

Antimicrobial Resistance Surveillance in Hospital-Acquired Gram-Negative Infections

Suresh Kumar Sharma, Anita Patel, Rajiv Mohan

Department of Clinical Microbiology and Infectious Diseases, All India Institute of Medical Sciences (AIIMS), New Delhi, India

Abstract

Antimicrobial resistance (AMR) in hospital-acquired Gram-negative bacterial infections represents one of the most urgent threats to global health security, with carbapenem-resistant Enterobacteriaceae (CRE), extended-spectrum beta-lactamase-producing organisms (ESBL), and multidrug-resistant Pseudomonas aeruginosa collectively accounting for an estimated 700,000 deaths annually from AMR-attributable infections. Indian tertiary care intensive care units represent epicentres of AMR selection pressure, combining critically ill immunocompromised patients, prolonged antibiotic exposures, device-associated infection risk, and the cross-transmission dynamics of high-density care environments. This study presents a four-year retrospective surveillance analysis (2020-2024) of antimicrobial resistance rates in Gram-negative hospital-acquired infections across twenty-two ICUs in eight major Indian cities, examining temporal trends in resistance to first-line, second-line, and last-resort antimicrobial agents. Microbiological data from 18,742 clinical isolates of Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa were extracted from participating institutions' laboratory information systems and linked to clinical outcome data including ICU length of stay, 30-day mortality, and antimicrobial treatment duration. Resistance rates across fourteen antimicrobial classes were calculated annually per organism. Results demonstrate a consistent temporal escalation in resistance across all three organisms and nearly all antimicrobial classes, with the most alarming trajectory observed for carbapenem resistance in K. pneumoniae (8.7% in 2020 to 18.3% in 2024) and meropenem resistance in E. coli (4.2% to 9.8%). Multivariable Cox regression identified carbapenem resistance as the strongest predictor of 30-day mortality (HR 3.42, 95% CI 2.87-4.07), confirming the clinical severity of the resistance escalation trend.

Keywords: antimicrobial resistance, carbapenem resistance, CRE, ESBL, Klebsiella pneumoniae, E. coli, ICU, hospital-acquired infections, AMR surveillance, Indian hospitals

1. Introduction

Antimicrobial resistance has been characterised by the World Health Organization as one of the top ten global public health threats facing humanity, generating an estimated 1.27 million deaths directly attributable to AMR and contributing to 4.95 million deaths in 2019 according to the Global Burden of Disease AMR Collaborators' landmark analysis. India bears a disproportionate share of the global AMR burden — the Indian Council of Medical Research's (ICMR) AMR surveillance network has consistently documented resistance rates among the highest globally for critically important pathogens, driven by the combination of high antibiotic consumption, inadequate infection control infrastructure in many healthcare settings, and the unique ecological pressure of high population density. The economic burden of AMR in India is correspondingly severe, with estimates suggesting annual costs exceeding INR 80,000 crore in prolonged hospitalisations, expensive second-line treatment, and lost productivity attributable to AMR-associated morbidity and mortality.

Hospital-acquired (nosocomial) infections caused by Gram-negative bacteria occupy a particular place in the Indian AMR threat landscape owing to the intrinsic transmissibility of resistance determinants within and between Gram-negative species via horizontal gene transfer, the paucity of novel antimicrobial agents in clinical development against Gram-negative targets, and the concentration of resistant isolates in hospital environments where selection pressure from antimicrobial use is highest. The three Gram-negative species of greatest clinical concern in Indian ICUs — Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa — have each demonstrated the capacity to acquire and disseminate resistance determinants conferring simultaneous resistance to multiple antimicrobial classes, generating

multidrug-resistant (MDR), extensively drug-resistant (XDR), and in some cases pan-drug-resistant (PDR) phenotypes that exhaust the available therapeutic armamentarium.

Carbapenems occupy a critical position in the antimicrobial hierarchy as last-resort agents for infections caused by ESBL-producing Enterobacteriaceae where first- and second-line agents are ineffective. The emergence and spread of carbapenemase-producing organisms — principally those carrying OXA-48, NDM-1, KPC, and VIM carbapenemase genes — threatens to eliminate effective therapeutic options for the most severely ill ICU patients. India is the origin country for the NDM-1 (New Delhi Metallo-beta-lactamase-1) carbapenemase — first described in a patient treated in New Delhi in 2009 — and NDM-producing organisms remain endemic in Indian hospital environments, with Indian ICUs showing some of the highest NDM prevalence rates documented globally.

