Review Article

Antimicrobial Resistance Genes: Molecular Mechanisms, Dissemination, and Public Health Implications

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ABSTRACT

Antimicrobial resistance (AMR) is one of the most important global health problems of the twenty-first century. It threatens the effective prevention and treatment of an ever-increasing range of bacterial infections. At the heart of this phenomenon lie resistance genes, discrete genetic elements that confer upon bacteria the ability to survive exposure to antimicrobial agents that would otherwise be lethal or growth-inhibitory. This review summarizes the current knowledge on the molecular mechanisms of antimicrobial resistance genes, relevant gene families, such as the beta-lactamases, mecA, vanA/vanB, tetracycline and macrolide resistance genes, and the plasmid-mediated colistin resistance gene mcr-1. It also discusses the laboratory methods for their detection, their clinical and epidemiological importance and the One Health strategies being implemented for their control. Understanding the genetic basis of AMR is crucial for developing rational diagnostic, therapeutic and antimicrobial stewardship strategies.

Keywords: AMR, Beta-lactamases, Plasmid mediated resistance, Macrolide.

1. INTRODUCTION

Antibiotic resistance is a frequent challenge in clinical practice. Antimicrobial resistance (AMR) refers to the ability of microorganisms including bacteria, fungi, viruses, and parasites to withstand drugs that once effectively inhibited or killed them. Among these, bacterial resistance has escalated into a global public health crisis, with recent estimates linking hundreds of thousands to over a million deaths annually to drug-resistant infections. Among the different types of drug resistance, most microbiologists would agree that multi-drug resistance Gram negative bacteria pose the greatest threat to human health. In addition, there are fewer effective drugs developed specifically against Gram-negative bacteria. During the past decade the increase of antibiotic resistance in enterobacteriaceae has become a major concern worldwide. An evolution of antibiotic resistant bacteria has resulted in the need for new antibiotics. β-lactam based drugs are the most predominantly prescribed antibiotics to combat bacterial infections. However, production of β-lactamases, which catalyzes the hydrolysis of the β-lactam bond of this class of antibiotics, by *Bacillus cereus, Escherichia coli, Klebsiella pneumoniae* are rendering them useless[1].

Antimicrobial resistance (AMR) has emerged as one of the most pressing global health challenges. Recent analyses estimate that bacterial AMR was associated with 4–7.1 million deaths worldwide in 2021, and without strong interventions, annual deaths could double by 2050, potentially reaching 10 million. The economic burden is equally severe, with the World Bank projecting losses of up to US$3.4 trillion in yearly GDP by 2030 if AMR remains unchecked. Beyond mortality and cost, AMR threatens decades of medical progress, jeopardizing routine surgeries, cancer chemotherapy, and other treatments that depend on effective antimicrobial protection. Resistance mechanisms can be classified as intrinsic, naturally present in certain species regardless of prior drug exposure, or acquired, which develops in previously susceptible populations through chromosomal mutations or the acquisition of foreign genetic material[2]. This review focuses on the second category, which involves acquired resistance driven by specific resistance genes, because these genes act as the units of selection, inheritance, and horizontal transfer that ultimately dictate the speed and extent to which resistance spreads through microbial populations.

2. MOLECULAR MECHANISMS OF RESISTANCE ENCODED BY AMR GENES

The molecular mechanisms of AMR in bacteria are highly complex as shown in Fig. 1. Together, these mechanisms reduce the efficacy of key therapies. Resistance is often mediated by antibiotic-binding targets, active efflux systems that pump drugs out of cells and enzymatic degradation or modification of antibiotics, e.g. β-lactamases. AMR genes provide resistance through four general and sometimes overlapping molecular strategies[2].

2.1 Enzymatic Inactivation or Modification of the Drug

Enzymatic inactivation remains one of the most sophisticated bacterial defense strategies against antibiotic treatment. β-Lactamases are the most extensively studied enzymes, classified into four Ambler classes: Class A (CTX-M-15 extended-spectrum β-lactamases [ESBLs]), Class B metallo-β-lactamases (NDM, VIM), Class C (AmpC cephalosporinases), and Class D (OXA-type carbapenemases)[2]. Many resistance genes encode enzymes that chemically destroy or modify the antimicrobial agent before it can reach its target. The beta-lactamase family,

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encoded by genes such as blaTEM, blaSHV, blaCTX-M, blaNDM, and blaKPC, hydrolyses the β-lactam ring common to penicillins, cephalosporins, and carbapenems, rendering these drugs inactive [2,7].

Aminoglycoside-modifying enzymes, encoded by aac (aminoglycoside acetyltransferases), aph (aminoglycoside phosphotransferases) and ant (aminoglycoside nucleotidyltransferases) genes, chemically modify aminoglycoside antibiotics by acetylation, phosphorylation or adenylation. These modifications prevent the drug from binding to the bacterial ribosome and abolish its antibacterial activity[2].

