

Antimicrobial Resistance in the Modern Era: Advances in Laboratory Detection, Emerging Mechanisms, and Diagnostic Challenges

Aneela Naik

Department of Biochemistry & Pathology, University of Agriculture Faisalabad, Pakistan

[\(aneelanaik@gmail.com\)](mailto:aneelanaik@gmail.com)

Nayyar Fatima

Department of Allied Health Sciences, University of Okara, Okara, Pakistan

[\(nayyerfatima691@gmail.com\)](mailto:nayyerfatima691@gmail.com)

Muhammad Hammad

Department of Allied Health Sciences, University of Okara, Okara, Pakistan

[\(mh9464022@gmail.com\)](mailto:mh9464022@gmail.com)

Madiha Ahmad Khan

Department of Allied Health Sciences, University of Okara, Okara, Pakistan

[\(madihaahmadkhan35@gmail.com\)](mailto:madihaahmadkhan35@gmail.com)

Laiba Shahadat

Department of Allied Health Sciences, University of Okara, Okara, Pakistan

[\(laibashahadat796@gmail.com\)](mailto:laibashahadat796@gmail.com)

Nida Tehreem

Department of Allied Health Sciences, University of Okara, Okara, Pakistan

[\(nidanaisr334@gmail.com\)](mailto:nidanaisr334@gmail.com)

Muhammad Adnan Jaffer (Corresponding Author)

Department of Biochemistry, University of Okara, Okara, Pakistan:

[\(adnanjaffar45@gmail.com\)](mailto:adnanjaffar45@gmail.com)

Muhammad Abdullah Butt (Corresponding Author)

Department of Food Sciences, Government College University Faisalabad, Pakistan

[\(muhammadabdullahbuttfst@gmail.com\)](mailto:muhammadabdullahbuttfst@gmail.com)

Abstract

Author Details

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Corresponding E-mail & Author*:**Muhammad Adnan Jaffer**

Department of Biochemistry, University of Okara, Okara, Pakistan: (adnanjaffar45@gmail.com)

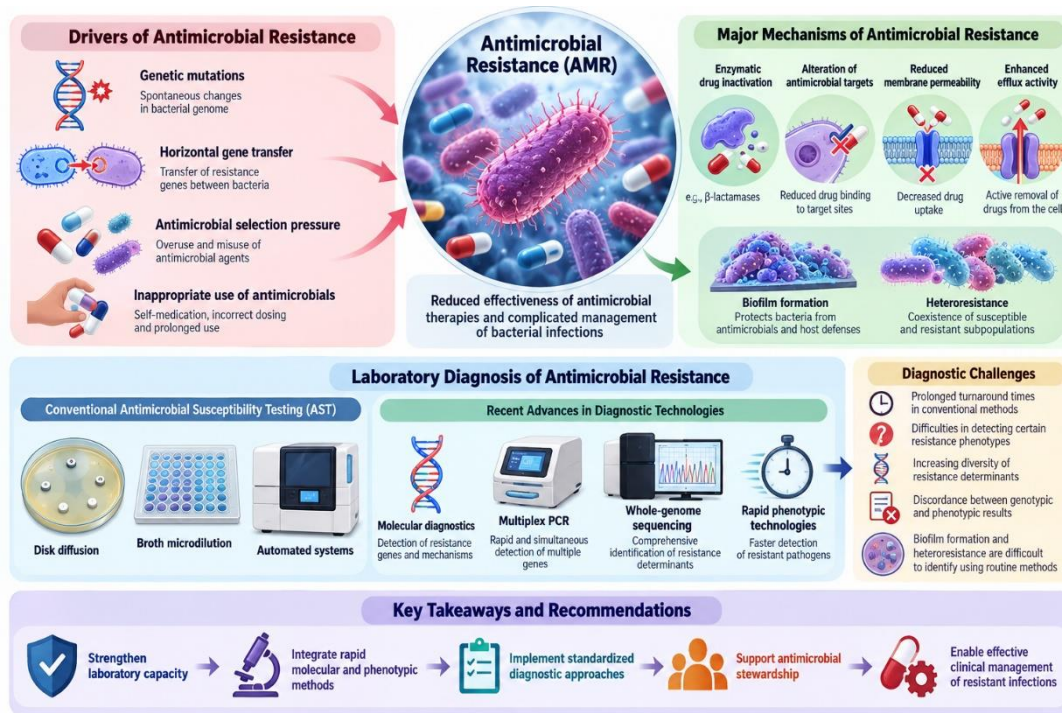
Muhammad Abdullah Butt

Department of Food Sciences, Government College University Faisalabad, Pakistan (muhammadabdullahbuttfst@gmail.com)

Antimicrobial resistance (AMR) has emerged as a major global health challenge, reducing the effectiveness of antimicrobial therapies and complicating the management of bacterial infections. The rapid emergence and dissemination of resistant microorganisms are driven by genetic mutations, horizontal gene transfer, antimicrobial selection pressure, and inappropriate use of antimicrobial agents. Laboratory diagnosis plays a critical role in identifying resistant pathogens and guiding appropriate therapeutic decisions. Conventional antimicrobial susceptibility testing methods, including disk diffusion, broth microdilution, and automated systems, remain widely used; however, their limitations include prolonged turnaround times and difficulties in detecting certain resistance phenotypes. Recent advances in molecular diagnostics, multiplex polymerase chain reaction, whole-genome sequencing, and rapid phenotypic technologies have improved the detection of resistance-associated genes and mechanisms. Nevertheless, the increasing diversity of resistance

determinants presents significant diagnostic challenges, particularly when genotypic resistance markers do not directly correspond with phenotypic susceptibility. Emerging mechanisms, including enzymatic drug inactivation, alteration of antimicrobial targets, reduced membrane permeability, and enhanced efflux activity, further complicate laboratory detection. In addition, biofilm formation and heteroresistance may contribute to treatment failure while remaining difficult to identify using routine diagnostic approaches. This review highlights recent advances in laboratory-based AMR detection, examines major and emerging mechanisms of antimicrobial resistance, and discusses diagnostic limitations affecting timely and accurate identification of resistant pathogens. Strengthening laboratory capacity, integrating rapid molecular and phenotypic methods, and implementing standardized diagnostic approaches are essential for improving antimicrobial stewardship and supporting effective clinical management of resistant infections.