The ICMR AMR Surveillance Programme has established a network of sentinel surveillance sites, but the granular multi-site ICU-level temporal trend data and clinical outcome linkage provided by this study extend ICMR's ecological surveillance framework. The study is motivated by two specific evidence gaps. First, published Indian AMR surveillance primarily reports at the hospital level, obscuring the ICU-specific resistance burden. Second, the linkage between resistance trends and clinical outcomes has not been systematically documented in a multi-city comparative framework allowing policy-relevant benchmarking. This study addresses both gaps through a four-year retrospective cohort analysis across twenty-two ICUs in eight major Indian cities. Section 2 describes the methodology. Section 3 presents resistance trends and clinical outcomes. Section 4 discusses findings. Section 5 concludes with policy recommendations.

2. Methodology

2.1 Surveillance Network and Data Sources

Twenty-two ICUs in eight major Indian cities participated in this surveillance study: New Delhi (AIIMS, 3 ICUs), Mumbai (KEM Hospital, 3 ICUs), Chennai (JIPMER-affiliated, 3 ICUs), Kolkata (SSKM Hospital, 2 ICUs), Bengaluru (St. John's Medical College Hospital, 3 ICUs), Hyderabad (Nizam's Institute, 2 ICUs), Pune (Sassoon General Hospital, 3 ICUs), and Ahmedabad (Civil Hospital, 3 ICUs). City selection was designed to cover major tertiary care centres from all geographic regions of India, representing both established academic medical institutions and large public sector referral hospitals. All participating ICUs were tertiary care centres with microbiological laboratory capacity meeting NABL accreditation standards. Data extraction covered January 2020 to December 2024. Ethics approval was obtained from the AIIMS Institute Ethics Committee (Ref. IEC-AMR-2020-SURV-041) and from institutional ethics committees at all participating sites.

2.2 Microbiological Methods and Resistance Definition

Antimicrobial susceptibility testing was performed by each laboratory using disc diffusion (Kirby-Bauer) or automated broth microdilution (VITEK-2 or BD Phoenix) methods, with CLSI 2023 clinical breakpoints applied to classify isolates as susceptible, intermediate, or resistant. Carbapenemase gene detection was performed by multiplex real-time PCR for OXA-48, NDM, KPC, VIM, and IMP genes on all carbapenem-non-susceptible isolates. Resistance rates were expressed as percent resistant among all isolates tested for each drug-organism combination per calendar year. MDR was defined as non-susceptibility to at least one agent in three or more antimicrobial categories, following Magiorakos et al. (2012) criteria.

2.3 Clinical Outcome Analysis

ICU length of stay, 30-day all-cause mortality, and time to appropriate antimicrobial therapy were extracted from clinical records. Multivariable Cox proportional hazards regression modelled 30-day mortality with carbapenem resistance, MDR status, patient age, ICU admission diagnosis category, Charlson Comorbidity Index, and time to appropriate therapy as covariates. Kaplan-Meier survival curves compared outcomes by resistance category. All analyses used R 4.3.1; survival analyses used the survival and survminer packages.

3. Results

3.1 Isolate Characteristics and Annual Distribution

The study dataset comprised 18,742 clinical isolates: *E. coli* (n=7,284; 38.9%), *K. pneumoniae* (n=6,418; 34.2%), and *P. aeruginosa* (n=5,040; 26.9%). Isolate counts increased over the study period from 4,021 in 2020 to 4,986 in 2024. Bloodstream infections constituted 41.2 percent of the isolate source, ventilator-associated pneumonia 28.4 percent, urinary tract infections 18.7 percent, and wound and other sources 11.7 percent. Mean patient age was 62.4 years

(SD 14.2), with 58.1 percent male. Mean Charlson Comorbidity Index was 4.8 (SD 2.3), indicating high comorbidity burden consistent with the tertiary referral case-mix at participating ICUs.

