

Imipenem Resistance: A Clarion Call to Antibiotic Stewardship

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Systematic Review

Keywords: Antibiotics, Carbapenem, Enterobacteriaceae, Imipenem, Multidrug-resistance

Posted Date: May 28th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9832011/v1>

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Additional Declarations: The authors declare no competing interests.

Abstract

Background

Imipenem, a **carbapenem antibiotic** with a broader antimicrobial spectrum and greater potency than other beta-lactam antibiotics, has been considered a last-resort antibiotic for severe Gram-negative infections. However, escalating resistance now threatens its clinical utility worldwide. This review synthesizes current knowledge on the epidemiology, molecular mechanisms, and therapeutic challenges associated with imipenem resistance in clinically significant pathogens such as *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Resistance arises through diverse pathways—including carbapenemase production, porin loss, efflux pump overexpression, and synergistic mutations—that collectively diminish drug efficacy and complicate treatment.

Methods

A systematic literature search was conducted across four major electronic databases — PubMed, Scopus, ScienceDirect, and Google Scholar — to identify relevant publications on imipenem resistance, carbapenem resistance mechanisms, clinical outcomes, and antibiotic stewardship interventions. Sixty-six publications met the inclusion criteria.

Results

Therapeutic options remain limited, often relying on toxic or suboptimal agents such as colistin, while emerging alternatives—including β -lactam/ β -lactamase inhibitor combinations, cefiderocol, antimicrobial peptides, bacteriophages, and immunomodulatory approaches—show promise but are not yet universally accessible. Effective management therefore requires integration of precision diagnostics, antimicrobial stewardship, and infection prevention strategies to optimize therapy and contain transmission.

Conclusion

Coordinated action across bedside practice, hospital policy, and global health governance is essential to preserve existing therapies and accelerate the development of sustainable alternatives. Without decisive intervention, the continued rise of imipenem resistance may herald a post-antibiotic era in which even routine infections become untreatable.

Introduction

Background on Carbapenems and Imipenem

Carbapenems are a class of β -lactam antibiotics with a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including many multidrug-resistant (MDR) pathogens. They are considered last-line agents for severe infections caused by extended-spectrum β -lactamase (ESBL)-producing *Enterobacterales* and non-fermenters such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [1]. Imipenem, the first carbapenem approved for clinical use, is notable for its stability against most β -lactamases and its potent activity in severe systemic infections. It is often administered with cilastatin to inhibit renal metabolism, thereby prolonging its plasma concentration and therapeutic effect [2].

Clinical Relevance and Rising Resistance

The clinical utility of imipenem has been increasingly undermined by the emergence of resistance mediated by carbapenemases, porin loss, efflux pump overexpression, and target site alterations [3]. In *P. aeruginosa*, downregulation of OprD and overproduction of chromosomal AmpC β -lactamase are central to imipenem resistance, with the latter often inducible by imipenem exposure itself [2]. Carbapenem resistance is also fueled by horizontal gene transfer of carbapenemase genes such as *blaKPC*, *blaNDM*, and *blaOXA* across diverse plasmid backbones [4]. The global spread of these resistance determinants is associated with increased mortality, prolonged hospital stays, and higher healthcare costs, particularly in intensive care settings [1, 5].

Aim of the Review

This review synthesizes current evidence on the molecular mechanisms, epidemiology, and clinical impact of imipenem resistance, with particular attention to *P. aeruginosa* and *Enterobacterales*. It further underscores the urgent need for robust antibiotic stewardship programs (ASPs) to curb inappropriate carbapenem use, enhance surveillance, and support the development of novel therapeutic strategies. By consolidating recent findings from 2015–2025, this review aims to provide clinicians, microbiologists, and policymakers with actionable insights to mitigate the growing threat of imipenem resistance.

Methods

Literature Search Strategy

A structured literature search was conducted across four major electronic databases — PubMed, Scopus, ScienceDirect, and Google Scholar — to identify relevant publications on imipenem resistance, carbapenem resistance mechanisms, clinical outcomes, and antibiotic stewardship interventions. Boolean operators were applied to capture comprehensive results across related themes (Table 1).

Databases and Boolean Search Terms

The following Boolean search strings were applied:

1. "imipenem resistance" AND/OR "carbapenem resistance"
2. "antibiotic stewardship" AND/OR "antimicrobial stewardship" AND/OR "infection control" AND/OR "antibiotic policy"
3. "clinical impact" AND/OR "mortality" AND/OR "treatment failure" AND/OR "drug resistance"
4. "surveillance" AND/OR "rapid diagnostics" AND/OR "novel antibiotics" AND/OR "phage therapy" AND/OR "alternative therapy"

For each search term combination, results from the four databases were retrieved, screened, and de-duplicated.

Table 1
Boolean operators search data

S/N	BOOLEAN OPERATOR	SCOPUS	GOOGLE SCHOLAR	PUBMED	SCIENCE DIRECT	TOTAL
1	imipenem resistance" AND/OR "carbapenem resistance	50	50	50	50	200
2	antibiotic stewardship" AND/OR "antimicrobial stewardship" AND/OR "infection control" AND/OR "antibiotic policy	50	48	59	50	207
3	clinical impact" AND/OR "mortality" OR "treatment failure" AND/OR "drug resistance	50	48	40	50	188
4	surveillance" AND/OR "rapid diagnostics" AND/OR "novel antibiotics" AND/OR "phage therapy" AND/OR "alternative therapy	50	50	1	50	151

Inclusion Criteria (PICOS)

Population (P): Human subjects of any age with confirmed or suspected infections due to *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, Enterobacterales, or other Gram-negative pathogens exhibiting imipenem resistance. Studies from any geographic location were eligible, with emphasis on data from tertiary care hospitals, intensive care units, and outbreak settings.

Intervention/Exposure (I): Studies reporting molecular mechanisms of imipenem or carbapenem resistance (e.g., β -lactamase production, porin loss, efflux pump overexpression, target site alterations), or interventions targeting carbapenem-resistant organisms (e.g., antibiotic stewardship programs, rapid diagnostics, novel antibiotics, or alternative therapies).