Graphical Abstract



Introduction:

The introduction of antimicrobial drugs in the mid-twentieth century brought about a revolutionary transformation in healthcare, dramatically reducing the risk of infections associated with injuries, childbirth, and invasive surgical procedures. This breakthrough fundamentally changed the practice of medicine, making once life-threatening infections treatable and enabling the safe performance of complex medical interventions. However, the initial optimism surrounding the rise of antimicrobials gradually faded over time due to the alarming emergence of antimicrobial resistance (AMR) in clinical settings. The escalation of drug resistance acquired by pathogens can be attributed to several interconnected factors, including injudicious antimicrobial use, inappropriate drug or dose selection, poor adherence to treatment regimens, and the lack of effective diagnostic methods. While mismanagement undoubtedly accelerates the crisis, the global rise in AMR is also an inherent consequence of the widespread adoption of antibiotic therapies and expanded access to healthcare (Ahmad et al., 2024). The successful integration of antimicrobials into modern medicine provides a persistent, large-scale selective pressure on microbial populations, making resistance a global challenge even alongside appropriate clinical use. The advent of AMR is limiting the potential of existing drugs and other treatment options, thereby increasing the risk of illness spread and infection-associated death. In addition to morbidity and mortality, AMR also imposes a significant economic burden attributable to prolonged hospital stays, expensive medicines, and complex drug regimens. Misuse and overuse of existing antibiotics have resulted in the accelerated development of bacterial resistance, surpassing the pace at which novel drugs can be developed. Consequently, the emergence of AMR has been accompanied by a decline in the antimicrobial development pipeline and a shortage of innovative drugs. In response to this AMR challenge, the World Health Organization (WHO) published a list of antibiotic-resistant "priority pathogens" in 2017 and again in 2024 in order to encourage intensive research and development against antimicrobial-resistant organisms (Elbehiry et al., 2025). The pathogens collectively known as ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) were mentioned in the WHO bacterial priority pathogens list. In this list, antibiotic-resistant ESKAPE pathogens were ranked as the most important pathogens. These include Gram-negative bacteria such as carbapenem-resistant *A.*

baumannii (CRAB) and *P. aeruginosa* (CRPA), and third-generation cephalosporin-resistant *K. pneumoniae* (CRKP) and Enterobacteriaceae (CRE), as well as Gram-positive bacteria, including vancomycin-resistant *E. faecium* (VRE) and methicillin-resistant *S. aureus* (MRSA) and/or vancomycin intermediate/resistant *S. aureus* (VISA/VRSA) (Hassall et al., 2024). ESKAPE pathogens account for substantial numbers of nosocomial infections, and they make up the vast majority of isolates whose antimicrobial resistance poses significant therapeutic challenges in clinical practice. Furthermore, a recently published study showed that ESKAPE pathogens developed resistance within 60 days of an evolutionary experiment conducted in vitro. While antibiotics are crucial for fighting infections, their widespread use has led to significant challenges, such as growing resistance, collateral damage to the microbiome, and the development gap. The process of discovering, developing, and getting a new antibiotic to market is long and expensive. Consequently, antibiotic research and development has seen a significant decline due to low return on investment for pharmaceutical companies, creating a critical gap in the exploration of therapeutic options. Therefore, accelerated development of alternative strategies is essential to address the issue. These strategies focus on different approaches that can bypass the limitations of traditional antibiotics, such as circumventing resistance mechanisms, targeting specific pathogens, enhancing host immunity, and using a combination of antibiotics. Through this survey, we aim to provide in-depth knowledge about ESKAPE pathogens, their antibiotic-resistant patterns, and newly discovered traditional and alternative therapies to fight them. In this analysis, we have thoroughly discussed the prevalence and antibiotic-resistant mechanisms of Gram-positive (VRE, MRSA, VISA/VRSA) and Gram-negative (CRAB, CRE, CRKP, and CRPA) antibiotic-resistant ESKAPE pathogens, along with the scientific and socioeconomic measures that need to be adopted to combat them (Leonard et al., 2018).

The Global Threat of antimicrobial Resistance

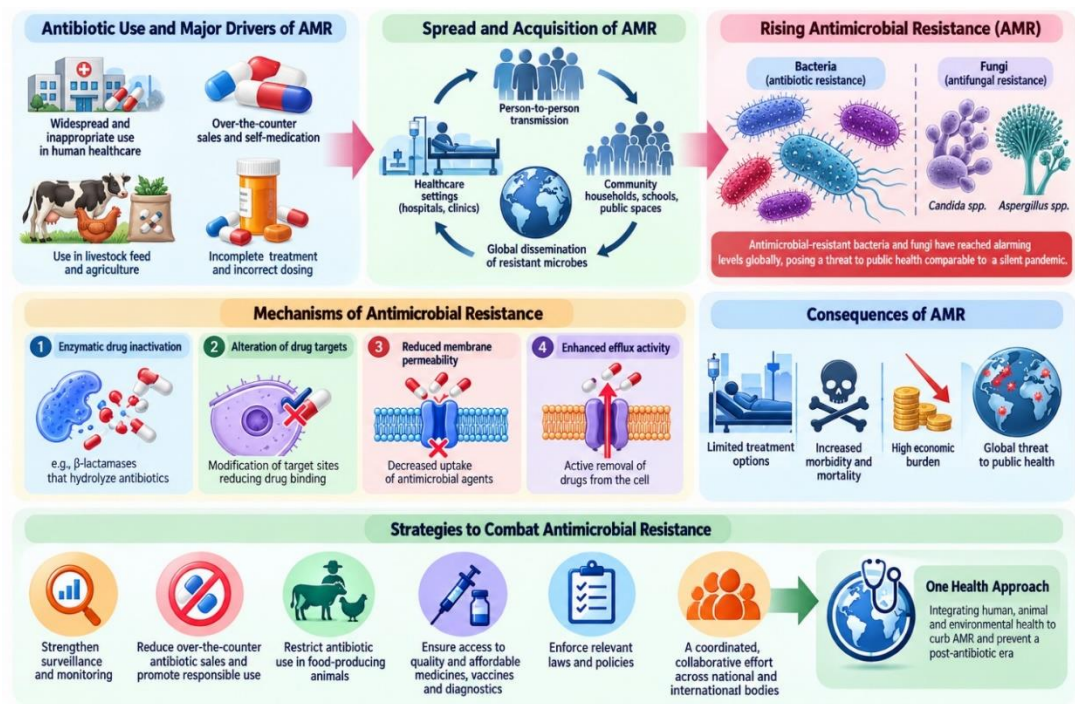
Antibiotics rank among the most significant medical breakthroughs of the 20th century, having prevented countless deaths from infectious diseases. However, the widespread and often inappropriate use of these drugs over time has created intense selective pressure, leading microbes to develop acquired antimicrobial resistance (AMR). The spread and acquisition of AMR happen mainly through person-to-person contact, both in healthcare settings and in the community. Numerous interconnected factors tied to healthcare practices and agricultural use drive the emergence of AMR through various resistance mechanisms (Oliveira et al., 2024). A major contributor has been the emergence and dissemination of AMR resulting from the unchecked use of antimicrobials in livestock feed. Today, antimicrobial-resistant bacteria have reached alarming levels globally, posing a threat to public health comparable to a silent pandemic and demanding immediate action. Treatment choices for infections caused by these resistant bacteria are scarce, leading to considerable illness, death, and economic burden. The shortage of new antimicrobial drugs in development and supply for life-threatening resistant infections stands in stark contrast to the growing need (Oliveira et al., 2024). Urgent measures to curb AMR include strengthening surveillance and monitoring, reducing over-the-counter antibiotic sales and antibiotic use in food-producing animals, ensuring access to quality and affordable medicines, vaccines, and diagnostics, and enforcing relevant laws. A coordinated, collaborative effort across multiple national and international bodies is urgently needed; otherwise, a post-antibiotic era could become a genuine reality rather than a distant fantasy for the 21st century. This narrative review examines the mechanisms and factors behind microbial resistance and outlines key strategies to tackle antimicrobial resistance (Rentschler et al., 2021). Fungal infections, known as mycoses, can lead to severe invasive and systemic diseases, sometimes fatal. In recent years, epidemiological data have shown a rise in severe fungal infection cases, driven largely

by an increasing number of immunocompromised patients and the appearance of fungal pathogens that are increasingly resistant to antifungal treatments. As a result, mortality from fungal infections has also risen. Among the most drug-resistant fungi are species belonging to *Candida* and *Aspergillus*. Some pathogens are found worldwide, while others are endemic to specific regions. Additionally, certain pathogens may pose a health risk only to particular subpopulations rather than the general public(Sinha & Upadhyay, 2025).

