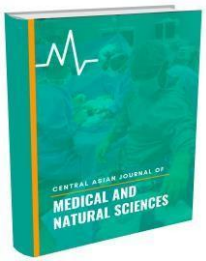

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Article

Antimicrobial Resistance Genes, Mechanisms, and Next-Generation Antibiotics: A Review for the Effective Treatment of Multidrug-Resistant Pathogens

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Abstract: Antimicrobial resistance (AMR) has become a growing global health concern due to the overuse and misuse of antibiotics in human medicine, agriculture, and animal care. This review aims to examine the major resistance genes, underlying mechanisms, and the potential of new-generation antibiotics in treating infections caused by multidrug-resistant (MDR) pathogens. A structured literature search was conducted using six databases—Scopus, Web of Science, PubMed, Google Scholar, ResearchGate, and Mendeley—focusing on studies published between 2015 and 2025. After applying inclusion criteria, 162 peer-reviewed articles were selected for analysis. These studies reported a wide range of resistance genes, with blaZ being the most common, found in approximately 64% of the reviewed literature. Other frequently mentioned genes included mecA (52%), erm (48%), tet (41%), and vanA/B (37%). Common MDR pathogens identified were Staphylococcus aureus (MRSA), Enterococcus (VRE), Enterobacteriaceae (CRE), and Pseudomonas aeruginosa. Resistance was found to occur through various mechanisms such as enzymatic degradation of antibiotics, altered binding targets, efflux pumps that remove antibiotics from bacterial cells, and the development of biofilms that reduce drug effectiveness. Several new treatment options—including cefiderocol, eravacycline, and silver/zinc-based nanoparticles—have shown encouraging results in overcoming resistance. Natural plant compounds and genomic-based drug discovery also offer promising directions. Overall, the findings highlight the urgent need for responsible antibiotic use, better diagnostic tools, and continued investment in alternative therapies. Without immediate action, AMR could make previously treatable infections far more dangerous and difficult to manage in the near future.

Keywords: Antimicrobial Resistance, Multidrug-Resistant Pathogens, Resistance Genes, Next-Generation Antibiotics, Biofilm, Efflux Pumps.

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1. Introduction

Antibiotics have been proven to be beneficial for human life since their discovery until now [1]. However, their continued and irrational use can cause several problems. The main problem in the use of antibiotics is the occurrence of antibiotic resistance. This incident causes antibiotic therapy to no longer be efficient and increases the cost of therapy [2]. Antibiotic resistance is defined as the ability of microorganisms to inhibit the action of antimicrobial agents and this phenomenon occurs when antibiotics lose their efficiency to inhibit bacterial growth. The increasing use of antibiotics in various health and agricultural sectors has led to the emergence of antibiotic resistance worldwide [3].

Antibiotics are natural or synthetic compounds used to combat infections caused by bacteria. Overuse of these medications favors the development of bacteria resistant to different groups of antibiotics (multidrug-resistant bacteria) [4]. Bacterial resistance is the ability of bacteria to survive in the presence of an antibiotic and represents an advantage for expanding their ecological niche and enabling their proliferation, 1 whether in hospitals or the environment. This reduces therapeutic options, which directly impacts the success of antimicrobial therapy in combating secondary infections caused by these pathogens, in addition to causing high rates of morbidity, mortality, and hospital costs [5]. Antibiotics intervene in molecules of essential biological processes in bacteria, for example: a) DNA gyrase in DNA replication, b) RNA polymerase in RNA synthesis, c) ribosomes in protein synthesis and d) transpeptidases (PBPs) in the synthesis of peptidoglycan that makes up the cell wall. Antibiotics act at different levels, quinolones inhibit DNA replication, rifampicin suppresses RNA synthesis and aminoglycosides, macrolides, tetracyclines and chloramphenicol cancel protein synthesis. The group of beta-lactam antibiotics (penicillins, cephalosporins, monobactams and carbapenems) inhibits cell wall synthesis [6], [7].

Antimicrobial resistance (AMR) has emerged as a global health issue due to the development of resistant microorganisms caused by the inappropriate and excessive use of antibiotics. The rise in infections caused by multi-drug-resistant organisms poses significant challenges for healthcare systems worldwide [8], [9], [10]. The overuse and misuse of antibiotics in human and animal health, as well as in agriculture, contribute to the spread of resistance genes—pushing deaths caused by microbial resistance ahead of many other causes of death. Microorganisms neutralize antibiotics through various mechanisms, including enzymatic modification and biofilm formation. Today, the limited effectiveness of existing antibiotics has made even routine medical procedures risky, sometimes leading to fatalities [8]. The growing global spread of bacterial diseases that are resistant to current antibiotics highlights the urgent need for investment in, and access to, new drugs, vaccines, and diagnostic tools. Historically, investments in drug development have been driven by expectations of high returns [9]. However, this is often not economically viable and likely to fail without sufficient incentives. Protecting the effectiveness of antibiotics depends on rapid and accurate diagnosis of infections. Yet, widespread adoption of diagnostic technologies faces barriers related to cost, technology, and human behavior [10].

According to recent global estimates, more than 1.14 million people died directly due to bacterial antimicrobial resistance (AMR) in 2021, with a further 4.71 million deaths associated with AMR-related infections in the same year [11]. Forecasts suggest that by 2050, the annual number of direct AMR-related deaths could reach 1.91 million, while associated deaths may increase to approximately 8.22 million [12]. These alarming figures highlight the urgent need for coordinated global action to reduce the rising health and economic burden caused by antimicrobial resistance.

This resistance occurs in several types of microorganisms with high prevalence that threaten human health. This problem has become one of the main public health threats, currently and WHO has estimated that there will be 10 million deaths by 2050 [10] due to increasing antimicrobial resistance. Antibiotic resistance involves the transfer of bacteria and genes between humans, animals and the environment. Antibiotic resistance can arise from mutations in pre-existing bacterial genomes. Mutations due to the external environment contribute less to the occurrence of resistance. Environmental resistance factors are caused by water, soil and other environmental factors with highly variable ecological niches providing genetic variation in bacteria [13].

Antimicrobial resistance mechanisms typically involve the enzymatic modification or breakdown of antibiotics, preventing them from entering bacterial cells or accumulating within them. Other strategies include altering metabolic pathways, modifying binding

sites—such as ribosomes—to reduce drug effectiveness, and increasing the activity of efflux pumps that expel antibiotics from the cell [14], [15].

Antimicrobial resistance genes are associated with mobile genetic elements such as plasmids, transposons, and integrons [16]. The latter are gene expression elements that incorporate promoterless genes, converting them into functional genes [17]. Consequently, the integron acts as an expression cassette for inserted genes, and more than one gene is frequently integrated. Class 1 integrons are the most studied and are primarily identified in clinical isolates. Cassette mobilization is mediated by the action of integrase, which has generated numerous cassette reconfigurations and combinations and selected for different antibiotics, making multidrug resistance possible through transposons or plasmids. Genomics emerged with the development of molecular biology techniques that allow the sequencing of entire genomes, which involves the analysis of the gene content of a microorganism such as bacteria. To date, 770 microbial genomes have been sequenced, and 1,287 are in progress. Analysis of bacterial genomes indicates that a large number of genes have been acquired through horizontal transfer [18]. The genes in a bacterial genome are very similar in terms of their base composition and codon usage pattern. Some of the sequences that are new to a bacterial genome, and that were introduced through horizontal transfer, vary in their total G+C content and can, in certain cases, be differentiated from native sequences because they maintain the characteristics of the donor genome. Consequently, the opportunity to identify conserved sequences linked to undescribed mobile genetic elements has increased, as is the case with integrons and their relationship with transposons. These studies have generated new knowledge about horizontal gene transfer and suggest a widespread distribution in the natural environment. From the analysis of bacterial genome sequences, genes and proteins essential for bacterial survival can be identified (see an example below) and, based on this information, new antibiotics can be "designed" to inhibit bacterial growth [19].

This review addresses a critical gap by bringing together data from 2015 to 2025 across multiple global databases to provide a comparative overview of resistance genes, mechanisms, and emerging treatments. While previous reviews often focus on specific pathogens or regions, this work offers a broader synthesis—highlighting gene prevalence trends (e.g., blaZ, mecA), newer therapeutics like cefiderocol, and region-specific resistance patterns. It integrates findings from both developed and developing countries, offering a more inclusive perspective on AMR progression and response strategies [20], [21].

2. Materials and Methods

The literature for this review was collected through a controlled search process guided by the PRISMA framework [22] to ensure clarity and consistency. Searches were carried out across six major databases—Scopus, Web of Science, PubMed, Google Scholar, ResearchGate, and Mendeley. The search terms included combinations such as “resistance genes,” “antibiotic resistance,” “incidence,” “next-generation antibiotics,” “multidrug-resistant,” and “antibiotics,” using Boolean operators (AND/OR) to refine the results. The review focused on studies published between January 2015 and May 2025 and considered only English-language articles.