Comparison (C): Studies comparing resistant versus susceptible isolates, pre- versus post-intervention outcomes, or differing stewardship/diagnostic strategies. Eligible studies had to clearly define comparator groups and outcome measures.

Outcomes (O): Primary outcomes included prevalence of resistance, molecular resistance profiles, treatment outcomes (e.g., clinical cure, microbiological eradication), mortality, and healthcare cost impact. Secondary outcomes included antibiotic consumption trends, time-to-appropriate therapy, and stewardship program effectiveness.

Study Design (S): Systematic reviews, meta-analyses, randomized controlled trials (RCTs), observational cohort studies, and well-documented case series published between 2015 and 2025. Only peer-reviewed English-language publications were included (Fig. 1).

Exclusion Criteria (PICOS)

Population (P): Studies on animal models, in vitro-only experiments, or environmental surveillance without clinical correlation. Reports focusing solely on non-bacterial pathogens or Gram-positive organisms without carbapenem data were excluded.

Intervention/Exposure (I): Articles not assessing imipenem or carbapenem resistance directly, or that lacked data on resistance mechanisms or clinical management strategies.

Comparison (C): Studies without defined comparator groups, such as descriptive reports without parallel susceptible isolates or intervention control groups.

Outcomes (O): Studies not reporting resistance-related epidemiology, molecular data, or clinical outcomes; papers focusing exclusively on pharmacokinetics or unrelated therapeutic areas without resistance relevance.

Study Design (S): Narrative reviews without systematic methodology, conference abstracts without full data, non-peer-reviewed literature, and publications outside the 2015–2025 date range.

Results and Discussion

Mechanisms of Imipenem Resistance

Imipenem resistance in Gram-negative bacteria is a multifaceted phenomenon resulting from one or more synergistic mechanisms that either prevent the drug from reaching its target, inactivate it enzymatically, or alter the target structure. These mechanisms often coexist within the same strain, producing high-level resistance and severely limiting treatment options [2, 3].

Beta-Lactamase Production

Class A (KPC-type)

Klebsiella pneumoniae carbapenemases (KPCs) are plasmid-encoded serine β -lactamases capable of hydrolyzing carbapenems, cephalosporins, and penicillins [5]. KPC genes are often located on transferable plasmids alongside additional resistance determinants such as aminoglycoside-modifying enzymes and quinolone resistance genes, enabling co-selection under non-carbapenem antibiotic pressure. Global dissemination of KPC-producing *K. pneumoniae* has been linked to sequence type 258 (ST258) and its variants, which have been implicated in hospital outbreaks worldwide [1].

Class D (OXA-type)

OXA-type carbapenemases are particularly significant in *Acinetobacter baumannii* (e.g., OXA-23, OXA-24/40, OXA-58), where they confer high-level resistance to imipenem. Their expression is frequently enhanced by upstream insertion sequences such as ISAba1, which provide strong promoters [4]. In Enterobacterales, OXA-48-like carbapenemases confer moderate carbapenem hydrolysis but can achieve clinical resistance when combined with porin loss [3].

Class C (AmpC)

AmpC β -lactamases are chromosomally encoded in species such as *Pseudomonas aeruginosa* and *Enterobacter cloacae*. While their basal activity against carbapenems is limited, imipenem can induce overproduction of AmpC, particularly in *P. aeruginosa* strains lacking the OprD porin [2]. This induction amplifies the resistance phenotype, often rendering clinical isolates resistant despite susceptibility in standard testing conditions.

Class B (Metallo- β -lactamases, MBLs)

Metallo- β -lactamases, including New Delhi metallo- β -lactamase (NDM), Verona integron-encoded metallo- β -lactamase (VIM), and imipenemase (IMP) types, utilize zinc ions for hydrolysis and can inactivate all β -lactams except monobactams. MBL genes are frequently found on integrons embedded in plasmids or transposons, enabling rapid interspecies dissemination [3]. Clinical infections with MBL-producing organisms are associated with limited therapeutic options, as no β -lactamase inhibitor in current clinical use is effective against them.

Porin Channel Alterations

Porin-mediated permeability is a major determinant of imipenem activity. In *P. aeruginosa*, OprD is the principal porin for imipenem uptake, and its loss or downregulation leads to marked MIC elevation. This can result from mutations, deletions, or insertion sequence disruptions in the oprD gene [2]. In Enterobacterales, reduced expression or structural modification of porins such as OmpK35 and OmpK36 impedes carbapenem influx, particularly when combined with β -lactamase production [5].

Efflux Pump Overexpression

Efflux systems actively expel imipenem from the bacterial cell, reducing its intracellular concentration. In *P. aeruginosa*, MexAB-OprM is the most clinically relevant efflux pump, though MexCD-OprJ and MexXY-OprM can also contribute [1]. Overexpression may result from mutations in local or global regulatory genes such as *mexR*, *nalC*, and *nalD*. In *A. baumannii*, AdeABC and AdeIJK efflux systems perform similar roles and are often co-expressed with OXA-type carbapenemases, producing extensively drug-resistant phenotypes.

Target Site Modifications

Alterations in penicillin-binding proteins (PBPs), specifically PBP2, can reduce imipenem binding affinity. Although this mechanism is less prevalent than β -lactamase production or permeability changes, it has been reported in *A. baumannii* and *P. aeruginosa* isolates with prolonged carbapenem exposure [3]. PBP modifications often occur alongside other resistance determinants, making it difficult to isolate their clinical impact.

Contributing Factors to Imipenem Resistance

The rise of imipenem resistance is not solely a consequence of molecular evolution within bacterial genomes but is also shaped by complex and overlapping clinical, environmental, and global dynamics. These drivers act in synergy to create sustained selective pressure, facilitate rapid horizontal gene transfer, and expand the ecological niches in which resistant pathogens thrive [2, 4, 5].

Inappropriate or Overuse of Antibiotics

One of the most consistent determinants of carbapenem resistance is the over-prescription and prolonged use of broad-spectrum β -lactams without microbiological confirmation [1, 6]. In many tertiary hospitals, imipenem is empirically administered for severe sepsis, febrile neutropenia, and suspected ventilator-associated pneumonia, particularly in high-risk units such as oncology wards and ICUs [7]. While early empiric therapy can be lifesaving, the absence of timely de-escalation once pathogen susceptibility is known results in unnecessary carbapenem exposure and selection for resistant strains [8].