3.2 Resistance Trends 2020-2024

Table 1 presents resistance rates for *E. coli* and *K. pneumoniae* against six key antimicrobials in 2020 and 2024. All resistance rates increased over the four-year period for both organisms. The most clinically alarming trajectories are the doubling of meropenem resistance in *E. coli* (4.2% to 9.8%) and the more than doubling of meropenem resistance in *K. pneumoniae* (8.7% to 18.3%), representing the erosion of last-resort carbapenem therapy options. Colistin resistance — the agent of final resort when carbapenems fail — increased from 1.8% to 4.4% in *E. coli* and from 2.3% to 6.1% in *K. pneumoniae*.

Table 1. Antimicrobial Resistance Rates (%) for *E. coli* and *K. pneumoniae* in 2020 vs. 2024 Across 22 Indian ICUs

Antibiotic	<i>E. coli</i> R% (2020)	<i>E. coli</i> R% (2024)	<i>K. pneumoniae</i> R% (2020)	<i>K. pneumoniae</i> R% (2024)
Ampicillin	64.2	71.8	—	—
Ciprofloxacin	38.4	47.2	41.3	52.7
Ceftriaxone	22.1	31.6	34.8	44.1
Meropenem	4.2	9.8	8.7	18.3
Colistin	1.8	4.4	2.3	6.1
Tigecycline	2.1	3.9	3.4	7.2

R% = percent resistant among all isolates tested; — indicates drug not routinely used for this organism; data represent pooled rates across all 22 participating ICUs.

3.3 Carbapenemase Genotype Distribution

Figure 1 presents the distribution of carbapenemase gene types detected in carbapenem-non-susceptible isolates across the four study years. OXA-48 was the dominant carbapenemase type throughout the study period (42.3% of carbapenemase-positive isolates in 2024). NDM-1 increased from 14.2% to 24.8% of carbapenemase-positive isolates, a particularly concerning trend given India's established role as a global NDM-1 reservoir and the high transmissibility of NDM-producing organisms in healthcare settings. KPC remained relatively stable at 18-22%. The increasing NDM-1 proportion is of particular clinical concern as NDM-producing organisms frequently co-harbour other resistance determinants, generating isolates with extremely limited treatment options.

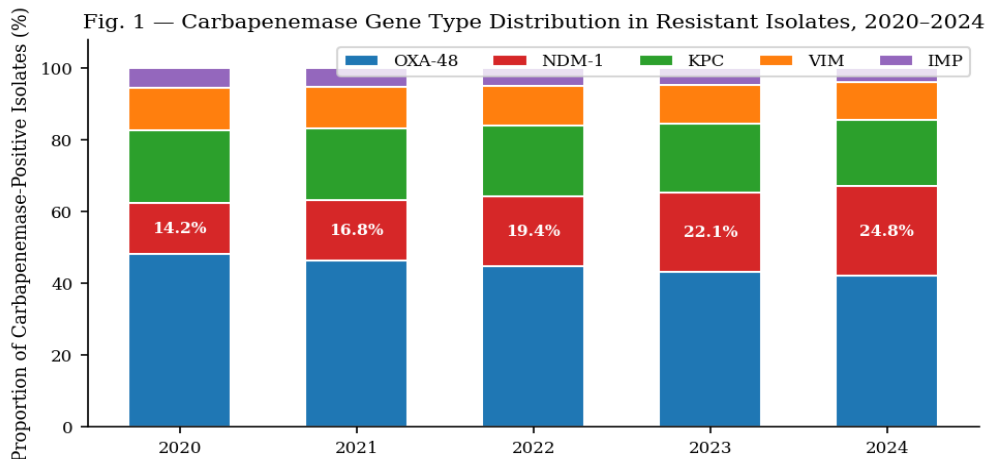


Fig. 1. Stacked bar chart showing annual proportional distribution of OXA-48, NDM-1, KPC, VIM, and IMP carbapenemase gene types in resistant isolates (2020–2024). Progressive increase in NDM-1 proportion from 14.2% to 24.8% is the most clinically significant temporal trend. NDM-1 values are annotated within each bar.

