



Antimicrobial Resistance: from Evolution to Clinical Impact and Strategies for Combating Drug-Resistant Infections

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Abstract

Antimicrobial resistance has emerged as a major global health threat, challenging the effective prevention and treatment of infectious diseases. Its evolution spans from the pre-antibiotic era through the early and golden era of antibiotic discovery to the present phase, characterized by a high prevalence of resistance and a limited pipeline of new agents. This review presents a comprehensive overview of epidemiology and the global burden of antimicrobial resistance, projecting its increasing impact on healthcare systems. It discusses common pathogens associated with resistance and key mechanisms involved, including enzymatic drug inactivation, target modification, decreased permeability, efflux pumps, and biofilm formation. The major clinical implications of antimicrobial resistance, such as treatment failure, increased morbidity and mortality, and prolonged hospitalization, are also discussed. Furthermore, the review examines major risk factors that contribute to the emergence and spread of resistance, such as irrational use of antibiotics, inadequate infection control, and lack of awareness. Strategies to combat antimicrobial resistance, such as international initiatives, national policies and committees, and interventions at the community and patient levels, are discussed. The role of pharmacists in antimicrobial stewardship, patient education, and optimization of therapy is also highlighted. Recent advances in antimicrobial research have presented innovative approaches to mitigate the increasing antimicrobial resistance, which comprise nanotechnology-based antimicrobial development, computational methods, including in silico modelling and fragment-based drug design, and drug repurposing. These approaches offer potential for the discovery of novel therapeutic agents with improved stability, efficacy, and reduced resistance development.

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1. Introduction

Antimicrobial agents are essential therapeutic tools used to prevent and treat infectious diseases caused by bacteria, fungi, viruses, and parasites. They include antibiotics, antifungal agents, antivirals, and antiparasitic drugs, which act by killing microorganisms or inhibiting their growth and replication. However, the effectiveness of these medicines is increasingly threatened by antimicrobial resistance (AMR), a phenomenon in which microorganisms acquire the ability to survive exposure to antimicrobial agents that would previously have been effective against them. Although AMR encompasses resistance across bacterial, fungal, viral, and parasitic pathogens, bacterial resistance to antibacterial agents remains a major focus of scientific and clinical concern because of its extensive impact on human health, healthcare systems, and public health [1].

The emergence and global dissemination of antimicrobial-resistant pathogens have substantially reduced the effectiveness of many conventional therapies. Infections caused by resistant bacteria may become more difficult to treat, require alternative or combination therapies, and lead to prolonged illness, increased healthcare utilization, and greater clinical complexity. The problem is further intensified by the ability of resistant microorganisms and resistance determinants to circulate between humans, animals, and environmental reservoirs [2]. Antibiotic-resistant bacteria can disseminate through agricultural manure, municipal and hospital wastewater, contaminated soil, surface water, and other environmental pathways. These interconnected routes facilitate the continuous exchange and maintenance of resistant microorganisms and resistance genes across different ecosystems [3].

The consequences of antimicrobial resistance extend beyond human medicine. Resistant infections can adversely affect animal health, increase morbidity and mortality, and contribute to animal suffering. In agricultural systems, infectious diseases and resistance-related treatment limitations may reduce farm productivity and increase economic losses. The presence of resistant microorganisms in livestock, crops, water, and food production systems can also create additional opportunities for exposure and transmission. Consequently, AMR represents a complex and interconnected challenge that cannot be adequately addressed through human healthcare interventions alone. It requires coordinated consideration of human, animal, agricultural, and environmental health [4].

The development of antimicrobial resistance is driven by multiple interacting factors, including inappropriate antimicrobial use, unnecessary prescribing, incomplete or incorrect treatment, self-medication, inadequate infection prevention, poor sanitation, and insufficient surveillance. In healthcare settings, inappropriate antibiotic selection, excessive use of broad-spectrum agents, and inadequate diagnostic support may accelerate the selection of resistant organisms. Similar pressures may occur in veterinary practice and agriculture, where antimicrobial exposure can create selective conditions favoring resistant populations. The persistence of resistant pathogens in communities and environmental reservoirs further complicates efforts to limit their transmission [5].