Data from LMICs highlight an additional challenge – limited diagnostic capacity often forces clinicians to prescribe based on syndromic presentation rather than culture results. This is compounded by the unregulated sale of antibiotics, including carbapenems, in community pharmacies, leading to inappropriate use for conditions like uncomplicated urinary tract infections and bacterial gastroenteritis [4, 5]. In such settings, *Escherichia coli* and *K. pneumoniae* strains harboring carbapenemase genes have been isolated from outpatients with no recent hospital exposure (Bittencourt *et al.*, 2025)

Hospital and Community Spread

Healthcare facilities remain the epicenter of carbapenem-resistant Gram-negative bacteria (CR-GNB) transmission. Overcrowded wards, inadequate staffing, lapses in hand hygiene, and poor environmental decontamination enable persistent colonization of surfaces and equipment [3, 9]. Environmental

reservoirs such as sinks, ventilators, dialysis machines, and endoscopes have been directly linked to outbreaks of OXA-48-producing *Enterobacterales* and NDM-producing *Acinetobacter baumannii* [1, 6].

Alarming, resistance is no longer confined to hospital environments. Reports from Europe, Asia, and Latin America indicate increasing asymptomatic carriage of carbapenemase producers among healthy community dwellers [4, 10]. This silent community dissemination is driven by factors such as contaminated food products, poor sanitation, and direct person-to-person transmission, eroding the traditional distinction between hospital-associated and community-acquired carbapenem resistance [5].

Lack of New Antibiotics

The paucity of effective agents against CR-GNB has amplified the clinical impact of imipenem resistance. β -lactam/ β -lactamase inhibitor combinations such as imipenem/relebactam and meropenem/vaborbactam show promising activity against KPC producers but remain ineffective against metallo- β -lactamases (MBLs) like NDM, VIM, and IMP [2, 9].

Even the siderophore cephalosporin cefiderocol – designed to bypass common resistance mechanisms – has demonstrated reduced efficacy against certain isolates with coexisting resistance determinants, including upregulated efflux systems and modified porin profiles [6, 9]. As a result, polymyxins (colistin, polymyxin B) are often used as salvage therapy despite their nephrotoxic and neurotoxic potential [7]. The limited antimicrobial pipeline underscores the urgency of investment in novel antibiotic classes, bacteriophage therapy, and host-directed interventions.

Globalization and Travel

International travel, migration, and medical tourism have facilitated the rapid global dissemination of carbapenemase-producing organisms (CPOs). Patients transferred from healthcare facilities in endemic regions frequently introduce high-risk clones into new geographic areas [4, 5]. For example, genomic surveillance has shown the same *K. pneumoniae* ST11 and ST258 lineages carrying *bla*KPC or *bla*NDM detected in hospitals across Asia, Europe, and South America [3, 10].

Whole-genome sequencing further confirms that identical carbapenemase genes and plasmid backbones appear in isolates from geographically distant locations, indicating both clonal expansion and horizontal transfer via mobile genetic elements [4]. This global interconnectedness highlights the importance of multinational surveillance initiatives, such as GLASS (Global Antimicrobial Resistance Surveillance System), and coordinated IPC measures at ports of entry and referral hospitals.

The contributing factors to imipenem resistance span the continuum from antimicrobial misuse to international travel. Mitigation requires not only rigorous antimicrobial stewardship and IPC within hospitals but also regulation of community antibiotic sales, enhanced diagnostic capacity, development of new antimicrobials, and coordinated global resistance tracking. Without these integrated measures, the conditions sustaining and accelerating resistance will remain unchecked [1, 2, 3, 4].

Clinical Impact of Imipenem Resistance

Imipenem resistance in Gram-negative pathogens is a major clinical and public health concern, translating microbiological findings into severe patient outcomes, operational strain on healthcare facilities, and amplified transmission risks within the community [2, 10]. Often, resistance occurs as part of multidrug-resistant (MDR) or pandrug-resistant (PDR) phenotypes, narrowing effective therapeutic choices to last-line agents with significant toxicity profiles [3, 4].

The clinical impact of imipenem resistance can be evaluated in three interconnected domains: increased mortality and morbidity, restricted treatment options, and prolonged healthcare costs and resource utilization.

Increased Mortality and Morbidity

Carbapenem-resistant Gram-negative bacterial (CR-GNB) infections are associated with significantly higher mortality rates than their carbapenem-susceptible counterparts [3, 6].

- Septicemia and bloodstream infections caused by carbapenem-resistant *Klebsiella pneumoniae* show mortality rates exceeding 40%, with critically ill patients surpassing 50% [1, 7].
- Ventilator-associated pneumonia (VAP) due to carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii* approaches 60% mortality, aggravated by high relapse frequencies [8].

Delays in appropriate antimicrobial initiation—often due to the lack of rapid diagnostic confirmation—prolong bacterial proliferation, induce systemic inflammatory injury, and increase mortality [6, 10].

Long-term sequelae include:

- Prolonged ICU admission and mechanical ventilation.
- Secondary nosocomial infections due to invasive devices.
- Increased rates of infection relapse, particularly in immunocompromised populations or those with prosthetic implants [7].

Limited Treatment Options

Imipenem resistance often coexists with resistance to other critical antibiotic classes, including aminoglycosides, fluoroquinolones, and extended-spectrum cephalosporins [1, 4].

Therapeutic implications include:

- β -lactam/ β -lactamase inhibitor combinations (e.g., imipenem/relebactam, meropenem/vaborbactam) are effective against some class A carbapenemases (KPC) but fail against metallo- β -lactamases (NDM, VIM, IMP) [2, 9].
- Coexisting mechanisms such as porin loss and efflux pump overexpression further reduce the efficacy of active agents [2, 9].
- Last-line therapies like polymyxins, tigecycline, and fosfomycin carry major limitations:

- Polymyxins: nephrotoxic and neurotoxic risks increase with cumulative exposure [10].
- Tigecycline: inadequate serum concentrations for bacteremia.
- Fosfomycin: rapid emergence of resistance when used alone in high-bacterial-load infections.