Figure No 01. Major drivers, transmission pathways, mechanisms, consequences, and control strategies of antimicrobial resistance (AMR).

Mechanism Of Antimicrbioal Resistance

The molecular mechanisms underlying bacterial antibiotic resistance encompass several critical processes that enable pathogens to survive exposure to antimicrobial agents. These mechanisms include genetic mutations that alter the structure or function of target proteins, enzymatic modification or degradation of antibiotics that renders them ineffective, alteration of drug targets to prevent antibiotic binding, and the overexpression of drug efflux pumps that actively expel antibiotics from bacterial cells, as illustrated in Figure 2. Each of these mechanisms contributes to the ability of bacteria to evade the lethal effects of antibiotics, leading to treatment failure and persistent infections. Antimicrobial resistance (AMR) exhibits pathogen-specific molecular profiles and epidemiological behaviors, meaning that different bacterial species employ distinct resistance strategies and spread at varying rates depending on local conditions, healthcare practices, and population dynamics(Trotter et al., 2019). This diversity necessitates differentiated surveillance approaches tailored to specific pathogens and treatment strategies customized to address the unique resistance mechanisms of each organism. Table 1 summarizes key pathogen-specific resistance mechanisms, their



clinical and public health implications, and the available treatment options for each, providing a comprehensive overview that can guide clinicians and public health officials in making informed decisions regarding infection management and resistance containment(Vasala et al., 2020).

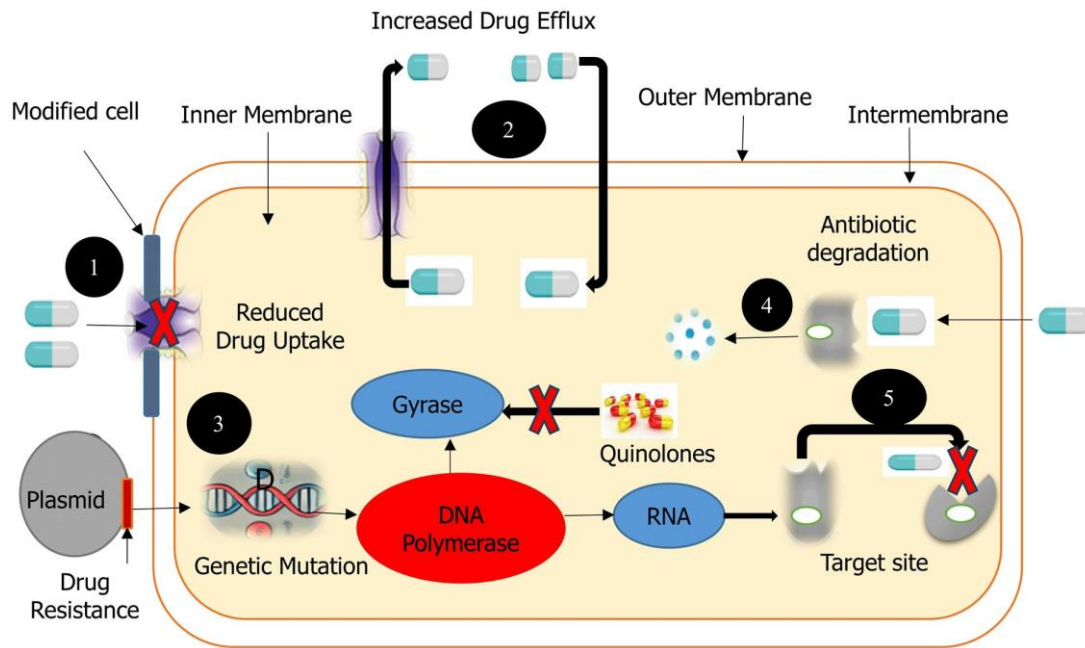


Figure No: 03. This diagram illustrates the key strategies employed by bacteria to resist the effects of antibiotics. These mechanisms include:

(1) **Reduced Drug Uptake:** Alterations in the bacterial cell envelope, such as modifications to porin channels, limit the entry of antibiotics into the bacterial cell. By reducing permeability, bacteria can prevent sufficient concentrations of the drug from reaching their intracellular targets, thereby evading its lethal effects.

(2) **Efflux Pumps:** Transmembrane protein pumps actively export antibiotics from the bacterial cytoplasm, reducing intracellular drug concentrations. These efflux systems, which may be specific to certain antibiotics or broad-spectrum in nature, effectively lower the amount of drug that accumulates inside the cell, allowing the bacterium to survive exposure.

(3) **Genetic Mutation and Target Modification:** Mutations in chromosomal genes, such as those encoding DNA polymerases or gyrase as observed with quinolone resistance, or the acquisition of resistance genes via plasmids, can alter the antibiotic's molecular target, preventing effective binding. These genetic changes ensure that the drug can no longer interact with its intended target, thereby preserving the bacterium's essential cellular functions.

(4) **Antibiotic Degradation:** Enzymes produced by the bacterium chemically modify or degrade the antibiotic molecule, rendering it inactive. A well-known example is the production of beta-lactamases, which hydrolyze the beta-lactam ring of penicillins and cephalosporins, thereby abolishing their antimicrobial activity(Alara & Alara, 2024).

(5) **Target Site Modification:** Structural changes at the antibiotic's binding site within the bacterial cell prevent the drug from exerting its inhibitory effect, even if it successfully enters the cell. These modifications may involve alterations in ribosomal RNA, penicillin-binding proteins, or other molecular targets, ensuring that the antibiotic can no longer recognize and bind to its intended site of action.

Antimicrobial Resistance Mechanisms:

In the context of antimicrobial resistance (AMR), bacteria are among the most extensively studied microorganisms, primarily because of their remarkable ability to develop multiple mechanisms that allow them to survive exposure to antibiotics. One such mechanism, known as target modification, involves bacteria altering their molecular targets for antibiotics, thereby preventing the drugs from binding effectively.

For example, mutations in bacterial ribosomal RNA (rRNA) can hinder the binding of aminoglycosides, enabling the bacteria to continue protein synthesis even in the presence of the antibiotic. A recent study by Babosan and co-workers demonstrated the importance of nonessential transfer RNA (tRNA) and rRNA modifications in the bacterial response to antibiotic stress, proposing that differential translation and codon decoding play an essential role in this stress response. In some bacteria, efflux pumps actively transport a broad range of drugs outside the cytoplasm, reducing their intracellular concentrations and allowing the bacteria to survive at higher antibiotic concentrations. These membrane proteins are particularly significant in resistance to tetracyclines, fluoroquinolones, and macrolides. Bacteria also produce enzymes, often involved in the biosynthesis of the cell wall, nucleic acids, and metabolites, which serve as direct targets for antibiotics (Alara & Alara, 2024). Structural changes in these enzymes can alter the bacteria's resistance profiles. For instance, β -lactamases hydrolyze the β -lactam ring in penicillin, cephalosporin, and carbapenems (which are relatively resistant to β -lactamase), making these antibiotics ineffective. As a result, β -lactam antibiotics are frequently used in combination with beta-lactamase inhibitors. Nevertheless, continuous bacterial evolution and mutation lead to the appearance of new β -lactamases that can resist these inhibitors. Some bacteria, especially Gram-negative ones, possess a mechanism that reduces cell membrane permeability, preventing antibiotics from entering the cell. The bacterial outer membrane acts as a selective diffusion barrier, limiting antibiotic influx through two main pathways: diffusion using protein channels (for hydrophilic antibiotics) and a lipid-mediated pathway (for hydrophobic antibiotics). Modifications in the lipid and protein compositions of the outer membrane can significantly impact bacterial sensitivity to antibiotics. A better understanding of the molecular basis of outer membrane permeability and the physicochemical parameters influencing antibiotic translocation through porins is essential for combating antibiotic resistance (Alara & Alara, 2024). (Show in figure 3)