To ensure quality and relevance, only peer-reviewed research and review articles that were fully accessible were included. Studies were excluded if they lacked full-text access, were not published in English, or did not specifically address antimicrobial resistance in clinically relevant bacteria. After applying these criteria and removing duplicates, a total of 162 articles were selected for detailed analysis.

The selected studies offered a wide range of insights into antibiotic resistance across different pathogens and settings. Most reported on resistance gene prevalence, patterns of

antibiotic use, and associated bacterial defense mechanisms. Many also highlighted the clinical consequences of resistance, such as treatment failure, prolonged illness, and increased healthcare costs. This structured approach allowed for a comprehensive understanding of current trends in antimicrobial resistance and emerging therapeutic strategies.

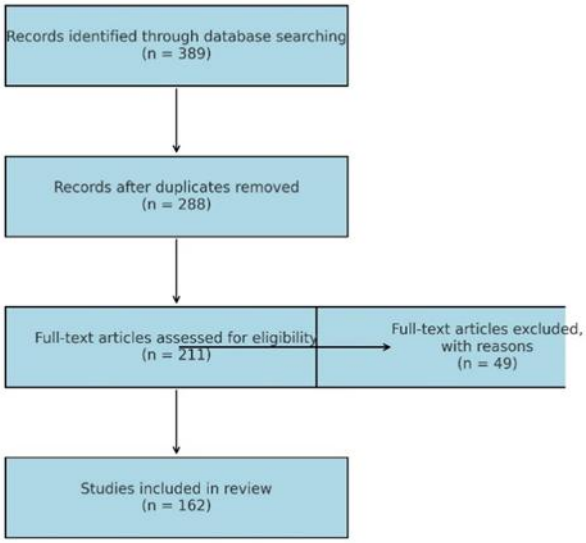

Figure 1. PRISMA Flow Diagram for the Selection of Studies in the AMR Review (2015–2025).

Figure 1 illustrates the selection process of studies included in the review. Out of 389 records initially identified through database searches, 288 remained after removing duplicates. After screening full texts, 49 were excluded based on relevance or accessibility. Finally, 162 peer-reviewed articles were included for analysis.

3. Results

Bacterial resistance continues to pose a serious threat to global health, especially with pathogens like *Vancomycin-Resistant Enterococcus* (VRE), *Methicillin-Resistant Staphylococcus aureus* (MRSA), *Carbapenem-Resistant Enterobacteriaceae* (CRE), *Multidrug-Resistant Pseudomonas aeruginosa* (MRPA), and *Multidrug-Resistant Escherichia coli* (MREC). VRE evades vancomycin by replacing the D-Ala-D-Ala cell wall terminus with D-Ala-D-Lac, reducing drug affinity. In contrast, MRSA acquires resistance through the mecA gene, producing an altered penicillin-binding protein (PBP2a) that reduces β-lactam effectiveness [23]. CRE uses carbapenemases to break down even last-resort β-lactams, while MRPA and MREC rely on efflux pumps, porin mutations, and biofilm formation to resist multiple drugs.

To combat these superbugs, treatment strategies include both existing and innovative solutions. Clinically approved drugs like daptomycin, ceftazidime-avibactam, and polymyxins remain central, but resistance is rising. Therefore, alternative approaches like natural products—such as curcumin, flavonoids, and berberine—offer promising antibacterial and anti-biofilm effects. Nanoparticles (NPs), particularly silver and zinc oxide-based, are being developed for their ability to disrupt bacterial membranes and deliver drugs effectively. Additionally, novel drugs like cefiderocol and eravacycline are entering clinical pipelines with targeted actions against resistant strains. These strategies highlight the urgent need for integrated efforts in drug development and antibiotic stewardship [23].

A recent comparative study of *Staphylococcus aureus* strains isolated from clinical mastitis in six countries reveals significant variations in antimicrobial resistance genes and virulence profiles. In all regions, the blaZ gene, which confers β-lactam resistance, was widespread—most notably in Italy (82.4%) and Germany (47.1%). The mecA gene, indicative of methicillin resistance, appeared at low levels across the countries, suggesting limited MRSA presence. Erythromycin and lincomycin resistance were notable in Argentina and Germany, likely linked to the presence of erm genes such as *ermC* and *ermB*. Interestingly, South African isolates showed 100% resistance to spiramycin and high virulence gene carriage, including sak and sea, hinting at a potentially more aggressive strain profile.

Table 1. Antimicrobial Resistance Genes and Virulence Profiles of *S. aureus* Isolated from Clinical Mastitis in Six Countries.

Country	Resistance Genes	% Resistance (Phenotypic)	Virulence Genes (Most Prevalent)
Argentina [25].	blaZ (18.8%), ermC (dominant), mecA (low)	Erythromycin 43.8%, Lincomycin 31.3%, Penicillin 6.3%	hla (100%), hlb (93.8%), sea (56.3%)
Brazil [26].	blaZ (46.7%), mecA (present), erm genes (absent)	Lincomycin 46.7%, TMP-SMX 20%, Penicillin 20%	hla (100%), hlb (100%), sea (53.3%)
Germany [24].	blaZ (47.1%), mecA (5.9%), ermB (35.3%)	Erythromycin 35.3%, Lincomycin 29.4%, Penicillin 5.9%	hla (100%), hlb (64.7%), sea (88.2%)
Italy [24].	blaZ (82.4%), mecA (5.9%), ermC (29.4%)	Penicillin & Ampicillin 58.8%, Spiramycin 58.8%	hla (100%), hlb (94.1%), sea (58.8%)
USA (NY State) [24].	blaZ (41.2%), mecA (low), erm genes (absent)	Spiramycin (high), Erythromycin (low)	hla (100%), hlb (88.2%), sea (52.9%)
South Africa [24]	blaZ (36.4%), ermB (36.4%), mecA (present)	Spiramycin 100%, Erythromycin 36.4%, Penicillin 27.3%	hla (100%), hlb (63.6%), sea (90.9%), sak (100%)

Across all countries (Table 1), *hla* was universally present, emphasizing the strain's cytotoxic potential. Genes such as hlb and sea were also common but varied in frequency. The USA and Brazil showed moderate resistance profiles and virulence gene presence, whereas Italy and South Africa had the highest overall burden. These findings highlight the importance of localized surveillance in guiding mastitis treatment and understanding pathogen evolution across regions [24].

The data presented in the table 2 highlight the widespread nature and complexity of antibiotic resistance among major bacterial pathogens. *Escherichia coli*, *Klebsiella spp.*, and

Enterobacter spp. exhibit high resistance to third-generation cephalosporins and carbapenems, primarily due to extended-spectrum β-lactamases (e.g., TEM, SHV, CTX-M) and carbapenemases such as KPC, NDM, and OXA-48 [27]. Similarly, *Acinetobacter baumannii* shows multidrug resistance through a combination of β-lactamases, efflux pumps (AdeABC), and membrane protein mutations [28]. *Pseudomonas aeruginosa* utilizes a broad array of resistance strategies, including porin loss, efflux systems, and aminoglycoside-modifying enzymes [29].

Table 2. Bacteria, Antibiotic Resistance, and Associated Genes [28], [29], [30].

Bacterium	**Antibiotic(s) Resistant To**	***Key Resistance Genes / Mechanisms***
Escherichia coli, Klebsiella spp., Enterobacter spp.	3rd-gen cephalosporins, carbapenems	*TEM-1, TEM-2, SHV-1, CTX-M, OXA, AmpC, KPC, NDM, VIM, OXA-48, IMP*
Acinetobacter baumannii	β-lactams, carbapenems, aminoglycosides, tetracycline	*TEM-1, SCO-1, CARB-4, GES-11, CTX-M, AmpC, OXA types, AdeABC, CarO, Omp22-33, DNA gyrase, PBPs, integrons*
Pseudomonas aeruginosa	Penicillins, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones	*AmpC, ampR, ampG, ampD, ampE, APHs, AADs, AACs, DNA gyrase, topoisomerase IV, NorM, porins*
Helicobacter pylori	Clarithromycin	*23S rRNA (A2142G/C, A2143G), ribosomal protein L22, IF-2, efflux pumps*
Campylobacter spp.	Fluoroquinolones	*gyrA (C257T), cmeABC, mfd, cmeR-cmeABC IR*
Salmonella spp.	Fluoroquinolones, cephalosporins, TMP-SMX, ampicillin	*gyrA, parC (QRDR mutations), Qnr, aac(6')-Ib-cr, oqxAB, qepA*
Neisseria gonorrhoeae	3rd-gen cephalosporins, fluoroquinolones	*penA (including mosaic), mtrR, penB, gyrA (91, 95, 102), parC, NorM*
Haemophilus influenzae	*Ampicillin, amoxicillin-clavulanate, cephalosporins*	*TEM-1, ROB-1, ftsI (PBP3 mutations), BLNAR, BLPAR, BLPACR*
Shigella spp.	*Fluoroquinolones*	*gyrA, gyrB, parC, parE (QRDR), Qnr, mdfA, tolC, ydhE, marA*

In pathogens like *Helicobacter pylori* and *Campylobacter spp.*, target site mutations in 23S rRNA and gyrA, respectively, underlie macrolide and fluoroquinolone resistance [31].

