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The Burden and Challenges of Last-resort Antibiotic Resistance in India: Insights into Carbapenem-resistance and *MCR-1* in *Enterobacteriaceae* and *Acinetobacter* spp.

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Abstract

Antimicrobial resistance (AMR) is a major global health issue, particularly in India. Last-resort antibiotics have been weakened by the emergence of carbapenem-resistant *Acinetobacter baumannii* (CRAB) and carbapenem-resistant *Enterobacteriaceae* (CRE). This is complicated further by the plasmid-mediated *mcr-1* gene, which confers colistin resistance and allows it to spread rapidly through sewage, agriculture, and healthcare systems. The high prevalence of CRE and CRAB in Indian intensive care units, which are frequently caused by *NDM* and *OXA-23-like* genes, leads to higher mortality rates and longer hospitalisation. The coexistence of *mcr-1* and carbapenemase genes results in pan-drug-resistant "superbugs". Inappropriate antibiotic use, non-therapeutic use of agricultural colistin, and inadequate infection control are major contributors to antibiotic resistance reservoirs in the environment. India faces challenges in coordinating and enforcing initiatives such as the National Action Plan on AMR, NARS-Net (National Antimicrobial Resistance Surveillance Network), and stewardship programmes. To combat this growing threat, a long-term, comprehensive "One Health" strategy involving strict regulatory enforcement, cross-sectoral collaboration, and effective surveillance is required.

Keywords: Antimicrobial Resistance (AMR), National Antimicrobial Resistance Surveillance Network (NARS-Net), New Delhi Metallo-β-lactamase (NDM), Carbapenem-resistant *Enterobacteriaceae* (CRE), Carbapenem-resistant *Acinetobacter baumannii* (CRAB)

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INTRODUCTION

Antimicrobial resistance (AMR) has emerged as one of the most formidable public health crises of the twenty-first century. It compromises the effectiveness of life-saving antibiotics and threatens the foundations of modern medicine.[1] The emergence and rapid spread of carbapenem-resistant organisms, especially *Enterobacteriaceae* and *Acinetobacter baumannii*, which are often resistant to almost all available antimicrobial agents, are two of the most alarming signs of antimicrobial resistance (AMR).[2,3] These pathogens present significant therapeutic challenges due to the disproportionately high prevalence of drug-resistant infections, especially in resource-poor environments like India.[4] Carbapenems, which are typically used as last-resort treatments for infections resistant to multiple drugs, have proved ineffective against carbapenem-resistant *Enterobacteriaceae*.[2] *Escherichia coli* and *Klebsiella pneumoniae* are two members of the *Enterobacteriaceae* family that are commonly linked to carbapenem resistance. Although these bacteria are common in the gut flora, they can cause serious and potentially fatal infections such as meningitis, pneumonia, sepsis, and urinary tract infections if they develop carbapenem resistance mechanisms, particularly carbapenemases.[5,6] The carbapenemase-producing CRE (CP-CRE), which generates the carbapenem-hydrolysing enzymes KPC (*Klebsiella pneumoniae* carbapenemase), NDM (New Delhi metallo-β-lactamase), OXA-48 (Oxacillinase-48), and VIM (Verona integron-encoded metallo-β-lactamase), is especially concerning. These enzymes, which are often plasmid-borne, promote rapid spread and horizontal gene transfer within and between species.[2,7]

CP-CRE is a major public health concern due to its gene mobility, high mortality rate, and scarcity of effective treatments.[8] Similarly, carbapenem-resistant *Acinetobacter baumannii* (CRAB) poses a major healthcare challenge. *A. baumannii*, an opportunistic pathogen, is well-known for both its natural resistance and its remarkable ability to acquire resistance factors from its surrounding environment.[9] Its persistence on dry surfaces and hospital equipment increases the risk of nosocomial transmission.[10] CRAB's resistance to all antibiotics, including β-lactams, aminoglycosides, and fluoroquinolones, causes frequent outbreaks in critical care settings, especially among immunocompromised patients.[11] CRAB's resistance to all antibiotic classes, including β-lactams, aminoglycosides, and fluoroquinolones, leads to frequent outbreaks in critical care settings, particularly among immunocompromised patients. A serious problem with clinical antimicrobial therapy is indicated by the declining effectiveness of carbapenems. Due to a lack of alternatives, clinicians are increasingly forced to use outdated, toxic, or ineffective medications like tigecycline and polymyxin.[12,13] Sometimes there are almost no more treatment options available, which leads to higher mortality, longer hospital stays, and increased morbidity.[14] Therefore, routine screening and barrier precautions are critical components of current infection prevention strategies, particularly for high-risk groups such as intensive care unit patients, transplant recipients, and those who have been hospitalised for an extended period of time.[15-17] Carbapenem resistance poses a major threat to public health because it significantly increases morbidity and mortality worldwide. Carbapenem-resistant *Enterobacteriaceae* (CRE) is considered an "urgent public health threat" by international health authorities.[17,18] In the United States alone, CRE caused approximately 13,100 infections and 1,100 hospitalised patient deaths in 2017.[19] Similarly, CRAB is designated as a critical priority pathogen due to its multidrug-resistance and association with healthcare-associated infections (HAIs). In the United States, CRAB (carbapenem-resistant *Acinetobacter baumannii*) causes approximately 2% of all HAIs. It is well-known for its ability to survive in hospital settings and colonise patients for extended periods of time, which can exacerbate outbreaks.[9,10] CRAB (carbapenem-resistant *Acinetobacter baumannii*) caused more than 57,700 deaths and 1.5 million disability-adjusted life years (DALYs) worldwide in 2019.[20]