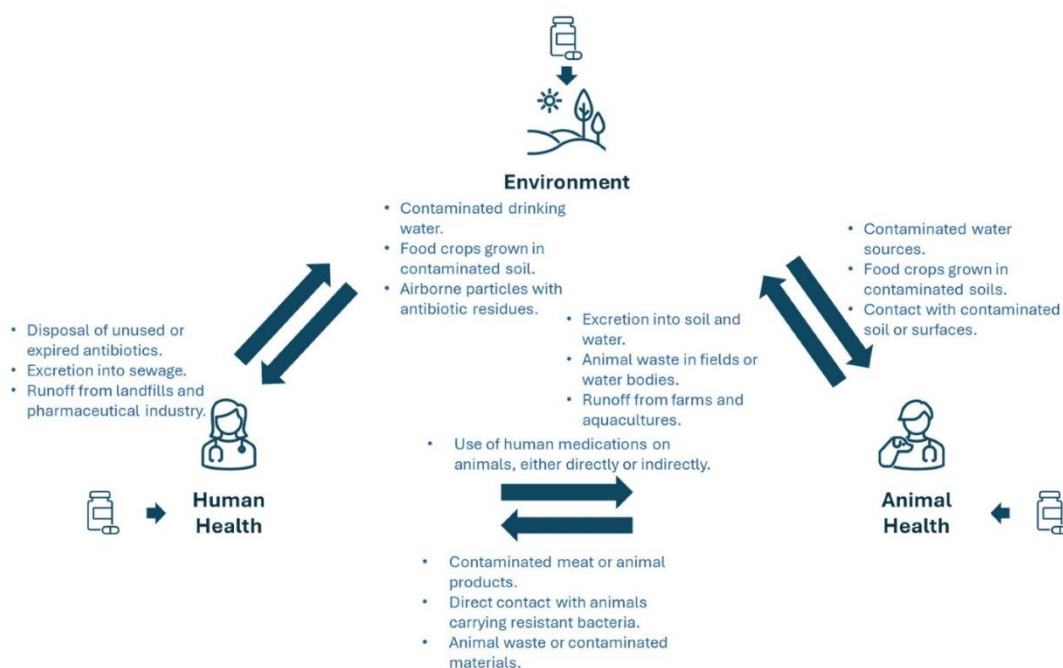


Figure No :03 The molecular mechanisms driving AMR in bacteria are intricately complex, as illustrated in Figure 3, and collectively undermine the efficacy of essential therapies. Resistance often arises through enzymatic degradation or modification of antibiotics, such as β -lactamases,

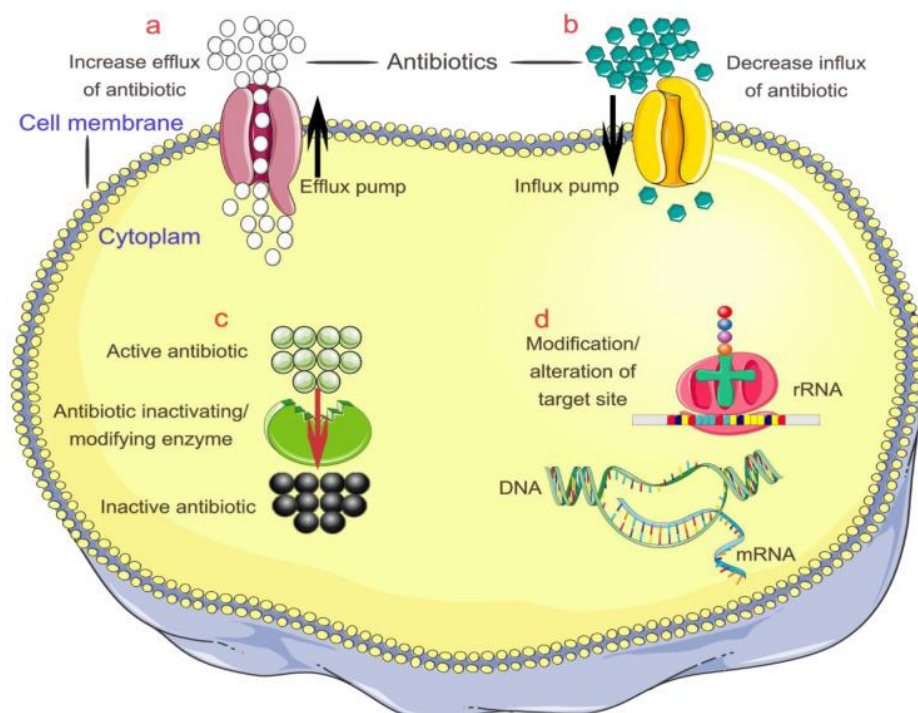


Figure No: 04 Antibiotic resistance occurs through reduced drug uptake, increased efflux, enzymatic inactivation, and modification of antibiotic target sites. These mechanisms decrease antibiotic effectiveness and allow resistant bacteria to survive and multiply.

alteration of antibiotic-binding targets, and active efflux systems that expel drugs from cells. Furthermore, changes in membrane permeability reduce drug uptake, and biofilm formation shields bacterial communities from antimicrobial agents, thereby promoting persistent infection.

Methicillin-Resistant *S. Aureus* (MRSA) and Vancomycin-Intermediate/Resistant *S. Aureus* (VISA/VRSA)

Staphylococcus aureus is a Gram-positive, round-shaped (coccus) bacterium that is frequently found as a part of the normal human skin microbiota. It is a versatile organism capable of surviving under both aerobic and anaerobic conditions, which contributes to its ability to colonize diverse anatomical sites and persist in various environmental niches (Mahrous et al., 2026). Once *S. aureus* strains enter the human body, they can lead to severe infections, including pneumonia, osteomyelitis, endocarditis, arthritis, sepsis, and toxic shock syndrome. Moreover, its ability to form biofilms further complicates antibiotic therapy in patients, as biofilms create a protective barrier that reduces drug penetration and enhances bacterial survival. In current clinical settings, *S. aureus* has become resistant to several commonly used antibiotics. Within two years of the introduction of methicillin in 1959 for the treatment of penicillin-resistant *S. aureus*, the first case of methicillin-resistant *S. aureus* (MRSA) was reported in England. The widespread presence of MRSA in the 1980s led to the accelerated usage of vancomycin in healthcare as empiric treatment for staphylococcal infections. During this time, the growing cases of *Clostridium difficile* and coagulase-negative staphylococci infections in the United States also led to increased consumption of vancomycin. In the 1990s, a strong selective pressure was established, which led to the emergence of strains less susceptible to glycopeptides, including vancomycin,

