Revista Geográfica de Chile Terra Australis, Vol.61, No. 1 (2025) 101-122 ISSN 0719-9562
https://doi.org/10.23854/07199562.2025611.sanchez

GLOBAL DISTRIBUTION AND EPIDEMIOLOGICAL RELEVANCE OF NDM, KPC, VIM, IMP AND OXA-48-LIKE CARBAPENEMASES

DISTRIBUCIÓN GLOBAL Y RELEVANCIA EPIDEMIOLÓGICA DE LAS CARBAPENEMASAS NDM, KPC, VIM, IMP Y OXA-48-LIKE

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ABSTRACT

Carbapenemase-mediated resistance, driven by enzymes that inactivate lastresort carbapenem antibiotics, has emerged as a critical global health threat. To delineate its true scope, we conducted an exhaustive review of the past five years' literature, focusing on the five principal carbapenemases (KPC, NDM, VIM, IMP, and OXA-48-like) in human clinical isolates. All relevant studies were synthesized into a unified database, which served as the basis for generating individual world maps for each enzyme and a composite map illustrating their co-occurrence. These visual tools illuminate the uneven yet interconnected nature of carbapenemase dissemination, underscoring the value of spatially resolved data in combating antimicrobial resistance. Our findings reveal distinct regional patterns: KPC dominates much of the Americas and Western Europe; NDM is most burdensome in the Indian subcontinent and North Africa; VIM remains concentrated in Southern Europe; IMP is endemic in Japan and parts of China; and OXA-48-like enzymes prevail around the Mediterranean and in the Middle East. These disparities reflect local genetic transfer dynamics, via plasmids, integrons, and other mobile elements, as well as variations in antibiotic use practices and surveillance capacity. Accurate, up-to-date distribution maps are therefore indispensable for tailoring surveillance strategies, optimizing antimicrobial stewardship, and directing research funding, all of which are vital for slowing the spread of these formidable resistance determinants.

Keywords: Carbapenemases, antimicrobialresistance, multidrug-resistant bacteria, epidemiologicalsurveillance

RESUMEN

La resistencia mediada por carbapenemasas, enzimas capaces de neutralizar los carbapenémicos, antibióticos considerados de última línea terapéutica, constituye una amenaza sanitaria de alcance global. Para caracterizar su verdadero alcance, realizamos una búsqueda exhaustiva de la literatura científica de los últimos cinco años, enfocada en la detección de las cinco carbapenemasas principales (KPC, NDM, VIM, IMP y OXA-48-like) en aislamientos humanos, y se consolidó la información obtenida en una base de datos unificada. A partir de ella se generaron mapas de distribución individual para cada enzima y un mapa compuesto que refleja la co-ocurrencia de todas. Los resultados revelan patrones geográficos distintivos: KPC domina en gran parte de América y Europa occidental; NDM presenta su mayor carga en el subcontinente indio y el norte de África; VIM se concentra en el sur de Europa; IMP mantiene su endemia en Japón y China; y OXA-48-like es especialmente prevalente en la región del Mediterráneo y Oriente Medio. Estas diferencias responden tanto a dinámicas locales de transferencia genética, plásmidos, integrones y elementos móviles, como a prácticas de uso de antibióticos y niveles de vigilancia microbiológica. Disponer de mapas precisos y actualizados resulta crucial para adaptar las políticas de vigilancia, optimizar estrategias de control y orientar la asignación de recursos y esfuerzos de investigación, con el fin de contener la diseminación de estas enzimas y preservar la eficacia de los tratamientos de última línea.

Palabras clave: Carbapenemasas, resistencia antimicrobiana, bacterias multirresistentes, vigilancia epidemiológica

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1. INTRODUCTION

Antimicrobial resistance (AMR) has become a critical threat to global public health, sustainable development, and health security in the twenty-first century. The World Health Organization (WHO) lists AMR among the top ten immediate health challenges, stressing that it is already affecting millions worldwide. Drug-resistant pathogens, which evolve new defenses against existing treatments, compromise our ability to manage common infections. Of greatest concern is the swift global spread of multidrug- and pan-resistant superbugs that render standard antibiotics ineffective. This trend places tremendous strain on healthcare systems, hampering outbreak control and eroding decades of progress in infectious-disease management (Assembly, 2015; Dutescu& Hillier, 2021).

Addressing AMR demands urgent, coordinated international efforts in antibiotic stewardship, surveillance, and the development of sustainable new therapies (Munkholm& Rubin, 2020). AMR has garnered considerable attention in recent decades and has been identified as a significant public health concern by the WHO. It is imperative that significant effort and proactive strategies to combat this global health crisis be implemented, as otherwise 10 million lives are estimated to be lost by 2050 (Antimicrobial Resistance Collaborators, 2022; Salam et al., 2023). AMR is an inherent survival mechanism exhibited by bacteria. However, the increase in AMR can be attributed to several factors, including the inappropriate use of antibiotics in humans and livestock, as well as the presence of antibiotics in the environment.

Bacterial resistance involves multiple mechanisms, such as reduced membrane permeability, efflux pumps, enzymatic degradation, target modification, and biofilm formation, that affect nearly all antibiotic classes (Ho et al., 2025). Among these, carbapenemases pose a major threat due to their ability to inactivate carbapenems and other β-lactams (Hammoudi-Halat& Ayoub-Moubareck, 2020). These enzymes compromise treatment for infections caused by multidrug-resistant Gram-negative pathogens like *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Their global spread has limited therapeutic options, increasing patient morbidity, mortality, and healthcare costs (Martin et al., 2018). This calls for urgent global coordination in surveillance, antimicrobial stewardship, and drug development to preserve effective treatments.

2. CARBAPENEMS

Carbapenems are broad-spectrum antibiotics regarded as a last-line therapy due to their effectiveness against multidrug-resistant pathogens (Boyd et al., 2022; Hansen, 2021; Tenover et al., 2022). Their potent bactericidal activity stems from a distinctive beta-lactam core that disrupts bacterial cell wall synthesis (Armstrong et al., 2021; Kim et al., 2023). These drugs are especially valuable in treating severe Gram-negative infections, often seen in critically ill or immunocompromised patients (Alvisi et al., 2025). However, the rise of carbapenemase-producing organisms has severely compromised their efficacy, leading to increased reliance on older, less ideal antibiotics like colistin and tigecycline (Cantón& Bou, 2017; Tamma et al., 2022).

Although alternatives exist, they present significant limitations. Colistin is linked to nephrotoxicity and neurotoxicity (Cantón& Bou, 2017), while tigecycline shows suboptimal efficacy in severe infections (Zha et al., 2020). These drawbacks emphasize the urgent need for innovative therapeutic strategies and stricter infection control measures in healthcare settings. Preserving the clinical utility of carbapenems is essential, not only because they remain one of the few effective options against resistant infections, but also because their diminished efficacy directly threatens patient outcomes, prolongs hospital stays, and increases healthcare costs.