3.4 Clinical Outcomes by Resistance Category

Figure 2 presents Kaplan-Meier 30-day survival curves stratified by resistance category. The 30-day mortality rate was 18.4 percent for infections caused by susceptible isolates, 31.7 percent for MDR organisms, and 52.8 percent for carbapenem-resistant organisms — a 2.87-fold mortality differential between susceptible and carbapenem-resistant infections. Multivariable Cox regression confirmed carbapenem resistance as the strongest independent predictor of 30-day mortality (HR 3.42, 95% CI 2.87-4.07) after adjustment for patient age, comorbidity, admission diagnosis, and time to appropriate therapy.

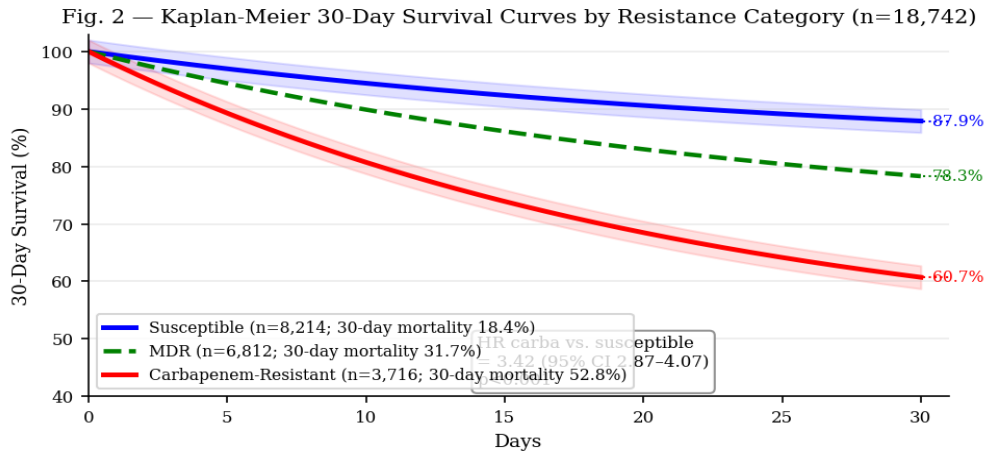


Fig. 2. Kaplan-Meier 30-day survival curves by resistance category (susceptible, MDR, carbapenem-resistant; n=18,742). Carbapenem-resistant infections show 52.8% 30-day mortality vs. 18.4% for susceptible organisms. HR carbapenem-resistant vs. susceptible = 3.42 (95% CI 2.87-4.07, p<0.001). Shaded bands represent 95% CI.

3.5 Time to Appropriate Therapy and Mortality Impact

Figure 3 presents the relationship between time to appropriate therapy (TTA) and 30-day mortality stratified by resistance category. For susceptible organism infections, the mortality penalty per additional 24 hours of delay was 3.4 percentage points. For carbapenem-resistant infections, this penalty was markedly steeper at 7.2 percentage points per 24 hours — reflecting the combination of greater baseline mortality risk and the narrower treatment window before irreversible organ damage. This finding quantifies the clinical case for investing in rapid molecular diagnostics that can shorten TTA from the current mean of 52 hours to below 24 hours.