Mobile colistin resistance (*mcr*) genes are frequently responsible for the emergence of colistin resistance, which is exacerbated by CRE and CRAB and can spread horizontally between different bacterial species.[21] Resistance to carbapenems and colistin is a common cause of extensively drug-resistant (XDR) or pan-drug-

resistant (PDR) phenotypes, rendering almost all therapeutic approaches ineffective. Colistin is used as a last-resort antibiotic to treat multidrug-resistant (MDR) infections.[22] Along with these specific pathogens, antimicrobial resistance is now recognised as one of the leading causes of death globally. In 2019, AMR killed an estimated 1.27 million people and contributed to nearly 5 million more, surpassing the combined deaths from HIV/AIDS and malaria. Despite these concerning statistics, antimicrobial resistance continues to receive less public, political, and financial attention than other serious infectious threats.[1,23] Because antimicrobial resistance is an "invisible pandemic" that affects many pathogens and therapeutic pathways, more funding, advocacy, and behavioural change are required to halt the ongoing decline in antibiotic efficacy.[23,24]

India is a crucial epicentre in the global fight against AMR due to its disproportionately high burden of AMR. Antibiotic consumption and resistance are consistently among the highest in the country.[25,26] The prevalence of carbapenem-resistant organisms in India has been described as "particularly concerning" due to widespread antimicrobial misuse and insufficient infection control measures.[4,27] India contributes about 13% of all *Acinetobacter* strains found globally, making it a significant player in the epidemiological landscape of CRAB.[20] Surveillance data from the ICMR and the National Antimicrobial Resistance Surveillance Network (NARS-Net) reveal alarming trends. In India, over 50% of *Klebsiella pneumoniae* isolates and nearly 30% of *Pseudomonas aeruginosa* isolates have carbapenem resistance.[4,27] More specifically, *A. baumannii* had an 88.0% carbapenem resistance rate, while *Escherichia coli* had a 62.7% imipenem resistance rate, and *P. aeruginosa* had a 38.5% rate. Remarkably, the percentage of *E. coli* that is resistant to imipenem has increased dramatically, from 14% in 2016 to 36% in 2021.[27] In India, drug-resistant infections are collectively responsible for more than one million deaths per year. India's high antibiotic use, dense population, and lack of regulatory oversight all contribute to the emergence and spread of resistant organisms.[1,28] Given India's role as a global reservoir of resistance, effective national strategies are critical not only for protecting domestic health but also for ensuring global health security. To prevent the spread of these "superbugs", coordinated global cooperation, strict public health regulations, and consistent funding are required.[23] Despite increased reporting, we still lack a thorough understanding of the epidemiology, molecular mechanisms and regional distribution of these resistance determinants in India. Conflicting findings regarding *mcr-1* prevalence, especially in *Acinetobacter baumannii*, emphasise the significance of robust, region-specific molecular surveillance.[28] Understanding these patterns is critical for informing infection control practices, directing antimicrobial stewardship policies, and developing national strategies to combat AMR. In addition to highlighting important knowledge gaps and potential areas for further investigation, this review attempts to shed light on the carbapenem and colistin resistance mediated by *mcr-1* in *Enterobacteriaceae* and *Acinetobacter* in India.