2.1. History of carbapenems

The discovery of β-lactam antibiotics in the 1960s, including penicillins and cephalosporins, marked a significant advance in antimicrobial therapy (Drawz et al., 2010). These agents inhibit bacterial cell wall synthesis, making them highly effective against a wide range of pathogens (Massova et al., 1998). Among them, carbapenems emerged as a distinct subclass, initially derived from imipenem, an antibiotic originally isolated from *Streptomyces* species (Aminov, 2009). In 1967, researchers at Merck & Co. developed one of the first carbapenems, ertapenem, laying the foundation for a new generation of broad-spectrum antibiotics. Due to their ability to combat a wide array of severe bacterial infections, carbapenems were soon recognized as “very broad-spectrum” antibiotics and

became essential tools in treating complicated and resistant infections.

In 1985, imipenem, a carbapenem antibiotic developed by Merck & Co., received clinical approval and was marketed under the brand name Primaxin (Zhanel et al., 1998). This represented a major breakthrough in the treatment of multidrug-resistant infections, especially those caused by *Pseudomonas aeruginosa* and members of the *Enterobacteriaceae* family. One of imipenem's key features was its stability against most β-lactamases, enzymes produced by bacteria to inactivate traditional β-lactam antibiotics (Hellinger et al., 1999), making it a powerful option against resistant pathogens.

During the 1990s and early 2000s, the rise of AMR drove the need for more advanced carbapenem agents. In 2000, meropenem was introduced, offering lower nephrotoxicity than imipenem, which translated into improved safety for patients. It also showed enhanced efficacy against *Pseudomonas* species and other resistant bacteria. Later, in 2005, doripenem and ertapenem entered the market, each tailored to specific types of infections and optimized for better dosing schedules and pharmacokinetics, further expanding the clinical utility of the carbapenem class.

2.2. Clinical relevance of carbapenems

One of the key strengths of carbapenems lies in their broad-spectrum antibacterial activity. These agents are highly effective against a diverse array of pathogens, including Gram-positive, Gram-negative, and anaerobic bacteria, making them particularly valuable for treating polymicrobial infections or those involving resistant organisms (Alvisi et al., 2025). Their clinical utility is especially evident against members of the *Enterobacteriaceae* family, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter spp.*, as well as problematic non-fermenters like *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. Additionally, they are active against *Streptococcus pneumoniae*, *Staphylococcus aureus* (including some methicillin-resistant strains), and *Bacteroides spp.* (Cantón& Bou, 2017), reinforcing their essential role in managing complex and severe infections.

They are primarily used to treat urinary tract infections, pneumonia, intra-abdominal infections, and sepsis, especially when the causative pathogens display multiple resistance mechanisms (Alvisi et al., 2025; Botelho et al., 2020; Martin et al., 2018). Due to their effectiveness and broad-spectrum activity, carbapenems play a critical role in managing severe infections in hospital settings, where resistant organisms are more frequently encountered. Their use has become standard practice for serious nosocomial infections, particularly those associated with invasive medical devices or occurring in immunocompromised patients.

Their empirical use in severe clinical scenarios, where resistant pathogens are suspected and immediate antibacterial action is required, buys crucial time while the causative organisms and their susceptibility profiles are identified (Hansen, 2021; Nordmann &Poirel, 2019). Being designated as a last-line therapy, means their effectiveness must be preserved, as losing this therapeutic option would severely compromise the treatment of complex infections (Alvisi et al., 2025; Martín et al., 2018; Nordmann &Poirel, 2019).

3. **CARBAPENEMASES**

The most critical threat to the clinical use of carbapenems comes from carbapenemases, which are enzymes that hydrolyze and neutralize these antibiotics (Bonomo et al., 2017). The global spread of carbapenemase-producing bacteria, particularly among *Enterobacteriaceae*, has led to a significant crisis in the treatment of resistant infections (Cantón& Bou, 2017).

Carbapenemase-mediated resistance not only renders carbapenems ineffective but also often coexists with resistance to other antibiotic families, significantly reducing available therapeutic options. This situation is further exacerbated in organisms that carry multiple carbapenemases, which favor co-resistance and make treatment particularly challenging, especially when last resort antibiotics such as colistin or fosfomycin also prove ineffective (Giske, 2015).

Carbapenemases are a class of β-lactamase enzymes that confers bacteria the ability to resist carbapenems (Cantón& Bou, 2017), and thus, significantly undermines therapeutic options (Aurilio et al., 2022). The Ambler classification, based on the structure of β-lactamase proteins, is a widely utilized system for the categorization of carbapenemases according to their structural characteristics and

mechanisms of action (Nath & Karthikeyan, 2017). Carbapenemases are classified into distinct classes (A, B, C, and D) based on the configuration of their active site and the nature of their mechanism of action (see **Table 1** for a detailed overview). The molecular characteristics that distinguish each class of carbapenemases include the presence of specific residues in the amino acid sequence, the formation of disulfide bridges, and the requirement of a metal for enzymatic activity. The molecular mechanisms that enable this classification are described below.

Class A carbapenemases are enzymes that utilize a serine residue in their active site to catalyze the hydrolysis of β-lactam antibiotics (Alvasi et al., 2025; Cantón& Bou, 2017; Hansen 2021). These enzymes, including *Klebsiella pneumoniae* carbapenemase (KPC), typically function by means of a mechanism that involves the nucleophilic attack of a serine residue on the β-lactam ring. This process leads to the opening and inactivation of the antibiotic. In molecular terms, class A carbapenemases share a similar amino acid sequence that forms an active site with a serine residue at its catalytic center (Queenan& Bush 2007). The ability of these enzymes to hydrolyze carbapenems depends on the structural conformation of the active site, which is adapted to allow substrate binding and facilitate the hydrolysis reaction.

Table 1. Ambler Classification of Carbapenemases. The characteristics of each class are described. Source: Own elaboration based on Ambler (1980) and Drawz & Bonomo (2010).

Classification	TypeofCarbapenemase	Group	Examples
Class A	Carbapenemase class A	Beta-lactamases	KPC (*Klebsiellapneumoniae*carbapenemase), GES (Guiana extended-spectrum beta-lactamase)
Class B	Metalo-beta-lactamases (MBL)	Beta-lactamases	NDM (New Delhi metallo-beta-lactamase), IMP (imipenemase), VIM (Verona integron-encodedmetallo-beta-lactamase)
Class C	AmpC Beta-lactamases	Beta-lactamases	CMY (Cephamycinase), FOX (Beta-lactamasetype AmpC)
Class D	Carbapenemase class D (OXA-type)	Beta-lactamases	OXA-23, OXA-24, OXA-48 (specifically carbapenemases oxacillin)

Class B carbapenemases, also known as metallo-bactamases, are zinc-dependent enzymes that require the presence of metal ions, typically Zn^{2+}, to exhibit catalytic activity. The histidine residues present in the active site coordinate with the metal ion, thereby facilitating the hydrolysis of the β-lactam ring. In molecular terms, class B carbapenemases are characterized by the presence of an active site in which zinc is essential for enzymatic activity. In this type of enzyme, the metal ion facilitates the activation of nucleophilic water, allowing it to attack the β-lactam ring. An example of a class B carbapenemase is the well-known New Delhi metallo-β-lactamase (NDM-1) (Oelschlaeger et al., 2023).