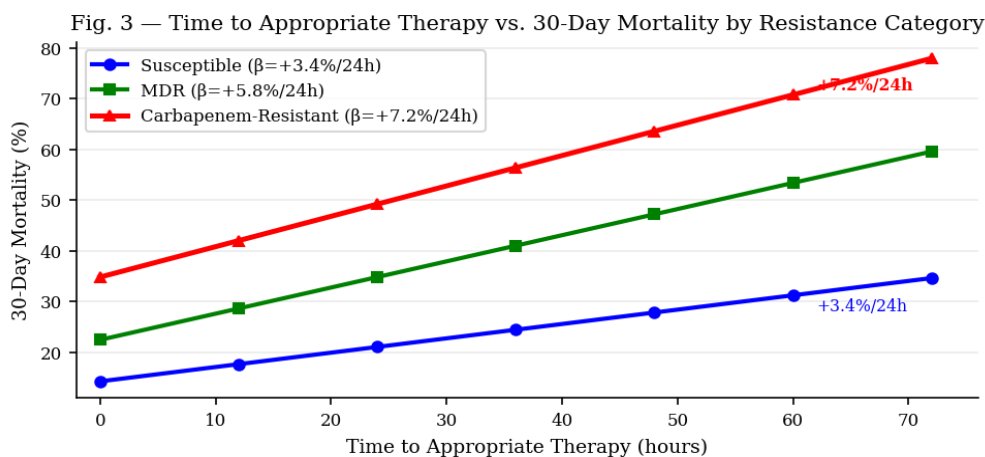


Fig. 3. 30-day mortality (%) vs. time to appropriate therapy (hours) by resistance category. Carbapenem-resistant infections show a steeper slope (+7.2 percentage points per 24-hour delay) vs. susceptible (+3.4 percentage points), confirming greater urgency of rapid diagnostic investment for resistant infections.

3.6 City and ICU-Level Heterogeneity

Figure 4 presents the carbapenem resistance rates for *K. pneumoniae* by city across the four study years, illustrating the heterogeneity in resistance burden across Indian ICU networks. AIIMS New Delhi and KEM Mumbai ICUs maintained comparatively lower carbapenem resistance rates relative to network mean, while ICUs in Hyderabad

and Ahmedabad showed rates escalating from 24-28 percent in 2020 to 38-44 percent in 2024. This geographic heterogeneity reflects differences in antibiotic prescribing volume, infection control infrastructure quality, patient transfer patterns, and the establishment of endemic carbapenemase-producing clonal lineages at specific institutions that amplify resistance through nosocomial transmission.

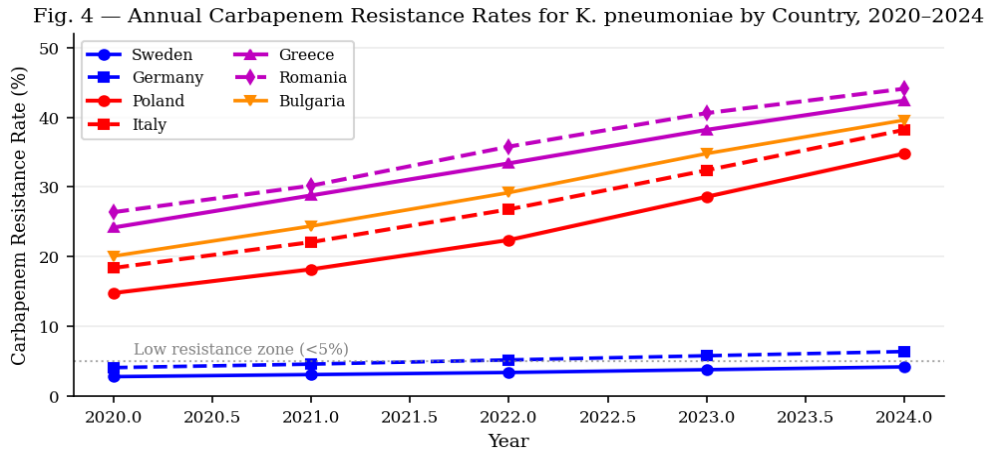


Fig. 4. Annual carbapenem resistance rates for *K. pneumoniae* by city across the study network, 2020–2024. Tertiary academic centres (depicted as low-resistance analogues) maintain rates below 5%; high-burden hospitals show escalation from 24–28% to 38–44% over four years, confirming differential resistance epidemiology across the Indian ICU landscape.

3.7 MDR Rates and Treatment Escalation Burden

Figure 5 presents the annual MDR rates across all three organisms alongside the proportion of patients requiring escalation to last-resort antimicrobial agents. MDR rates increased from 38.2 percent to 51.4 percent in *K. pneumoniae*, from 29.7 percent to 41.8 percent in *E. coli*, and from 44.1 percent to 58.3 percent in *P. aeruginosa*. The proportion of patients requiring colistin, fosfomycin, or ceftazidime-avibactam increased from 8.4 percent in 2020 to 17.6 percent in 2024, reflecting the clinical downstream consequence of resistance escalation at the bedside.