Additionally, resistance in *Salmonella* and *Shigella* is driven by plasmid-mediated genes (e.g., qepA, Qnr) and chromosomal mutations [32]. These findings confirm that resistance is not confined to one mechanism or region—it is a global, multifactorial challenge requiring urgent and tailored antimicrobial stewardship strategies.

The table 3 outlines the antibiotic resistance patterns and mechanisms among clinically important Gram-positive bacteria. *Staphylococcus spp.*, including *S. aureus*, show resistance to a broad range of antibiotics—such as β-lactams, fluoroquinolones, and glycopeptides—mainly due to the presence of *mecA*, *vanA*, and efflux-related genes like *norA* and *tetK* [33]. Biofilm formation and aminoglycoside-modifying enzymes (AMEs) further complicate treatment. *Enterococcus faecium* also exhibits high-level resistance to penicillins, vancomycin, and aminoglycosides, driven by genes such as *vanA*/*B* and *pbp5* [34]. *Streptococcus spp.* develop resistance through altered penicillin-binding proteins (PBPs) and ribosomal methylation via *erm(B)* and *mef(A)* genes. Meanwhile, *Clostridium difficile* strains, particularly hypervirulent types like RT027/078, show multidrug resistance, although specific genes remain underexplored [35]. *Bacillus cereus* produces β-lactamases, whereas *B. anthracis* remains largely susceptible. Less commonly discussed pathogens, such as *Corynebacterium diphtheriae* and *Listeria monocytogenes*, also harbor resistance genes like *tet(W)* and use efflux pumps or conjugative transposons. These findings reflect a diverse and evolving resistance landscape, emphasizing the need for targeted surveillance, updated treatment protocols, and global antimicrobial stewardship.

Table 3. Overview of Antibiotic Resistance Mechanisms in Clinically Relevant Gram-Positive Bacteria [36].

Bacterium	Resistant Antibiotics	Genes / Mechanisms	Ref.
Staphylococcus spp. (*S. aureus*, *S. epidermidis*, *S. saprophyticus*)	Methicillin, Vancomycin, Teicoplanin, Fluoroquinolones, Linezolid, Daptomycin, TMP-SMX, Tetracyclines, Clindamycin, Fusidic acid, Aminoglycosides, β-lactams, Quinolones	*mecA*, *vanA*, 23S rRNA, *gyrB*, *grlA*, *norA*, *dfrA*, *tet(K/L/O/M)*, *erm*, *fusA*, *fusB*, AMEs, biofilm matrix	[37]
Enterococcus faecium	Ampicillin, Penicillin, Cephalosporins, Vancomycin, Aminoglycosides, Fluoroquinolones, Quinupristin–Dalfopristin	*pbp5*, *CroR*, *IreK*, *IreP*, *vanA*/*B*/*D*/*M*, *aac*, *ant*, *aph*, *gyrA*, *parC*, *NorA*, *erm*, *vat*, *vgb*	[38]
Streptococcus spp. (*S. pneumoniae*, *S. viridans*, *S.*	Penicillin, Macrolides, TMP-SMX, Clindamycin, Tetracyclines, MLS	Altered PBPs, *erm(B)*, *mef(A/E)*, *mel*, 23S rRNA,	[39]

pyogenes, *S. agalactiae*)		*linB*, ribosomal protection	
Clostridium spp. (*C. difficile*, *C. perfringens*)	Fluoroquinolones, Clindamycin, Cephalosporins, Streptomycin, TMP-SMX, Ciprofloxacin, Cefotaxime	Hypervirulent strains (RT027/078); genes not specified	[40]
Bacillus spp. (*B. cereus*, *B. anthracis*)	β-lactams, TMP (B. cereus); none major (B. anthracis)	β-lactamase production (B. cereus); Penicillin-susceptible (B. anthracis)	[41]
Corynebacterium diphtheriae	Chloramphenicol, Sulfonamides, Tetracyclines	*cmx*, *sul1*, *tet(W)*	[42]
Listeria monocytogenes	Tetracyclines, Fluoroquinolones, Streptomycin, Chloramphenicol	Conjugative transposons, efflux pumps	[43

Figure 2 illustrates the diverse mechanisms of antibiotic resistance in Gram-positive and Gram-negative bacteria, including efflux pump overexpression, drug target modification, enzymatic degradation, and plasmid-mediated gene transfer—mechanisms that collectively reduce drug efficacy and complicate treatment [21].

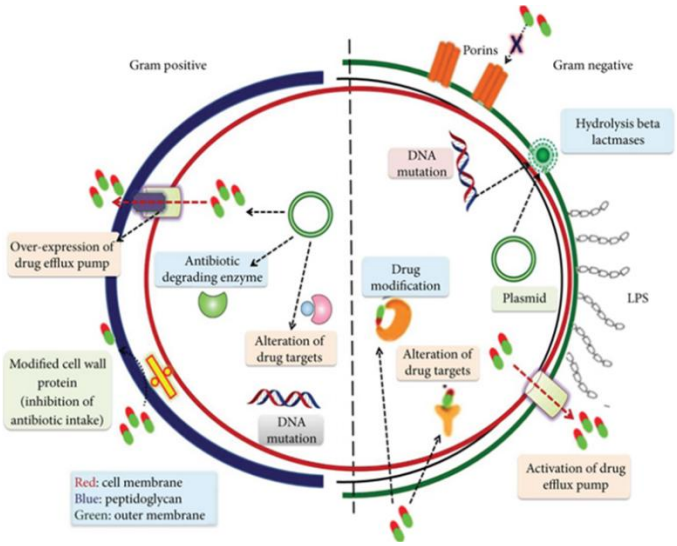

Figure 2. Antimicrobial-resistant Organism-Gram-positive and negative bacteria [44].

Table 4 summarizes major mechanisms of antibiotic resistance in clinically important bacteria, detailing the antibiotics affected and the genes or targets involved. *Staphylococcus*

aureus and *S. epidermidis* resist methicillin via the *mecA* gene, which encodes a modified penicillin-binding protein (PBP2a) that reduces β-lactam binding [45]. Similarly, vancomycin resistance in *Staphylococcus* and *Enterococcus* species is mediated by *vanA* and *vanB*, which alter peptidoglycan precursors to reduce drug binding. Gram-positive and Gram-negative bacteria often inactivate aminoglycosides enzymatically via AMEs, while macrolide resistance commonly involves rRNA methylation encoded by *erm* genes. Linezolid and chloramphenicol resistance in *Staphylococcus* arises from mutations in the 23S rRNA or the *cfr* gene. Gram-negative pathogens like *E. coli* exhibit resistance to nitrofurantoin and trimethoprim through gene overexpression or mutation, while *Pseudomonas aeruginosa* resists fluoroquinolones by downregulating porins such as *oprD*. Rifampicin resistance in *M. tuberculosis* results from mutations in *rpoB*. Additionally, biofilm formation and metabolic dormancy contribute to multi-class resistance across various chronic infections. These findings underscore the genetic adaptability of bacteria and the urgent need for targeted diagnostic tools and therapies [45].

Table 4. Mechanisms of Antibiotic Resistance and Associated Genetic Determinants in Clinically Relevant Bacteria [48].