Class C carbapenemases are a type of AmpC-type β-lactamases, which are serine-like enzymes. However, unlike class A carbapenemases, their main action is the hydrolysis of third-generation β-lactams, such as cephalosporins (Bush & Jacoby 2010). However, they also have the capacity to inactivate carbapenems. These enzymes share structural similarities with AmpC-type β-lactamases, featuring a serine-containing active center and an amino acid sequence that enables interaction with antibiotics analogous to conventional β-lactamases. While class C carbapenemases do not require metals for their activity, their ability to hydrolyze carbapenems may depend on structural changes in their active site due to the acquisition of mutations (Bush & Bradford, 2020).

Class D carbapenemases, on the other hand, are serine-enzymes harboring a distinct structural and

functional characteristic that differentiate them from class A carbapenemases. Enzymes of this class, including OXA-carbapenemases, possess an active center with serine residues that facilitate the hydrolysis of carbapenem antibiotics (HammoudiHalat& Ayoub Moubareck, 2020). These enzymes are most prevalent in gram-negative bacteria, such as *Acinetobacter baumannii*, and are characterized by their ability to hydrolyze a wide range of β-lactams, including carbapenems (Evans & Amyes, 2014). The active site of these enzymes exhibits specific structural features that facilitate efficient interaction with the β-lactam ring.

Carbapenemase-mediated resistance has been observed not only in *Enterobacteriaceae*, but also in *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. In the *Enterobacteriaceae* family, the most prevalent classes of carbapenemases include KPC, NDM, and OXA-48-like. In contrast, carbapenemase resistance is predominantly associated to class D β-lactamases, including blaOXA-23, blaOXA-24/40, and blaOXA-58 in *Acinetobacter baumannii*; however, class B β-lactamases such as NDM-1, have also been identified in some *Acinetobacter baumannii* strains. On the other hand, class B carbapenemases such as VIM and IMP predominate in *Pseudomonas aeruginosa*, with a less prevalence of KPC and OXA-like carbapenemases. These disparities are indicative of species-specific genetic adaptations and geographical dissemination patterns, which complicates the formulation of universal control and treatment strategies

During the last years, both carbapenem-resistant *Enterobacteriaceae* (CRE) and other bacterial pathogens resistant to carbapenems have proliferated rapidly on a global scale, primarily attributable to the production of carbapenemases. Evidence indicates that mobile genetic elements, that include plasmids, integrative and conjugative elements, transposons, and insertion sequences, among other elements, are the most important factors implicated in the dissemination of carbapenemase-encoding genes among diverse bacterial species. Indeed, these mobile genetic elements play a pivotal role in horizontal gene transfer (HGT) within bacterial populations, thereby promoting rapid evolutionary adaptation. **Table 2** lists several examples of the most significant carbapenemases genes associated with mobile genetic elements.

3.1. Carbapenemases spreading

The spread of carbapenemases is driven by both horizontal gene transfer and bacterial evolution (Botelho et al., 2020). Resistance determinants move between strains via plasmids (Botelho et al., 2020; Boyd et al., 2022), transposons (Cantón& Bou, 2017; Hansen, 2021), and other mobile genetic elements (Ji et al., 2024), enabling once-susceptible bacteria to deactivate carbapenems. Inappropriate and excessive antibiotic use, especially in hospital settings, has accelerated this process, allowing resistant organisms to survive standard treatments and ignite hard-to-control nosocomial outbreaks (Cantón& Bou, 2017).

Global travel, international trade, and urbanization further facilitate the dissemination of carbapenemase-producing strains across regions with differing prevalence levels. Compounding this issue, many health systems lack adequate infrastructure, and access to high-quality antimicrobials remains limited, creating environments where resistant pathogens gain a foothold. In these contexts, infections caused by carbapenemase producers are not only more common but also more severe, as therapeutic options become increasingly scarce.

3.2. Co-production of carbapenemases

The co-production of carbapenemases occurs when a single bacterial strain synthesizes two or more enzymes capable of inactivating carbapenems, a phenomenon referred to as “redundant carbapenemase-producing” (RCP) bacteria (Bush & Bradford, 2020; Contreras et al., 2020; Kumarasamy&Kalyanasundaram, 2012; Solgi et al., 2017; Yuan et al., 2024). This genetic feature significantly amplifies resistance mechanisms, as each enzyme degrades carbapenems through distinct hydrolytic pathways, often encoded on highly promiscuous plasmids and integrons. Clinically, RCP strains are critical due to their association with multidrug-resistant or extensively drug-resistant phenotypes, which drastically narrow therapeutic options. The global spread of these strains has steadily increased over recent decades, expanding from early hotspots in Asia and Europe to nearly every continent (Bush & Bradford, 2020; Yuan et al., 2024).

Geographically, co-production cases are particularly concentrated in Asia, namely China, India, South

Korea, Turkey, and Iran, though significant reports also exist from Europe (Spain, Greece, Italy), South America (Argentina, Brazil, Colombia), and, to a lesser extent, Africa and North America (Baek et al., 2019). The most commonly implicated species belong to the Enterobacterales order, led by *Klebsiella pneumoniae* (accounting for 70% of RCP–Enterobacterales reports), followed by *Escherichia coli* (10–15%), *Enterobacter cloacae*, *Citrobacter freundii*, and *Acinetobacter baumannii*. Cases have also been described in *Pseudomonas aeruginosa*, *Serratia marcescens*, and *Raoultellaplanticola*, underscoring the versatility of mobile genetic elements that shuttle these resistance genes across diverse bacterial hosts.

Table 2. Examples of some of the most important carbapenemases disseminated through Horizontal Gene Transfer.