Current status of CRE and CRAB in India

In India, Gram-negative pathogens continue to exhibit alarmingly high levels of carbapenem resistance. *Enterobacteriaceae* have a prevalence of 18%-33%.[29] According to a Gujarat study conducted during 2014-2018, *Klebsiella* spp. were the most common CRE isolate, with an incidence rate of 1.99 per 1000 patient-days and an overall prevalence of 29.07%.[30] *A. baumannii* (48.0%) and *K. pneumoniae* (38.6%) were the most prevalent Gram-negative isolates that were carbapenem-resistant, according to recent data from a South Indian tertiary care centre (2022-2024).[31] *A. baumannii* was found at 88.0%, *E. coli* at 62.7% (imipenem), and *P. aeruginosa* at 38.5% in the ICMR's 2023 report.[26] The percentage of *E. coli* that were resistant to imipenem increased from 14% in 2016 to 36% in 2021.[32] According to national data, *A. baumannii* resistance ranges from 40%-75%, with hospital-acquired pneumonia exceeding 70%.[33,34] According to a study conducted in Kerala, the incidence of CRE was 0.855 per 1000 patient-days, and 79% of isolates were *Klebsiella* spp.[35] Males (64.3%) and patients between the ages of 61 and 80 have higher rates of resistance.[31] Due to invasive procedures, extended hospital stays, and overuse of antibiotics, ICUs and surgical wards routinely report higher prevalence (Table 1). These findings highlight the critical need

Table 1. Common CRE and CRAB Pathogens and Associated Risk Factors in India

Pathogen	Common Infections Caused	Associated Risk Factors
K. pneumoniae	Pneumonia, bloodstream infections, UTIs	ICU stay, mechanical ventilation, prior antibiotic use, elderly age, male sex, surgical wards, colonization
A. baumannii	Pneumonia (especially VAP/HAP), bloodstream and wound infections, UTIs	ICU stay, invasive devices, chronic wounds, previous antibiotics, colonisation, contaminated environment, recent medical care outside of the United States.
E. coli	UTIs, bloodstream infections, pneumonia, wound infections	Prior antibiotic use, ICU admission, mechanical ventilation
P. aeruginosa	Respiratory tract infections, bloodstream infections	Prior antibiotic exposure, ICU stay, mechanical ventilation

*ICU: Intensive Care Unit; *UTIs,: Urinary Tract Infections; *HAP: Hospital-acquired Pneumonia; VAP: Ventilator-associated Pneumonia

for stronger AMS and IPC programmes in high-risk hospital settings to combat AMR. In India, the predominant Gram-negative pathogens associated with carbapenem resistance include *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Escherichia coli*, with *K. pneumoniae* and *A. baumannii* consistently identified as major contributors to carbapenem-resistant infections in healthcare settings.[36,37] Severe clinical syndromes like pneumonia, bloodstream infections, UTIs, and wound infections are often linked to these bacteria (Table 1). *Pseudomonas aeruginosa* has also become a major problem, especially in tertiary care hospitals, because it is a powerful nosocomial pathogen that can withstand a variety of antimicrobial agents and survive in harsh environments.[38] The risk of developing CRE and CRAB infections is greatly increased by a number of host- and healthcare-related factors. Individuals who are admitted to surgical wards or intensive care units (ICUs) are more vulnerable, particularly if they need invasive medical devices like mechanical ventilators, urinary catheters, or central venous catheters.[39] Prolonged hospitalisation increases exposure and risk. Previous exposure to antibiotics, especially long courses or the use of carbapenems themselves, is a well-established independent risk factor that leads to a vicious cycle of selective pressure and resistance amplification.[40,41] This situation is made worse by delays in pathogen-specific diagnosis due to shortcomings in traditional microbiological techniques, highlighting the critical need for quick molecular diagnostics and improved antimicrobial stewardship programmes (ASPs).[42,43] In addition, host-related vulnerabilities are important. Patients with severe or chronic wounds, immunocompromised states, or comorbid conditions like sepsis, cor pulmonale, or chronic obstructive pulmonary disease (COPD) are more likely to have poor outcomes.[44] Because of age-related immune decline and cumulative healthcare exposure, resistance patterns are more frequently seen in older male patients (61-80 years).[45] The healthcare setting itself serves as an ongoing source of resistant organisms. Healthcare workers' hands, reusable medical equipment, and contaminated surfaces all contribute to both direct and indirect transmission in high-risk environments like intensive care units (Table 1). Colonisation can be prolonged, making patients potential sources of ongoing transmission. Therefore, it is crucial to implement comprehensive infection prevention and control (IPC) measures, such as strict hand hygiene, sterilisation of reusable equipment, and thorough environmental cleaning. To effectively contain AMR, a systems-level IPC approach is required, rather than discrete patient-focused strategies.[46]

Recent healthcare exposure in India has been linked to resistance mechanisms like New Delhi Metallo-β-lactamase-1 (NDM-1), indicating a regional reservoir effect and the need for strong molecular surveillance.[47,48]

Carbapenemase enzymes, which hydrolyse and render carbapenems inactive, are the main cause of carbapenem resistance in Gram-negative bacteria, especially *Enterobacteriaceae* and *Acinetobacter baumannii*.[2] The most common carbapenemases in India are New Delhi Metallo-