known as vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA). The first strain of vancomycin-resistant *S. aureus* (VRSA) was isolated in the year 2002 in the United States, and strains of vancomycin-intermediate *S. aureus* (VISA) have been reported from across the globe. To understand the statistical prevalence of vancomycin resistance in *S. aureus*, an in-depth meta-analysis was performed, demonstrating that before 2010, the overall prevalence of VRSA and VISA was 1.2%, and it had reached 2.4% and 4.3% in 2020, respectively. The frequency of VRSA and VISA has increased 2-fold and 2.6-fold, respectively, over the years as compared to what it was prior to 2010. Results from subgroup analysis show that VISA is highly prevalent in Asia as compared to the United States, with a frequency of 2.1%. However, VRSA occurs with the highest frequency in the USA, which is approximately 3.6%. Hasanpour and colleagues have shown that the global prevalence of MRSA was 14.69% in 2023. In this analysis, 119 studies were considered, involving 164,717 participants from 29 different countries. Antibiotic-resistant *S. aureus* ranks second among other leading pathogens for antimicrobial resistance-associated deaths (Anderson, 2026).

Resistance Mechanisms: MRSA

Methicillin, a β -lactam antibiotic, inhibits the binding of penicillin to penicillin-binding protein (PBP), which is essential for the synthesis of the peptidoglycan layer in the bacterial cell wall. MRSA is caused by two genes, *mecA* and *mecC*, which code for PBP2a and PBP2c enzymes, respectively. Both genes confer resistance against β -lactam antibiotics, such as penicillin G (penicillinase-labile), methicillin (penicillinase-stable), and cefoxitin (a cephalosporin). It was further validated that *mecC*-MRSA was naturally selected in the wild during the pre-antibiotic era and not due to the clinical abuse of antibiotics, as β -lactam antibiotics producing the dermatophyte *Trichophyton erinacei* provided the necessary selective pressure in the natural environment, in which MRSA had a growth advantage over its susceptible counterpart. Later, the extensive usage of antibiotics in livestock imparted a selective advantage for MRSA to emerge in domesticated animals, which later jumped to humans. This is supported by the discovery and isolation of the *mecC*-MRSA gene from domesticated cows in Europe initially. Also, studies from different parts of Europe confirmed that a low frequency of MRSA was found in other domesticated animals such as goats, horses, and sheep (da Silva Dantas, 2022).

Resistance Mechanisms: VISA and VRSA

To date, at least eleven *van* gene clusters have been identified to confer vancomycin resistance, namely *vanA*, *vanB*, *vanD*, *vanF*, *vanI*, *vanM*, *vanC*, *vanE*, *vanG*, *vanL*, and *vanN*. Of these eleven genes, only the *vanA* cluster has been identified to be associated with resistance in isolated VISA/VRSA strains. VISA shows intermediate resistance with a minimum inhibitory concentration (MIC) of 4–8 $\mu\text{g/mL}$, while VRSA exhibits full resistance to the drug with an MIC greater than 16 $\mu\text{g/mL}$, making them difficult to treat with standard antibiotic regimens. The strain acquired the *vanA* operon encoded on transposon Tn*1546*, which was originally associated with the VRE conjugative plasmid, and *S. aureus* must have acquired enterococcal plasmids during conjugation. The vast majority of clinical VRSA isolates harbor the *vanA* operon. The presence of the resistant gene *vanA* in *S. aureus* represents a serious epidemiological concern, given its ability to acquire and express resistance genes from the *Enterococcus* reservoir (Howard et al., 2026). (Show in figure 5)

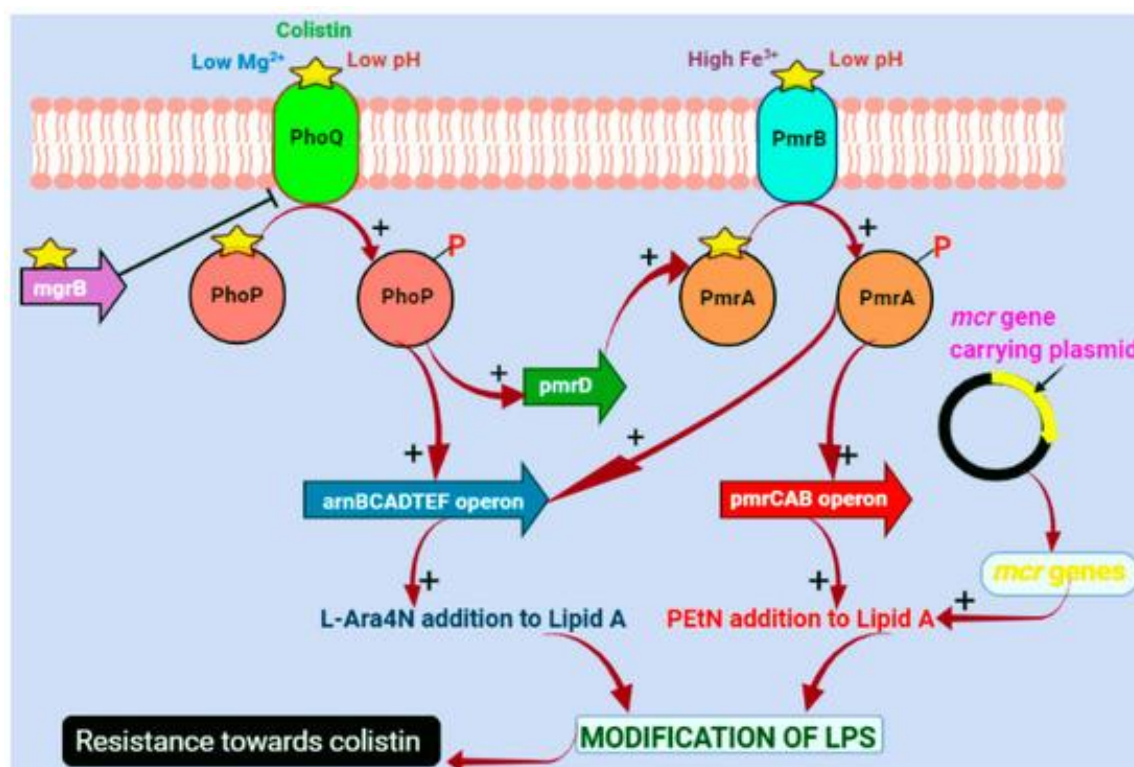


Figure No: 05 Resistance towards colistin.