Carbape-nemasec lass	Enzyme family	Representative carbapenemase s	Organism(s)	Genetic basis ofresistance	MGE associ-ated	SelectedReferences
A	KPC	KPC-1, KPC-2, KPC-3	*Klebsiella pneumoniae* *Pseudomonas aeruginosa* *Acinetobacter baumanii* *Serratia marcescens* *Citrobacter freundii*	Self-conjugative plasmids	Tn*4401a* Tn*4401b* Tn*4401d*	Yigit et al., 2001;Bratu et al., 2005; Woodford et al., 2004; Nordmann et al., 2011; van Beek et al., 2019; Giddins et al., 2018; Balm et al., 2012; Naas et al., 2008; Galetti et al., 2019; Hu et al., 2019; Gomez et., 2011; Mojica et al., 2012; Cuzon et al., 2010; Andrade et., 2011; Cerdeira et al., 2019;Tavares et al., 2015; Barría-Loaiza et al., 2016
B	IMP	IMP-1, IMP-2, IMP-2, IMP-3, IMP-4, IMP-5	*Pseudomonas aeruginosa* *Acinetobacter baumanii* *Klebsiella. pneumoniae*	Conjugative plasmids	Gene-cassette s in Class I integrons	Watanabe et al., 1991; Riccio et al., 2000; Limbago et al., 2011; McCarthy et., 2017; Elena et al., 2018; Lincopan et al., 2005
	VIM	VIM-1-like, VIM-2-like, VIM-7-like	*Pseudomonas aeruginosa* *Klebsiellapneu moniae*	Chromosom al/ Plasmids	Gene-cassette s in Class I integrons	Lauretti et al., 1999; Poirel et al., 2000; Toleman et al., 2004; DeBelder et al., 2017; Campos et al., 2015; Silva et al., 2015
	NDM	NDM-1, NDM-2, NDM-3, NDM-4, NDM-5	*Klebsiellapneu moniae* *Acinetobacterb aumanii* *Escherichiacoli* *Enterobacterhor maechei* *Providencia rettgeri*	Chromosom al/ Plasmids	ISA*ba125* Tn*3000* Tn*125* Tn*5393*	Yong et al., 2009; Kaase et al., 2011; Tada et al., 2014;Nordmann et al., 2012; Hornsey et al., 2011; Pasteran et al., 2014; Rojas et al., 2016; Escobar et al., 2013; Carvalho-Assef et al., 2013-2014; Campos et al., 2015; Romero-Alvarez et al., 2017,
D	OXA	OXA-48 like	*Klebsiellapneu moniae*	Plasmids	pOXA-48a Tn*1999* IS*4321*-IS*4*	Poirel et al., 2004-2011-2013; Turton et al., 2016; Gomez et al., 2013; Sampaio et al., 2014; Reyes et al., 2019

MGE: mobile genetic elements. Source: Own elaboration based on selected references.

Among more than 28 described carbapenemase combinations, five account for nearly 70 % of global reports: NDM+OXA (67 %), KPC+NDM, VIM+OXA, KPC+VIM, and KPC+OXA. NDM and OXA-48-like co-occur in most NDM-positive isolates, while the KPC+NDM pairing is especially prevalent in South America, representing 93% of KPC-producing RCP strains in Argentina. RCP bacteria can even harbor three or four carbapenemases simultaneously (e.g., NDM+VIM+OXA-48), further complicating clinical

and epidemiological management. Clinically, these strains cause infections that are harder to eradicate, necessitate expensive and potentially toxic combination therapies, and exhibit higher rates of treatment failure and complications, particularly in critically ill patients.

3.3. Horizontal gene transfer of carbapenemases

HGT is a pivotal mechanism driving the spread of carbapenemase-mediated resistance in bacteria, undermining last-line antibiotic therapies. three main HGT pathways are particularly important, plasmids, natural transformation and integrative and conjugative elements.

Firstly, plasmids are self-replicating, circular extrachromosomal DNA molecules. Plasmids carrying blaNDM and blaKPC genes, and others, have been identified as major vehicles for carbapenemase dissemination (Zhang et al., 2024).

Secondly, in *Acinetobacter baumannii*, natural transformation can capture “resistance islands” up to 30 kb in size. These large DNA segments integrate into the bacterial chromosome, often carrying virulence and resistance determinants such as blaOXA-23, aminoglycoside, and fluoroquinolone resistance genes, thereby fostering multidrug-resistant strains (Godeux et al., 2022).

Thirdly, integrative and conjugative elements combine features of conjugative plasmids and bacteriophages. In pathogens like *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, 66 carbapenemase genes, predominantly metallo-β-lactamases (IMP, NDM), have been linked to these elements, which readily transfer resistance across species (Botelho et al., 2020). The human gut microbiota is proposed as a critical reservoir for both commensal and pathogenic bacteria, providing an ideal environment for such gene exchanges (McInnes et al., 2020). Hospital settings further amplify HGT events, facilitating the rapid emergence and spread of carbapenemase producers.

This review has highlighted the escalating threat posed by carbapenemase-producing bacteria and underscored the critical need for a clear, evidence-based picture of their global distribution. To address this, the following section outlines the systematic approach we employed to gather and organize the most recent data on the five principal carbapenemases, NDM, KPC, VIM, IMP, and OXA-48-like, across human clinical isolates worldwide. By synthesizing these findings, we aim to provide a robust foundation for interpreting regional trends, guiding surveillance efforts, and informing targeted interventions against these formidable resistance mechanisms.

4. METHODOLOGY

In order to identify reports of carbapenemase-producing bacteria in human clinical samples from the past five years, anextensive literature review was conducted. Searches were carried out in PubMed and Google Scholar using combinations of enzyme names (“carbapenemase,” “NDM,” “KPC,” “VIM,” “IMP,” “OXA-48”) and country identifiers. Any study reporting the detection of one or more of these enzymes, regardless of sample type, was included.

Extracted data were compiled into country-specific tables, including more than 200 countries, for each of the five key carbapenemases using NotebookLM, then merged into a single Excel database. To fill gaps, a targeted secondary search (“Country[title] carbapenemase”) was performed for nations initially marked as having no available information. This step added 58 countries to the dataset, confirming carbapenemase presence in 27 countries. The completed database then served as the basis for generating both individual and composite world maps illustrating the global distribution of each enzyme.

The geographic prevalence of carbapenemases varies widely across continents, reflecting differences in surveillance, infection-control practices, and antibiotic pressure. The following data represent the main findings related to carbapenem resistance over the world.

This review has some limitations. The search was based on specific keywords (“carbapenemase,” “NDM,” “KPC,” “VIM,” “IMP,” “OXA-48”), which may have excluded relevant studies that did not use these exact terms, introducing search bias. Additionally, the secondary search (“Country[title] carbapenemase”) relied on the mention of the country in the title, likely omitting pertinent research. There is also a significant limitation due to the limited availability of data from countries that do not report or publish prevalence information, affecting geographic representativeness.