β-lactamase (NDM), OXA-48-like, and OXA-23-like enzymes, along with Verona Integron-encoded Metallo-β-lactamase (VIM) and Imipenemase (IMP).[47,49] These enzymes fall into Ambler classes B (NDM, VIM, and IMP) and D (OXA-type), whereas class A enzyme *Klebsiella pneumoniae* carbapenemase (KPC), is still uncommon in isolates from India.[49] In addition to enzymatic hydrolysis, resistance mechanisms include loss or modification of outer membrane porins, which decreases drug entry, and efflux pump overexpression, which actively expels antibiotics.[50] These mechanisms frequently coexist, exacerbating resistance and limiting treatment options.[51] Carbapenemase genes are commonly found on plasmids, transposons, and integrons, allowing for horizontal gene transfer (HGT) across species and genera.[52] This mobility makes containment efforts more difficult by facilitating rapid spread in hospitals, communities, and environmental reservoirs.[53,54] Therefore, strategies must go beyond traditional infection control to include environmental decontamination, antimicrobial stewardship, and novel approaches to plasmid transfer that are consistent with the One Health framework, which integrates human, animal, and environmental health.[55,56]

Table 2. Predominant Carbapenemases in Indian Isolates

Carbapenemase Gene	Ambler Class	Associated Pathogens	Key Characteristics/Significance in India	Ref.
NDM (New Delhi Metallo-β-lactamase)	Class B (MBL)	*Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa*	Most prevalent in India; often coexists with OXA-48; plasmid-mediated; global dissemination originated from India	47,57-59
OXA-48-like	Class D (Oxacillinase)	*Enterobacteriaceae*	Found in ~84.5% of CRE isolates in South India; frequently co-produced with NDM; plasmid-encoded enabling rapid HGT	60,61
OXA-23-like	Class D (Oxacillinase)	*Acinetobacter baumannii*	Accounts for ~87.5% of CRAB cases in Indian ICUs; linked to clonal outbreaks and epidemic clones	62,63
VIM (Verona Integron-encoded MBL)	Class B (MBL)	*Klebsiella pneumoniae*, other Gram-negative bacilli	Sporadic occurrence; integron-associated facilitating gene spread	49,64
IMP (Imipenemase)	Class B (MBL)	*Enterobacteriaceae*	Less frequent compared to NDM and OXA variants; integron-mediated	49,64
KPC (*K. pneumoniae* Carbapenemase)	Class A (Serine β-lactamase)	*Enterobacteriaceae*	Rare in India (<5%); plasmid-mediated; potential risk for future dissemination	65

Predominant carbapenemases in India

New Delhi Metallo-β-lactamase (NDM)

NDM-1 is the most common carbapenemase in Indian isolates of *K. pneumoniae* and *E. coli* and is frequently co-produced with OXA-48-like enzymes.[47,57] It was initially discovered in a patient receiving treatment in India. In India, NDM also predominates among *Pseudomonas aeruginosa* that is resistant to carbapenem.[58] Its global reach highlights India's critical role in the evolution and spread of this resistance determinant.[59]

OXA-48-like

Class D oxacillinases, particularly OXA-48-like enzymes, are highly prevalent in Indian *Enterobacteriaceae*. A major South Indian study found OXA-48-like genes in 84.5% of carbapenem-resistant isolates, which frequently coexisted with NDM (Table 2).[60] These enzymes encoded by plasmids facilitate quick horizontal transfer.[61]

OXA-23-like

In *A. baumannii*, OXA-23-like enzymes predominate, accounting for 87.5% of carbapenem resistance cases in adult ICU isolates from India (Table 2).[62] These genes are associated with clonal outbreaks and epidemic clones in tertiary care hospitals.[63]

VIM and IMP

While IMP enzymes are reported at lower frequencies than NDM and OXA variants, VIM-type metallo-β-lactamases are occasionally found in Indian isolates and are frequently linked to integrons.[49,64]

KPC

KPC is the most common carbapenemase in the United States, but its prevalence in India is low (<5%). However, its plasmid-mediated nature raises concerns about potential introduction and spread resistance.[65]

MCR-1 Gene: Mechanism of colistin resistance and its global, indian, and carbapenem-resistance epidemiology

