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Review Paper

Modern treatment approaches and effective early diagnosis in reducing antibiotic resistance mortality: A review

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ABSTRACT

Antibiotic resistance (ABR) has emerged as a critical global health challenge, posing considerable threats to effective infection management and public health. Antibiotics are increasingly ineffective against a wide range of pathogens because of the rising rate of microbial resistance. Misuse and overuse of antibiotics in both clinical and agricultural settings have contributed to the proliferation of resistant strains. A substantial number of deaths are attributable to drug-resistant infections, underscoring the urgency of addressing this crisis. This review aims to inform stakeholders in mitigating the impact of antibiotic resistance on global health. It focuses on the multifaceted nature of ABR, highlighting mechanisms by which bacteria avoid antibiotic action, including horizontal gene transfer, genetic mutations, and biofilm formation. The review also emphasizes the need for an integrated, modern approach to reduce antibiotic resistance, incorporating advances in diagnostic techniques and novel therapeutic strategies to protect public health.

Keywords: *Antibiotic resistance, Antibacterial, Bacteria, Genetic transfer, Mortality*

1 INTRODUCTION

Antibiotic resistance (ABR) is a critical global health challenge that directly involves humans, animals, and environmental factors. Addressing this challenge requires a collaborative, integrated strategy to manage health risks at the animal–human–environment interface across multiple disciplines and sectors [1, 2]. ABR is a major, growing crisis and a global health threat of the 21st century, according to reports from the International Monetary Fund (IMF), the Group of Eight (G8), the World Health Organization (WHO), and the World Bank [3]. Antibiotics were once considered highly effective treatments for bacterial infections [4]. However, misuse and overuse have promoted antibiotic resistance in bacteria. This phenomenon occurs when bacteria evolve and adapt to antibiotics, rendering these drugs less effective or even ineffective in treating infections they once cured [5]. Sources of resistance have emerged due to the widespread use of antibiotics in both human and animal communities, leading to the continuous presence of drug-resistant genes in the environment [6]. Environmental reservoirs include farm waste, hospital waste, water, soil, polluted ecological environments, and industrial waste [7]. Microorganisms have acquired antimicrobial resistance (AMR), a phenomenon in which viruses, parasites, fungi, and bacteria can thrive despite exposure to drugs intended to eradicate them [8]. Antibiotics, a subset of antimicrobials, are primarily used to treat bacterial infections and are more commonly used than other antimicrobials. AMR represents an inevitable evolutionary process observed in all organisms, manifesting as genetic mutations that counteract the lethal effects of selection pressures. In response to environmental stressors, bacteria adapt by developing resistance to antibacterial treatments, thereby rendering these medications less effective [9, 10]. Recent

studies highlight the environment's significance in spreading resistant bacteria and in the emergence of resistant pathogens. Yet, there remains a gap in understanding the evolutionary adaptations and ecological mechanisms underlying the expression of antimicrobial resistance genes in clinical settings, as well as limitations in understanding environmental barriers to dispersal [11, 12]. Resistance outcomes are closely related to antibiotic use, meaning that unnecessary drug use can significantly increase resistance. Therefore, maintaining the effectiveness of existing antimicrobials is imperative, as there have been no substantial findings of modern biomolecules in recent years [13, 14]. The absence of effective antibiotics could lead to a marked increase in the annual mortality rate, potentially reaching millions if left unattended. Additionally, the economic impact of AMR is substantial, with financial burdens of trillions of dollars affecting both the agricultural and healthcare systems [15]. This review discusses the connection between mortality and antibiotic resistance. It focuses on epidemiological trends, mechanisms, and public health implications across different healthcare settings. The review also provides a critical overview of the indirect and direct effects of antimicrobial resistance on healthcare costs, patient outcomes, and mortality rates. It explores challenges in modern diagnostic technologies and treatments, as well as future research directions.

2 ANTIBIOTIC IMPORTANCE AND SCOPE OF THE PROBLEM

The overuse, abuse, and misuse of antibiotics in modern medicine have inadvertently contributed to the emergence of ABR. This has led to the proliferation of resistant bacteria through natural selection, as antibiotics can inadvertently eliminate their drug-sensitive counterparts [16]. The threat of ABR is not limited to prolonged illness, increased healthcare costs, and an increased risk of severe disease, but also includes death due to infections. Annually, the estimated mortality from bacterial infections is 7.7 million deaths. In 2019 alone, 1.27 million fatalities were linked to drug-resistant bacterial pathogens. Additionally, nearly 4.95 million deaths were linked to these infections in some way. Alarmingly, projected fatality rates could rise to 10,000,000 deaths by 2050, far exceeding mortality from cancer. This underscores the urgent need for action to safeguard global health and minimize antimicrobial resistance [17–19].

A recent study in Iraq indicated that, among children, multidrug-resistant Gram-negative bacteria accounted for 60.8% and multidrug-resistant Gram-positive bacteria for 39.2%. In comparison, in adults, multidrug-resistant Gram-negative bacteria accounted for 48.9% and Gram-positive multidrug-resistant bacteria for 51.1% of clinical isolates from a total of 11,592 clinical specimens. The most prevalent isolates reported in adults were *Staphylococcus aureus*(40.8%) and *Klebsiella pneumoniae* (30.1%), whereas in children the most prevalent isolates were *Staphylococcus haemolyticus* (41.8%) and *K. pneumoniae* (37.9%). Isolates from children were highly resistant to ampicillin, benzylpenicillin, cefoxitin, and nafcillin, whereas oxacillin and ampicillin were ineffective therapies in adults [20, 21].

Moreover, a descriptive analysis of 1,384 patients from general hospitals in Basra indicated that resistance to cefixime, cefuroxime, amoxicillin, and penicillin G was highest. The widespread occurrence of ABR in Basra can be attributed to the limited range of antimicrobial agents available against resistant bacteria, such as *Enterococcus faecalis, Proteus mirabilis*, and *K. pneumoniae* [22]. In numerous Iraqi hospitals, most physicians prescribed antibiotics empirically and frequently, without relying on laboratory sensitivity tests. In contrast, pharmacists often dispense to patients various types of antibiotic therapies without appropriate prescriptions from physicians, indicating misuse and self-medication of antibiotics in Iraq [22]. Various factors contribute to the spread of antibiotic resistance in Iraq, as shown in Figure 1.