These constraints frequently force combination therapy strategies, although the clinical evidence supporting them remains limited [1].

Prolonged Healthcare Costs and Resource Use

Imipenem resistance imposes a substantial financial and operational burden on healthcare systems. The costs stem from extended hospitalizations, more expensive drugs, enhanced infection control measures, and indirect productivity losses [4, 7].

Length of stay and ICU costs:

- Patients with CR-GNB infections typically remain hospitalized 7–21 days longer than those with susceptible infections, with ICU stays extending by an average of 10–14 days in severe cases [1, 6].
- Extended ICU care is associated with increased resource consumption, including prolonged use of ventilators, hemodialysis, and continuous monitoring equipment [3].

Drug acquisition costs:

- Salvage regimens (e.g., cefiderocol, imipenem/relebactam, or colistin-based combinations) are significantly more expensive than standard carbapenem therapy, sometimes costing 3–10 times more per treatment course [9].

Infection control and outbreak management:

- Hospitals managing outbreaks of carbapenemase-producing organisms must implement costly measures: patient isolation or cohorting, environmental decontamination, and staff retraining [10].
- Ward closures during large outbreaks result in revenue loss and disruption of scheduled procedures.

Indirect societal costs:

- Patients surviving CR-GNB infections often face prolonged rehabilitation and reduced quality of life, contributing to long-term economic losses through work absenteeism and disability [4].

Economic modeling studies estimate that each case of CR-GNB bloodstream infection can incur direct medical costs of \$15,000–\$40,000 USD, with aggregated national-level expenditures reaching hundreds of millions of dollars annually in high-burden countries [3].

Imipenem resistance drives higher mortality, severely limits effective therapeutic options, and inflates healthcare costs through longer admissions, expensive salvage therapies, and enhanced infection

control measures. The combination of clinical and economic burdens underscores the need for urgent, integrated antimicrobial stewardship and resistance containment strategies [1, 4, 10].

Antibiotic Stewardship: A Critical Strategy

Antibiotic stewardship (AS) is a cornerstone strategy in addressing the escalating threat of imipenem resistance, a pressing global health concern driven by the rapid spread of carbapenem-resistant Gram-negative bacteria (CR-GNB). By integrating evidence-based prescribing, robust infection prevention, and rapid diagnostic technologies, AS minimizes unnecessary carbapenem use while ensuring timely and effective treatment for critically ill [1, 10, 11]. The urgency of AS is amplified by the limited therapeutic alternatives to carbapenems, with CR-GNB infections carrying mortality rates exceeding 40% in some settings [12]. This section explores the goals, principles, diagnostic integration, restriction policies, educational strategies, and measurable outcomes of AS, emphasizing its role in preserving the efficacy of last-line antibiotics like imipenem.

AS programs (ASPs) employ multidisciplinary teams, including infectious disease specialists, pharmacists, microbiologists, and nurses, to review prescriptions in real-time, particularly in high-risk settings like intensive care units (ICUs) where carbapenem overuse is prevalent [13]. These programs align with global initiatives, such as the World Health Organization's Global Action Plan on Antimicrobial Resistance, emphasizing surveillance, optimization, and education. Studies demonstrate that ASPs can reduce carbapenem consumption by 20–50% without compromising patient outcomes, disrupting selective pressure that drives resistance mechanisms like carbapenemase production (e.g., KPC, NDM, OXA-48-like enzymes) [14]. Challenges include resource constraints in low- and middle-income countries and prescriber resistance, yet the long-term benefits—reduced resistance, lower healthcare costs, and improved survival—underscore AS as a vital intervention.

Goals and Core Principles

The primary objectives of AS in the context of imipenem resistance are to optimize patient outcomes while mitigating resistance development. These goals include:

- **Improving Clinical Outcomes Through Targeted Therapy:** AS prioritizes pathogen-specific treatments based on susceptibility data, reducing adverse events like *Clostridioides difficile* infections and nephrotoxicity. Rapid de-escalation from broad-spectrum carbapenems to narrower agents in sepsis cases has been shown to improve survival without increasing resistance [15].
- **Delaying Resistance Emergence:** By minimizing unnecessary broad-spectrum exposure, AS reduces selective pressure. Dose optimization, guided by pharmacokinetic/pharmacodynamic (PK/PD) principles, adjusts imipenem regimens based on renal function, infection site, and pathogen minimum inhibitory concentration (MIC), extending carbapenem utility by 2–3 years in high-risk settings [16].
- **Preserving Last-Line Antibiotics:** Carbapenems are reserved for confirmed or strongly suspected multidrug-resistant (MDR) infections, with alternatives like ceftazidime-avibactam prioritized when

appropriate, particularly in regions with high CRE prevalence [13].

- Optimizing PK/PD Parameters: Patient-specific factors, such as organ dysfunction, guide dosing decisions. In ICUs, combining AS with therapeutic drug monitoring (TDM) has reduced mortality in *Pseudomonas aeruginosa* bacteremia by 15–20% by ensuring therapeutic levels without overuse [15].

These goals are operationalized through core principles outlined by the Centers for Disease Control and Prevention (CDC), including leadership commitment, accountability, drug expertise, action, tracking, reporting, and education. Metrics like defined daily doses (DDD) per 1,000 patient-days provide benchmarks, with studies showing 30–40% reductions in carbapenem use correlating with decreased resistance in *Klebsiella pneumoniae* [17].

Diagnostic Stewardship as a Partner Strategy

Diagnostic stewardship enhances AS by ensuring microbiological data guide prescribing, reducing reliance on empirical carbapenem therapy. Key components include:

- Rapid Molecular Testing: Multiplex PCR panels detecting carbapenemase genes (e.g., KPC, OXA-48, NDM) within 1–2 hours enable immediate escalation or de-escalation, shortening hospital stays by 2–4 days [17]. Phenotypic assays like RAPIDEC® CARBA NP further accelerate control of carbapenemase producers in outbreaks [14].
- Surveillance Cultures: Routine screening in high-risk wards (e.g., ICUs, transplant units) identifies asymptomatic CR-GNB colonization, enabling preemptive isolation and reducing transmission by up to 50% [12].
- Electronic Decision Support Systems: Real-time integration of microbiology data into electronic health records delivers alerts, decreasing inappropriate carbapenem prescriptions by 25–35% [18].