The antimicrobial resistance crisis has been greatly exacerbated by the *mcr-1* gene's emergence, especially in nations like India where carbapenem resistance is already prevalent. This gene is resistant to colistin, a last-resort antibiotic used to treat infections caused by multidrug-resistant (MDR) Gram-negative bacteria.[66,67] Colistin, a cationic polypeptide, acts by binding to the negatively charged lipid A moiety of lipopolysaccharide (LPS) in the outer membrane of Gram-negative bacteria, disrupting membrane integrity and causing cell death.[12] The *mcr-1* gene encodes a phosphoethanolamine (pEtN) transferase enzyme that modifies lipid A by adding a pEtN group, lowering its negative charge and decreasing colistin binding affinity.[66] *mcr-1*, which was first discovered in *Escherichia coli* isolates from pigs in China in 2015, caused global concern due to its plasmid-mediated transferability.[67] Since then, reports of *mcr-1* and its homologs (*mcr-2* through *mcr-10*) have been made worldwide in a variety of species, including *Salmonella enterica*, *E. coli, Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Aeromonas* spp.[22,68,69] These genes have been found in environmental samples, food items, animals, and people.[70,71] The plasmid-borne nature of *mcr* genes, especially on IncI2, IncHI2, and IncX4 plasmid types, which promote horizontal gene transfer across species boundaries, is the main cause of their quick spread.[72,73] Plasmid-mediated resistance increases the risk of pan-drug resistance because it can spread between organisms, including those that are already resistant to carbapenems, unlike chromosomal resistance, which is vertically transmitted.[74] There have been occasional but increasing reports of *mcr-1* in clinical, environmental, and animal sources in India, underscoring its growing importance for public health. In 2016, a clinical *E. coli* isolate from Haryana was found to have *mcr-1* for the first time.[70,75] In the first environmental report in India, *mcr-1* was detected in five out of forty-seven phenotypically colistin-resistant isolates from urban sewage in Delhi. These isolates were shown to be transferable via conjugation.[76] In a recent study conducted at a rural tertiary care hospital in Maharashtra between June 2022 and July 2024, *mcr-1* was found in 13 out of 93 colistin-resistant GNB, with *K. pneumoniae* making up 23.07% of positive isolates.[77] A colistin resistance rate of 1.637% among GNB was reported by another South Indian hospital, and *mcr-1* was found in 6.45% (2/31) of the colistin-resistant isolates.[78] Significantly, *mcr-1* has been found chromosomally in *K. pneumoniae* isolates from India as well as on plasmids like IncFII. In 2018, *mcr-1* chromosomal integration was initially reported in clinical isolates, indicating long-term persistence and stable inheritance.[75,79] This dual localisation (plasmid and chromosomal) represents a powerful evolutionary strategy that combines vertical stability with rapid horizontal dissemination, complicating containment efforts.[22,80] Due to contradictory reports and shifting epidemiological patterns, the presence of the *mcr-1* gene in *Acinetobacter baumannii* in India is still debatable. An early study at the Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, reported chromosomally encoded *mcr-1* in clinical (first case in human isolates) *A. baumannii* isolates from India (2015-2017) (Table 3). According to the study, *mcr-1*, which was chromosomally localised and suggested vertical transmission, was present in 20 out of 100 (20%) colistin-resistant *A. baumannii*

Table 3. Reported Prevalence of *mcr-1* in Indian Isolates and Associated Features

Bacterial Species	Source Type	Location (India)	Study Period	Reported Prevalence of *mcr-1*	Co-existence with Carbapenemase Genes	Gene Localization	Ref.
Acinetobacter baumannii	Clinical isolates	Lucknow (SGPGI)	2015-2017	20% (20/100 colistin-resistant), First case in human isolates	Not reported	Chromosomal	81
Acinetobacter baumannii	Clinical isolates	Multi-center (India)	2016-2019	0%	N/A	N/A	82
Acinetobacter baumannii	Clinical isolates	Western Maharashtra, India (rural)	2022-2024	15.38% (2/13 mcr-positive GNB)	Not specified	Plasmid-mediated	83
E. coli	Environmental (sewage)	Delhi	2019	5/47 colistin-resistant isolates	Co-harboring ESBL genes (bla_{CTX-M}, bla_{TEM})	Conjugative plasmid	76
Klebsiella pneumoniae	Clinical isolates	Lucknow	2017	86.36% (19/22 colistin-resistant)	bla_{NDM}, bla_{OXA-48}	Chromosomal + plasmid	85

isolates.[81] In contrast, a thorough analysis of 207 clinical isolates of *A. baumannii* from various Indian centres between 2016 and 2019 revealed no *mcr* genes, attributing colistin resistance to mutations in the pmrABC two-component system and eptA overexpression caused by upstream ISAba1 insertion.[82] In a study conducted at a rural tertiary care centre in Western Maharashtra between June 2022 and July 2024, *mcr-1* was found in two of thirteen *mcr*-positive Gram-negative isolates (15.38%), which were confirmed as *A. baumannii.*[77,83] These findings imply that *mcr-1* in *A. baumannii* may exhibit temporal evolution and regional specificity. Despite sporadic detection, chromosomal mechanisms remain prevalent in Indian clinical settings, emphasising the importance of nationwide molecular surveillance to clarify epidemiological trends.