Infections caused by multidrug-resistant pathogens place a substantial burden on healthcare systems, resulting in extended hospital stays and significantly poorer clinical outcomes. This urgent issue must be addressed to safeguard public health [23]. Prolonged AMR is associated with a higher likelihood of recurrent infections and treatment failure [24]. Numerous antibiotic-resistant bacteria contribute to increased mortality, particularly in high-risk healthcare settings, through the infections they cause, as shown in Table 1 [21–25].

3 MECHANISMS OF ANTIBIOTIC RESISTANCE

Bacteria can acquire resistance, which primarily develops through mechanisms that enable them to evade the effects of antibiotics [26, 27]. Bacterial cells can also withstand both older and newly developed antibiotics through diverse resistance mechanisms [28, 29].

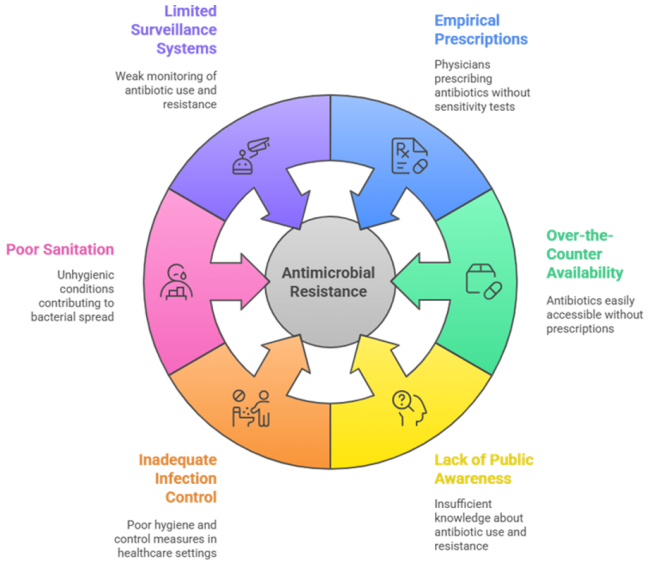

Fig. 1 Underlying Causes and Contributing Factors of Antibiotic Resistance Spread in Iraq

3.1 Enzymatic modification or degradation

This mechanism involves enzymatic modification of structural elements targeted by antibiotics, such as ribosomal methylation by methyltransferases. A major group of enzymes can alter or inactivate antibiotic molecules, rendering them ineffective. Additionally, enzymes that catalyze metabolic processes and activate or modify prodrugs of modern antimicrobial drugs also contribute to the development of ABR. The bacterial enzymes that confer resistance typically belong to large superfamilies and may have originally served different functions. Genes encoding these enzymes, along with their capacity to mutate, are predominantly located on mobile genetic elements (MGEs), allowing resistance to spread rapidly between microorganisms [26, 30].

3.2 Decreasing permeability

The Gram-negative outer membrane is an essential barrier that protects the microorganism while still permitting the passage of materials required for survival. The outer membrane is a complex macromolecular structure whose intricacies have only recently been fully understood. It is composed of highly hydrophobic phospholipid layers and pore-forming proteins; it functions as a selective permeability barrier. The permeability characteristics of the outer membrane influence antibiotic sensitivity in Gram-negative bacteria by controlling the entry of antimicrobial agents, particularly those targeting intracellular processes [31, 32]. Macrolides and other hydrophobic antibiotics can diffuse across phospholipid layers, whereas small hydrophilic antibiotics, such as β-lactams, enter the cell through porins. The prevalence of drug-resistant species in numerous bacterial strains, resulting from modifications in outer-membrane protein composition or lipid content, underscores the critical role of the outer membrane barrier in antibiotic susceptibility [33, 34].

3.3 Altered target site

Various bacteria can alter the targets of antibiotics through different mechanisms, rendering these drugs ineffective. This prevents antibiotics from disrupting the bacterial processes they target, as seen in macrolide resistance. Resistance mechanisms include changes at the ribosomal target site, efflux pump activity, and substrate-inactivating enzymes (e.g., esterases). Alterations at ribosomal binding sites, such as methylation of 23S rRNA in macrolide resistance, typically prevent antibiotic binding and thereby reduce inhibition of protein synthesis [34].

3.4 Formation of biofilm

This structure serves to shield and protect bacterial colonies. The established symbiotic association between bacteria and humans is mutually advantageous. The human microbiome, comprising bacteria, fungi, and viruses, is vast and primarily located on the skin, in the oral mucosa, and in the gastrointestinal tract [35]. When bacteria adhere to a surface, they undergo genetic changes and produce exopolysaccharides (EPS), also known as "slime," which form a protective barrier. Bacterial biofilms act as a shield against external threats, including host immune defenses and antibiotics [36].

3.5 Antibiotic inactivation

Drug-resistant bacteria can produce enzymes that render antibiotics ineffective through processes encoded on plasmids or chromosomes. These enzymes include modifying, hydrolytic, and inactivating types. Their production, which dismantles or deactivates antibiotics, contributes substantially to bacterial resistance by destroying antimicrobial drugs or reducing their effectiveness. In Gram-negative bacteria, antibiotic inactivation is commonly mediated by β-lactamases, which cleave the amide bond in the β-lactam ring of specific antibiotics, thereby rendering them ineffective [37]. Additionally, aminoglycoside antibiotics are often rendered ineffective by enzyme-mediated modification. Aminoglycosides can be modified by enzymes such as nucleoside phospho-