Bacteria	Resistant Antibiotic(s)	Mechanism of Resistance	Affected Genes / Targets	References
Staphylococcus aureus, *Staphylococcus epidermidis*	Methicillin	Acquisition of a resistance gene	*mecA* (PBP2a)	[46]
Staphylococcus spp., *Enterococcus spp.*	Glycopeptides (Vancomycin)	Peptidoglycan precursor alteration	*vanA*, *vanB* clusters (D-Ala-D-Lac)	[47]
General Gram-positive & Gram-negative bacteria	Aminoglycosides	Enzymatic inactivation / ribosomal modification	AMEs (AAC, ANT, APH); 30S ribosomal subunit	[48], [49]
General Bacteria	Macrolides (e.g., Erythromycin)	rRNA methylation	*erm* gene	[50]
Staphylococcus spp.	Linezolid, Clindamycin, Chloramphenicol	Domain V mutation / rRNA methylation	*cfr* gene, 23S rRNA	[48]
Enterobacteriaceae (e.g., E. coli)	Trimethoprim, Nitrofurantoin	Enzyme overexpressio	*nfsA*, *nfsB*, *ribE*, DHFR overexpression	[48]

		n/target mutation		
Enterococcus spp.	Trimethoprim-Sulfamethoxazole	Metabolic bypass	Folinic acid salvage pathway	[48]
Pseudomonas aeruginosa, other Gram-negative rods	Fluoroquinolones, Aminoglycosides	Porin loss / decreased permeability	Downregulation of *oprD*	[48]
Mycobacterium tuberculosis	Rifampicin	Target site mutation	*rpoB* (β-subunit of RNA polymerase)	[48]
Various Gram-negatives (e.g., Haemophilus spp.)	Chloramphenicol	Drug acetylation	*cat* gene	[48]
Various clinical pathogens	β-lactams	Enzymatic degradation	β-lactamases (e.g., TEM, SHV, CTX-M)	[48]
Various bacterial species	Tetracyclines	Efflux pump activation	*tet* genes	[48]
All species (esp. chronic infections)	Multiple classes	Biofilm formation, reduced penetration	EPS genes, metabolic dormancy pathways	[48]

Antimicrobial resistance (AMR) is a growing global concern, with resistance mechanisms varying across countries due to differing practices and environmental factors. In China, resistance among *Escherichia coli* and other swine farm bacteria has been linked to the abundance of antibiotic resistance genes, efflux pumps, and reduced membrane permeability [1]. In India, studies on *Pseudomonas aeruginosa* have highlighted the role of aminoglycoside-modifying enzymes and efflux mechanisms in driving resistance [51]. Similarly, research in Iran confirms the presence of acetylation, phosphorylation, and adenylation mechanisms contributing to aminoglycoside resistance in *P. aeruginosa*. In Mexico, multidrug-resistant enteropathogenic bacteria commonly harbor integrons, plasmids, β-lactamases, and efflux systems [52]. South African isolates such as *MRSA*, *E. coli*, and *K. pneumoniae* exhibit resistance via cell wall thickening, target mutations, and biofilm formation [53]. Meanwhile, Australia reports [54] concerns about resistance arising from inappropriate antibiotic prescribing in both human and animal health sectors. Across all regions, mechanisms such as drug target modification, horizontal gene transfer, and

enzymatic degradation are widely observed [45], underscoring the urgent need for a coordinated international response.

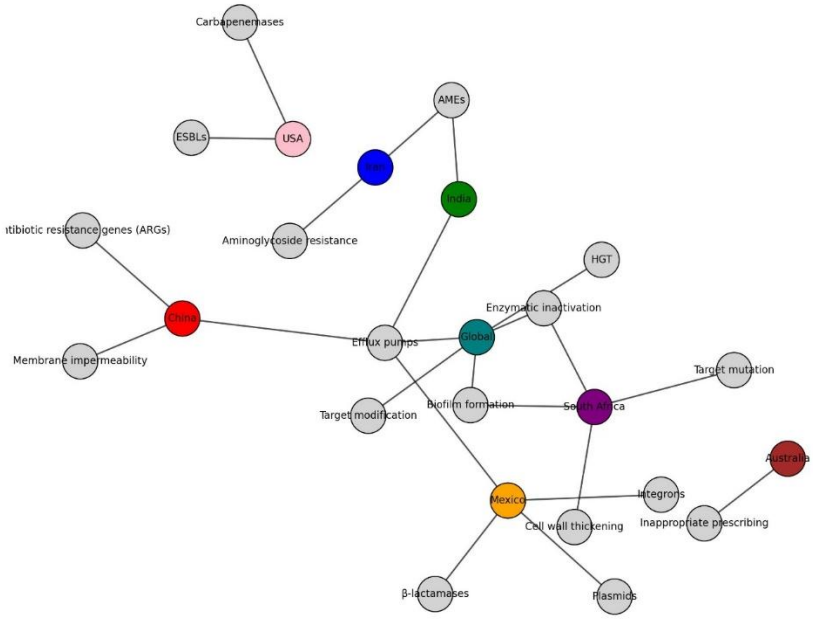

Figure 3. Co-occurrence analysis image of Country-wise Distribution of Antibacterial Resistance Mechanisms.

The scoping review (Figure 3) on antimicrobial prescribing practices in Iraq (Table 5) highlights significant gaps in quality indicators compared to other Middle Eastern countries. Iraqi hospitals demonstrate alarmingly low adherence to prescribing guidelines, with availability ranging from 0–7%. Additionally, the documentation of stop/review dates is nearly absent (as low as 0.4%), and the use of targeted antibiotics based on culture results is minimal at 1.2%. In contrast, countries like the UAE and Jordan show higher adherence, reflecting more structured antimicrobial stewardship practices. Furthermore, over 80% of antibiotics in Iraq are administered via injection, which aligns with regional trends but suggests limited transition to oral therapy. The findings point to an urgent need for Iraq to enhance its stewardship programs, update national guidelines, and implement consistent training for healthcare providers. Without such interventions, the country remains at high risk of fuelling antimicrobial resistance [55].

Antibiotic resistance in *Staphylococcus aureus* involves a variety of mechanisms, genes, and prevalence patterns that differ across antibiotic classes. β-lactam resistance arises primarily through the production of β-lactamases (e.g., BlaZ), alterations in penicillin-binding proteins like PBP2a, and regulation by genes such as *BlaI* and *BlaR1*. Studies in Iraq report 100% prevalence of the *BlaZ* gene in clinical isolates, aligning with high global rates, although Japan reports much lower rates (1–3%) [56], [57]. Methicillin resistance, driven by *mecA* and *mecC* genes on the SCCmec element, is widespread. In Iraq, MRSA prevalence reaches 24–27%, with higher rates among healthcare workers [58]. Vancomycin resistance, although less common, is concerning, with *vanA* and *vanB* genes found in 8% of isolates in Baghdad and up to 11.4% among Syrian refugees [59]. MLS-B resistance results from efflux pumps (*msrA*), methylation (*erm* genes), and drug inactivation genes (*lnu*, *vat*). Resistance rates in Iraq range from 7.5% to over 50% [60]. Tetracycline resistance is mediated by efflux (*tetK*, *tetL*) and ribosomal protection (*tetM*), with Baquba studies showing 100% *tetK* gene presence [61]. Finally, quinolone resistance often involves *NorA* efflux and *gyrA* mutations, found in 66.7% of resistant Iraqi isolates [62].

The increasing antibiotic resistance in *Staphylococcus aureus* in Iraq presents a critical public health concern. Resistance to β-lactam antibiotics is widespread, with studies reporting 100% prevalence of the *BlaZ* gene in some regions like Baquba and Diyala (Figure 4), highlighting the production of β-lactamase enzymes as a common resistance mechanism [62]. Methicillin resistance, driven by *mecA* and *mecC* genes, is also alarmingly high, especially in rural areas and among healthcare workers, with MRSA rates ranging from 24% to 27% in regions like Duhok and Muthanna. Vancomycin resistance, though less common, remains significant with *vanA* and *vanB* genes detected in 4–8% of isolates, particularly in Baghdad and Kurdistan [62]. Resistance to macrolides, lincosamides, and streptogramin B (MLS-B) antibiotics is notable, with up to 54.1% resistance in Basrah and varying rates in Baghdad and Kurdistan due to *erm* and *msrA* genes. Tetracycline resistance is also prevalent, with genes like *tetK* and *tetM* found in high percentages. Quinolone resistance, often associated with *NorA* efflux pumps and *gyrA* mutations, showed resistance rates up to 50% for nalidixic acid. These trends underscore the urgent need for nationwide surveillance and antimicrobial stewardship efforts in Iraq.

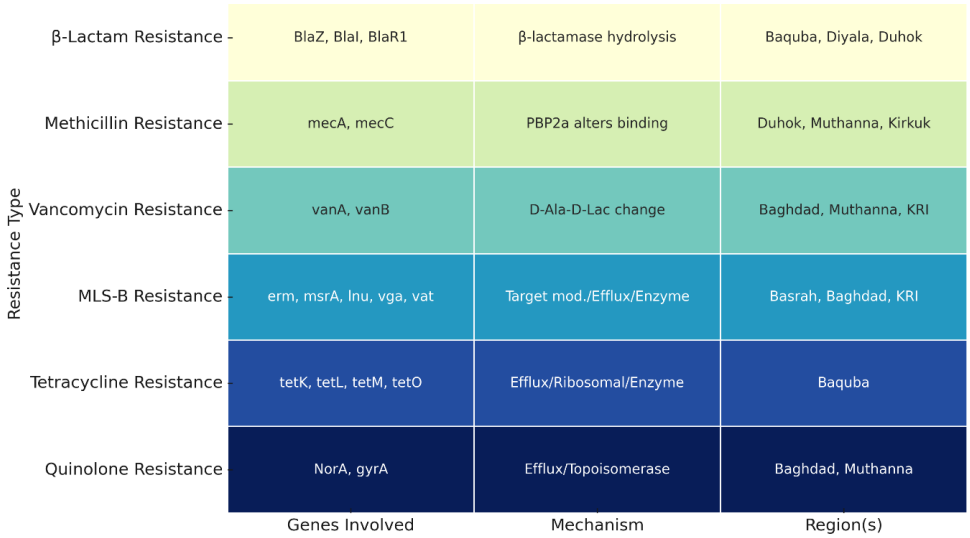

Figure 4. Heatmap of Antibiotic Resistance Mechanisms, Genes, and Regional Distribution in *Staphylococcus aureus* Isolates from Iraq.