5. GEOGRAPHIC PREVALENCE OF CARBAPENEMASES

Global carbapenemase distribution varies significantly by region as shown in figure 1. In North and Latin America, KPC is the most prevalent enzyme, while OXA-48-like and NDM occur less frequently (Bush & Bradford, 2020; Wise et al., 2024). Europe exhibits greater diversity, with OXA-48-like carbapenemases common in Mediterranean and Eastern countries, alongside widespread KPC and NDM (Boyd et al., 2022; van Duin& Doi, 2017). OXA-48-like enzymes are endemic in the Middle East, and NDM variants predominate in the Indian subcontinent (Boyd et al., 2022; Kedišaletše et al., 2023). In Africa and Asia, NDM and OXA-48-like are reported, while Oceania shows sporadic detections (Alvisi et al., 2025; Stewart et al., 2018) (Figure 1).
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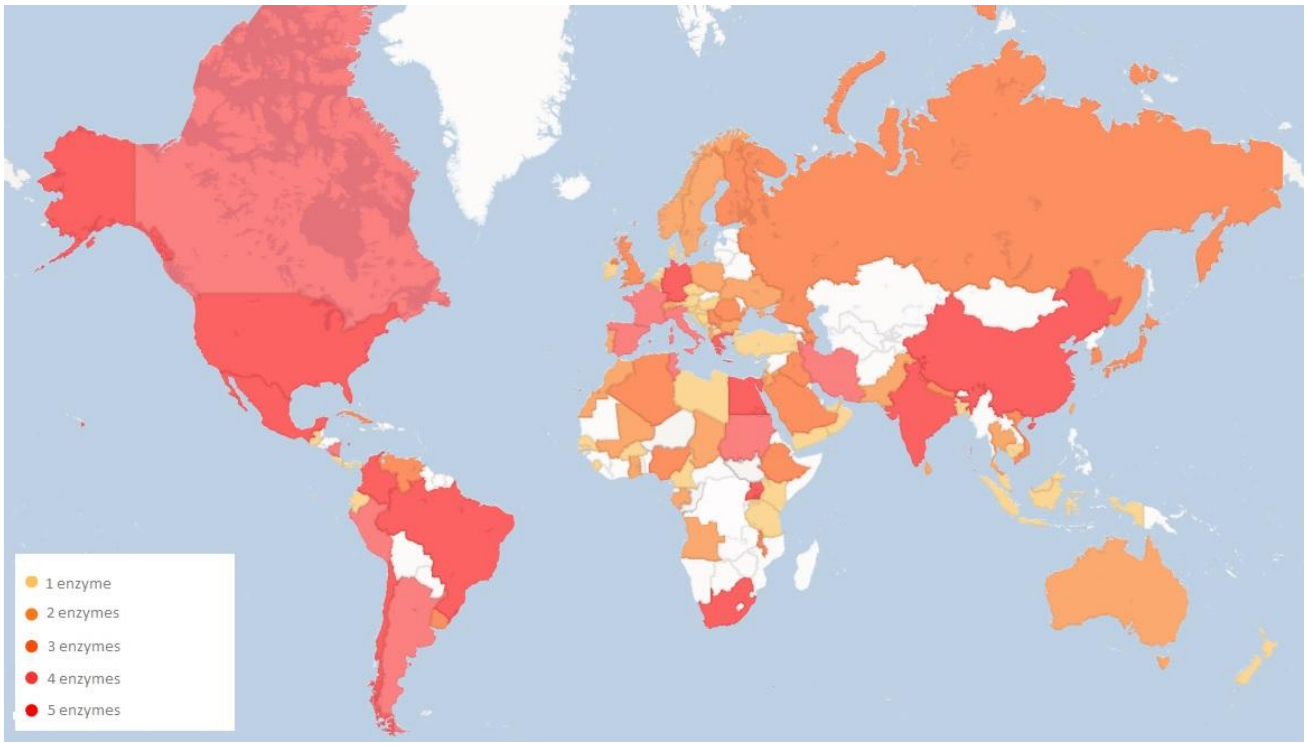

Figure 1. World map illustrating the global distribution of the five main carbapenemases (KPC, NDM, VIM, IMP, and OXA-48-like) in human clinical isolates. Countries are color-coded by the number of distinct carbapenemases reported: yellow for one, orange for two, dark orange for three, red for four, and maroon for all five. Source: Own elaboration based on selected articles.

5.1. Global distribution of kpc

The KPC carbapenemase (*Klebsiella pneumoniae* carbapenemase) was first identified in 1996 in North Carolina, USA, from a clinical *Klebsiella pneumoniae* isolate (Yigit et al., 2001). Since then, its spread has accelerated via horizontal gene transfer mediated by plasmids and other mobile elements, enabling the dissemination of *bla*KPC across diverse Enterobacterales species (Diene & Rolain, 2014). What began as a localized threat in the U.S. Northeast has evolved into a global crisis: recent analyses indicate that KPC is now the most frequently detected carbapenemase worldwide (Ma et al., 2023). This rapid expansion has posed significant clinical and public health challenges, undermining the effectiveness of last-line antibiotics and necessitating more stringent infection-control and surveillance strategies (**Figure 2A**).

Today, KPC exhibits an extremely broad geographic distribution. In the United States, particularly within the New York–New Jersey corridor, it is endemic (Bradford et al., 2004). In Latin America, Brazil and Colombia report over 80 % of carbapenem-resistant Enterobacteriaceae isolates harboring *bla*KPC (van

Duin & Doi, 2017). Europe also grapples with high incidence rates, with Italy and Greece serving as epicenters where KPC is the primary driver of carbapenem resistance (Boyd et al., 2022). In Asia, China has recorded moderate increases (Qin et al., 2024), whereas India shows much lower prevalence, dominated instead by NDM-type enzymes. Data from Africa and Oceania remain limited but suggest comparatively low KPC incidence, likely reflecting both reduced prevalence and gaps in molecular surveillance (Mushi et al., 2014; Stewart et al., 2018).