Table 1 Mortality rate and primary causes due to Antibiotic-Resistant Bacteria

Types of Pathogens	Common Infections Caused	Causes of Mortality	Resistance Type	High-Risk healthcare	Mortality Rate
Neisseria gonorrhoeae	Gonorrhea	Pelvic inflammatory disease, infertility, and neonatal blindness	MDR, cephalosporinresistant	Sexually transmitted infections	2%
Sabmonella spp.	Typhoid fever, a foodborne illness	Septicemia, intestinal perforation	MDR, fluoroquinoloneresistant	Contaminated food/water	3%
Enterococcus faecium	Urinary tract, intra-abdominal, bloodstream infections	Persistent bloodstream infections, infective endocarditis	Vancomycin-resistant	Oncology wards, post-surgery	4%
Streptococcus preumoniae	Pneumonia, meningitis, otitis media	Pneumonia-related respiratory failure, meningitis	Penicillin and macrolide-resistant	Children, the elderly, and immunocompro mised	6%
Pseudomonas aeruginosa	Respiratory, urinary, and wound infections	Lung infections in immunocompromise d patients, septicemia	MDR, Carbapenemresistant	Burn units, ventilators, catheters	7%
Acinetobacter baumannii	Pneumonia, wounds, and bloodstream infections	Respiratory failure, prolonged sepsis	MDR, carbapenemresistant	Intensive Care Units, mechanical ventilation	8%
Mycobacterium tuberculosis	Tuberculosis	Lung destruction, respiratory failure, systemic spread	MIDR tuberculosis and XDR tuberculosis	Community and healthcare settings	10%
Klebsiella pneumoniae	Pneumonia, bloodstream infections	Severe pneumonia, sepsis, multiorgan failure	CarbapenemResistant, ExtendedSpectrum BetaLactamases	Intensive Care Units, ventilatorassociated infections	11%
Staphylococcus aureus (MRS.A)	Slain infections, pneumonia, sepsis	Necrotizing pneumonia, sepsis, endocarditis	MRSA	Hospitals, wound infections, dialysis units	18%
Escherichia coli	Urinary tract infections, sepsis	Septic shock, lidney failure, bloodstream infections	Extended-Spectrum Beta-Lactamases, carbapenem-resistant	Hospitals, elderly care, and post-surgery	23%

transferases and

acetyltransferases through O-adenylation, O-phosphorylation, and N-acetylation. These modifications disrupt antibiotic binding to ribosomal targets, leading to a loss of activity. In this regard, methicillin-resistant Staphylococcus aureus (MRSA) can produce various enzymes that confer resistance to multiple antibiotics [38].

3.6 Genetic mutations

Multidrug resistance (MDR) can occur through two genetic mechanisms: the acquisition of new mutations (such as duplications, deletions, insertions, or point mutations) or bacterial recombination, which involves the transfer of DNA from one bacterium to another via mechanisms other than vertical transmission [39, 40]. Genotypic and phenotypic analyses have revealed fluoroquinolone resistance in Pseudomonas aeruginosa via several mutations in the gyrA gene, which encodes DNA gyrase. Mutations in gyrA that affect DNA gyrase reduce the binding affinity of fluoroquinolones, thereby leading to resistance [41,42]. Thus, transcriptional inhibition and mutations during DNA replication can occur at any time and are often harmful rather than beneficial. Over time, descendants tend to accumulate more harmful mutations, which can slow adaptation. This phenomenon does not occur in populations that undergo recombination, because recombination can combine beneficial mutations onto a single chromosome [26].

3.7 Efflux pumps

Efflux pumps are MDR components encoded by bacterial genomes that can actively transport a wide range of antimicrobial agents. They often serve as a major contributor to resistance in both Gram-negative and Gram-positive bacteria, contributing to intrinsic, acquired, and phenotypic resistance in bacterial pathogens. In addition to their roles in ecosystems, efflux pumps also play a role in determining antibiotic resistance. Most Gram-negative bacteria possess natural resistance to many drugs due to multidrug efflux pumps that span both the inner and outer membranes. Efflux pumps can expel β-lactam compounds that are unable to cross the cytoplasmic membrane. When these pumps are overproduced, they can significantly increase the minimum inhibitory concentrations (MICs)

of antibiotics. This mechanism contributes to bacterial resistance by expelling antimicrobial compounds such as antibiotics, dyes, antiseptics, and detergents. These efflux pump genes are found in resistant *Klebsiella pneumoniae* strains [40]. Despite extensive research, several gaps persist in understanding how antibiotic resistance determinants disseminate across bacterial and environmental populations. Addressing these gaps requires integrating epidemiological, ecological, and molecular perspectives to develop effective strategies.

3.8 Common pathogens of antibiotic-resistant infections

Multidrug-resistant *Escherichia coli, Acinetobacter spp., Staphylococcus aureus, Klebsiella pneumoniae, Enterococcus spp.,* and *Pseudomonas aeruginosa* are considered to be among the primary causes of nosocomial infections in the world. These pathogens (ESKAPE) employ multiple ABR mechanisms against many antibiotics, especially those considered a last line of defense, such as polymyxins and carbapenems [43]. Moreover, antibiotic-resistant nosocomial infections caused by *E. coli* contribute to the development of urinary tract infections (UTIs), meningitis, and intestinal infections. In contrast, *Acinetobacter* causes bloodstream infections, UTIs, and severe pneumoniae in different parts of the body. Even after water treatment, residual bacteria in hospital wastewater can transmit ABR to the environment through various antibiotic resistance genes and mobile genetic elements [42]. The presence of antibiotic resistance genes (ARGs) in wastewater residual bacteria indicates, in particular, extended-spectrum β-lactamases and carbapenemase-producing Enterobacteriaceae. Resistance genes for colistin and carbapenem resistance were also detected in various *Salmonella* strains, thereby increasing the risk of infection with resistant bacteria through foodborne transmission [44].

3.9 Developing alternatives to antibiotics

The prolonged and widespread use of antibiotics has negatively affected both ecological biodiversity and human health [45]. Numerous approaches have been proposed to address these issues, including exploring alternative compounds with antimicrobial properties, effectively managing existing antimicrobials, and promptly detecting antimicrobial-resistant pathogens [46, 47]. Scientists emphasize the importance of using antibiotics prudently, but the exact meaning of "prudent use" is not consistently defined. Developing effective alternatives to antibiotics is therefore crucial for prudent antibiotic use. Successful implementation of these alternatives can reduce antibiotic consumption and help prevent the emergence of bacterial resistance (Figure 2) [48].

