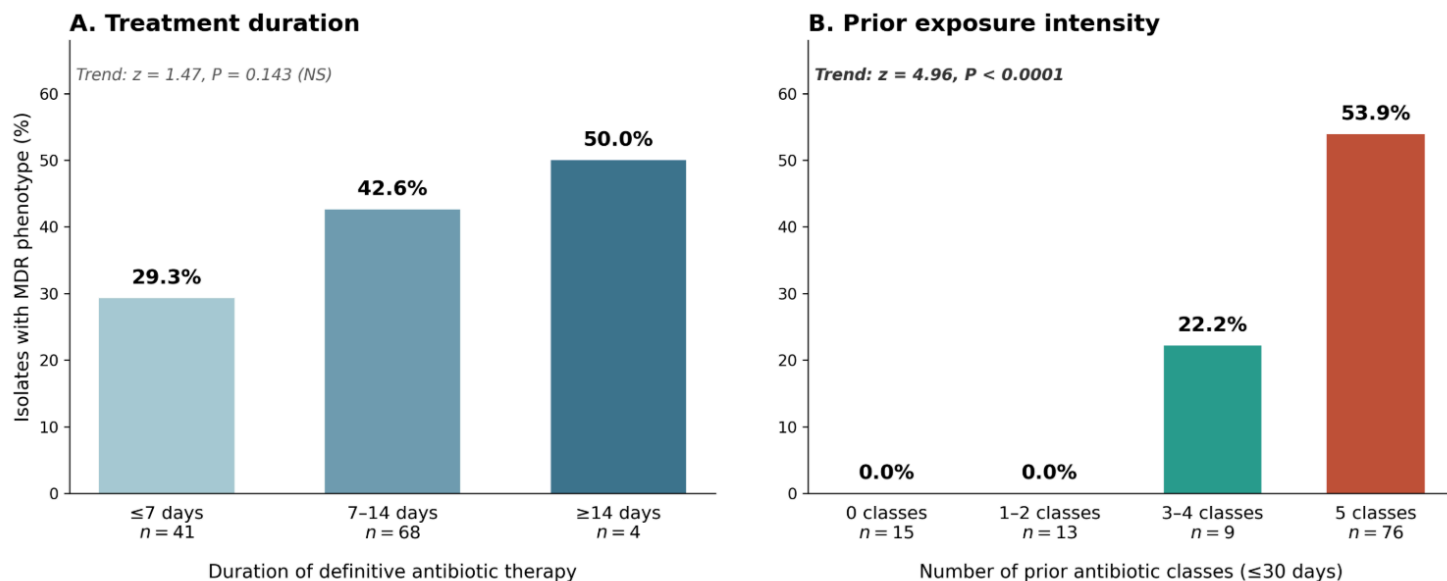


Figure 2

Proportion of isolates with a multidrug-resistant phenotype according to (A) duration of definitive antibiotic therapy for the index episode and (B) the number of prior antibiotic classes received within 30 days of isolation. Only the prior-exposure gradient in panel B is statistically significant (Cochran–Armitage $z=4.96$, $P<0.0001$).

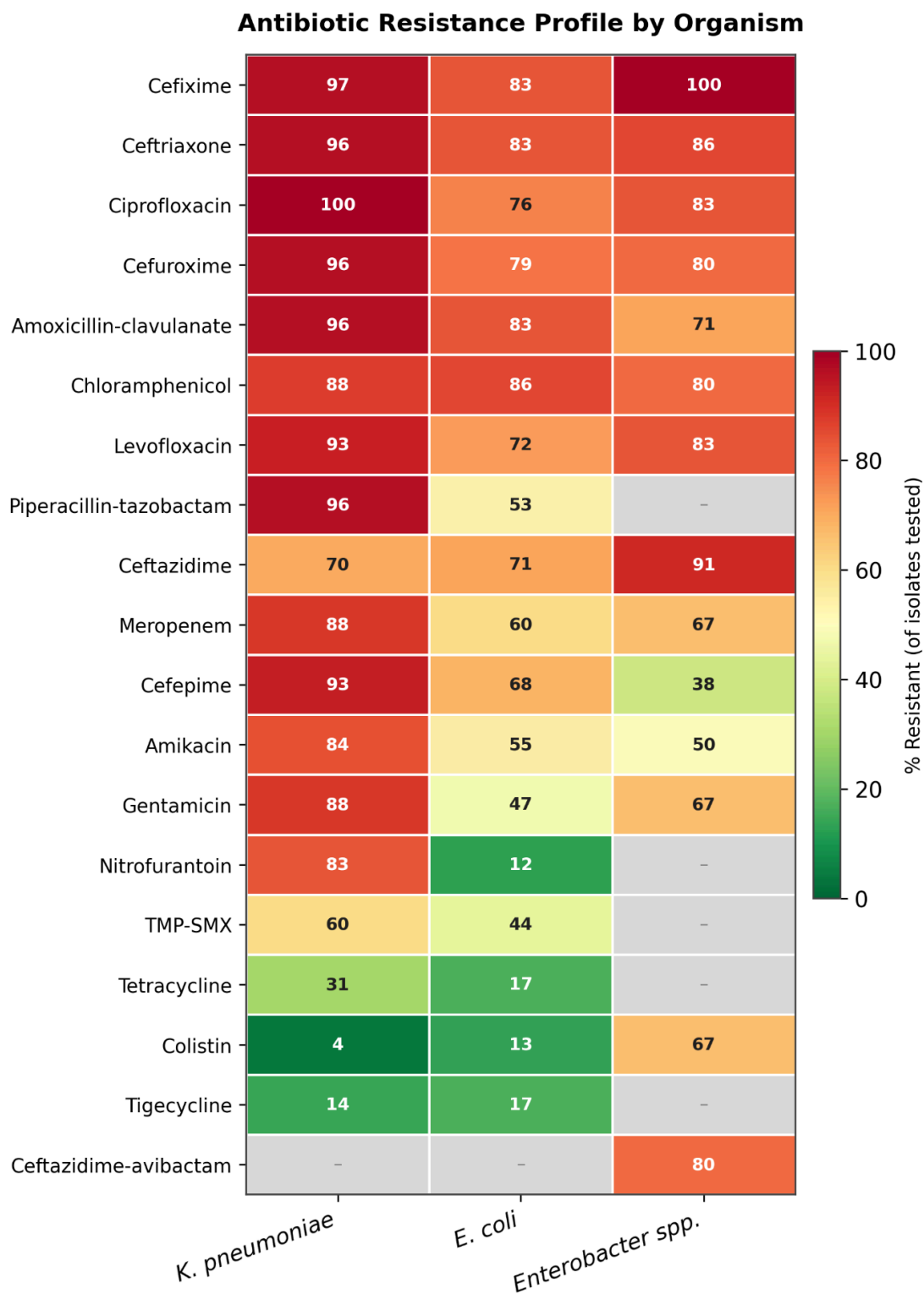


Figure 3

Percentage resistance by antimicrobial agent and organism, restricted to agents with at least 10 isolates tested overall. Cells are shaded from green (low resistance) to red (high resistance); “–” indicates fewer than five organism-specific isolates tested.