Despite challenges like test cost and accessibility, cost-effectiveness analyses highlight savings from reduced antibiotic use and shorter hospitalizations, making diagnostic stewardship a critical partner to AS.

Restriction and Pre-Authorization Policies

Restriction policies, such as pre-authorization and post-prescription reviews, are effective in curbing carbapenem overuse. Pre-authorization requires infectious disease approval before initiating imipenem, while post-prescription audits reassess therapy at 48–72 hours. Multicenter studies report 20–40% reductions in carbapenem consumption without increased mortality [13]. A “carbapenem time-out” at 72 hours facilitates de-escalation or discontinuation, reducing treatment duration by 2–3 days [17]. In high-prevalence regions, patients on empirical carbapenems are isolated pending susceptibility results, preventing nosocomial spread [12].

Pharmacist-led reviews and electronic restrictions achieve acceptance rates above 80% when paired with education, with long-term data showing a 66% drop in carbapenem use post-intervention [14]. These policies balance access with stewardship, preserving imipenem for true MDR cases.

Education and Prescriber Engagement

Education is pivotal to AS success, driving behavioral change through targeted interventions. Interactive workshops and case-based learning, combined with audit-and-feedback, improve guideline adherence, reducing inappropriate prescriptions by 30–40% [11]. Embedding infectious disease pharmacists in ward rounds increases appropriate carbapenem use and shortens treatment durations, as evidenced in Asian and European [16, 18]. Digital tools, such as e-learning modules, achieve 39% reductions in overall antibiotic use [18]. Multiprofessional education involving nurses and pharmacists fosters a team-based approach, addressing knowledge gaps and enhancing patient education on resistance [13].

Measurable Outcomes of Stewardship

Robust ASPs yield significant benefits, validated through key metrics:

- **Reduced Carbapenem Use:** Programs achieve 20–66% reductions in carbapenem consumption, with stable or improved outcomes in bloodstream infections and ventilator-associated pneumonia [15].
- **Lower Resistance Rates:** Resistance in *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* declines by 10–30% within 2–3 years post-implementation [17].
- **Cost Savings:** Shorter hospital stays and reduced reliance on salvage therapies save \$200–500 per patient, alongside lower *C. difficile* rates [12].

ASPs thus represent a high-value intervention, mitigating imipenem resistance while enhancing patient care and resource efficiency.

Future Directions

The battle against imipenem resistance demands a multifaceted approach, advancing simultaneously on three key fronts: (i) developing smarter drugs and optimized dosing regimens to circumvent dominant resistance mechanisms; (ii) exploring non-traditional therapeutics that evade conventional β -lactam vulnerabilities; and (iii) implementing precision guidance systems, including rapid genomics, AI-driven decision support, and host-directed strategies to deliver targeted therapies more efficiently at the bedside [1, 3, 9]. This integrated strategy is essential given the escalating global burden of carbapenem-resistant Gram-negative bacteria (CR-GNB), which contribute to over 700,000 deaths annually and are projected to cause 10 million deaths by 2050 without intervention [19]. Recent modeling studies highlight a persistent treatment gap for CR-GNB infections, with undertreatment rates exceeding 50% in some regions, underscoring the need for innovative solutions [20]. The World Health Organization's (WHO) updated Bacterial Priority Pathogens List (BPPL) 2024 emphasizes critical threats like carbapenem-resistant *Acinetobacter baumannii* (CRAB), *Pseudomonas aeruginosa* (CRPA), and *Enterobacterales*, prioritizing research into novel agents and diagnostics [21].

Progress in these areas is accelerating, driven by initiatives like the Gram-Negative Antibiotic Discovery Innovator (Gr-ADI) program, which funds early-stage discovery for Gram-negative pathogens [22]. Challenges include regulatory hurdles, economic disincentives for antibiotic development, and the rapid evolution of resistance, but collaborative efforts between academia, industry, and governments are paving the way [23]. Ultimately, combining new therapeutics with precision tools could restore efficacy against imipenem-resistant strains, reducing morbidity, mortality, and healthcare costs while buying time for truly disruptive innovations.

New Antibiotics (and Smarter β -Lactam Strategies)

Next-generation β -lactam/ β -lactamase inhibitor (BL/BLI) combinations and siderophore-conjugated cephalosporins are expanding the armamentarium against prevalent resistance mechanisms, though vulnerabilities persist in scenarios involving metallo- β -lactamases (MBLs) or efflux/porin defects.

Optimized BL/BLI Use: Agents like imipenem/relebactam and meropenem/vaborbactam effectively restore susceptibility against KPC-producing Enterobacterales, with efficacy rates up to 80% in clinical trials when guided by rapid carbapenemase detection and local resistance patterns [2, 10]. The Infectious Diseases Society of America (IDSA) 2024 guidance recommends these for extended-spectrum β -lactamase (ESBL) and carbapenem-resistant Enterobacterales (CRE) infections, preferring them over older agents like colistin due to lower toxicity [24]. Ceftazidime-avibactam (CAZ-AVI) demonstrates synergistic activity with other antimicrobials against CR-GNB, achieving bactericidal effects in combination therapies [25]. However, resistance emergence during therapy remains a concern, necessitating de-escalation protocols informed by molecular epidemiology.

Cefiderocol and Siderophore Strategies: As a "Trojan-horse" antibiotic, cefiderocol exploits iron uptake pathways to bypass outer membrane barriers, showing superior activity against CRPA and CRAB isolates, with cure rates comparable to best-available therapies in randomized trials [9, 26]. Its performance wanes in efflux-overexpressing strains, highlighting the importance of concurrent molecular profiling to identify co-resistance mechanisms [27]. Pipeline candidates like taniborbactam-combined BLs target MBLs, offering hope for broader [28].

PK/PD-Driven Administration: Prolonged or continuous infusions of β -lactams, coupled with therapeutic drug monitoring (TDM), optimize time above MIC in critically ill patients with altered pharmacokinetics, such as those with augmented renal clearance or sepsis [1, 15]. Bayesian model-informed precision dosing overcomes TDM barriers, improving target attainment by 30–50% and potentially suppressing resistance [29]. Randomized trials comparing standard versus double dosing in ICU settings are underway, aiming to balance efficacy and toxicity [30]. These strategies could extend the lifespan of existing carbapenems like imipenem by minimizing subtherapeutic exposures that drive selection pressure.