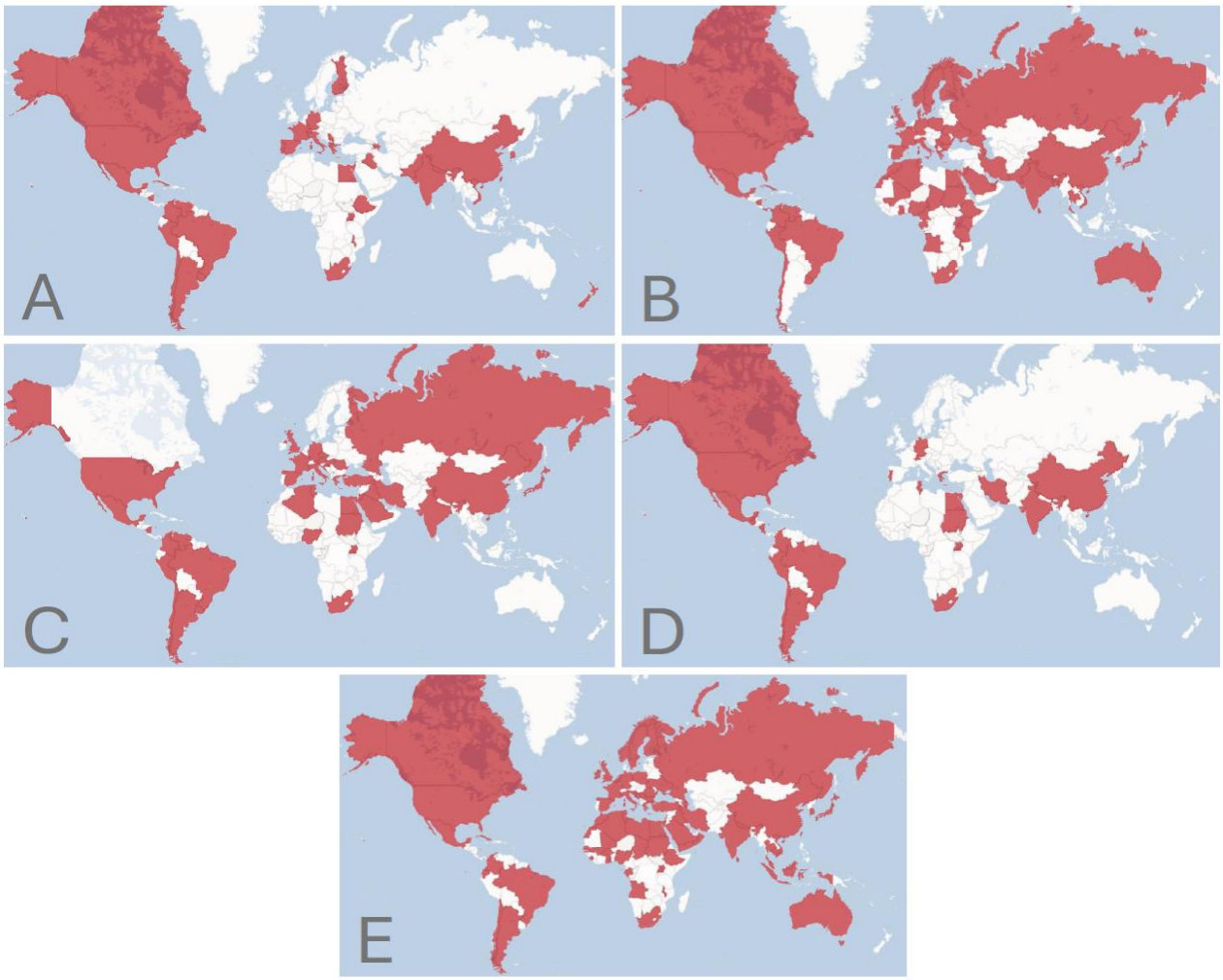

Figure 2. Global distribution maps of the five principal carbapenemases. (A) KPC, (B) NDM, (C) VIM, (D) IMP, and (E) OXA-48-like. In each subpanel, countries that have reported the detection of the respective carbapenemase are highlighted in red. Source: Own elaboration based on selected articles.

5.2. Global distribution of ndm

The metallo-β-lactamase NDM was first identified in 2008 in a Swedish patient treated in India, although retrospective studies confirmed the presence of the *bla*NDM-1 gene there as early as 2006 (Yong et al., 2009). Within a decade, this class B enzyme spread worldwide without reliance on high-risk clones or epidemic plasmids, highlighting its remarkable capacity to disseminate across diverse bacterial species. Unlike other carbapenemases, NDM circulates via multiple genetic variants and transfer vehicles, demonstrating notable promiscuity (Logan & Weinstein, 2017). To date, at least 24 variants have been described, with NDM-1 being the most prevalent (HammoudiHalat& Ayoub Moubareck,

2020), and its rapid expansion severely complicates the treatment of infections caused by multidrug-resistant pathogens (**Figure 2B**).

NDM prevalence peaks in the Indian subcontinent (India, Pakistan, and Bangladesh), where it outstrips other carbapenemases (Cantón & Bou, 2017). It has also become endemic in North Africa, the Balkans, and the Arabian Peninsula (Nordmann &Poirel, 2019), dominating in countries such as Egypt, South Africa, Nigeria, Tanzania, and Morocco (Kedišaletše et al., 2023). In Latin America, NDM has overtaken KPC in nations including Venezuela, Brazil, Mexico, and Chile (Wise et al., 2024), and in the Asia-Pacific region it is predominant in China, South Korea, and Thailand (Antequera et al., 2020; Bush & Bradford, 2020; Ma et al., 2023). Although reported less frequently, cases have also been documented in Canada and Russia (Ma et al., 2023). By contrast, NDM detection remains low or sporadic in the United States and much of Oceania, including Pacific island nations, underscoring the need to strengthen surveillance and diagnostic capacities in these areas (Cantón et al., 2017; Wailan et al., 2015).

5.3. Global distribution of vim

The Verona integron-encoded metallo-β-lactamases (VIM) were first detected in Europe: VIM-2 in *Pseudomonas aeruginosa* in France (1996) and VIM-1 in Italy (1997), both embedded within class 1 integrons (Lauretti et al., 1999). Initially confined to *Pseudomonas aeruginosa*, VIM enzymes began emerging in Enterobacterales such as *Klebsiella pneumoniae* by the late 1990s and early 2000s, particularly across Southern Europe and parts of Asia. Despite their global dissemination, VIM variants remain less common overall than carbapenemases like NDM or KPC. To date, at least 46 *bla*VIM alleles have been identified, with VIM-1 and VIM-2 the most prevalent worldwide (Logan & Weinstein, 2017). Their spread has been propelled by broad-host-range plasmids (Botelho et al., 2020), enabling interspecies transfer and fueling the expansion of carbapenem resistance, especially within hospital settings.

Today, VIM carbapenemases are highly endemic in Europe, most notably in Greece, Spain, Hungary, and Italy (Alvisi et al., 2025; Cantón & Bou, 2017). Greece serves as the primary epicenter, having experienced multiple nosocomial outbreaks of VIM-1–producing Enterobacterales (Logan & Weinstein, 2017). In Spain, VIM-1 ranks as the second most common carbapenemase after OXA-48, while VIM-2 predominates in *Pseudomonas aeruginosa*. VIM-4 has also been reported in Hungary and the Czech Republic (Matsumura et al., 2017). In contrast, VIM occurrence is low in North and Latin America, where NDM and KPC are far more prevalent (van Duin& Doi, 2017). Data from Africa and the Asia-Pacific region are limited, sporadic reports exist in countries like South Africa, Tunisia, and select Southeast Asian nations, but without widespread endemicity (Hansen, 2021). Oceania shows similarly sparse VIM detection, suggesting very limited circulation (Bell et al., 2019). These patterns underscore that, although VIM has achieved global reach, its epidemiological impact remains primarily concentrated in Europe (**Figure 2C**).

5.4. Global distribution of imp

The metallo-β-lactamase IMP, a zinc-dependent class B enzyme, was first identified in Japan in 1990–1991 in *Pseudomonas aeruginosa* carried on a conjugative plasmid, which facilitated its rapid spread (Alvisi et al., 2025). Soon thereafter, IMP emerged in *Serratia marcescens* and other Enterobacteriaceae during hospital outbreaks, marking it as the first plasmid-encoded carbapenemase discovered in this family. Since then, horizontal gene transfer via plasmids and class I integrons has driven the evolution of over 52 *bla*IMP variants (with 88 catalogued in databases), demonstrating sustained diversification (Logan & Weinstein, 2017). Although IMP can hydrolyze most β-lactams, its endemic presence in Japanese hospitals heralded its intercontinental dissemination, underscoring the ability of mobile genetic elements to jump across bacterial species.

Globally, IMP prevalence remains highest in Asia, with Japan accounting for roughly 25% of reports and China 17%, followed by Thailand and Singapore at 7% each. The most common hosts are *Pseudomonas aeruginosa*, followed by *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* (Pongchaikul & Mongkolsuk, 2022). Outside Asia, IMP-producing strains appear predominantly in isolated cases or sporadic outbreaks. In the United States, Canada, and much of Europe, IMP metallo-β-lactamases are far less frequent than NDM or VIM (van Duin& Doi, 2017). Data from Latin America and Africa are scarce and limited to a handful of reports, where other carbapenemases such as KPC, NDM, and OXA-48-like predominate (Kedišaletše et al., 2023;

Pongchaikul & Mongkolsuk, 2022) (**Figure 2D**).