2.2 Modification of the Drug Target

Bacteria evade antimicrobials through structural alterations in their target drugs. Ribosomal modifications, particularly in 16S rRNA and ribosomal proteins, compromise the binding of aminoglycosides and tetracyclines[2]. Resistance genes can alter the very molecule that an antibiotic is designed to bind, reducing the drug's affinity for its target while preserving the target's normal cellular function. The mecA gene, carried by methicillin-resistant Staphylococcus aureus (MRSA), encodes an alternative penicillin-binding protein, PBP2a, with markedly reduced affinity for beta-lactam antibiotics[2]. The vanA and vanB gene clusters alter the terminal residues of the peptidoglycan precursor from D-alanine–D-alanine to D-alanine–D-lactate, weakening vancomycin binding [10,11]. Ribosomal methylation, mediated by erm genes, methylates 23S rRNA and blocks macrolide, lincosamide, and streptogramin binding [2].

2.3 Reduced Drug Uptake and Efflux

Active efflux pumps, which are another major mechanism by which bacteria decrease intracellular antibiotic levels. Bacteria can limit intracellular drug accumulation either by reducing membrane permeability, often through loss or modification of porin channels, or by actively pumping the drug back out of the cell using efflux pump systems such as AcrAB-TolC, MexAB-OprM, and tetA/tetB[12]. Efflux pumps are frequently multi-drug transporters, and their overexpression can confer simultaneous resistance to structurally unrelated antibiotic classes [2,12].

2.4 Bypass and Protection Mechanisms

Some genes provide resistance not by altering the drug or its target directly, but by physically shielding the target. The plasmid-mediated quinolone resistance genes qnrA, qnrB, and qnrS encode proteins that bind DNA gyrase and topoisomerase IV, protecting them from fluoroquinolone inhibition [2]. Biofilm formation, though not itself encoded by a single resistance gene, further compounds these mechanisms by creating a physical and physiological barrier that limits antibiotic penetration and promotes genetic exchange within densely packed bacterial communities [5].

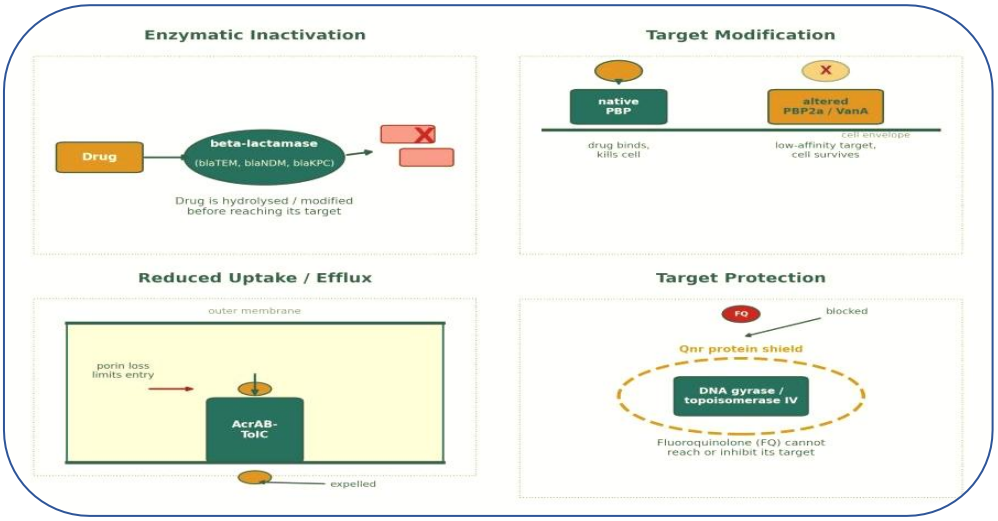


Figure 1: Four molecular strategies by which AMR genes confer resistance.

3. CLASSIFICATION AND GENETIC LOCATION OF AMR GENES

AMR genes can be broadly classified according to their location within the bacterial genome, a distinction that has significant implications for how readily resistance spreads (Fig-2).

i. Chromosomal resistance genes are typically transmitted vertically, from a bacterial cell to its daughter cells during division, and often arise through spontaneous point mutations, for example in the gyrA and parC genes conferring fluoroquinolone resistance, or in rpoB conferring rifampicin resistance[1].

ii. Plasmid borne resistance genes reside on extrachromosomal, self-replicating DNA elements that can transfer between bacterial cells, even across different species and genera, through conjugation. Genes such as blaNDM, mcr-1, and many tet and sul genes are frequently plasmid-associated, which greatly accelerates their dissemination [4,8].

iii. Transposon and integron-associated genes are embedded within mobile genetic elements that can "jump" between plasmids and the chromosome, and in the case of integrons, capture and express cassettes of multiple resistance genes simultaneously, often

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producing multidrug-resistant phenotypes in a single genetic event [5,13].