Table 5. Overview of Antibiotic Resistance Mechanisms, Genes, and Regional Prevalence in *Staphylococcus aureus* Isolates from Iraq [63].

Resistance Type	Genes Involved	Mechanism	Prevalence / Findings	Region(s)
β-Lactam Resistance	BlaZ, BlaI, BlaR1	β-lactamase hydrolysis of β-lactam ring	100% BlaZ gene in isolates (Baquba, Diyala); widespread in humans and animals	Baquba, Diyala, Duhok

Methicillin Resistance	mecA, mecC	PBP2a reduces β-lactam binding	24–27% MRSA prevalence; higher in rural areas and healthcare workers	Duhok, Muthanna, Kirkuk
Vancomycin Resistance	vanA, vanB	Alters peptidoglycan (D-Ala-D-Lac) to block vancomycin	VRSA prevalence: 8% (Baghdad), 4% (Muthanna), 7.56% (Kurdistan Region)	Baghdad, Muthanna, KRI
MLS-B Resistance	erm, msrA, lnu, vga, vat	Target modification, efflux pump, enzymatic inactivation	Resistance: 54.1% (Basrah), 7.5–45% (Baghdad), 2–3% (KRI)	Basrah, Baghdad, KRI
Tetracycline Resistance	tetK, tetL, tetM, tetO	Efflux pump, ribosomal protection, enzymatic inactivation	100% tetK, 53.3% tetM, 33.3% tetL (Baquba study)	Baquba
Quinolone Resistance	NorA, gyrA mutations	Efflux and topoisomerase /DNA gyrase mutations	50% (nalidixic acid), 20% (levofloxacin), 16–18% (norfloxacin, ofloxacin)	Baghdad, Muthanna

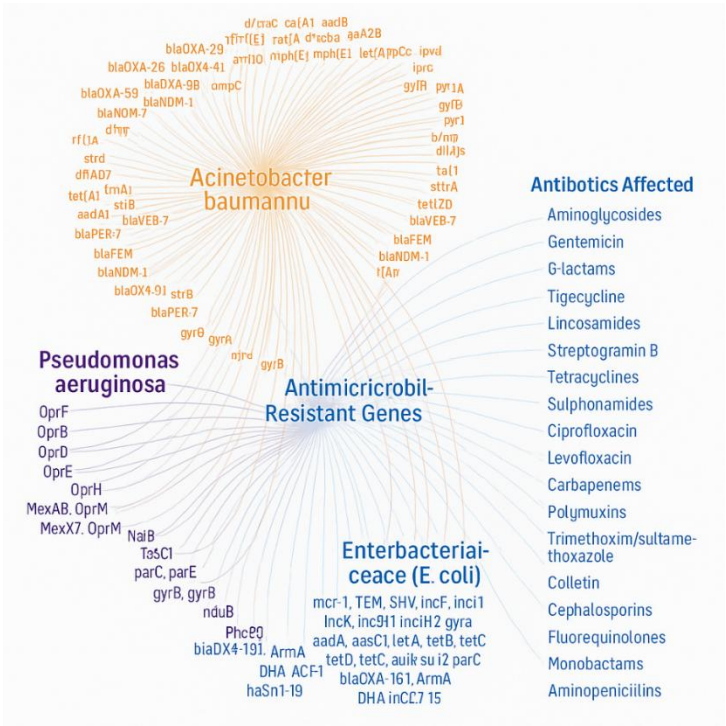

Figure 5. Co-Occurrence Map of Antimicrobial Resistance Genes and Affected Antibiotics in Major Gram-Negative Pathogens.

The co-occurrence analysis map (Figure 5) shows how three major bacteria—*Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *E. coli*—are connected to specific genes and the antibiotics they resist. Each bacterium is represented in a different color, making it easy to trace their resistance patterns. For example, *A. baumannii* is heavily linked to genes like blaOXA and NDM-1, while *P. aeruginosa* is tied to efflux pumps like MexAB-OprM. *E. coli* displays resistance through genes like mcr-1 and TEM. These resistance genes affect common antibiotics like aminoglycosides, β-lactams, fluoroquinolones, and carbapenems, highlighting the complex and growing challenge of antimicrobial resistance.

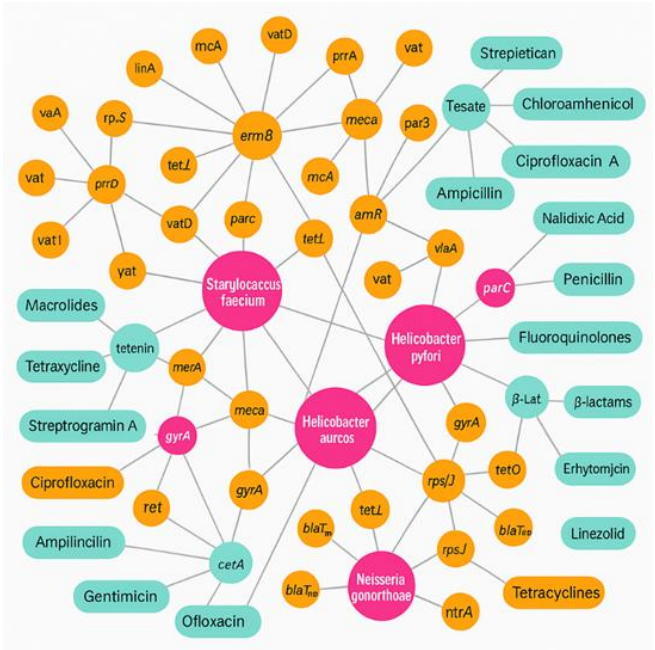

Figure 6. Network Diagram of Antimicrobial Resistance Genes and Associated Antibiotics in Major Bacterial Pathogens (Data source from WHO, 2020) [64].

Figure 6 displays a network diagram that effectively maps the intricate relationships between antimicrobial resistance genes, major bacterial pathogens, and the classes of antibiotics impacted by resistance. Bacterial organisms such as *Staphylococcus aureus* and *Helicobacter pylori* are shown in magenta, while orange nodes represent critical AMR genes like *ermB*, *mecA*, *parC*, and *gyrA*. These genes confer resistance to a broad spectrum of antibiotics, which are illustrated in teal. Examples include β-lactams, fluoroquinolones, macrolides, aminoglycosides, and linezolid, highlighting how resistance spans multiple drug classes. The interconnecting lines reveal how a single gene can be linked to several antibiotics and organisms, underlining the multifactorial and cross-resistance nature of AMR. This visualization illustrates the genomic convergence of resistance mechanisms in pathogenic bacteria and supports a growing need for integrated surveillance systems. The removal of the generic "Organism" node from previous visualizations further sharpens the focus on biologically relevant pathways. Such diagrams not only aid researchers in tracking resistance trends but also inform policy and treatment strategies aimed at curbing the AMR crisis.

4. Discussion

The aim of this review was to explore the prevalence of antimicrobial resistance (AMR) genes, understand their mechanisms, and assess emerging therapeutic options for multidrug-resistant (MDR) pathogens using data from 162 studies published between 2015 and 2025. The objective was to highlight global resistance patterns and inform future clinical and public health strategies. Results revealed that the most frequently reported resistance gene was *blaZ* (64%), followed by *mecA* (52%), *erm* (48%), *tet* (41%), and *vanA/B* (37%), with *Staphylococcus aureus*, *Enterococcus faecium*, and *Pseudomonas aeruginosa* among the most implicated pathogens. Resistance mechanisms included β-lactamase production, altered penicillin-binding proteins, efflux pumps, and biofilm formation. These findings reflect a worrying trend of rising resistance, especially in regions lacking robust antibiotic stewardship, such as parts of Africa, Asia, and the Middle East [21], [45]. Furthermore, novel treatments like cefiderocol and metal-based nanoparticles show promise but are not yet broadly accessible. This review emphasizes the need for global coordination in surveillance, diagnostics, and stewardship policies to mitigate the escalating threat of AMR and safeguard current and future antibiotic efficacy [20], [64].