5.5. Global distribution of OXA-like

The OXA-48–like oxacillinases were first identified in carbapenem-resistant *Klebsiella pneumoniae* isolates from Turkey in 2001 (Poirel et al., 2004). Initially confined to that country, they rapidly spread across Europe, the Mediterranean, and beyond. This dissemination is largely driven by a self-conjugative IncL/M plasmid carrying *bla*OXA-48, as well as related variants such as OXA-181, OXA-232, and OXA-244 (Pitout et al., 2019). Diagnostically, these enzymes pose challenges due to their moderate hydrolytic activity against carbapenems, often resulting in under-detection. By 2013, the number of European countries reporting endemic OXA-48-like producers had surged, and in Spain they became the most frequently encountered carbapenemase that same year (Cantón & Bou, 2017). Today, OXA-48-like enzymes rank as the second or third most common carbapenemases in Enterobacterales globally, with growing reports of chromosomal integration in *Escherichia coli* lineages, notably ST38 (Pitout et al., 2019).

Geographically, OXA-48-like prevalence is highest in Turkey, where these enzymes are endemic (Boyd et al., 2022), and in Western Europe, especially Spain, France, Italy, and the Balkans (Hansen, 2021). They are also widespread in the Middle East and North Africa (Kedišaletše et al., 2023) and have established footholds in the Indian subcontinent, predominantly as OXA-181 and OXA-232 variants (Boyd et al., 2022). In the Asia-Pacific region, these variants have triggered outbreaks in South Korea, China, and India (Pitout et al., 2019). Although OXA-232 has been reported in Latin America, KPC remains the dominant carbapenemase there (Boyd et al., 2022). In contrast, reports from the United States and Canada are sporadic and low in number (Bush & Bradford, 2020). Data from sub-Saharan Africa and Oceania remain scarce, likely reflecting limited molecular surveillance, and suggest that the true global burden of OXA-48-like producers may still be underestimated (**Figure 2E**).

6. MORBIDITY AND MORTALITY ASSOCIATED WITH CARBAPENEMASES

Infections caused by carbapenemase-producing bacteria are linked to markedly higher morbidity and mortality, driven by both the increased frequency and severity of hospital-acquired infections (Bonomo, 2017; Bush & Bradford, 2020).

6.1. Morbidity

Carbapenemase producers are implicated in complex clinical syndromes such as ventilator-associated pneumonia, bloodstream infections, urinary tract infections, and surgical-site infections (Bush & Bradford, 2020; Cantón & Bou, 2017; Nordmann & Poirel, 2019). These infections predominantly occur under high antibiotic pressure, intensive treatments, invasive procedures, and prior colonization or use of devices like catheters and urinary catheters all facilitate their emergence. Unlike susceptible strains, resistant pathogens prolong symptoms, complicate clinical resolution, and introduce additional complications that impair patient function even when not immediately fatal (Cantón & Bou, 2017; Martin et al., 2018). Consequently, carbapenemase infections pose a significant clinical challenge, with lasting impacts on individual health.

The burden of these infections on morbidity is further intensified by the occurrence of co-infections and related clinical complications. Strains harboring multiple carbapenemases, for example, NDM plus OXA-48-like, often exhibit co-resistance to several antibiotic classes, severely narrowing effective treatment options (Boyd et al., 2022; Bush & Bradford, 2020; Cantón & Bou, 2017). As a result, clinicians are forced to rely on last-line agents or complex combination regimens that carry substantial toxicity risks, such as colistin or aminoglycosides, leading to increased rates of nephrotoxicity and other adverse events (Bonomo, 2017; Cantón & Bou, 2017; Martin et al., 2018; Wise et al., 2024). Initiating suboptimal therapy, whether due to inappropriate empirical choices or undetected resistance, can prolong infection, facilitate spread to additional organs, and amplify the clinical burden of each episode (Alvisi et al., 2025; Cantón& Bou, 2017; Martin et al., 2018; Rocha et al., 2015). The need for frequent adjustments in antimicrobial regimens, combined with intensive microbiological monitoring, underscores the significant clinical challenge these infections pose, even in patients not initially at highest risk.

Critically ill, immunocompromised, elderly patients, as well as those with major trauma, undergoing surgery, or requiring prolonged use of invasive devices, are at heightened risk for infections by

carbapenemase-producing pathogens (Bush & Bradford, 2020; Martin et al., 2018; Nordmann & Poirel, 2019). These infections severely hinder the recovery of vulnerable individuals, complicating rehabilitation and often extending the need for specialized medical support (Bush & Bradford, 2020; Kedišaletše et al., 2023; Martin et al., 2018). Consequently, their impact on morbidity extends beyond the acute infectious episode, interfering with the patient's overall clinical trajectory and long-term outcomes.

Moreover, the increased morbidity associated with carbapenemase producers directly strains hospital resources. Such infections lengthen hospital stays, escalate intensive care requirements, and drive up the use of costly, often more toxic antibiotic regimens that demand close monitoring for adverse effects and frequent microbiological testing. This translates into significantly higher healthcare expenditures, from expensive drugs to prolonged bed occupancy in critical units. Additionally, the inability to discharge patients colonized or infected with multidrug-resistant strains reduces bed availability, delays elective procedures, and heightens the risk of in-hospital outbreaks. In sum, the morbidity burden imposed by these infections extends beyond individual patient care, undermining the efficiency and sustainability of healthcare systems.

6.2. Mortality

Infections caused by CRE carry a significantly higher risk of death compared to those caused by carbapenem-susceptible strains. A meta-analysis found that CRE infections are associated with a 3.39-fold increase in the odds of mortality (95% CI: 2.35–4.89) (Martin et al., 2018). This elevated risk is partly due to the use of antibiotics that lack efficacy against these pathogens. For instance, bloodstream infections by KPC-producing Klebsiella pneumoniae have reported mortality rates as high as 54.3% (Bonomo et al., 2018), while carbapenem-resistant Acinetobacter baumannii can raise mortality from 8% to 40% in healthcare settings (Bush & Bradford, 2020). Globally, Klebsiella pneumoniae and Acinetobacter baumannii ranked among the leading causes of AMR-associated deaths in 2019, underscoring that carbapenem resistance represents one of the deadliest pathogen-drug combinations in modern clinical practice (Vásquez-Ponce et al., 2025; Bush & Bradford, 2020).

A key driver of increased mortality is the frequent co-resistance exhibited by these bacteria. Carbapenemase producers often carry resistance determinants against multiple antibiotic classes, severely constraining therapeutic options and complicating clinical management. Strains harboring more than one carbapenemase, such as NDM+OXA or KPC+VIM in *Klebsiella pneumoniae*, have demonstrated mortality rates as high as 56.7% (Bonomo et al., 2018; Bush & Bradford, 2020). Resistance to lastresort agents like colistin or fosfomycin, frequently mediated by plasmid-borne genes, further exacerbates the problem. These complex resistance profiles not only hinder the efficacy of available treatments but also elevate the risk of therapeutic failure, particularly in settings where new antibiotics are scarce or pathogen identification is delayed.