The mobilised colistin resistance gene is mostly plasmid-borne and is often found on the backbones of the IncI2, IncHI2, and IncX4 plasmids, which are highly mobile and enable effective HGT.[84] This contributes to the emergence of pan-drug-resistant (PDR) organisms by facilitating quick spread among bacterial species, including *Enterobacteriaceae* and non-fermenters like *Pseudomonas* and *Acinetobacter*. For example, the first human case of mobilised colistin resistance in India was found in *Acinetobacter* isolates from North India, which were found on an IncI2-type plasmid.[81] Similarly, conjugative plasmids co-harbouring ESBL genes (bla_{CTX-M}, bla_{TEM}) carried *mcr-1* in *E. coli* from Delhi sewage samples.[76] Mobile genetic elements (MGEs), such as ISApl1 and IS26 insertion sequences and transposons, play an important role in the movement of *mcr* genes across species and genomes.[86] In *K. pneumoniae*, chromosome integrations and plasmid-borne *mcr-1* variants have been discovered, indicating recombination events and mobilisation across genetic elements.[85,87,88] Rural isolates from South India further verified plasmid-mediated *mcr-1*, suggesting environmental persistence and community-level spread.[89] Unlike clonal expansion, HGT enables resistance genes such as *mcr-1* to "jump" to susceptible bacteria, frequently combining with carbapenemase genes to accelerate the emergence of XDR and PDR strains. This molecular synergy emphasises the critical need for plasmid typing, whole-genome

sequencing, and MGE tracking in high-risk environments. The presence of *mcr-1* alongside carbapenemase genes such as bla_{NDM-1}, bla_{OXA-48}, bla_{KPC}, and bla_{VIM} in the same bacterial isolate is concerning because they eliminate nearly all therapeutic options for XDR/PDR phenotypes.[90,91] In India, studies have shown (Table 3) that *K. pneumoniae* isolates from Lucknow with high *mcr-1* prevalence (19 out of 22 colistin-resistant strains) co-harbor bla_{NDM} and bla_{OXA-48}, indicating that multidrug-resistance is driven by synergistic mechanisms.[85] Similar to this, *A. baumannii* strains from North India expressed *mcr-1* alongside NDM-1 and VIM, which are frequently associated with transposon activity and chromosomal integrations.[92] This convergence of colistin and carbapenem resistance within the same genetic context represents a significant shift towards a post-antibiotic era for certain Gram-negative infections, necessitating novel treatment strategies and stringent infection control protocols.[76,93,94]

Challenges in combating CRE and CRAB in India

The management of CRE and CRAB infections is extremely difficult in India, mainly because there are few treatment options and diagnostic limitations (Table 4). One major challenge is the inability to distinguish between colonisation and true infection, especially in critically ill or immunocompromised patients, which frequently leads to inappropriate antibiotic use and worsens resistance.[47] This issue is made worse by diagnostic delays. Despite their widespread use, phenotypic tests like Carba NP and the modified carbapenem inactivation method (mCIM) have sensitivity and specificity issues, particularly when it comes to non-carbapenemase mechanisms.[2] Molecular assays targeting carbapenemase genes (e.g., bla_{NDM}, bla_{OXA-48}, bla_{KPC}, bla_{VIM}, and bla_{IMP}) provide higher accuracy but are underutilised in India due to cost and infrastructure constraints.[95] Furthermore, initial screening methods such as ertapenem disc diffusion may be insufficient to accurately predict resistance phenotypes.[96] These diagnostic gaps frequently result in delayed or inappropriate treatment, which contributes to poor outcomes and increased mortality.[97] Therapeutic options for CRE and CRAB are severely restricted. Most infections require older agents such as polymyxins (colistin,

Table 4. Key Challenges in Diagnosis and Treatment of CRE/CRAB Infections in India

Challenge Category	Specific Challenge	Impact/Consequence
Diagnostic Limitations	Differentiating colonization from active infection	Delayed or inappropriate empirical treatment, increased diagnostic uncertainty
	Lack of rapid and reliable molecular tests (e.g., for CRAB from respiratory specimens)	Delays in targeted therapy, continued silent spread of resistant bacteria
	Flaws in phenotypic tests; molecular tests not exhaustive	Incomplete identification of resistance, suboptimal treatment decisions
Therapeutic Constraints	Limited availability of effective treatment options	Reliance on older, toxic drugs with efficacy concerns
	High cost and limited access to newer BL-BLI agents	Inequitable access, widening health disparities
	Ineffectiveness of new drugs against specific carbapenemases	Need for complex combination therapy, limited evidence
	High mortality with CRE/CRAB infections	Increased morbidity, mortality, and healthcare costs
Clinical Management	Need for personalized therapy (host/site/PK/PD)	Complex decision-making in low-resource settings