3.1. Epidemiology and Mechanisms of Resistance

The alarming rise in antibiotic resistance rates, combined with the increasing risk of infections in immunocompromised patients and the widespread use of invasive diagnostic and therapeutic methods globally, is responsible for a staggering number of deaths attributable to bacterial infections each year, with 13.7 million infection-associated deaths recorded in 2019, of which 7.7 million were attributable to 33 bacterial pathogens, accounting for 13.6% of all global deaths and 56.2% of deaths due to sepsis. The most important bacterial pathogens associated with mortality were *Staphylococcus aureus*, a major cause of infections reported across 135 countries and responsible for more than 1 million deaths, particularly among individuals older than 15 years; *Streptococcus pneumoniae*, most frequently linked to deaths in the pediatric population under 5 years; *Salmonella enterica* serovar Typhi, associated with deaths in the 5–14 year age group; and *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, each of these three Gram-negative bacilli being responsible for more than 500,000 deaths in 2019 (Yu et al., 2023). In the same year, three major infectious syndromes were predominantly associated with mortality: lower respiratory tract infections, primarily caused by *S. pneumoniae*, and sepsis, dominated by *S. aureus*, each responsible for over 2 million deaths, as well as intra-abdominal infections most frequently caused by *E. coli*, resulting in over 1 million deaths, with the highest infection-related mortality rate recorded in Central Africa at 394 deaths per 100,000 population and the lowest in Iceland at 35.7 deaths per 100,000 population (Jian et al., 2021). To these figures must be added the growing concern over the escalation of global antimicrobial resistance, which is leaving increasingly limited therapeutic resources for the management of bacterial infections, with multidrug resistance (MDR) referring to resistance against at least three classes of antibiotics, extensive drug resistance (XDR) defined as resistance to at least one agent in all but two or fewer antimicrobial classes, and pandrug resistance (PDR) referring to resistance to all agents in all antimicrobial classes; by 2050, it is estimated that antimicrobial resistance will be responsible for more than 10 million deaths annually, prompting the WHO to release, on 17 May 2024, a list of 15 priority families of pathogens requiring surveillance and urgent therapeutic

solutions, stratified into critical, high, and medium priority groups. The critical priority group includes *Acinetobacter baumannii* (carbapenem-resistant) and Enterobacterales resistant to third-generation cephalosporins and/or carbapenems, which are characterized by extremely limited or even absent therapeutic options, high morbidity and mortality, rapidly increasing resistance trends, and transmission mechanisms that are difficult to control; the high priority group comprises *Salmonella* Typhi (fluoroquinolone-resistant), *Shigella* spp (Jian et al., 2021). (fluoroquinolone-resistant), *Enterococcus faecium* (vancomycin-resistant), *Pseudomonas aeruginosa* (carbapenem-resistant), non-typhoidal *Salmonella* (fluoroquinolone-resistant), *Neisseria gonorrhoeae* (third-generation cephalosporin- and/or fluoroquinolone-resistant), and *Staphylococcus aureus* (methicillin-resistant), which are also highly challenging to treat, associated with elevated morbidity and mortality, demonstrate alarming upward trends in resistance, spread rapidly, and have only a few available or pipeline therapeutic options; and the medium priority group, which has a significant impact on global health, particularly among vulnerable populations in low-resource settings, includes group A and group B streptococci, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, against which moderate therapeutic resources remain available, with intermediate levels of morbidity and mortality, moderate increases in resistance, and more effective control through preventive and transmission-reduction strategies (Vitiello et al., 2024). In Europe, data provided by the European Centre for Disease Prevention and Control (ECDC) indicate an increasing trend in resistance to third-generation cephalosporins and carbapenems among *Klebsiella pneumoniae*, with carbapenem resistance exceeding 25% in 33% of reporting countries, and *Escherichia coli*, while carbapenem resistance was also common among *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, particularly in countries from Southern and Eastern Europe; for *E. coli* isolates obtained in 2021 from blood and urine cultures in Northern European countries such as Finland and Norway, resistance to fluoroquinolones and third-generation cephalosporins remained below 10%, by contrast, resistance rates in Russia, Turkey, North Macedonia, and Cyprus exceeded 50%, and carbapenem resistance among *E. coli* isolates was reported at below 1% in eight European countries, while for *K. pneumoniae* isolated from blood, urinary, and respiratory infections, resistance rates to third-generation cephalosporins remained below 10% in Northern European countries including Iceland, Norway, Sweden, Switzerland, Denmark, Finland, and Austria but exceeded 50% in Eastern and Southern Europe, with carbapenem resistance below 1% in 14 countries, whereas 15 countries reported resistance rates of 25% or higher, and eight countries, namely Romania, Moldova, Serbia, Russia, Ukraine, Georgia, Belarus, and Greece, documented resistance exceeding 50%; for *P. aeruginosa*, most frequently isolated from healthcare-associated infections in immunocompromised patients, carbapenem resistance was below 5% in Denmark and Finland but exceeded 50% in Moldova, Serbia, Ukraine, Russia, Georgia, and Belarus, while the highest resistance levels were reported for *A. baumannii*, isolated from blood cultures, ventilator-associated respiratory infections, and wound infections, with resistance reaching at least 50% in 25 European countries; among *S. aureus* isolates from Europe in 2021, there was a marked increase in community-acquired MRSA, representing 25% or more of isolates in 13 countries including Romania, Italy, Turkey, and Ukraine, and an increasing trend in penicillin resistance among *Streptococcus pneumoniae* strains was observed in several countries including Romania, France, Serbia, Turkey, and Belarus where resistance rates were 25% or higher, while for *Enterococcus faecium*, vancomycin resistance was below 1% in France, the Netherlands, Norway, Luxembourg, Sweden, and Finland in 2021 but exceeded 50% in Malta, Cyprus, North Macedonia, Serbia, and Lithuania, with 17 other European countries reporting resistance rates above 25%. Most bacterial pathogens exhibit multiple acquired resistance mechanisms against the same antimicrobial agent, with the most relevant mechanisms including enzymatic or chemical inactivation, target modification such as

alterations in penicillin-binding proteins (PBPs), reduced permeability through porin loss, overexpression of efflux pumps, and the continuous identification of new resistance gene families, all of which add to the background of intrinsic resistance already present in many organisms (The, 2024); Gram-positive bacteria, lacking an outer membrane, generally display higher permeability, which allows the entry of certain antibiotics that are unable to cross the double membrane of Gram-negative bacteria, while in Gram-negatives, resistance is further enhanced by porin loss and by modifications in fatty acid and phospholipid content, both of which reduce antibiotic penetration, and at the level of porins, antibiotic entry occurs by passive rather than active diffusion and is influenced by pore size and the molecular weight of the antibiotic, with non-specific porins such as OmpF and OmpC facilitating easier passage of antibiotics compared to substrate-specific porins such as PhoE and LamB, which allow permeation primarily for molecules with molecular weights below 600 Da, and structural modifications of OmpK35 and OmpK36 have been shown to underlie carbapenem resistance in *Klebsiella pneumoniae*; structural modifications of OmpC have also been identified in *Escherichia coli* strains, conferring resistance to cephalosporins, carbapenems, and aminoglycosides, while porins likewise play a critical role in resistance among *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, permitting entry of molecules smaller than 200 Da while rendering the outer membrane impermeable to larger, hydrophilic antibiotics, and synergy between multiple resistance mechanisms and complete porin loss in *P. aeruginosa* effectively prevents the intracellular penetration of antibiotics (Millar et al., 2026); efflux pumps represent another major resistance determinant, as these transmembrane proteins extrude diverse substances including antibiotics from the periplasmic space, and of the six efflux pump families, the resistance–nodulation–division (RND) family is the most significant, being a key driver of multidrug resistance in Gram-negative bacteria, while the emergence of MDR frequently involves the interplay of several resistance mechanisms, for instance, increased antibiotic efflux in Enterobacterales may be associated with deletion or inhibition of the *acrAB* gene, leading to reduced expression of specific porins such as OmpF and consequently diminished intracellular antibiotic penetration, and in *K. pneumoniae*, plasmid-mediated resistance has been shown to enhance the transcription of efflux-associated genes, thereby contributing further to drug resistance; modification of the cellular target reduces antibiotic efficacy, as for fluoroquinolones, structural changes in topoisomerase caused by amino acid substitutions impair drug binding, and genetic alterations leading to structural changes in penicillin-binding proteins (PBPs) are similarly associated with reduced β -lactam activity, with a recent example being the modification of PBP3 in *Escherichia coli*, which confers resistance to aztreonam/avibactam, while ribosomal RNA methylation is another mechanism conferring resistance to macrolides, streptogramins, and lincosamides, as well as to aminoglycosides through the action of 16S rRNA methyltransferases; structural modifications of lipopolysaccharide (LPS) represent the major mechanism of resistance to colistin in Gram-negative bacteria, occurring primarily through the activity of phosphoethanolamine (pEtN) transferases or *mcr* (mobile colistin resistance) genes, explaining the rapid emergence of colistin resistance, and for quinolones, high-level resistance often arises from the combination of multiple mechanisms, for instance, acquisition of a *qnr* gene, which encodes Qnr proteins that protect topoisomerases from quinolone action, coupled with chromosomal mutations (Reza et al., 2025). (Show in figure 6)