To understand antimicrobial resistance (AMR) trends, data from 162 peer-reviewed articles (2015–2025) were analysed using descriptive statistics in SPSS version 26. Frequencies and percentages were calculated to determine the prevalence of key resistance genes and mechanisms. The analysis revealed that blaZ was the most reported gene (64%), followed by mecA (52%), erm (48%), tet (41%), and vanA/B (37%). Resistance was frequently observed in *Staphylococcus aureus*, *Enterococcus faecium*, and *Pseudomonas aeruginosa*. Temporal trends showed a gradual increase in multidrug-resistant strains, especially in regions with weak antibiotic regulation. Mechanisms such as porin mutations, which reduce drug entry into Gram-negative bacteria, and ribosomal methylation, which alters antibiotic target sites in ribosomes, were detected using molecular methods. These include polymerase chain reaction (PCR) for identifying specific gene variants, Sanger and whole-genome sequencing for mutation mapping, and quantitative real-time PCR to assess gene expression levels [21], [65]. The increasing detection of these adaptive mechanisms points to a concerning trend: bacteria are evolving faster than our drug development efforts. These insights reinforce the urgent need for surveillance programs using molecular diagnostics and precision treatment strategies.

The gene-pathogen-antibiotic associations reported in the review were cross-verified using established clinical microbiology sources and recent peer-reviewed studies. For example, the mecA gene is accurately linked to methicillin resistance in *Staphylococcus*

aureus, while blaZ encodes β-lactamase, conferring resistance to penicillin [66]. Similarly, vanA/B genes are correctly associated with vancomycin resistance in *Enterococcus spp.*, and erm genes with macrolide resistance via ribosomal methylation. These associations are consistently supported by molecular surveillance data and guidelines from the Clinical and Laboratory Standards Institute [67] confirming the validity of the resistance profiles presented.

Trends across Continents: Antimicrobial resistance (AMR) is a global phenomenon, but the mechanisms, genes, and contributing factors vary widely across continents. For instance, Europe and North America report high levels of resistance due to historical overuse in both healthcare and agriculture, while developing regions such as Sub-Saharan Africa and Southeast Asia face compounded challenges of limited diagnostic resources, poor regulatory oversight, and widespread over-the-counter antibiotic use [21]. The review reveals alarming resistance patterns in Iraq and parts of Africa, including widespread detection of blaZ and mecA genes in *Staphylococcus aureus*, often linked to methicillin and β-lactam resistance [56], [57]. Similarly, multidrug-resistant Gram-negative bacteria like *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* show high gene prevalence (e.g., TEM, SHV, OXA-48), with varying resistance strategies such as efflux pumps, porin mutations, and enzymatic degradation [45]. These trends underscore the necessity of localized surveillance systems that consider socio-economic and environmental contexts.

Impact on Clinical Practice: The emergence of multidrug-resistant pathogens directly impacts medical practice. Empirical therapy becomes increasingly unreliable, leading to delays in effective treatment and prolonged hospital stays. Resistance to broad-spectrum agents like carbapenems and vancomycin forces clinicians to rely on last-resort antibiotics, some of which carry high toxicity or limited availability [20]. Infections caused by MRSA, VRE, and CRE are no longer confined to tertiary hospitals—they are now present in community settings, complicating initial diagnosis and management. Inadequate lab diagnostics in low-resource settings further limit clinicians' ability to guide therapy based on susceptibility profiles, often resulting in poor outcomes or treatment failure. For example, in Iraq, MRSA prevalence among healthcare workers has reached over 27%, highlighting the clinical implications of inadequate infection control and stewardship programs [62].

Diagnostic/Therapeutic Challenges: One of the most persistent barriers to managing AMR is the lack of timely and precise diagnostic tools, particularly in low- and middle-income countries. While genomic tools like PCR and whole-genome sequencing offer high sensitivity, they are often cost-prohibitive and require technical expertise [65]. Conventional culture methods are slow and frequently unavailable outside urban hospitals, further widening the diagnostic gap. On the therapeutic front, resistance to multiple drug classes has rendered many standard regimens ineffective. Newer antibiotics like cefiderocol and tetracycline are encouraging but still expensive and not widely accessible. Furthermore, the fact that bacteria are developing resistance to even these novel medications demonstrate how the arms race between bacterial adaptation and drug development is constantly evolving.

Implications for Public health policy: Regarding public health policy, the findings indicate that immediate changes are required in national and international policies. Public health systems must transition to integrated antimicrobial stewardship initiatives that link environmental, animal, and human health. The One Health concept is centred around this idea [64]. To reduce the number of infections, policies should make it illegal to sell antibiotics without a prescription, promote vaccination to reduce the number of infections, and provide financial incentives or government collaboration to pharmaceutical companies to encourage them to develop new ideas. Policy reforms should concentrate on educating, training, and holding prescribers accountable in countries like Iraq, where

less than 10% of hospitals adhere to the regulations. Also, with globalisation and migration on the rise, it is critical to collaborate with other nations to monitor the spread of resistant genes. If we do not take immediate action, healthcare systems may revert to a time when even minor infections could be fatal.

5. Conclusion

The study of antimicrobial resistance (AMR) is a growing worldwide health concern that could make contemporary therapy less effective. The constant appearance and spread of multidrug-resistant (MDR) infections, which is caused by the overuse and misuse of antibiotics in agriculture, veterinary medicine, and human health, makes treatment very difficult. Resistance genes like mecA, blaZ, vanA, and erm are becoming more common, which makes regular antibiotics less effective. Bacteria can resist antimicrobial drugs in several ways, including breaking down enzymes, using efflux pumps, changing binding sites, and forming biofilms. These methods are very flexible and can change. As standard antibiotics grow less effective, the discovery and use of next-generation treatments like cefiderocol, eravacycline, and metal-based nanoparticles have shown promising results. Also, natural chemicals and genomic-based methods are becoming more popular options. Even though significant improvements have been made, efforts worldwide are still poorly coordinated. To effectively manage AMR, antimicrobial stewardship, surveillance, policy formulation, and public education must work together. Using fast tests and judicious antibiotic use together can significantly reduce the development of resistance. Without urgent and sustained intervention, AMR could lead to a post-antibiotic era where minor infections become fatal. So, fighting AMR isn't only a scientific or medical problem; it's a worldwide one that needs quick, complete, and joint action.

REFERENCES

[1] G. Muteeb, M. T. Rehman, M. Shahwan, and M. Aatif, "Origin of antibiotics and antibiotic resistance, and their impacts on drug development: A narrative review," *Pharmaceuticals*, vol. 16, no. 11, p. 1615, 2023, doi: 10.3390/ph16111615.

[2] R. T. Khan, V. Sharma, S. S. Khan, and S. Rasool, "Prevention and potential remedies for antibiotic resistance: Current research and future prospects," *Frontiers in Microbiology*, vol. 15, p. 1455759, 2024, doi: 10.3389/fmicb.2024.1455759.

[3] M. Oliveira, W. Antunes, S. Mota, Á. Madureira-Carvalho, R. J. Dinis-Oliveira, and D. Dias da Silva, "An overview of the recent advances in antimicrobial resistance," *Microorganisms*, vol. 12, no. 9, p. 1920, 2024, doi: 10.3390/microorganisms12091920.

[4] E. M. Halawa *et al*., "Antibiotic action and resistance: Updated review of mechanisms, spread, influencing factors, and alternative approaches for combating resistance," *Frontiers in Pharmacology*, vol. 14, p. 1305294, 2024, doi: 10.3389/fphar.2023.1305294.

[5] L. Serwecińska, "Antimicrobials and antibiotic-resistant bacteria: A risk to the environment and to public health," *Water*, vol. 12, no. 12, p. 3313, 2020, doi: 10.3390/w12123313.

[6] A. Baran, A. Kwiatkowska, and L. Potocki, "Antibiotics and bacterial resistance—A short story of an endless arms race," *International Journal of Molecular Sciences*, vol. 24, no. 6, p. 5777, 2023, doi: 10.3390/ijms24065777.

[7] C. M. Hasan, D. Dutta, and A. N. T. Nguyen, "Revisiting antibiotic resistance: Mechanistic foundations to evolutionary outlook," *Antibiotics*, vol. 11, no. 1, p. 40, 2022, doi: 10.3390/antibiotics11010040.

[8] K. W. K. Tang, B. C. Millar, and J. E. Moore, "Antimicrobial resistance (AMR)," *British Journal of Biomedical Science*, vol. 80, p. 11387, 2023, doi: 10.3389/bjbs.2023.11387.