Alternative Therapies (Beyond Classical Antibiotics)

Non-traditional approaches, including adjuncts that disrupt bacterial fitness or enhance antibiotic penetration, offer pathways to combat CR-GNB without relying solely on β -lactam targets.

Antimicrobial Peptides (AMPs): Engineered AMPs target bacterial membranes, providing rapid bactericidal action against Gram-negative pathogens while evading β -lactamases [31]. Recent advancements include AMP-Designer, an LLM-based tool for generating peptides with broad-spectrum activity, demonstrating efficacy against MDR strains in preclinical models [32]. Only a few AMPs, like polymyxins, are clinically available for Gram-negatives, but pipeline candidates focus on anti-biofilm properties and reduced host toxicity [33]. Fusion protein technologies and molecular engineering are enhancing production scalability [34].

Anti-Virulence & Combination Adjuvants: Efflux pump inhibitors (EPIs) resensitize resistant phenotypes to β -lactams by blocking antibiotic extrusion, with RND-family inhibitors showing promise in Gram-negatives [35]. Anti-virulence agents targeting quorum sensing or toxin production could complement carbapenems, though clinical data are nascent [2, 8]. Berberine hydrochloride, a natural adjuvant, modulates virulence factors in CRE, potentially restoring susceptibility [36]. Plasmapheresis and other host-directed therapies are emerging to remove toxins and enhance immune responses [37].

Diagnostics as Therapy Enablers: Rapid diagnostics enable judicious use of alternatives, preventing overuse that accelerates resistance [17]. Integration with stewardship ensures these modalities are deployed only when β -lactams fail.

Phage Therapy

Bacteriophages provide targeted, strain-specific lysis, biofilm disruption, and synergy with β -lactams, making them ideal for CRPA and CRAB infections [11]. Compassionate-use cases report success rates over 70% in MDR cases, with phages like vAbaIN10 showing no lysogeny risks [38]. Combinations with meropenem exhibit synergy, clearing biofilms and preventing regrowth [39]. Phage cocktails, such as those against CRAB, demonstrate in vivo efficacy in animal models [40]. Challenges include standardization, regulatory approval, and resistance evolution, addressed through rapid genomics for phage matching and stewardship integration. Controlled trials and manufacturing guidelines are priorities to transition from compassionate use to routine therapy [41].

Pharmacogenomics, Precision Dosing, and AI-Assisted Care

Precision medicine leverages host and pathogen data to tailor therapies, minimizing resistance selection.

Host- and Pathogen-Level Precision: Carbapenemase genotyping within hours guides BL/BLI selection, differentiating KPC from MBLs [17, 65]. Pharmacogenomics identifies variants affecting β -lactam metabolism, enabling personalized dosing [42].

TDM-Guided β -Lactam Therapy: Algorithms incorporating MIC, organ function, and infection site boost target attainment, reducing toxicity and resistance [15, 61]. Systematic reviews confirm clinical benefits in critically ill patients [43].

AI Decision Support: AI-based clinical decision support systems (CDSS) integrate EHR data for real-time antibiotic recommendations, reducing mismatches by 40% [44]. Tools like UTI Smart-Set and Bayesian DSS enhance stewardship, with meta-analyses showing improved outcomes [45, 46].

Surveillance Genomics: Whole-genome sequencing (WGS) tracks resistance plasmids and clones (e.g., ST258), informing infection prevention and policy [5, 62]. Global platforms like amr.watch monitor trends from 620,000 genomes, enabling early detection [47]. One Health frameworks integrate human-animal surveillance for comprehensive AMR tracking [64].

In summary, integrating novel agents with precision tools offers the most expedient path to reclaiming control over imipenem-resistant CR-GNB, while scaling phages and AMPs for long-term sustainability.

Summary

The escalation of imipenem resistance among Gram-negative bacteria represents both a molecular and public health crisis. This review has outlined the multifactorial drivers—from enzymatic hydrolysis and efflux overexpression to inappropriate prescribing practices and international dissemination—that collectively undermine imipenem's status as a last-resort agent. Synthesizing these insights underscores several urgent themes.

First, the molecular versatility of resistance mechanisms is striking. Carbapenemases remain the most significant contributors, with KPC, OXA-48, and NDM producers driving hospital outbreaks worldwide [5, 62]. Yet resistance is often compounded by porin loss and efflux activation, creating layered defenses that reduce the efficacy even of novel β -lactam/ β -lactamase inhibitor (BL/BLI) combinations [8, 60]. This redundancy explains why resistance often persists despite therapeutic escalation, highlighting the need for therapies that target multiple bacterial vulnerabilities simultaneously.

Second, the clinical toll of imipenem resistance is profound. Mortality in bloodstream infections and ventilator-associated pneumonia caused by carbapenem-resistant *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa* routinely exceeds 40–50%, particularly when delays in appropriate therapy occur [6, 65]. Survivors frequently endure prolonged ICU admissions, device-associated complications, and recurrent infections [7]. These outcomes are exacerbated by limited treatment options, forcing reliance on nephrotoxic polymyxins or suboptimal agents such as tigecycline [59]. Thus, resistance not only worsens survival but also inflates healthcare costs through longer hospital stays and the need for high-cost salvage therapies [61].

Third, while new therapeutics are emerging, they are insufficient to offset the crisis fully. BL/BLI combinations such as imipenem/relebactam and meropenem/vaborbactam offer reliable coverage against KPC producers but remain ineffective against MBLs [64]. Cefiderocol provides activity against

multiple difficult-to-treat pathogens, yet reduced efficacy in the presence of efflux or porin alterations illustrates that bacteria can rapidly adapt [65]. Alternative modalities, including antimicrobial peptides, bacteriophages, and host-directed therapies, are promising but remain experimental [11, 30]. Collectively, these gaps demonstrate that drug innovation alone cannot solve the resistance crisis.