These approaches and therapies have the potential to reduce the high ABR rate by expanding the spectrum of chemical and physical applications of currently approved antibiotics [49].

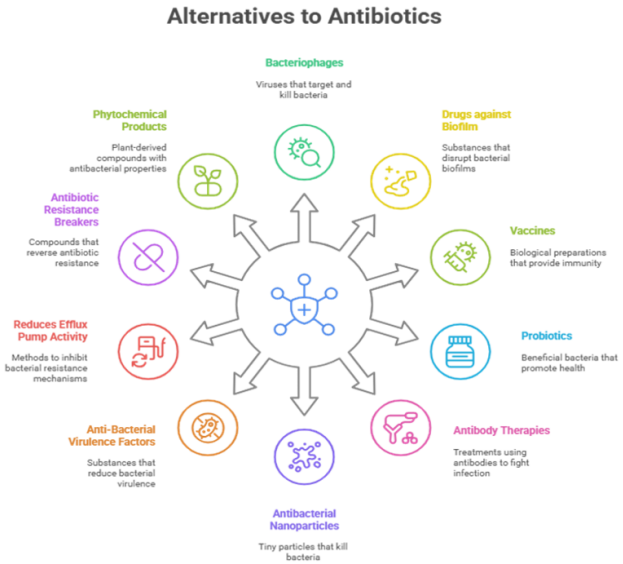

Fig. 2 Therapeutic alternative approaches for combating antibiotic resistance

3.10 Bacteriophages

Before antibiotics, bacteriophages were used to treat many bacterial infections. Phages are viruses that can specifically target and destroy bacteria without harming the body's cells. In certain Eastern European countries, a variety of products using phage therapy are available for purchase [50]. Engineered endolysins can target specific bacterial species, such as multidrug-resistant *Enterobacter spp., Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella spp.,* and *Escherichia coli* [51]. Notably, an increasing number of clinical trials have evaluated bacteriophages as alternatives to antibiotics, describing the efficacy and safety of phage treatment for many infection cases. A single bacteriophage, such as phage P100, can kill more than 90% of highly conserved strains of *Listeria monocytogenes* [52]. Furthermore, future use of phage therapy may help protect against *Staphylococcus aureus* infections if systematic strategies are developed to enhance effectiveness and

safety in humans, thereby supporting the development and acceptance of phage treatment as an alternative therapy [53, 54]. A recent study indicated that bacteriophage treatment (bacteriophages PlySs2, SJ2, Φ2, and a cocktail e11/2, e4/1c, pp01) might be a potential option against multidrug-resistant bacterial infectious diseases such as *Campylobacter jejuni, Streptococcus dysgalactiae, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus sanguinis, Streptococcus equi, E. coli O157:H7, Streptococcus pneumoniae, group E streptococci,* and *Salmonella enteritidis* [55].

3.11 Drugs against biofilm

Consequently, traditional antibiotics are often ineffective against biofilm-related infections. The first stage in biofilm formation is the initial attachment of a bacterial cell to a surface. Targeting the bacterial attachment process may therefore be a viable strategy for preventing biofilm formation. In this regard, small biomolecules such as mannosides are used to target the E. coli FimH gene, which encodes the type 1 pili adhesion protein. Peptides such as DJK-6, DJK-5, and IDR-1018 have demonstrated the ability to reduce biofilm formation in various bacteria by targeting and breaking down guanosine tetraphosphate, a key molecule involved in nutrient sensing, antibiotic resistance, and biofilm formation. These anti-biofilm peptides offer promising new strategies for combating biofilm-related issues [56]. Because bacterial biofilms are a serious concern, recent studies have evaluated direct treatment of medical equipment using antibiotics such as rifampicin, daptomycin, linezolid, minocycline, cephalosporins, vancomycin, or tigecycline, which may minimize biofilm growth [57, 58]. Despite the difficulties in managing biofilms with standard antibiotic treatments, combination therapies, particularly those using antibiotic adjuvants or higher-dose topical applications, have been implemented. Research indicates that, when administered topically in higher doses, polymyxins, cephalosporins, monobactams, aminoglycosides, tetracyclines, and glycylcyclines can effectively combat biofilms [59]. Antibiotic resistance in biofilm communities is a direct consequence of their multicellular structure and adaptive strategies. These include slow or incomplete antibiotic penetration, altered chemical microenvironments within the biofilm, and the presence of specific microbial subpopulations that display cell differentiation similar to spore formation. The multicellular nature of biofilms fundamentally enhances resistance, thereby compounding conventional mechanisms. This dynamic significantly undermines the effectiveness of treatment strategies and can lead to treatment failure [60, 61].

3.12 Probiotics

Several probiotic genera, including *Enterococcus, Propionibacterium spp., Streptococcus, Lactococcus, Pediococcus, Bifidobacterium,* and *Lactobacillus*, are used in pharmaceutical formulations and fermented dairy products. The use of probiotics as supplements is widely recognized as a beneficial health practice worldwide, although scientific evidence supporting the purported effects remains limited [62]. The protective effects of probiotics are currently understood through several mechanisms, including competition with pathogenic bacteria for nutrients, support of the immune system, strengthening of intestinal epithelial barriers, and bacteriocin-mediated interference [63, 64]. Bacitracin (an antimicrobial peptide) disrupts cell wall formation in MRSA and other Gram-positive bacteria. However, in a prospective study in which healthcare workers received a 5-day course of treatment, bacitracin was less effective than mupirocin in suppressing nasal *Staphylococcus aureus* [14, 65]. Collectively, these probiotic actions may help maintain microbial balance and reduce the risk of ABR development [66]. The physicochemical properties and peptide structure of several bacteriocins exhibit specific antibacterial spectra against closely related species of the producer, whereas other bacteriocins show broad antibacterial activity [67]. Furthermore, these peptides show considerable promise in inhibiting the proliferation of specific resistant strains. However, caution is warranted, as the structural characteristics of many bacteriocins remain inadequately defined. In addition, assessments of antimicrobial efficacy are often limited to well-established reference isolates, which may not fully represent the diverse array of bacterial species encountered in clinical settings [68].