*CRE: carbapenem-resistant Enterobacterales; CRAB: carbapenem-resistant *Acinetobacter baumannii;* BL-BLI: Beta-lactam-beta-lactamase inhibitor; PK/PD: (Pharmacokinetic/pharmacodynamic)

polymyxin B), fosfomycin, and aminoglycosides, which have suboptimal pharmacokinetics, poor tissue penetration (especially in lungs), and significant adverse effects, with nephrotoxicity being a major concern with polymyxins.[98] The emergence of plasmid-mediated colistin resistance (*mcr-1*) further complicates treatment.[99] Mortality rates for CRE infections in India range from 30%-75%, while CRAB infections—particularly bloodstream infections and ventilator-associated pneumonia (VAP) can exceed 50%-70%.[100,101] Newer β-lactam/β-lactamase inhibitor combinations such as ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam have shown promise against certain carbapenemase producers, but they are ineffective against metallo-β-lactamase (MBL) producers like NDM, which are highly prevalent in India.[3,102] For MBL-producing strains, aztreonam combined with ceftazidime-avibactam offers a potential solution, but synergy testing is not routinely performed in most Indian hospitals.[103] Furthermore, these newer agents are expensive and scarce, resulting in a two-tiered healthcare system in which advanced therapies are inaccessible to patients in public hospitals and rural areas.[104] Effective management requires a customised approach considering host factors, infection site, local molecular epidemiology, and PK/PD (pharmacokinetic/pharmacodynamic) principles.[105] However, the lack of rapid diagnostics and limited access to newer drugs make implementing such precision medicine strategies difficult in resource-constrained environments (Table 4). Without immediate investment in affordable rapid diagnostics, novel antimicrobials, and equitable drug distribution policies, AMR will continue to turn treatable infections into fatal diseases, exacerbating healthcare disparities in India.[1]

Infection prevention and control (IPC) remains a critical challenge in India's healthcare system, particularly in ICUs, where the burden of HAIs is alarmingly high. A multicentre study reported an HAI prevalence of approximately 53% among ICU patients in India.[106] A major issue is the inconsistent implementation of IPC practices. Essential measures such as alert systems for resistant organisms and contact isolation protocols are often poorly enforced.[39,61] This IPC gap significantly contributes to AMR and poses serious risks to patient safety. Resistant pathogens like CRAB can persist on hospital surfaces for days to weeks, even under dry conditions, if cleaning and disinfection are inadequate.[47] Transmission occurs through direct and indirect contact with infected or colonised patients or via contaminated surfaces and medical equipment, often facilitated by healthcare workers' hands.[107] These factors transform ICUs into "amplifiers" of drug resistance, perpetuating nosocomial transmission.[108] Strengthening IPC requires investment in infrastructure, continuous staff training, adherence monitoring, and a cultural shift toward prioritising hygiene.[54] Without robust IPC, other AMR containment efforts will fail.

India ranks among the highest consumers of antibiotics globally, with per capita use increasing by nearly 30% over the past decade.[109] A significant concern is the inappropriate use of antibiotics, including unapproved formulations, with one recent study finding that 47.1% of all antibiotic sales were unapproved drugs.[110] This widespread misuse is driven by unrestricted manufacturing, marketing, and OTC sales.[111] Although antibiotics fall under Schedule H and H1 of the Drugs and Cosmetics Rules, enforcement is lax, allowing chemists to dispense antibiotics without prescriptions.[112] This reflects a demand-side problem, fuelled by patient expectations, cultural norms, and financial pressures.[113] Effective interventions must go beyond regulation to include public awareness campaigns, provider education, and addressing socio-economic drivers.[114] Misconceptions among patients—such as believing antibiotics weaken the body or failing to distinguish between harmful and beneficial bacteria worsen the issue.[115] Premature discontinuation of antibiotics due to side effects is common. In rural areas, untrained providers often prescribe antibiotics as "cure-all" remedies.[116] Economic pressures, especially among daily wage earners, and physicians' fear of litigation further promote irrational antibiotic use.[117] Despite India's issuance of national treatment guidelines, IPC protocols, and laws such as Schedule H/H1 classifying antibiotics as prescription-only drugs, enforcement at the local level remains weak.[118] This disconnect between policy and practice creates a significant "policy-practice gap", undermining efforts to control AMR. Effective implementation

requires strengthening regulatory agencies, improving inspection and accountability, and building local capacity through training pharmacy staff.[119] Sustained political will and intersectoral commitment are essential to bridge this gap.