Instead, the evidence strongly supports antibiotic stewardship and infection prevention as the frontline defense. Successful stewardship programs consistently reduce carbapenem use without compromising patient survival, lower resistance rates in *P. aeruginosa* and *Enterobacterales*, and generate measurable cost savings [13, 14, 18]. Effective programs integrate rapid molecular diagnostics, therapeutic drug monitoring, and behavioral interventions to promote prescriber adherence [15, 61]. However, stewardship cannot succeed in isolation: without parallel investment in surveillance, regulatory control of community antibiotic sales, and global genomic networks to track high-risk clones, resistant strains will continue to spread across borders [11, 62].

Finally, this crisis illustrates a broader tension in modern medicine: our capacity to innovate is outpaced by bacterial adaptability. Imipenem resistance highlights the fragility of relying solely on pharmaceutical solutions without structural interventions in prescribing culture, diagnostics, and infection prevention. The future must embrace a more integrated approach, combining stewardship, novel agents, precision pharmacology, and global health coordination.

In summary, imipenem resistance is not merely a molecular curiosity but a clarion call to global stewardship. Without decisive and coordinated action, we risk a post-antibiotic era where even routine Gram-negative infections become lethal. Stewardship interventions have already proven effective, but their reach must expand beyond tertiary hospitals to encompass communities and international networks. Only through a combination of stewardship, innovation, and global collaboration can imipenem's clinical utility be preserved for the next generation.

Conclusion and Call to Action

Imipenem resistance among Gram-negative pathogens stands as one of the most daunting obstacles in contemporary infectious disease management, emblematic of the broader antimicrobial resistance (AMR) crisis that threatens global health security. This resistance arises from a complex interplay of molecular mechanisms—such as the production of carbapenemases (e.g., KPC, NDM, OXA-48-like enzymes), loss of outer membrane porins, and overexpression of efflux pumps—that render these bacteria impervious to carbapenems, a class once hailed as last-resort antibiotics [3, 11, 62]. These mechanisms are amplified by clinical practices like empirical antibiotic overuse in hospitals, environmental reservoirs including wastewater and agricultural settings, and global factors such as international travel and trade that facilitate the rapid dissemination of resistant clones [59, 60]. Recent surveillance data underscore the severity: carbapenem-resistant *Enterobacterales* (CRE) have seen a dramatic rise, with cases of New Delhi metallo- β -lactamase (NDM)-positive CRE increasing from 58 in 2019 to 388 in 2024 in New York City alone, highlighting urban hotspots as epicenters of spread.

Globally, multidrug-resistant Gram-negative infections contribute to approximately 5 million AMR-associated deaths annually, with projections estimating up to 10 million by 2050 if unchecked [21]. In high-acuity environments like intensive care units (ICUs), these infections yield mortality rates surpassing 50%, often necessitating fallback to toxic agents like colistin or tigecycline, which carry high risks of adverse effects and suboptimal efficacy [20, 49]. For instance, bloodstream infections (BSIs) due to carbapenem-resistant *Klebsiella pneumoniae* (CRKP) exhibit a 54.3% mortality rate, exacerbated by delays in effective therapy and underlying comorbidities [28].

The human and economic toll is profound: resistant infections prolong hospital stays, escalate treatment costs by up to 30–50% per case, and strain healthcare systems, particularly in low- and middle-income countries where access to diagnostics and novel agents is limited [19, 50]. Environmental dissemination further complicates containment, with carbapenem-resistant bacteria detected in rivers, soils, and animal reservoirs, underscoring the One Health paradigm that links human, animal, and environmental health [51]. Without intervention, this trajectory risks eroding advances in surgery, chemotherapy, and organ transplantation, where effective antibiotics are foundational.

Despite these challenges, therapeutic innovation offers glimmers of hope, though the pace lags behind resistance evolution. Next-generation β -lactam/ β -lactamase inhibitor (BL/BLI) combinations like imipenem/relebactam and meropenem/vaborbactam restore activity against many KPC producers, while siderophore cephalosporins such as cefiderocol provide novel mechanisms to penetrate resistant strains [18, 61]. Emerging modalities, including antimicrobial peptides (AMPs) with membrane-disrupting action, bacteriophage therapies for strain-specific targeting, and anti-virulence agents that disarm pathogens without killing them, are progressing through pipelines [30, 40]. Initiatives like the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) have invested over \$490 million since 2016 in 104 projects, fostering development of non-traditional therapies [52]. Precision diagnostics, pharmacogenomics to tailor dosing based on host genetics, and AI-driven decision support systems are pivotal in extending the lifespan of these agents by ensuring targeted use and minimizing selection pressure [53, 65]. However, barriers persist: high development costs, regulatory hurdles, and market failures deter investment, with only a handful of new antibiotics approved in the last decade [54]. The 2024 WHO Bacterial Priority Pathogens List emphasizes the need for innovation in diagnostics and scalable treatments to combat critical threats like carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [21].

Call to Action

Confronting imipenem resistance necessitates a unified, multi-tiered response that transcends individual efforts, demanding collaboration across sectors and borders. Drawing from the updated Global Action Plan on Antimicrobial Resistance (GAP-AMR), endorsed at the 78th World Health Assembly in May 2025, and the 2024 United Nations General Assembly High-Level Meeting on AMR, stakeholders must prioritize evidence-based strategies to curb this threat [55, 56]. The following imperatives outline a roadmap for action:

At the Bedside Level: Implement rapid diagnostics for organism identification and resistance profiling within hours, leveraging multiplex PCR and whole-genome sequencing to enable precise, pathogen-directed therapy and avoid empirical broad-spectrum use [17]. Integrate therapeutic drug monitoring (TDM) and pharmacogenomic testing to optimize dosing, reducing toxicity and resistance emergence in vulnerable patients [15]. Clinicians should adopt de-escalation protocols, transitioning from carbapenems to narrower agents based on susceptibility results, as supported by the Infectious Diseases Society of America (IDSA) 2024 guidance [48].