This review presents an integrated perspective on antimicrobial resistance by connecting its historical emergence with contemporary epidemiology, important resistant pathogens, underlying molecular and cellular resistance mechanisms, clinical consequences, modifiable risk factors, and current prevention and control measures. Particular attention is given to antimicrobial stewardship as a central strategy for optimizing antimicrobial use and reducing unnecessary selective pressure. The expanding role of pharmacists is also considered, especially in antimicrobial selection, dosage optimization, patient counseling, medication monitoring, adherence improvement, and stewardship programs [6].

A One Health framework is further emphasized because effective AMR control depends on coordinated interventions across human health, veterinary medicine, agriculture, food systems, and the environment. In parallel, the review discusses emerging approaches aimed at addressing limitations in the conventional antimicrobial pipeline. These include nanotechnology-based antimicrobial strategies, computational drug discovery, fragment-based drug design, and drug repurposing, which may facilitate the identification and development of innovative therapeutic options against resistant pathogens [7].

By integrating these complementary dimensions, this review emphasizes that antimicrobial resistance is not solely a microbiological or clinical problem but a multifaceted global challenge requiring sustained scientific, healthcare, regulatory, and environmental action. Understanding the interconnected drivers of resistance and developing coordinated strategies for prevention, surveillance, stewardship, and therapeutic innovation will be essential for preserving the

effectiveness of existing antimicrobial agents while supporting the discovery of new approaches for managing drug-resistant infections [8].

2. History of Antimicrobial Resistance

2.1 Pre-antibiotic era:

In this era, knowledge about microbes and infectious diseases was inadequate. The prevention and treatment of infectious diseases were ineffective, resulting in high mortality rates. Historically, infectious diseases such as plague were associated with substantial morbidity and mortality because effective antimicrobial therapy was unavailable [9]. In 1676, Antonie van Leeuwenhoek's discovery of microscopic living organisms, which he termed "animalcules," laid the groundwork for the eventual development of antibiotics [10]. In 1871, the inhibitory effect of *Penicillium glaucum* on bacterial growth was reported by Joseph Lister, providing early evidence of microbial antagonism and contributing to the emerging understanding of infectious diseases. Louis Pasteur's work on *Bacillus anthracis* and Robert Koch's studies on *Mycobacterium tuberculosis* established a clear association between specific bacterial species and disease. The seminal contributions of these pioneering microbiologists advanced the field of microbiology and paved the way for the modern development of antibiotics [11].

2.2 Early antibiotic era:

In 1893, Barto Lomeo Gosio discovered the first antibiotic, mycophenolic acid, which was isolated from *Penicillium glaucum* and inhibits the growth of *Bacillus anthracis*. Paul Ehrlich and his co-workers discovered Salvarsan (arsphenamine), which was the first synthetic arsenic-derived antibiotic effective against *Treponema pallidum* [12]. In 1932, Gerhard Domagk demonstrated the antibacterial activity of Prontosil, a sulfonamide-containing azo dye, marking

a major milestone in the development of sulfonamide chemotherapy. In 1928, Alexander Fleming accidentally discovered penicillin. The structure of Penicillin G was elucidated by Howard Walter Florey and Ernst Boris Chain in 1939. In 1961, staphylococci became resistant to methicillin (MRSA) and were described as the first "superbug" [13].

2.3 Golden antibiotic era:

In 1939, French microbiologist René Dubos marked a major milestone in antibiotic research by isolating tyrothricin, a mixture of gramicidin D and tyrocidine, from soil bacteria. The producing organism, *Bacillus brevis*, exhibited potent antibacterial activity against Gram-positive organisms. In 1949, Selman Waksman established a systematic framework for antibiotic discovery through microbial screening, leading to the identification of several important antibiotics and antifungal agents, including actinomycin, neomycin, streptomycin, clavacin, and fumigacin [14].