3.13 Antibacterial nanoparticles

Various nanoparticles exhibit potential bactericidal activity through multiple mechanisms, including disruption of DNA replication, induction of oxidative stress responses, alteration of bacterial metabolism, protein denaturation, and physical disruption [69, 70]. The envelope of a resistant bacterium typically carries a negative charge, and one way to interact with it is through positively charged nanoparticles. For instance, gold nanoparticles can induce bacterial cell lysis by increasing membrane tension and causing physical damage to the cell envelope [71]. Similarly, silver and copper nanoparticles

can disrupt bacterial cell walls or membranes. Nanomaterials offer the potential to enhance the pharmacokinetics and efficacy of therapeutic and imaging agents by accumulating at disease sites, persisting in the bloodstream for longer periods, and being readily functionalized due to their large surface area. Oxide-based nanoparticles have been reported to show improved durability, lower toxicity, and greater stability. Metal compounds are similar to antibiotics in that they can distinguish between mammalian and bacterial targets due to specific metal transport systems within cells and the unique roles of metalloproteins [72].

3.14 Vaccines

Unlike antibiotics, which face rapid resistance, vaccines offer the possibility of longer-term control of infections. Advanced methods, such as high-throughput cloning of human B cells from vaccinated or convalescent individuals, are enabling the identification of previously unrecognized protective antigens (Ags) that were not identified using traditional approaches. Vaccines remain the primary method for preventing infectious diseases. While numerous vaccines are available for viruses, there are relatively fewer options for bacterial infections [73]. In 2019, the U.S. Food and Drug Administration (FDA) approved 97 vaccines to prevent bacterial and viral diseases. In this context, bacterial infections included *Haemophilus influenzae, Mycobacterium tuberculosis, Vibrio cholerae, Salmonella typhi, Bacillus anthracis, Streptococcus pneumoniae, Yersinia pestis, Clostridium tetani,* and *Neisseria meningitidis* [74]. Additionally, vaccines affect antibiotic-resistant strains, such as *Streptococcus pneumoniae and Haemophilus influenzae type b* (Hib) [68, 75]. New research in vaccine technologies, including bioconjugation, MAPS, nanoparticles, and GMMA, enables the design of complex vaccines targeting distinct pathogenic mechanisms and diverse strains. However, challenges remain, such as the need for technological improvements in RNA vaccine platforms and the difficulty of identifying populations to demonstrate clinical efficacy. Emerging challenges include pre-existing immunity in targeted patients, which may affect the shift toward protective immunity and necessitate alternative vaccine approaches and formulations. While vaccines for tuberculosis are under clinical evaluation, there is a need to develop formulations with higher effectiveness against other ABR infections, such as *Acinetobacter baumannii* and *Enterococcus faecium*. Ongoing research aimed at identifying new antigens to prevent infections is progressing through advanced stages. However, as of now, none of the promising candidates have yet advanced to the clinical phase of development [76].

3.15 Antibody therapies

Recent studies have demonstrated the effectiveness of using egg yolk-derived (IgY) antibodies from immunized chickens as artificial passive immunization, administered topically, nasally, or orally, for treating bacterial pathogens in humans and animals [77]. By immunizing chickens with specific antigens, targeted antibodies can be produced that may combat a broad spectrum of ABR. Antibodies can be used to prevent and treat bacterial infections. Unlike many current clinical vaccines, only three FDA-approved monoclonal antibody treatments exist for bacterial infections, such as *Clostridioides difficile* and *Bacillus anthracis*. Two of these target monoclonal antibodies are human immunoglobulin G and can recognize secretory toxins [78, 79]. Animal models often poorly predict human outcomes, and many monoclonal antibodies (mAbs) showing efficacy in preclinical settings fail in clinical trials due to critical immunological and genetic differences between species [80]. High specificity can also be limiting for pathogens with diverse serotypes, and bacterial capsules may mask conserved antigens, reducing mAb binding effectiveness. While advances such as antibody, antibiotic conjugates, gene-delivered mAbs, and nanobody approaches are being explored, challenges remain in identifying predictive models, expanding strain coverage, penetrating intracellular infections, optimizing dosing, and addressing production costs, especially in low- and middle-income countries where the ABR burden is high [81].

3.16 Reduces efflux pump activity

Some potent efflux pump inhibitors (EPIs), such as carbonyl cyanide m-chlorophenylhydrazone (CCCP), have been described. These inhibitors increase intracellular antibiotic concentrations, ultimately leading to cell death. Phenylalanine-arginine β-naphthylamide, considered a broad-spectrum EPI, has been used against *Pseudomonas aeruginosa* and has been shown to significantly reduce resistance levels and the emergence of fluoroquinolone-resistant strains [82]. However, these inhibitors are not applicable in vivo due to their toxicity, which should be noted. Investigators in antibiotic resistance are therefore exploring ways to modify EPIs to improve safety and reduce toxicity for humans and animals, such as minimizing side effects, combining EPIs with other antibiotics,

using natural EPIs, employing nanoparticles targeted to infected tissue, developing gene-editing EPIs, designing less toxic EPIs, or using prodrugs [41, 83].