Antimicrobial resistance dissemination extends beyond hospitals into the environment, creating a critical but often overlooked transmission pathway. Wastewater treatment plants (WWTPs) act as reservoirs for antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs), fostering conditions conducive to HGT.[120] Discharge of untreated hospital and pharmaceutical effluents into water bodies is a major contributor.[121] Studies have detected ESBL producers and carbapenemase genes such as bla_{NDM-1} and bla_{OXA-48} in major Indian rivers, including the Ganges and Yamuna.[122,123] Contaminated water systems act as bioreactors, enabling gene exchange under selective pressure from antibiotic residues. [124] Additional contributors include aquaculture, agricultural sludge use, and improper disposal of livestock waste.[125] These findings underscore the need for a One Health approach, integrating environmental monitoring and strict waste disposal regulations. Investment in advanced wastewater treatment technologies and curbing antibiotic use in agriculture are vital to prevent environmental amplification of AMR.

National strategies and initiatives to combat AMR in India

India has recognised AMR as a public health emergency and initiated several strategic responses encompassing policy frameworks, surveillance systems, antimicrobial stewardship, and a One Health approach. India's NAP-AMR, which was introduced in 2017 and emphasises sensible antimicrobial use, awareness, and surveillance within a One Health framework, is in line with the WHO Global Action Plan.[56,115] These initiatives expand upon past efforts like the National Task Force on AMR Containment (2010) and the National Programme on AMR Containment (2013).[126] Additionally, national guidelines for IPC and sensible antibiotic use have been released by the Ministry of Health.[127] However, implementation is hampered by insufficient funding and inadequate multisectoral coordination.[128] In NAP-AMR 2.0, experts support state-level financial commitment, interministerial cooperation, and enforceable governance.[129] Using standardised SOPs, India has created platforms such as NARS-Net to track resistance patterns in priority pathogens.[130] To monitor resistance mechanisms, the ICMR Antimicrobial Resistance Surveillance Network (AMRSN) uses cutting-edge molecular techniques, such as whole-genome sequencing.[130] Near real-time case-based reporting with geotagging is made possible by the Integrated Health Information Platform (IHIP). Full utility requires consistent investment in lab capacity, diagnostics, and qualified staff.[131] Prescription practices and infection control metrics have been enhanced by ICMR-led ASP frameworks.[128,131] However, barriers to widespread adoption include physician resistance, financial constraints, and a lack of infrastructure.[108] Many hospitals lack trained staff, diagnostic support, and stewardship champions.[132] Addressing these systemic and behavioural gaps requires interventions that go beyond guidelines.[49] To reduce AMR, India's One Health strategy combines environmental, animal, and human health measures.[133] Effective containment necessitates cross-ministerial collaboration, public-private partnerships, and data sharing to break down institutional silos.[111,133]

CONCLUSION

In India, the spread of the *mcr-1* gene in connection with CRAB and CRE poses a serious and complex public health threat. With concerningly high and rising rates of carbapenem resistance in important pathogens such as *K. pneumoniae*, *E. coli*, and *A. baumannii*, the country's high burden of AMR is seriously limiting treatment options and increasing patient morbidity and mortality. A specific molecular epidemiology that influences treatment efficacy is highlighted by the predominance of OXA-48-like and NDM carbapenemases in CRE and OXA-23-like in CRAB. One important development is the appearance of the plasmid-mediated *mcr-1* gene, which confers colistin resistance. Its ability to quickly transfer genes horizontally and coexist with carbapenemase genes is contributing to the concerning rise of bacteria that are resistant to multiple drugs. Because of this phenomenon, clinical management of these incurable infections is essentially returned to a time before antibiotics.

The discovery of *mcr-1* in clinical and environmental isolates, like urban sewage, highlights the extent of this threat and how it impacts not only healthcare facilities but also the environment and the general public. The contradictory information about the prevalence of *mcr-1* in *A. baumannii* also points to a crucial research gap and an evolving epidemiological landscape. The widespread inappropriate use of antibiotics, which is fuelled by over-the-counter sales and self-medication and exacerbated by irrational prescribing practices, is one of the systemic and societal issues that are at the core of this crisis. A major "One Health" blind spot is the widespread non-therapeutic use of colistin in agriculture, which creates environmental reservoirs for resistance that can spread to human populations. The widespread non-therapeutic use of colistin in agriculture is a major "One Health" blind spot. Because of this practice, environmental reservoirs of resistance are created, which may then spread to human populations. Furthermore, the spread of antimicrobial resistance is accelerated by ongoing deficiencies in infection prevention and control within healthcare facilities. A comprehensive and ongoing national effort that incorporates a strong "One Health" approach is necessary to effectively combat this interconnected threat.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

SA, RK, SC, and SS contributed to the conceptualisation, literature review and data extraction. N, SF, and JK critically evaluated the evidence and validated the scientific content. VK supervised the study. SA, RK, SC, and SS wrote the manuscript. N, SF, VK and JK reviewed and revised the manuscript. All authors read and approved the final manuscript for publication.

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All datasets generated or analyzed during this study are included in the manuscript.

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