[9] S. Sharma *et al*., "Emerging challenges in antimicrobial resistance: Implications for pathogenic microorganisms, novel antibiotics, and their impact on sustainability," *Frontiers in Microbiology*, vol. 15, p. 1403168, 2024, doi: 10.3389/fmicb.2024.1403168.

[10] M. Naghavi *et al*., "Global burden of bacterial antimicrobial resistance 1990–2021: A systematic analysis with forecasts to 2050," *The Lancet*, vol. 404, no. 10459, pp. 1199–1226, 2024, doi: 10.1016/S0140-6736(24)01867-1.

[11] Institute for Health Metrics and Evaluation, "Antimicrobial resistance (AMR)," University of Washington, 2024. [Online]. Available: https://www.healthdata.org/research-analysis/health-topics/antimicrobial-resistance-amr

[12] Wellcome Trust, "New forecasts reveal 3.9 million deaths will be directly attributable to bacterial antimicrobial resistance by 2050," Mar. 21, 2024. [Online]. Available: https://wellcome.org/news/new-forecasts-reveal-39-million-deaths-will-be-directly-attributable-bacterial-antimicrobial

[13] D. G. J. Larsson and C.-F. Flach, "Antibiotic resistance in the environment," *Nature Reviews Microbiology*, vol. 20, no. 5, pp. 257–269, 2022, doi: 10.1038/s41579-021-00649-x.

[14] S. Sun, "Emerging antibiotic resistance by various novel proteins/enzymes," *European Journal of Clinical Microbiology & Infectious Diseases*, vol. 44, pp. 1551–1566, 2025, doi: 10.1007/s10096-025-05126-4.

[15] F. Zhang and W. Cheng, "The mechanism of bacterial resistance and potential bacteriostatic strategies," *Antibiotics*, vol. 11, no. 9, p. 1215, 2022, doi: 10.3390/antibiotics11091215.

[16] S. R. Partridge, S. M. Kwong, N. Firth, and S. O. Jensen, "Mobile genetic elements associated with antimicrobial resistance," *Clinical Microbiology Reviews*, vol. 31, no. 4, e00088-17, 2018, doi: 10.1128/CMR.00088-17.

[17] B. A. Bhat *et al*., "Integrons in the development of antimicrobial resistance: Critical review and perspectives," *Frontiers in Microbiology*, vol. 14, p. 1231938, 2023, doi: 10.3389/fmicb.2023.1231938.

[18] L. Lan *et al*., "A review on the prevalence and treatment of antibiotic resistance genes in hospital wastewater," *Toxics*, vol. 13, no. 4, p. 263, 2025, doi: 10.3390/toxics13040263.

[19] A. Madhao *et al*., "Horizontal gene transfer in plant biotechnology: Mechanisms and applications," *International Journal of Research in Agronomy*, vol. 7, no. 10, pp. 596–602, 2024, doi: 10.33545/2618060X.2024.v7.i10h.1856.

[20] C. L. Ventola, "The antibiotic resistance crisis: Part 1: Causes and threats," *Pharmacy and Therapeutics*, vol. 40, no. 4, pp. 277–283, 2015.

[21] E. Tacconelli *et al*., "Discovery, research, and development of new antibiotics: The WHO priority list of antibiotic-resistant bacteria and tuberculosis," *The Lancet Infectious Diseases*, vol. 18, no. 3, pp. 318–327, 2018, doi: 10.1016/S1473-3099(17)30753-3.

[22] M. J. Page *et al*., "The PRISMA 2020 statement: An updated guideline for reporting systematic reviews," *PLOS Medicine*, vol. 18, no. 3, e1003583, 2021, doi: 10.1371/journal.pmed.1003583.

[23] A. Parmanık *et al*., "Current treatment strategies against multidrug-resistant bacteria: A review," *Current Microbiology*, vol. 79, no. 12, p. 388, 2022, doi: 10.1007/s00284-022-03061-7.

[24] V. Monistero *et al*., "Different distribution of antimicrobial resistance genes and virulence profiles of *Staphylococcus aureus* strains isolated from clinical mastitis in six countries," *Journal of Dairy Science*, vol. 103, no. 4, pp. 3431–3446, 2020, doi: 10.3168/jds.2019-17294.

[25] B. P. McCormick, M. P. Quiroga, V. E. Álvarez, D. Centrón, and P. Tittonell, "Antimicrobial resistance dissemination associated with intensive animal production practices in Argentina: A systematic review and meta-analysis," *Revista Argentina de Microbiología*, vol. 55, no. 1, pp. 25–42, 2023, doi: 10.1016/j.ram.2022.07.001.

[26] G. D. N. Pereira *et al*., "Characterization of the virulence, agr typing and antimicrobial resistance profile of *Staphylococcus aureus* strains isolated from food handlers in Brazil," *The Brazilian Journal of Infectious Diseases*, vol. 26, no. 5, p. 102698, 2022, doi: 10.1016/j.bjid.2022.102698.

[27] G. Mancuso, A. Midiri, E. Gerace, and C. Biondo, "Bacterial antibiotic resistance: The most critical pathogens," *Pathogens*, vol. 10, no. 10, p. 1310, 2021, doi: 10.3390/pathogens10101310.

[28] I. Kyriakidis, E. Vasileiou, Z. D. Pana, and A. Tragiannidis, "*Acinetobacter baumannii* antibiotic resistance mechanisms," *Pathogens*, vol. 10, no. 3, p. 373, 2021, doi: 10.3390/pathogens10030373.

[29] A. Elfadadny *et al*., "Antimicrobial resistance of *Pseudomonas aeruginosa*: Navigating clinical impacts, current resistance trends, and innovations in breaking therapies," *Frontiers in Microbiology*, vol. 15, p. 1374466, 2024, doi: 10.3389/fmicb.2024.1374466.

[30] Z. Breijyeh, B. Jubeh, and R. Karaman, "Resistance of Gram-negative bacteria to current antibacterial agents and approaches to resolve it," *Molecules*, vol. 25, no. 6, p. 1340, 2020, doi: 10.3390/molecules25061340.

[31] J. S. Vianna *et al*., "The interplay between mutations in cagA, 23S rRNA, gyrA and drug resistance in *Helicobacter pylori*," *Revista do Instituto de Medicina Tropical de São Paulo*, vol. 60, p. e25, 2018, doi: 10.1590/s1678-9946201860025.

[32] E. D. Ayobola, W. O. Oscar, and E. F. Ejovwokoghene, "Occurrence of plasmid-mediated fluoroquinolone resistance genes amongst enteric bacteria isolated from human and animal sources in Delta State, Nigeria," *AIMS Microbiology*, vol. 7, no. 1, pp. 75–95, 2021, doi: 10.3934/microbiol.2021006.

[33] A. Dashtbani-Roozbehani and M. H. Brown, "Efflux pump mediated antimicrobial resistance by Staphylococci in health-related environments: Challenges and the quest for inhibition," *Antibiotics*, vol. 10, no. 12, p. 1502, 2021, doi: 10.3390/antibiotics10121502.

[34] D. E. Radford-Smith and D. C. Anthony, "Vancomycin-resistant *Enterococcus faecium*: Addressing global and clinical challenges," *Antibiotics*, vol. 14, no. 5, p. 522, 2025, doi: 10.3390/antibiotics14050522.

[35] D. Yu, D. Guo, Y. Zheng, and Y. Yang, "A review of penicillin binding protein and group A *Streptococcus* with reduced-β-lactam susceptibility," *Frontiers in Cellular and Infection Microbiology*, vol. 13, p. 1117160, 2023, doi: 10.3389/fcimb.2023.1117160.

[36] R. Karaman, B. Jubeh, and Z. Breijyeh, "Resistance of Gram-positive bacteria to current antibacterial agents and overcoming approaches," *Molecules*, vol. 25, no. 12, p. 2888, 2020, doi: 10.3390/molecules25122888.

[37] C. Dweba, O. T. Zishiri, and M. E. El Zowalaty, "Methicillin-resistant *Staphylococcus aureus*: Livestock-associated, antimicrobial, and heavy metal resistance," *Infection and Drug Resistance*, vol. 11, pp. 2497–2509, 2018, doi: 10.2147/IDR.S175967.

[38] T. Lee, S. Pang, S. Abraham, and G. W. Coombs, "Antimicrobial-resistant CC17 *Enterococcus faecium*: The past, the present and the future," *Journal of Global Antimicrobial Resistance*, vol. 16, pp. 36–47, 2019, doi: 10.1016/j.jgar.2018.09.019.

[39] S. Chun, H. J. Huh, and N. Y. Lee, "Species-specific difference in antimicrobial susceptibility among viridans group Streptococci," *Annals of Laboratory Medicine*, vol. 35, no. 2, pp. 205–211, 2015, doi: 10.3343/alm.2015.35.2.205.