Patients with underlying clinical conditions, such as immunosuppression, chronic diseases, advanced age, or those requiring invasive medical procedures, are especially vulnerable to the often-fatal consequences of carbapenemase-producing infections (Bush & Bradford, 2020; Kedišaletše et al., 2023; Logan et al., 2017; Ji et al., 2024). While it remains unproven that these infections directly exacerbate chronic illnesses like diabetes, evidence shows that individuals with such comorbidities or generally poor health are at heightened risk of developing severe, life-threatening infections. The host's diminished capacity to contain aggressive pathogens combines with the therapeutic challenges posed by AMR, creating a clinical scenario of extreme vulnerability (Alvisi et al., 2025; Bush & Bradford, 2020; Kedišaletše et al., 2023). Thus, beyond their direct pathogenic impact, carbapenemase-producing infections act as a destabilizing force in already compromised patients, significantly increasing the likelihood of fatal outcomes.

In summary, carbapenemase-mediated resistance not only narrows therapeutic options but also directly increases mortality, especially when multiple drug resistances or co-produced enzymes are involved. This impact is particularly severe in complex clinical settings and among patients with underlying conditions that heighten their vulnerability to complications. Medical response capabilities are constrained by both the rapid progression of these infections and the ineffectiveness of standard treatments, resulting in a higher attributable death rate (Alvisi et al., 2025; Cantón & Bou, 2017). Consequently, rigorous infection-control measures

and preventive strategies are essential not only to contain hospital outbreaks but also to reduce AMR-associated mortality.

7. FUTURE PERSPECTIVES

7.1. Health challenge

The sustained rise of carbapenemase-producing bacteria poses a critical threat to global health. The WHO has designated CRE as critical priority pathogens (Assembly, 2015; Munkholm& Rubin, 2020), highlighting *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* as particularly concerning due to their multidrug resistance (Hansen, 2021). In clinical settings, these infections lead to prolonged hospital stays and persistent nosocomial outbreaks that challenge infection-control measures (Yuan et al., 2024). Critically ill patients face mortality rates exceeding 50%, and in 2019, over 55,000 deaths were attributed solely to carbapenem-resistant *Klebsiella. pneumoniae* (Temkin et al., 2018). Beyond the human toll, the economic burden of containing and treating these outbreaks places immense strain on healthcare systems.

Looking ahead, it is imperative to enhance real-time epidemiological surveillance and diagnostic capacity for rapid detection and tracking of carbapenemase producers. Deploying dynamic global distribution maps alongside robust antimicrobial stewardship programs will guide the optimization of treatment protocols and resource allocation. Investment in research for novel antibiotics and alternative therapies, such as carbapenemase inhibitors and bacteriophage-based treatments, must be prioritized. Cross-cutting infection-control strategies, including stringent hospital sanitation, staff education, and the prudent use of antimicrobials in both human and veterinary medicine, are essential to curb the spread of these enzymes and safeguard the efficacy of last-line therapies (Assembly, 2015; WHO, 2019).

7.2. Addressing the challenge

AMR stands as one of the most urgent and complex challenges humanity will face in the coming decades. Far from a distant concern, it has become a full-blown health crisis jeopardizing the future of modern medicine and global well-being. The WHO lists AMR among the top ten immediate health threats, underscoring its current, and critical, status (Wise et al., 2024). The rapid spread of multidrug- and pandrug-resistant “superbugs” undermines therapies once regarded as gold standards, driving up both morbidity and mortality in infections that were previously manageable.

The recent emergence of strains co-expressing multiple resistance mechanisms, including carbapenemases, reveals an epidemiological landscape of escalating complexity, where outbreaks will be harder to contain and therapeutic options increasingly scarce (Bonomo, 2017; Bush & Bradford, 2020; Cantón& Bou, 2017). Preparing for tomorrow demands action today: strengthening microbiological surveillance, expanding early diagnostic capabilities, and forging international cooperation networks for effective outbreak control. AMR respects no borders; its containment requires coordinated, multidisciplinary responses that span sectors and nations.

The therapeutic outlook is further darkened by the stagnation in new antibiotic development. By 2019, barely thirty candidate molecules were in clinical trials targeting WHO priority pathogens, and only six of these offered truly innovative profiles (WHO, 2019). This reality highlights not only a scientific void but also a systemic failure in R&D incentives. Moving forward, it is urgent to establish sustainable financing models that drive therapeutic innovation while ensuring equitable, global access to high-quality antimicrobials. Absent such advances, the gap between bacterial evolution and medical response will only widen.

Meanwhile, irrational antimicrobial use, driven by inappropriate clinical practices, self-medication, and extensive application in agriculture and livestock, will remain the primary engine of resistance unless effective measures are enacted (Alvisi et al., 2025; Rocha et al., 2015). Over the coming decades, embracing a “One Health” approach offers the most promising strategy for confronting AMR comprehensively. This means simultaneous action across healthcare systems, environmental management, and social practices, guaranteeing hygiene, safe water, and infection control in both hospital and community settings (Alvisi et al., 2025; Rocha et al., 2015).

From an economic and social standpoint, AMR threatens to undo decades of progress in public health. Healthcare systems may soon face mounting pressure from rising rates of treatment failure,

extended hospital stays, and increased mortality and disability, burdens that fall hardest on vulnerable populations (Alvisi et al., 2025; Bush & Bradford, 2020; Rocha et al., 2015). The shift toward more expensive, last-resort therapies, coupled with lost productivity at both individual and societal levels, promises long-lasting financial repercussions (Rocha et al., 2015). Without decisive intervention, routine medical procedures, ranging from elective surgeries to cancer therapies, risk becoming impractical or even impossible to perform safely.

Securing a future in which infections remain treatable demands a profound transformation in how we discover, deploy, and steward antimicrobials. We must foster a paradigm shift toward rational antibiotic use, incentivize groundbreaking research, and bolster international health governance. Confronting AMR with forward-looking strategies is not only a scientific and public health imperative but also an ethical commitment to safeguard the wellbeing of generations to come.

8. CONCLUSIONS

In conclusion, the rapid global expansion of the five key carbapenemases, NDM, KPC, VIM, IMP, and OXA-48-like, has turned what was once a regional concern into a widespread international health crisis. Horizontal gene transfer via plasmids, integrons, and conjugative elements has enabled these resistance determinants to spread across diverse species such as Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, severely complicating both empirical therapy and infection-control efforts in hospitals. Without a clear understanding of each enzyme's geographic footprint, antibiotic stewardship policies and outbreak-response strategies lack the precision needed to be truly effective.

That is why generating detailed, enzyme-specific global distribution maps, and then integrating them into a composite overview, is relevant. These geospatial tools not only pinpoint high-burden areas but also guide the allocation of surveillance resources, the reinforcement of diagnostic laboratories, and the tailoring of treatment guidelines to local resistance profiles. In an era where the antibiotic development pipeline has declined, leveraging real-time distribution data is essential for anticipating emerging threats, driving targeted prevention campaigns, and ensuring that control measures evolve as dynamically as the pathogens they aim to contain.

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