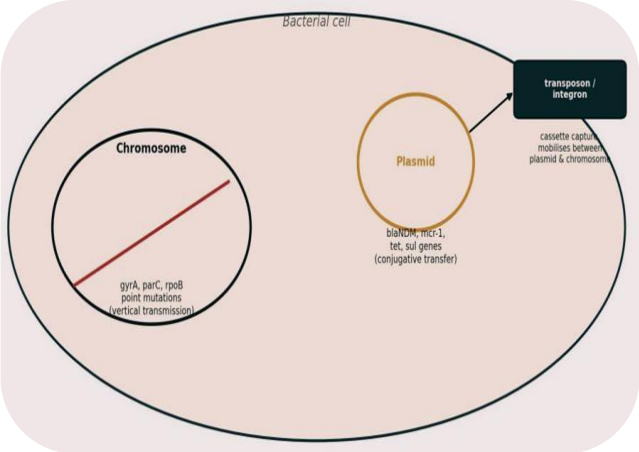


Figure 2: Genetic locations of AMR genes in Bacterial cell.

4. HORIZONTAL GENE TRANSFER AND MOBILE GENETIC ELEMENTS

A defining feature of bacterial AMR is its capacity to spread horizontally, that is, between unrelated or distantly related bacterial cells within a single generation, rather than solely through inherited vertical transmission. Three principal mechanisms drive this process (Fig.3).

4.1 Conjugation

Conjugation involves direct cell-to-cell contact, typically mediated by a pilus, through which a donor bacterium transfers a plasmid carrying resistance genes to a recipient. This is considered the most significant route for the dissemination of clinically important resistance genes, including many carbapenemase and colistin resistance determinants, because it can occur across species and even genus boundaries [4,14].

4.2 Transformation

Some bacterial species are naturally competent and can take up free DNA, including resistance genes released into the environment from lysed bacterial cells, directly from their surroundings and incorporate it into their own genome [13].

4.3 Transduction

Bacteriophages, viruses that infect bacteria, can inadvertently package fragments of bacterial DNA, including resistance genes, and introduce them into a new host cell during a subsequent infection cycle [13].

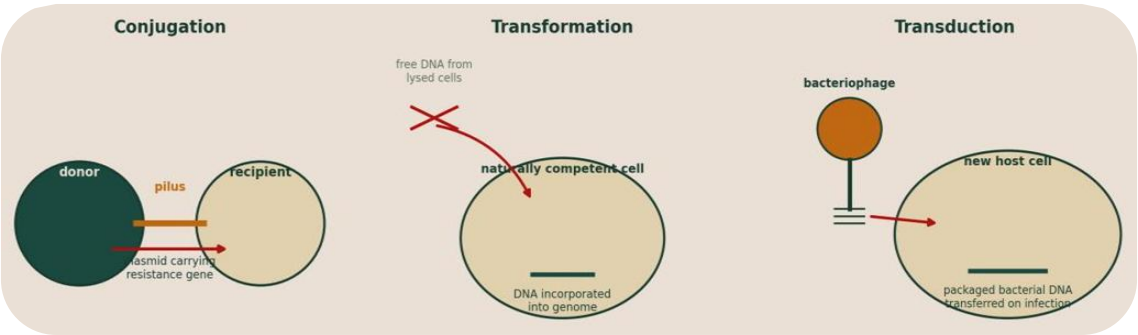


Figure 3: The three classical mechanisms of horizontal gene transfer: conjugation, transformation, and transduction.

Table 1: The gene family and resistance mechanism in clinically significant microorganisms

Gene / Family	Resistance Mechanism	Antibiotic Class Affected	Representative Organisms
blaTEM, blaSHV, blaCTX-M	Beta-lactamase hydrolysis of the beta-lactam ring	Penicillins, cephalosporins (ESBLs)	*E. coli*, *Klebsiella pneumoniae*
blaNDM, blaKPC, blaOXA-48	Carbapenemase production (metallo- and serine beta-lactamases)	Carbapenems	*Klebsiella pneumoniae*, *Acinetobacter baumannii*
mecA / mecC	Altered penicillin-binding protein (PBP2a) with low drug affinity	Methicillin, all beta-lactams	*Staphylococcus aureus* (MRSA)
vanA / vanB	Modified peptidoglycan precursor (D-Ala-D-Lac) reducing drug binding	Vancomycin (glycopeptides)	*Enterococcus faecium*, *E. faecalis*
tetA, tetB, tetM	Efflux pump extrusion or ribosomal protection	Tetracyclines	*E. coli, Salmonella spp.*
ermB, ermC	Ribosomal RNA methylation blocking drug binding	Macrolides, lincosamides, streptogramins	*Streptococcus, Staphylococcus spp.*
aac(6')-Ib, aph, ant	Aminoglycoside-modifying enzymes (acetylation, phosphorylation, adenylation)	Aminoglycosides	*Enterobacteriaceae, Pseudomonas spp.*
qnrA, qnrB, qnrS	Plasmid-mediated protection of DNA gyrase/topoisomerase IV	Fluoroquinolones	*E. coli, Klebsiella spp.*
sul1, sul2	Altered dihydropteroate synthase target enzyme	Sulfonamides	*E. coli, Salmonella spp*.
mcr-1	Modification of lipid A reducing colistin binding	Colistin (polymyxins)	*E. coli, Klebsiella pneumoniae*