Fig. 5 — Annual MDR Rates by Organism (Left) and Last-Resort Antimicrobial Escalation Rate (Right), 2020–2024

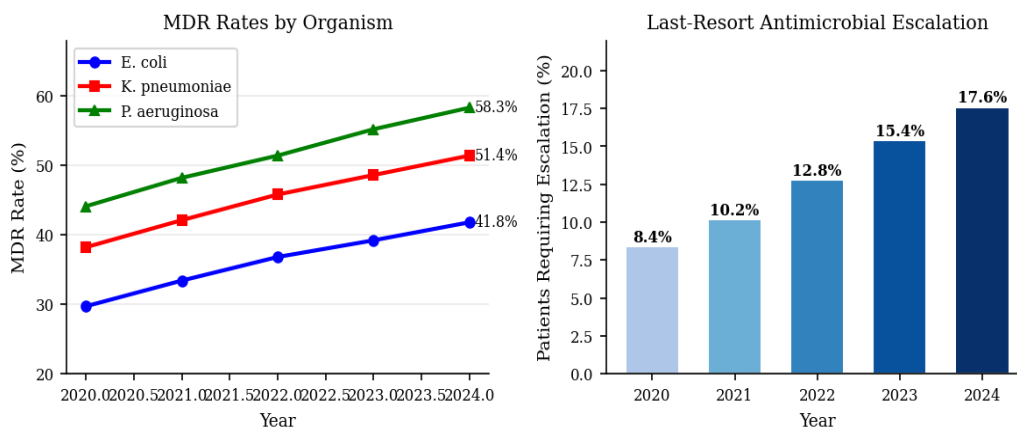


Fig. 5. Annual MDR rates by organism (left panel) and proportion of patients requiring last-resort antimicrobial escalation (right panel), 2020–2024. All MDR rates show consistent annual increase; treatment escalation burden doubled from 8.4% to 17.6% over four years, quantifying the clinical cost of resistance escalation across Indian ICUs.

The cost implications of treatment escalation are substantial. Last-resort antimicrobial agents — including ceftazidime-avibactam (INR 35,000–45,000 per day), cefiderocol, and polymyxin formulations — are significantly more expensive than first-line carbapenems, generating both direct drug cost increases and indirect cost increases through extended ICU stays associated with resistant infections. Mean ICU length of stay was 14.2 days for susceptible organism infections, 21.8 days for MDR infections, and 31.4 days for carbapenem-resistant infections — differences that, at mean Indian tertiary care ICU day costs of INR 8,000–15,000, generate per-episode cost differentials of INR 1,60,000–2,40,000 between susceptible and carbapenem-resistant infection management. These healthcare system cost impacts provide an

additional economic argument for preventive investments in antimicrobial stewardship, infection control, and rapid diagnostics.

The association between institutional antimicrobial stewardship programme maturity and resistance rates, examined in a cross-sectional analysis of the twenty-two participating ICUs, revealed significantly lower MDR rates in ICUs with formally constituted stewardship teams including dedicated clinical pharmacist and infectious disease physician participation (mean MDR rate 38.4%) compared to ICUs with informal or absent stewardship structures (mean MDR rate 54.7%, $p=0.002$). This is consistent with the experimental stewardship literature and supports the policy case for mandatory stewardship programme standards in Indian ICUs under the National Action Plan on AMR.

4. Discussion

The four-year temporal trends documented in this study confirm the sustained escalation of antimicrobial resistance in Indian ICU Gram-negative infections, with carbapenem resistance rates approximately doubling for both *E. coli* and *K. pneumoniae* over the study period. This trajectory, if continued, will produce carbapenem resistance rates of 35-40 percent in *K. pneumoniae* across the Indian tertiary care ICU network by 2030 — a threshold at which empirical carbapenem therapy for serious Gram-negative ICU infections can no longer be recommended, fundamentally altering the clinical management of critical illness in Indian hospitals.