3.17 Phytochemical products and plant extracts

Phytochemicals have antibacterial properties, including the synthesis of active components and interference with ABR mechanisms. Plant secondary metabolites, commonly referred to as phytochemicals, including alkaloids, phenols, coumarins, and terpenes, have considerable potential to address drug-resistant pathogens. Research has indicated that these plant extracts exhibit antimicrobial properties comparable to those of contemporary pharmaceuticals. Moreover, several phytochemicals have been shown to target molecular mechanisms that contribute to drug resistance in pathogens, such as membrane proteins, biofilms, efflux pumps, and bacterial communication systems [84, 85]. Polyphenols, flavones, and flavonols are active against a broad spectrum of resistant bacteria. The synergistic effect of amoxicillin and quercetin is an effective combination for inhibiting peptidoglycan biosynthesis in Gram-positive bacteria by increasing cell membrane permeability, inhibiting β-lactamases, and decreasing fatty acid levels. Additionally, galangin and sophoraflavanone G were found to influence the reversal of *Staphylococcus aureus* β-lactam antibiotic resistance [84]. Chanoclavine combined with tetracycline shows synergistic activity against multidrug-resistant *Escherichia coli*. Beyond their potential for bacterial killing, these products have recently been explored as adjunct agents to re-sensitize/re-potentiate antibiotics or to reverse drug resistance [85].

3.18 Anti-bacterial virulence factors

Alternative compounds can target adhesins or motility in numerous bacterial infections without inhibiting bacterial growth. Surface protein sortase A (SrtA) and bacterial biofilm adhesion proteins are considered potential targets for anti-virulence drug development. Depriving pathogens of essential virulence factors, such as motility and adhesins, could modulate bacterial pathogenesis, enabling the host immune system to clear virulence-attenuated bacteria. Investigating the effectiveness of adhesion-specific monoclonal antibodies to block bacterial infection and induce an immune response in vivo is worthwhile [86].

3.19 Antibiotic resistance breakers

One promising area of research involves antibiotic resistance breakers, which can resensitize resistant bacteria to antibiotics. While some antibiotic resistance breakers, such as β-lactam inhibitors, have been used in clinical settings, further research could lead to the development of a broader range of more effective therapeutic agents [41]. In addition to these alternative drugs, research has emphasized the importance of exploring other targets and therapies. These include combination therapies that inhibit kinase activity and intrinsic antibiotic resistance, as well as strategies such as anti-regulatory measures, anti-secretion systems, anti-signal transduction approaches, anti-quorum sensing mechanisms, anti-adhesion tactics, anti-motility interventions, microbiome modulation, engineered bacteriophages, and anti-toxin therapies to effectively combat multidrug-resistant (MDR) bacteria [87].

The current study summarizes alternative approaches to reducing the high rate of antibiotic resistance (Table 2).

4 EFFECTIVE DIAGNOSTIC METHODS FOR ANTIBIOTIC RESISTANCE DETECTION

Early diagnosis of pathogens is essential for treating bacterial infectious diseases. In medical technology, large-scale efforts have focused on shortening turnaround time (TAT) for the characterization and detection of bacterial pathogens, which can otherwise take several days [88]. Initial testing includes phenotypic techniques such as disk diffusion (Kirby–Bauer) and broth microdilution, which assess bacterial growth inhibition in the presence of antibiotics. These techniques provide a straightforward assessment of antibiotic susceptibility profiles. Genomic analysis methods can be applied to clinical specimens to directly detect resistance gene profiles, as well as gene expression and mutations. These molecular techniques have been developed as substitutes for, or adjuncts to, traditional antimicrobial susceptibility testing methods [89, 90]. Biotechnological advancements have enabled more sensitive genotypic profiling, such as polymerase chain reaction (PCR), which detects specific ABR genes in bacterial strains. In addition, next-generation sequencing (NGS) technologies provide comprehensive insights into mutation detection, identification of the genetic basis of ABR, and plasmid-mediated resistance mechanisms across different isolates [91, 92]. Rapid phenotypic antimicrobial susceptibility techniques also include meth-

Table 2 Non-antibiotic therapeutic contemporary options and their key features

Treatment Approach	Features
Bacteriophages	Used before antibiotics; specific drugs for multidrug-resistant bacteria; role in clinical trials
Drugs against Biofilm	Ineffective traditional antibiotics; targeting bacterial attachment; anti-biofilm peptides
Probiotics	Genera include Enterococcus, Propionibacterium, Streptococcus, Lactococcus, Pediococcus, Bifidobacterium, Lactobacillus; health benefits despite limited evidence
Antibacterial nanoparticles	Bactericidal activity; examples include gold, silver, copper nanoparticles
Vaccines	Long-term infection control; 97 vaccines approved by FDA
Antibody Therapies	Uses egg yolk-derived IgY antibodies; FDA-approved monoclonal antibodies
Reduces Efflux Pump Activity	Potent efflux pump inhibitors (EPIs) increase antibiotic concentration; effective against *P*. aeruginosa
Phytochemical products and plant extracts	Antibacterial properties; examples include alkaloids, phenols, coumarins, terpenes
Anti-Bacterial Virulence Factors	Targets include adhesins and motility; modulates pathogenesis and enhances immune response
Antibiotic resistance breakers	Research is promising; clinical use includes β-lactam inhibitors

ods such as surface plasmon resonance, fluorescence imaging, and innovative micro- and nanotechnology-based devices. Recent studies have reported several commercially available antimicrobial strips, including MIC Test Strip (Liofilchem Inc., Waltham, MA), Etest (bioMérieux AB BIODISK), Ezy MIC Strip (HiMedia Laboratories Pvt. Ltd., Mumbai, India), and MIC Evaluator (Oxoid, Basingstoke, UK) [40, 93]. Our study included various challenges, applications, and advantages of antibiotic resistance detection technologies (as shown in Table 3) [94, 95].