Building on Waksman's culture-based screening strategy, pharmaceutical companies subsequently adopted more systematic and increasingly rational screening approaches to identify novel antimicrobial compounds based on established mechanisms of action. Despite these advances, the discovery of new antibiotic classes progressively declined [15]. Major antibiotic classes introduced during this discovery era included tetracyclines in 1948, macrolides in 1952, nitrofurantoin in 1953, quinolones in 1960, and oxazolidinones in 1987. Since the introduction of oxazolidinones, the development of entirely new antibiotic classes has remained limited, highlighting the increasing challenges associated with the conventional antibiotic discovery pipeline. A schematic representation of the historical development of antibiotics is presented in Figure 1 [16].

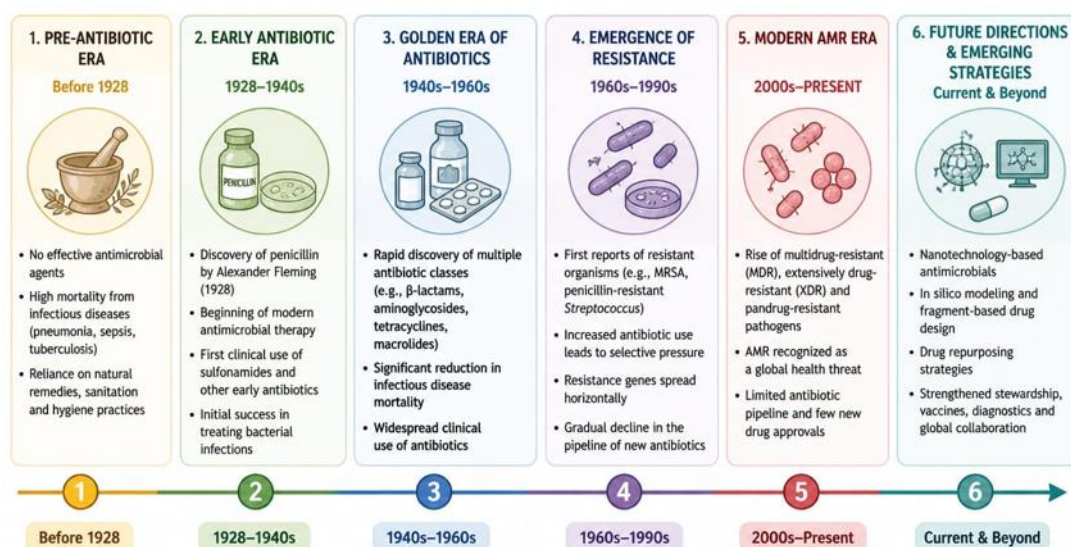


Figure 1: Evolution of antimicrobial therapy and resistance.

3. Epidemiology and Global Burden of Antimicrobial Resistance

Antimicrobial resistance represents a major global health crisis. In 2019, bacterial AMR was estimated to be directly responsible for approximately 1.27 million deaths globally and associated with 4.95 million deaths. More recent surveillance and epidemiological evidence indicates that the burden of resistant infections remains substantial across regions, with considerable variation in pathogen distribution, antimicrobial resistance patterns, and healthcare capacity. Epidemiological data show a high burden in Sub-Saharan Africa, where LRTI represents the leading syndrome affecting routine surgical procedures and medical care [17].

Low- and middle-income countries are disproportionately affected due to inadequate healthcare infrastructure, weak regulatory oversight, and limited access to antibiotics. Conversely, antimicrobial resistance in high-income countries is driven primarily by hospital-associated outbreaks and globalization-related factors [18].