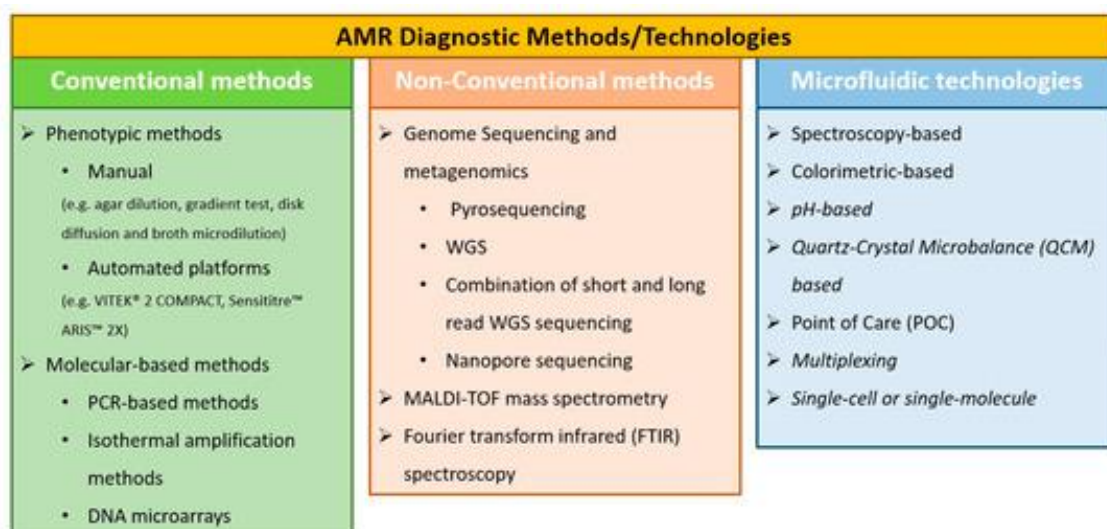


Figure No: 06. AMR diagnostic Method\Technologies.

Future Perspectives: Toward an Integrated-Sciences Framework for Antimicrobial Resistance

The future management of antimicrobial resistance (AMR) requires a fundamental transition from reductionist approaches toward a philosophy of integrated sciences, in which biological, technological, environmental, nutritional, agricultural, clinical, computational, and socioeconomic dimensions are considered as interconnected components of a single system. The expanding body of interdisciplinary research demonstrates that complex health challenges cannot be effectively addressed through isolated scientific disciplines. Developments in functional foods, probiotics, food safety, nutritional biochemistry, molecular biotechnology, artificial intelligence, environmental toxicology, computational science, and sustainable food systems collectively provide a broader conceptual foundation for understanding how microbial ecosystems, host health, environmental pressures, and human behaviour interact. Research on probiotic yogurt, plant-based functional foods, gut microbiota, dietary bioactives, and nutritional interventions illustrates the increasing importance of nutrition and microbiome science in maintaining metabolic and physiological resilience, while investigations into foodborne safety, adulteration, heavy-metal exposure, and microbial hazards demonstrate that microbial health is inseparable from the food system itself (Ahmed et al., 2024; Riaz et al., 2026a; Riaz et al., 2026b; Rashid et al., 2026; Nawaz et al., 2026; Shazif et al., 2026).

From this perspective, future AMR research should increasingly adopt a One Health–plus framework, extending beyond the conventional human–animal–environment triad to incorporate food systems, nutrition, biotechnology, digital technologies, economics, and social behaviour. The safety and sustainability of animal-derived foods, for example, are linked simultaneously with microbial contamination, antimicrobial exposure, agricultural practices, nutritional quality, and consumer health. Comparative studies of beef products, milk safety, plant-based meat analogues, and hybrid protein systems demonstrate the value of connecting food technology with microbiological and public-health considerations (Butt et al., 2024a; Riaz et al., 2026b; Butt et al., 2025a; Butt et al., 2025b). Similarly, investigations of dietary zinc, functional diets, nutritional biomarkers, cancer-related dietary bioactives, and metabolic health indicate that future preventive strategies may increasingly connect nutritional status with host resilience and disease susceptibility (Butt et al., 2026a; Butt et al., 2026b; Zaidi & Randhawa, 2025; Zaidi et al., 2026; Riaz et al., 2026c). Such integration does not imply that nutrition alone can control AMR; rather, it suggests that antimicrobial stewardship

should be situated within a broader understanding of host, microbial, dietary, and environmental interactions.

A particularly important future direction is the convergence of molecular biotechnology, genome engineering, precision fermentation, and computational biology. CRISPR-based genome editing has already demonstrated potential for manipulating biological systems with increasing precision, including disease resistance in crops and epigenetic regulation of stress-response pathways (Jabeen et al., 2025; Fatima et al., 2026). These technologies could eventually contribute to AMR research through improved characterization of resistance determinants, development of microbial surveillance platforms, engineering of beneficial microorganisms, and exploration of alternative antimicrobial strategies. Likewise, ultrasound-assisted protein modification, microbial transglutaminase crosslinking, sustainable meat-analogue development, and precision fermentation demonstrate how advanced biotechnology can be integrated with food and microbial sciences to develop safer and more sustainable biological systems (Butt et al., 2026c; Butt et al., 2026d; Butt et al., 2026e). Future research should therefore examine not only how microorganisms become resistant but also how biological systems can be deliberately redesigned to reduce selective pressures and improve resilience.

The philosophy of integrated sciences also places artificial intelligence (AI), machine learning, and computational modelling at the centre of future AMR research. AI should not be viewed merely as a diagnostic automation tool but as a connective layer capable of integrating heterogeneous datasets generated from microbiology, genomics, metabolomics, nutrition, clinical medicine, environmental monitoring, and epidemiology. Current research demonstrates the expanding use of AI in cardiovascular diagnostics, precision fermentation, nutrigenomics, business decision systems, cybersecurity, education, and adaptive technological environments (Arif et al., 2026; Butt et al., 2026e; Butt et al., 2026f; Naeem et al., 2026a; Naeem et al., 2026b; Naeem et al., 2026c; Faizi et al., 2026; Amanat & Butt, 2026). In the AMR context, this interdisciplinary computational architecture could support prediction of resistance emergence, identification of high-risk transmission networks, optimization of antimicrobial treatment strategies, interpretation of complex microbiological datasets, and early warning systems. The integration of AI with multi-omics approaches is particularly promising because biological resistance is rarely governed by a single variable; rather, it emerges from interactions among genes, metabolic pathways, microbial communities, host factors, environmental conditions, and antimicrobial exposure.