5 PHYSICAL DIAGNOSTIC METHODS OF ANTIBIOTIC RESISTANCE DETECTION

Advanced applications of physics for detecting and treating antibiotic resistance continue to evolve as researchers combine cutting-edge technologies from diverse fields, such as materials science, nanotechnology, and quantum physics. Physical methods for detecting and potentially treating antibiotic resistance have gained significant attention [96]. The use of MALDI-TOF MS technology in clinical microbiology has provided a reliable approach for rapidly identifying bacteria and their antibiotic resistance. This method has been used to detect antimicrobial resistance in various bacterial species and has the potential to help clinicians streamline antibiotic therapy, thereby improving outcomes. The Alfred 60 AST^{TM} system, which is CE-marked, uses MALDI-TOF MS to analyze bacterial samples directly from positive blood culture tubes and provides antimicrobial susceptibility results within 4–6 hours [97]. This method has been applied through various approaches, including detection of variations in mass spectra between resistant and susceptible isolates, use of classical isolate-typing methodologies, analysis of bacterial hydrolysis of β-lactam antibiotics, detection of stable (non-radioactive) isotope-labeled amino acids, and assessment of isolate growth in the presence and absence of antibiotics using standard methods. Moreover, MALDI-TOF MS technology has improved resistance detection in anaerobic and aerobic bacteria, Gram-negative and Gram-positive bacteria, mycobacteria, viruses, and fungi [98, 99]. Raman scattering is an inelastic process in which light passing through a transparent medium interacts with molecules, causing a change in the frequency of light. This process has made it a powerful analytical technique for bacterial studies. The SERS signal can be substantially enhanced through chemical and electromagnetic mechanisms, with the former described as the main contributor [100]. Optical biosensors, such as photonic crystals and fiber optics, can detect antibiotic resistance by using light to identify indicators such as β-lactamases. These biosensors have the potential to provide real-time monitoring of bacterial resistance in clinical samples by measuring changes in optical properties [101].

6 MOLECULAR TECHNIQUES FOR ANTIBIOTIC RESISTANCE DETECTION

Many molecular antimicrobial susceptibility testing methods include hybridization-based, amplification-based, and sequence-based strategies. In hybridization technologies, nucleic acid probes target specific gene sequences to enable detection, whereas in amplification techniques, the target gene sequence is amplified to enable detection [96, 102]. Sequence-based methods analyze genome sequences to detect resistance-conferring mutations or resistance genes (Figure 3) [103, 104].

Table 3 Classification and critical attributes of antibiotic resistance methods

Method Type	Description	Advantages	Challenges	Applications
Hybridization-based	Uses nucleic acid probes to target gene sequences for detection	Allows detection of specific resistance genes	May require further validation studies	Identifying antibiotic resistance genes
Amplification-based	Amplifies target gene sequences to allow detection	Higher sensitivity for detecting low levels of resistance	Potential for false positives	Used in PCR assays for resistance gene detection
Sequence-based	Analyzes genome sequences to detect resistance mutations	Rapid and precise detection of resistance mechanisms	Accuracy concerns compared to traditional methods	Whole-genome sequencing used to evaluate isolate relationships
Microarray	Simultaneous detection of many resistance genes	Predicts resistance to multiple antibiotic classes	Requires additional testing after culture	Clinical diagnostics for multidrug-resistant bacteria
Nanopore sequencing	Real-time sequencing of bacterial genomics	Rapid prediction of antibiotic resistance	May overlook some conventional resistance tests	Improving clinical decision-making and patient outcomes
Predictive AST	Predicts bacteria's response to antibiotics using analytics	Advances with increased sequencing data and reference AST	Still emerging in clinical applications	Enhancing accuracy in antibiotic resistance prediction
MALDI-TOF MS	Reliable identification of antibiotic-resistant bacteria	Rapid detection of antimicrobial resistance	N/A	Streamlining antibiotic therapy
Raman scattering	Inelastic light interaction with molecules	Powerful analytical technique for bacterial studies	N/A	Analytical applications in microbiology
Optical biosensors	Use of light to identify indicators of resistance	Real-time monitoring of bacterial resistance	N/A	Clinical sample analysis
Phenotypic techniques	Disk diffusion tests (Kirby-Bauer) and broth microdilution	Straightforward assessment of antibiotic susceptibility profiles	Time-consuming method; results may take days	Initial testing for bacterial pathogens
Genomic analysis	Detect profiles of resistant genes, gene expression, and mutations	Quicker results in hours compared to culture-based tests	May require specialized equipment and expertise	Substitute or addition to traditional susceptibility tests
PCR	Detect specific ABR genes of bacterial strains	High sensitivity	Need for specific reagents and training	Molecular diagnostics
NGS	Inclusive insights into mutations and resistance mechanisms	Comprehensive data	High cost and complexity	Research and clinical diagnostics
Rapid phenotypic AST	New methods like surface plasmon resonance and fluorescence imaging	Fast results	Emerging technology may not be widely adopted	Clinical testing
Commercial strips	Ready-to-use commercial strips like MIC Test Strip, Etest	Convenient for laboratories	Cost and availability may vary	Routine antimicrobial testing