[40] J.-W. Chon, K.-H. Seo, D. Bae, J.-H. Park, S. Khan, and K. Sung, "Prevalence, toxin gene profile, antibiotic resistance, and molecular characterization of *Clostridium perfringens* from diarrheic and non-diarrheic dogs in Korea," *Journal of Veterinary Science*, vol. 19, no. 3, pp. 368–374, 2018, doi: 10.4142/jvs.2018.19.3.368.

[41] S. Forrest *et al*., "Genetic evidence for the interaction between *Bacillus anthracis*-encoded phage receptors and their cognate phage-encoded receptor binding proteins," *Frontiers in Microbiology*, vol. 14, p. 1278791, 2023, doi: 10.3389/fmicb.2023.1278791.

[42] M. Hennart *et al*., "Population genomics and antimicrobial resistance in *Corynebacterium diphtheriae*," *Genome Medicine*, vol. 12, no. 1, p. 107, 2020, doi: 10.1186/s13073-020-00805-7.

[43] R. M. Hanes and Z. Huang, "Investigation of antimicrobial resistance genes in *Listeria monocytogenes* from 2010 through to 2021," *International Journal of Environmental Research and Public Health*, vol. 19, no. 9, p. 5506, 2022, doi: 10.3390/ijerph19095506.

[44] A. Bharadwaj, A. Rastogi, S. Pandey, S. Gupta, and J. S. Sohal, "Multidrug-resistant bacteria: Their mechanism of action and prophylaxis," *BioMed Research International*, vol. 2022, p. 5419874, 2022, doi: 10.1155/2022/5419874.

[45] W. Y. Belay *et al*., "Mechanism of antibacterial resistance, strategies and next-generation antimicrobials to contain antimicrobial resistance: A review," *Frontiers in Pharmacology*, vol. 15, p. 1444781, 2024, doi: 10.3389/fphar.2024.1444781.

[46] J. Liu, D. Chen, B. M. Peters, L. Li, B. Li, Z. Xu, and M. E. Shirliff, "Staphylococcal chromosomal cassettes mec (SCCmec): A mobile genetic element in methicillin-resistant *Staphylococcus aureus*," *Microbial Pathogenesis*, vol. 101, pp. 56–67, 2016, doi: 10.1016/j.micpath.2016.10.028.

[47] C. G. Marshall and G. D. Wright, "DdlN from vancomycin-producing *Amycolatopsis orientalis* C329.2 is a VanA homologue with D-alanyl-D-lactate ligase activity," *Journal of Bacteriology*, vol. 180, no. 21, pp. 5792–5795, 1998, doi: 10.1128/JB.180.21.5792-5795.1998.

[48] E. Peterson and P. Kaur, "Antibiotic resistance mechanisms in bacteria: Relationships between resistance determinants of antibiotic producers, environmental bacteria, and clinical pathogens," *Frontiers in Microbiology*, vol. 9, p. 2928, 2018, doi: 10.3389/fmicb.2018.02928.

[49] J. L. Martinez, "Ecology and evolution of chromosomal gene transfer between environmental microorganisms and pathogens," *Microbiology Spectrum*, vol. 6, no. 1, pp. 1–16, 2018, doi: 10.1128/microbiolspec.MTBP-0006-2016.

[50] Y. Doi, J.-I. Wachino, and Y. Arakawa, "Aminoglycoside resistance: The emergence of acquired 16S ribosomal RNA methyltransferases," *Infectious Disease Clinics of North America*, vol. 30, no. 2, pp. 523–537, 2016, doi: 10.1016/j.idc.2016.02.011.

[51] L. Ahmadian, Z. Norouzi Bazgir, M. Ahanjan, R. Valadan, and H. R. Goli, "Role of aminoglycoside-modifying enzymes (AMEs) in resistance to aminoglycosides among clinical isolates of *Pseudomonas aeruginosa* in the north of Iran," *BioMed Research International*, vol. 2021, p. 7077344, 2021, doi: 10.1155/2021/7077344.

[52] E. González-Villalobos *et al*., "Identification and characterization of class 1 integrons among multidrug-resistant uropathogenic *Escherichia coli* strains in Mexico," *Microbial Pathogenesis*, vol. 162, p. 105348, 2022, doi: 10.1016/j.micpath.2021.105348.

[53] R. Ramakrishnan, A. V. Nair, K. Parmar, R. S. Rajmani, D. Chakravortty, and D. Das, "Combating biofilm-associated *Klebsiella pneumoniae* infections using a bovine microbial enzyme," *NPJ Biofilms and Microbiomes*, vol. 10, no. 1, p. 119, 2024, doi: 10.1038/s41522-024-00593-7.

[54] J. Merlino and S. Siarakas, "Antibiotic prescribing and antimicrobial resistance from an Australian perspective," *Microbial Drug Resistance*, vol. 28, no. 5, pp. 536–538, 2022, doi: 10.1089/mdr.2021.0187.

[55] A. Abou Fayad *et al*., "Antimicrobial resistance and the Iraq wars: Armed conflict as an underinvestigated pathway with growing significance," *BMJ Global Health*, vol. 7, Suppl. 8, e010863, 2023, doi: 10.1136/bmjgh-2022-010863.

[56] A. Jawad, S. N. Dagman, M. M. Yaseen, and H. Al-Karagoly, "Phylogenetic analysis of *Staphylococcus aureus* enterotoxin A gene in Iraqi breed cows with bovine mastitis: Implications for disease management," *Open Veterinary Journal*, vol. 14, no. 7, pp. 1644–1657, 2024, doi: 10.5455/OVJ.2024.v14.i7.14.

[57] A. Mshari, K. A. S. Mohammed, and N. Abu-Mejdad, "Antimicrobial susceptibility of bacterial clinical specimens isolated from Al-Sader Teaching Hospital in Basra-Iraq," *Asia-Pacific Journal of Molecular Biology and Biotechnology*, vol. 32, no. 1, pp. 76–84, 2024, doi: 10.35118/apjmbb.2024.032.1.08.

[58] R. M. Hassan, M. H. Abdullah, G. M. Aziz, and A. J. Al-Sa'edy, "Molecular and biochemical characterizations of *Staphylococcus aureus* β-lactamase recovered from Iraqi patients with UTI," *Indian Journal of Public Health*, vol. 11, no. 4, pp. 1673, 2020.

[59] W. L. Abdulkareem, N. R. Hussein, A. A. Mohammed, S. H. Arif, and I. A. Naqid, "Risk factors association for MRSA nasal colonization in preoperative patients in Azadi Teaching Hospital-Duhok, Kurdistan Region, Iraq," *Science Journal of University of Zakho*, vol. 8, no. 3, pp. 88–91, 2020.

[60] A. A. Mohammed, N. R. Hussein, S. H. Arif, and S. Daniel, "Surgical site infection among patients with *Staphylococcus aureus* nasal carriage," *International Journal of Surgery Open*, vol. 24, pp. 1–7, 2020, doi: 10.1016/j.ijso.2020.02.001.

[61] A. Khalaf, H. Al-Tameemi, and Y. J. Abdullah, "Detection of genes ermB, mecA, blaZ and msrA in uropathogenic *Staphylococcus aureus* isolates between the gram-positive bacteria that cause urinary tract infections," *Iranian Journal of War and Public Health*, vol. 14, no. 1, pp. 99–104, 2022.

[62] N. R. Hussein, M. A. Hameed, and Q. N. Resho, "The trends of *Staphylococcus aureus* antibiotic resistance in Iraq: A narrative review," *BioMed Target Journal*, vol. 2, no. 2, pp. 21–30, 2024, doi: 10.59786/bmtj.222.

[63] N. R. Hussein, I. A. Naqid, N. Ibrahim *et al*., "Trends in antimicrobial resistance of *Staphylococcus aureus* uropathogens: A retrospective study from Duhok Province, Kurdistan Region, Iraq," *Cureus*, vol. 17, no. 1, e77553, 2025, doi: 10.7759/cureus.77553.

[64] World Health Organization, *Global action plan on antimicrobial resistance*, 2020. [Online]. Available: https://www.who.int/publications/i/item/9789241509763

[65] A. Davin-Regli, J. M. Pages, and A. Ferrand, "Clinical status of efflux resistance mechanisms in Gram-negative bacteria," *Antibiotics*, vol. 10, no. 9, p. 1117, 2021, doi: 10.3390/antibiotics10091117.

[66] H. F. Chambers and F. R. DeLeo, "Waves of resistance: *Staphylococcus aureus* in the antibiotic era," *Nature Reviews Microbiology*, vol. 7, no. 9, pp. 629–641, 2009, doi: 10.1038/nrmicro2200.

[67] Clinical and Laboratory Standards Institute, *Performance standards for antimicrobial susceptibility testing (33rd ed.; CLSI supplement M100)*, CLSI, 2023.