Future AMR surveillance should consequently evolve from isolated laboratory testing toward real-time, multi-scale intelligence systems. Multi-omics approaches in environmental and aquatic systems demonstrate how molecular information can be combined with ecological and toxicological data to understand complex biological responses (Ullah et al., 2026a; Ullah et al., 2026b). Similar principles could be applied to AMR surveillance by integrating genomic resistance markers with microbiological phenotypes, antimicrobial-use data, wastewater monitoring, food-chain surveillance, clinical outcomes, and environmental measurements. Advances in diagnostic testing, including molecular detection and rapid confirmatory technologies in other infectious diseases, further illustrate the potential of combining molecular assays with conventional diagnostic workflows rather than treating them as competing paradigms (Nadeem et al., 2026; Sarwar et al., 2026). Future diagnostic systems should therefore be designed as interoperable platforms in which laboratory results can be connected to clinical, epidemiological, environmental, and population-level information.

The integrated-sciences philosophy also requires greater attention to environmental sustainability and ecological feedback mechanisms. AMR does not occur in isolation from broader environmental pressures. Microplastics, nanoplastics, chemical contaminants, salinity stress, agricultural practices, and industrial processes can alter

biological systems and potentially influence microbial ecology and host susceptibility (Ullah et al., 2026a; Ullah et al., 2026b; Shafeeq et al., 2026). Future research should therefore investigate AMR within environmental systems rather than restricting surveillance to hospitals. Agricultural biotechnology and crop-resilience research, including CRISPR-mediated disease resistance and drought adaptation, may also contribute to reducing dependence on chemical and antimicrobial inputs in food production (Jabeen et al., 2025; Fatima et al., 2026). Similarly, sustainable protein systems, plant-based foods, and valorization of agricultural by-products provide opportunities to redesign food-production systems around principles of resource efficiency, microbial safety, nutritional adequacy, and reduced environmental pressure (Butt et al., 2025a; Butt et al., 2026g; Riaz et al., 2026a).

Another essential component of future integrated science is the recognition that AMR is simultaneously a biological and social problem. Scientific innovation alone cannot resolve antimicrobial misuse if economic incentives, healthcare practices, educational systems, workplace structures, and consumer behaviour remain disconnected from antimicrobial stewardship. Research on healthcare workforce sustainability, migration and health inequities, educational technologies, organizational performance, and AI-supported decision-making demonstrates that health outcomes are influenced by institutional and socioeconomic structures (Rehman et al., 2026; Riaz et al., 2026d; Faizi et al., 2026; Naeem et al., 2026c). The future AMR agenda should therefore incorporate behavioural science, health economics, public communication, education, governance, and equitable access to diagnostics and therapeutics. Research addressing gendered social structures and broader social dimensions of sustainability further reinforces the principle that technological interventions operate within complex human systems rather than independently of them (Fatima et al., 2026b; Khurshid et al., 2026). The same principle applies to governance and responsible innovation. As scientific systems become increasingly interconnected, the risks associated with technological complexity also increase. Research on risk governance, AI-generated code, AI adoption, and strategic decision systems highlights the necessity of establishing frameworks that balance technological innovation with accountability, security, transparency, and human oversight (Butt et al., 2026h; Ali & Butt, 2026; Saboor et al., 2026; Naeem et al., 2026a). In future AMR platforms, AI-generated recommendations, automated diagnostics, genomic predictions, and antimicrobial-use algorithms should therefore remain subject to validation, ethical oversight, data-quality assessment, and clinical accountability. Integrated science should not mean indiscriminate technological integration; it should mean purposeful integration under scientifically and ethically defined principles.

There is also considerable potential for integrating materials science, engineering, physics, and computational modelling into the future AMR ecosystem. Research in photonic devices, nonlinear mathematical modelling, and computational investigation of complex physical systems illustrates how engineering disciplines can contribute methods for sensing, modelling, communication, and system optimization (Butt & Ansar, 2026; Tahir et al., 2026; Shah & Butt, 2026). Similar interdisciplinary principles could support next-generation biosensors, point-of-care diagnostic devices, antimicrobial delivery systems, nanoscale detection platforms, and distributed surveillance networks. The future laboratory may therefore become less defined by conventional disciplinary boundaries and more by integrated platforms capable of generating, interpreting, and communicating biological information in real time.

The integration of food science, nutrition, microbiology, biotechnology, medicine, environmental science, and digital intelligence may ultimately enable a shift from reactive AMR management toward predictive and preventive health systems. Functional foods, probiotics, dietary bioactives, plant-derived compounds, and sustainable food technologies should be investigated not as substitutes for antimicrobial therapy but as components of broader strategies for maintaining host health and

reducing unnecessary antimicrobial exposure (Ahmed et al., 2024; Riaz et al., 2026a; Nawaz et al., 2026; Butt et al., 2026b; Butt et al., 2026g). Likewise, studies of nutritional and molecular determinants of disease, dietary patterns, and metabolic health suggest opportunities for developing personalized preventive frameworks in which nutrition and microbial ecology are considered alongside conventional medical interventions (Riaz et al., 2026c; Riaz et al., 2026e; Butt et al., 2026f).

Ultimately, the future of AMR research should be guided by a philosophy of scientific convergence rather than scientific isolation. The objective should not simply be to produce faster diagnostic tests, discover new antimicrobials, or generate larger datasets, but to construct an interconnected knowledge system in which discoveries in one discipline inform decisions in another. Food-production systems should communicate with public-health surveillance; genomic information should interact with clinical diagnostics; environmental monitoring should inform agricultural and healthcare policy; nutritional science should contribute to preventive health strategies; and AI should integrate these heterogeneous streams while remaining under human scientific and ethical oversight. Research across functional foods, sustainable proteins, precision fermentation, genome editing, AI, environmental toxicology, healthcare systems, education, governance, and computational science collectively demonstrates the feasibility of such interdisciplinary convergence (Ahmed et al., 2024; Butt et al., 2024a; Butt et al., 2025a; Jabeen et al., 2025; Fatima et al., 2026; Riaz et al., 2026a; Ullah et al., 2026a; Saboor et al., 2026). In this framework, AMR becomes not merely a microbiological problem requiring a microbiological solution, but a complex systems challenge requiring coordinated knowledge across the life sciences, physical sciences, computational sciences, food and agricultural sciences, health sciences, and social sciences. Such an integrated perspective offers a pathway toward more predictive, sustainable, equitable, and resilient approaches to antimicrobial stewardship and global health.

Conclusion

Antimicrobial resistance remains a rapidly evolving challenge that requires accurate and timely laboratory diagnosis. Advances in molecular, genomic, and rapid phenotypic technologies have improved the detection of resistant pathogens. However, complex resistance mechanisms and discrepancies between genotypic and phenotypic findings continue to create diagnostic challenges. Strengthening laboratory infrastructure, diagnostic capacity, and standardized susceptibility testing is essential for reliable AMR surveillance. Integrating advanced diagnostics with antimicrobial stewardship can support appropriate therapy and help limit the further spread of resistant microorganisms.

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