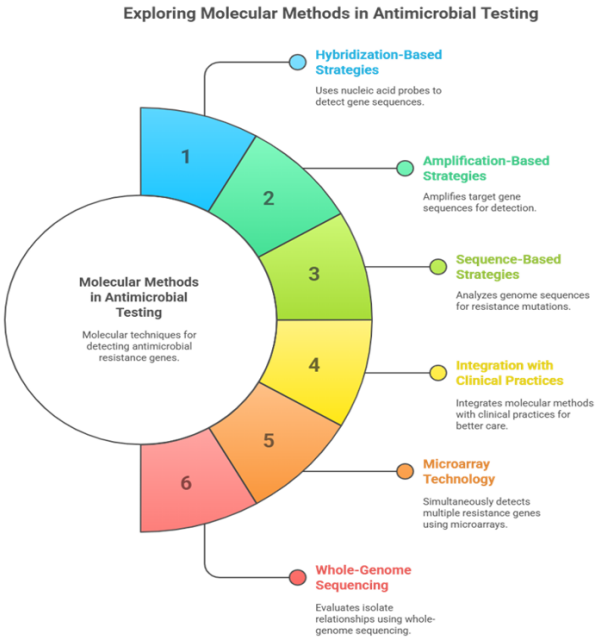

Fig. 3 Advanced molecular techniques in antimicrobial resistance testing

Integrating molecular characterization of resistant strains with precise identification of antibiotic resistance genes or mutations, and the genetic elements involved in their dissemination, is considered a practical approach to managing the spread of antibiotic resistance. Molecular methods also aid in determining gene location and in distinguishing between horizontal gene transfer and clonal spread [105, 106]. Numerous PCR assays have been developed to detect antibiotic resistance genes, and work is underway to create microarrays for the simultaneous detection of these genes and the genetic elements involved in their dissemination [106]. Molecular methods can provide a more accurate risk assessment for the use of antimicrobial substances. Furthermore, a better understanding of the transcriptional and translational expression of antibiotic-resistance genes could allow molecular methods to replace phenotypic measurements. Real-time bacterial genome sequencing using nanopore technology holds promise for rapid ABR prediction in clinical settings [107]. Nanopore sequencing is particularly relevant clinically, as it can reveal hidden or intermediate plasmid-mediated resistance that may substantially affect treatment choices. Thus, rapid use of genomics has significant potential to improve patient outcomes and enhance clinical decision-making [108].

This review highlights instances in which fast, cost-effective, real-time genomics outperformed traditional diagnostic methods in accurately predicting antibiotic resistance. There is strong potential to integrate this genomic technology into established hospital practices, thereby further improving patient care [108]. This technology can identify the antibiotic class associated with resistance, the underlying mechanisms, and whether resistance genes are inherent or acquired. For β-lactam antibiotics, it can also pinpoint the specific subclass of resistance genes. Microarray technology enables simultaneous detection of many resistance genes, helping to predict an isolate's resistance to multiple antibiotic classes. However, it primarily infers resistance phenotypes and may require additional testing after bacterial culture, with results typically taking 9–20 hours. Molecular methods are faster but have their own challenges [107]. Regular updates help ensure these tools guide effective treatment of infections caused by multidrug-resistant Gram-negative bacteria and help prevent treatment failures [109].

Whole-genome sequencing (WGS) is now standard practice in clinical microbiology laboratories for evaluating relationships between isolates. Using advanced analytics, the same sequencing data can also help predict bacterial responses to antibiotics. As the number of sequenced isolates and reference AST data continues to grow, along with our understanding of AMR, predictive AST is expected to advance, offering a promising avenue for future clinical applications [110].

7 STRATEGIES TO REDUCE ANTIBIOTIC RESISTANCE

To address AMR effectively, a one-health approach that considers environmental factors, animal health, and human health is crucial. This also includes enhancing surveillance systems, promoting stewardship programs, and investing in research and development for new antimicrobial options. International collaboration, public education, and awareness are necessary to reduce AMR and preserve the efficacy of antibiotics for future generations [16]. This awareness should be based on four key aspects: a robust regulatory environment, adequate awareness, material or emotional incentives, and an enabling social structure. Unless all these strategies are satisfactorily addressed, antibiotic resistance prevention programs will not bring about a discernible change in user behavior [111]. To minimize the high rate of antibiotic-resistant mortality, effective multifaceted strategies must be implemented urgently, supported by modern technologies and scientific research on alternative therapies (Table

4) [112, 113]. At both global and national levels, new technologies should be developed to enhance classical methods for detecting antimicrobial resistance. Governments require multidisciplinary alliances and coordinated initiatives to combat this global health crisis.

Table 4 Approaches and strategies to control the spread of antimicrobial resistance

Strategy	Description
Compounds that decrease mutagenesis	Reduce the likelihood of resistance emergence.
Resistance-resistant therapeutic strategies	Regimens that slow or stall the development of resistance in targeted pathogens.
Antibiotic cycling	Forces bacterial populations toward susceptibility to another antibiotic.
Machine learning and personalized medicine	Predicts the likelihood of resistance development based on patient factors.
Combination therapies	Sabotage defensive mechanisms and eliminate potentially resistant infections.
Biopolymers	High-performance, sustainable materials with intrinsic antibacterial performance.
Narrow-spectrum agents	Help prevent resistance by reducing selective pressure.

8 CONCLUSION

Antibiotic resistance is a major challenge that threatens the effectiveness of current therapies and poses risks to public health worldwide. Resistance involves genetic adaptations, environmental factors, and misuse of antibiotics in healthcare and agriculture. Surveillance should be strengthened, responsible antibiotic use promoted, and new treatment options, such as probiotics and bacteriophage therapy, investigated to address this crisis. It is also important to address environmental sources of resistance genes. Through collaboration across healthcare, research, policy, and public sectors, effective strategies can be strengthened to mitigate the impact of ABR and protect global health. Immediate and sustained action is essential to preserve the effectiveness of antibiotics.

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Author contributions

S.E.A. led the conceptualization and writing of the study, while L.A.G. supported the literature review and manuscript organization. L.A. focused on the environmental aspects of antibiotic resistance, and O.Y.S. assisted with data collection and editing. H.F.A. provided microbiology expertise and helped refine the final manuscript.

Abbreviations

ABR, Antibiotic resistance; Ags, Protective antigens; AMR, Antimicrobial resistance; CCCP, Carbonyl Cyanide M-Chlorophenylhydrazone; EPIs, Efflux pump inhibitors; EPS, Exopolysaccharides; ESKAPEE, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Acinetobacter* spp., *Enterococcus* spp., *Pseudomonas aeruginosa*, and *Escherichia coli*; FARA, Function-based Antibiotic Resistance Assay; FDA, Food and Drug Administration; FISH, Fluorescent in situ Hybridization; IMF, International Monetary Fund; MADM, Multiplexed automated digital microscopy; MBL, Metallo--lactamase; MDR, Multidrug Resistance; MGE, Mobile genetic elements; MHA, Mueller-Hinton agar; MICs, Minimum inhibitory concentrations; MRSA, Methicillin-resistant *Staphylococcus aureus*; NGS, Next-generation sequencing; PCR, Polymerase chain reaction; SERS, Surface-enhanced Raman Spectroscopy; SrtA, Sortase A; TAT, Turn-around time; WGS, Whole-genome sequencing; WHO, World Health Organization; XDR, extensively drug-resistant.

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