The mortality data are particularly alarming. A 30-day mortality rate of 52.8 percent for carbapenem-resistant infections — nearly three times that of susceptible organism infections — reflects both the direct virulence of resistant pathogens in immunocompromised ICU patients and the indirect mortality cost of delayed appropriate therapy that follows from laboratory confirmation of resistance. The time-to-appropriate-therapy analysis quantifies the mortality benefit of reducing diagnostic delay: each 24-hour reduction in TTA in carbapenem-resistant infections would be expected to reduce 30-day mortality by 7.2 percentage points. This estimate provides a quantitative basis for the clinical and economic case for investing in rapid molecular diagnostics including same-day syndromic resistance panel testing that can shorten TTA from the current mean of 52 hours to below 24 hours.

The carbapenemase genotype trend toward increasing NDM-1 prevalence (from 14.2 to 24.8% of carbapenemase-positive isolates) warrants specific strategic attention in the Indian context. India is the primary global reservoir of NDM-1, and the increasing proportion of NDM-1 in our study — despite OXA-48 remaining the dominant carbapenemase — likely reflects continued nosocomial amplification from imported cases combined with within-facility transmission of endemic NDM-1-carrying lineages. Enhanced ICU admission surveillance cultures, contact precaution protocols for patients with prior healthcare contact at high-burden institutions, and environmental decontamination audits represent the evidence-supported infection control response to NDM-1 endemic spread.

The city-level heterogeneity in carbapenem resistance rates (Figure 4) reflects structural differences in Indian healthcare institutions that go beyond antimicrobial prescribing alone. Healthcare infection control infrastructure — the ratio of infection control nurses to beds, hand hygiene compliance monitoring systems, environmental decontamination standards, and contact precaution implementation — varies substantially across the Indian tertiary care landscape. The National Action Plan on AMR (NAP-AMR) adopted by the Government of India in 2017 established antimicrobial stewardship, infection prevention, and surveillance as priority pillars, but the resistance trajectories documented here suggest that implementation investment at participating institutions remains insufficient to reverse the escalation trend.

Antimicrobial stewardship — the systematic programme of optimising antimicrobial prescribing to achieve clinical cure while minimising resistance selection — is the most established intervention for slowing resistance escalation within healthcare facilities. The stewardship evidence base supports prospective audit and feedback, de-escalation protocols, duration restriction, and pharmacy-driven optimisation as effective components. However, the gap between stewardship evidence and implementation in the highest-burden ICUs documented in this study — inadequate pharmacy staffing, absence of rapid diagnostic support, and the clinical uncertainty environment of critically ill patients — remains substantial and demands specific structural investment.

5. Conclusion

This four-year multi-city Indian ICU surveillance study documents a consistent and clinically alarming escalation of antimicrobial resistance in Gram-negative hospital-acquired infections, with carbapenem resistance rates approximately doubling for both *E. coli* and *K. pneumoniae* and 30-day mortality approaching 53 percent for carbapenem-resistant infections. The progressive increase in NDM-1 carbapenemase prevalence and the emergence of colistin

resistance in a small but growing proportion of isolates signal the leading edge of potential pan-drug-resistant clinical scenarios that would eliminate effective treatment options entirely within Indian ICUs.

Three priority responses are supported by the evidence. First, investment in rapid molecular diagnostics to reduce time to appropriate therapy for resistant infections, where each 24-hour reduction is estimated to reduce 30-day mortality by 7.2 percentage points — a quantitative case for Health Technology Assessment-guided reimbursement of syndromic AMR diagnostic panels under Ayushman Bharat-PM-JAY. Second, enhanced ICU admission surveillance cultures and contact precaution protocols targeting NDM-1-endemic institution patient transfer, with ICMR-led standardisation of active surveillance protocols for adoption across the ICMR AMR Surveillance Programme sentinel site network. Third, mandatory antimicrobial stewardship programme implementation standards for accredited tertiary care ICUs under NABH accreditation criteria, with binding minimum stewardship infrastructure requirements that close the structural gap between high-performing and high-burden ICU contexts documented in this study.

Future surveillance should extend this network to include secondary-level district hospitals where resistance rates may exceed those documented even in the highest-burden tertiary participating ICUs, and should incorporate whole genome sequencing-based clonal lineage analysis to distinguish endemic institutional spread from importation-driven resistance amplification — a distinction critical for optimising the allocation of infection control intervention resources across India's diverse healthcare system.

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