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Integrons deserve particular mention as genetic platforms that capture gene cassettes, frequently resistance genes, via site-specific recombination, and can express multiple cassettes from a single promoter. This allows for the rapid and simultaneous acquisition of resistance to several unrelated antibiotic classes and is a major contributor to the emergence of multidrug-resistant clinical isolates [5,13].

5. MAJOR CLINICALLY SIGNIFICANT AMR GENE FAMILIES

The table-1 below summarizes the resistance mechanism, drug class affected, and representative organisms for several clinically important gene families that are frequently encountered in both hospital and community settings.

6. DETECTION OF AMR GENES

Accurate identification of resistance genes underpins effective antimicrobial stewardship and infection control. Commonly used approaches include [15].

a) Phenotypic susceptibility testing, such as disc diffusion and broth microdilution, which infers resistance from observed bacterial growth in the presence of an antimicrobial agent.

b) Polymerase chain reaction (PCR) and multiplex PCR panels, which allow rapid, targeted detection of specific resistance genes such as mecA, vanA, or blaNDM directly from clinical isolates or samples.

c) Whole-genome sequencing (WGS) and metagenomic sequencing, increasingly used in reference laboratories and surveillance programmes, which can identify the full complement of resistance genes and mobile genetic elements carried by an isolate or a microbial community in a single assay.

d) Bioinformatics prediction tools and, increasingly, artificial intelligence–assisted pipelines, which compare sequencing data against curated resistance gene databases to predict phenotypic resistance profiles.

7. CLINICAL AND PUBLIC HEALTH IMPLICATIONS

Global deaths attributed to therapeutic failures caused by multidrug-resistant organisms reached 4.71 million in 2021, with methicillin-resistant infections significantly boosting mortality rates, particularly in patients with sepsis, by up to three times [2]. The clinical consequences of AMR gene carriage manifest across several interconnected domains. Infections caused by resistant organisms are often more difficult and time-consuming to diagnose accurately, since first-line empirical therapy may fail, delaying appropriate treatment. This, in turn, is associated with prolonged hospital stays, higher treatment costs, increased morbidity, and elevated mortality, particularly among vulnerable populations such as neonates, the elderly, and immunocompromised patients[3]. From a public health perspective, the rise of resistance genes on highly mobile plasmids capable of crossing species boundaries has transformed AMR from a localized clinical problem into an ecological and societal one, spanning human medicine, veterinary practice, agriculture, and the wider environment[4].

8. STRATEGIES TO COMBAT THE SPREAD OF AMR GENES

The key control strategies are as follows:

i. Early identification through molecular techniques, particularly real-time PCR, should be employed for the rapid detection of carbapenemase genes [1].

ii. Antimicrobial stewardship programmes that promote judicious and evidence-based prescribing in both human and veterinary medicine[16].

iii. Robust infection prevention and control practices in healthcare settings, including hand hygiene, isolation precautions, and environmental cleaning, to limit the transmission of resistant organisms.

iv. Strengthened surveillance systems, at local, national, and global levels, to track the emergence and spread of resistance genes across human, animal, and environmental reservoirs, consistent with the One Health approach[2,4].

v. Continued investment in the discovery of novel antimicrobial agents, alternative therapies such as bacteriophage therapy, and rapid point-of-care diagnostics that can guide targeted rather than empirical therapy.

vi. Regulation of antimicrobial use in agriculture and livestock production, where widespread use has been strongly linked to the emergence and environmental dissemination of resistance genes [4,16].

CONCLUSION

Antimicrobial resistance genes are the molecular currency of one of the defining public health challenges of our time. Their diversity of mechanism, from enzymatic drug inactivation to target modification, efflux, and target protection, combined with their remarkable capacity for horizontal transfer via plasmids, transposons, and integrons, has allowed resistance to spread rapidly across bacterial species and ecological niches[1,3]. A thorough understanding of the genetic basis of resistance is indispensable not only for clinical decision-making but also for the design of rational surveillance systems, novel therapeutics, and coordinated One Health interventions. Continued research into the molecular biology of these genes, coupled with responsible antimicrobial stewardship, remains essential to preserving the efficacy of existing antimicrobial agents for future generations.

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