At the Hospital and Healthcare System Level: Strengthen infection prevention and control (IPC) through rigorous hand hygiene, environmental cleaning, and contact precautions, particularly in ICUs and transplant units where CRE transmission is rampant [14]. Embed antibiotic stewardship programs (ASPs) with multidisciplinary teams, including infectious disease pharmacists for real-time prescription reviews, aiming to reduce carbapenem consumption by 20–40% [13]. Hospitals must invest in surveillance systems to track resistance patterns and respond to outbreaks promptly, aligning with the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (2020–2025) that emphasizes evidence-based interventions [57].

At the Policy and Global Health Level: Governments should enforce national AMR action plans, ensuring equitable access to new therapeutics and diagnostics, especially in resource-limited settings, through incentives like pull mechanisms for antibiotic development [58]. Bolster global genomic surveillance via platforms like the WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) to detect and contain high-risk clones before transnational spread [66]. Advocate for One Health approaches, regulating antibiotic use in agriculture and veterinary medicine to mitigate environmental reservoirs [63]. The AMR Industry Alliance and global coalitions call for urgent funding—targeting \$10 billion annually—to support R&D, access, and stewardship, as highlighted in the 2024 UN Political Declaration on AMR [55].

At the Research and Innovation Level: Accelerate funding for novel therapies, including phage banks, AMP engineering, and AI-optimized combinations, while addressing market failures through public-private partnerships [51]. Prioritize clinical trials for underserved populations and integrate equity into AMR strategies to prevent disproportionate impacts on low-income regions.

If left unaddressed, imipenem resistance could unravel decades of medical progress, heralding a post-antibiotic era where routine procedures become perilous. Yet, the arsenal of tools— from stewardship to genomics—exists today. What is required is resolute political will, institutional commitment, and clinical vigilance to deploy them. As echoed in the 2025 World AMR Awareness Week theme, "Preventing Antimicrobial Resistance Together," collective action is not optional but imperative to safeguard future generations [58].

Declarations

Funding

No organization or institution provided funding for this review.

Ethics and Consent to Participate declarations

Ethics and Consent to Participate declarations: not applicable.

Data Availability declaration

Not applicable. This manuscript does not report data generation or analysis.

Author contribution statement

MGO – Conceptualization, Investigation, Methodology, Validation, Writing- review and editing

AAS – Methodology, Writing-original draft, Data curation, Visualization

BOE – Methodology, Validation, Visualization, writing-review and editing

AOE – Supervision, Validation, writing-review and editing,

All authors reviewed the manuscript

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Figures

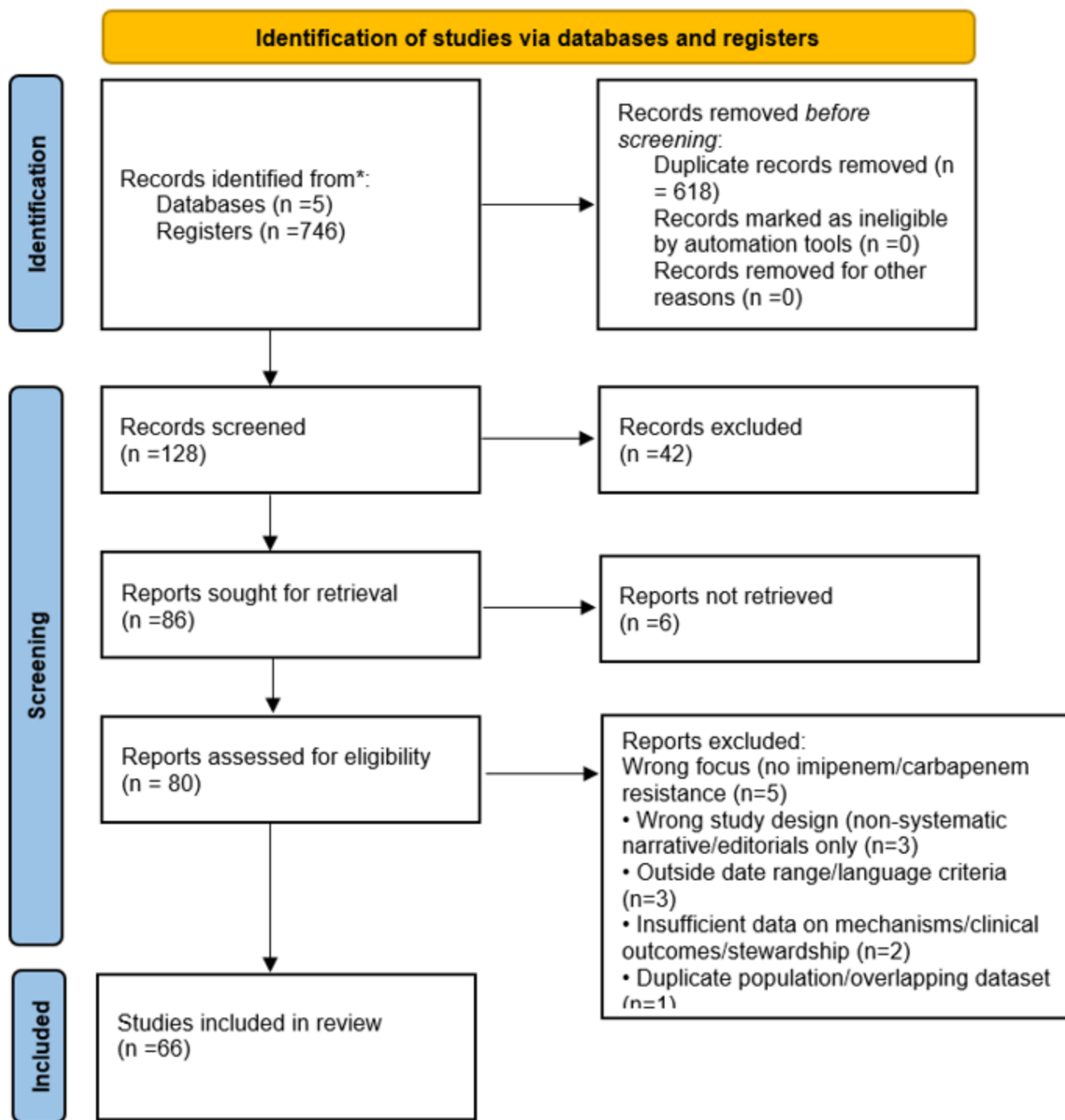


Figure 1

PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only