The economic impact of AMR is significant. Resistant infections raise healthcare expenditure through prolonged hospital stays, greater dependence on intensive care, and the use of costly last-resort antibiotics. The economic consequences of AMR are substantial, owing to prolonged hospitalization, increased healthcare utilization, intensive-care requirements, and the use of more expensive or toxic alternative antimicrobials. Economic modelling has suggested that uncontrolled AMR could substantially reduce global economic output by 2050 [19].

4. Common Pathogens Associated with Antimicrobial Resistance

Major pathogens implicated in antimicrobial resistance include *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*. These organisms are responsible for a wide range of severe community- and healthcare-associated infections and have been identified as important threats because of their increasing resistance to available antimicrobial therapies [20]. In 2017, the World Health Organization (WHO) published a priority list of antibiotic-resistant bacteria, categorizing pathogens into three groups according to the urgency of developing new antimicrobial therapies: critical, high, and medium priority [21].

The critical-priority group comprised multidrug-resistant organisms associated with substantial

therapeutic challenges, particularly carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant or third-generation cephalosporin-resistant Enterobacteriaceae, including *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter* spp. The high-priority group included vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus*, which represent important causes of difficult-to-treat infections [22].

The medium-priority group included *Streptococcus pneumoniae* and *Shigella* spp., for which resistance is a significant concern, although several effective therapeutic options remain available. This classification highlights differences in the clinical and public-health importance of resistant bacterial pathogens and helps guide research and development toward areas of greatest unmet therapeutic need [23].

4.1 *Acinetobacter baumannii*

Acinetobacter baumannii is a Gram-negative, aerobic, opportunistic bacterial pathogen predominantly associated with hospital-acquired infections. It develops resistance to antimicrobial agents through multiple complementary mechanisms. A major mechanism is the production of all four classes of β -lactamases, namely classes A, B, C, and D, which hydrolyze β -lactam antibiotics and contribute substantially to β -lactam and carbapenem resistance [24].

In addition, *A. baumannii* expresses several efflux-pump systems belonging to the major facilitator superfamily (MFS), resistance-nodulation-division (RND) superfamily, multidrug and toxic compound extrusion (MATE) family, and small multidrug resistance (SMR) family, which actively expel antimicrobial agents from bacterial cells. Resistance may also arise through antibiotic-modifying enzymes, including acetyltransferases, adenylyltransferases, and phosphotransferases, which chemically modify and inactivate antimicrobial compounds. Furthermore, alterations in outer-membrane porins reduce membrane permeability and limit the uptake of antibiotics, thereby enhancing the overall resistant phenotype [25].

4.2 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a Gram-negative, non-spore-forming rod-shaped bacterium capable of causing infections in both immunocompetent and immunocompromised individuals. Its intrinsic and acquired resistance is mediated by several mechanisms that reduce the activity of antimicrobial agents. A major mechanism involves overexpression of multidrug efflux pumps, which actively export

antibiotics from the bacterial cell and decrease their intracellular concentrations [26]. Reduced outer-membrane permeability further limits the penetration of antimicrobial agents and contributes to intrinsic resistance. In addition, mutations in resistance-associated genes encoding proteins involved in the regulation of antibiotic entry and passive diffusion across the outer membrane can alter membrane permeability and reduce antimicrobial uptake. Collectively, these mechanisms facilitate the development of multidrug-resistant *P. aeruginosa* strains and complicate the treatment of serious infections [27].

4.3 *Staphylococcus aureus*

Staphylococcus aureus is a Gram-positive, non-motile, non-spore-forming coccus that typically appears as grape-like clusters under microscopic examination and is responsible for a wide range of community- and hospital-acquired infections. Its antimicrobial resistance is mediated through several well-established mechanisms. Penicillin resistance is primarily associated with production of plasmid-encoded β -lactamase, which hydrolyzes the β -lactam ring of penicillin and inactivates the antibiotic [28]. Methicillin resistance in methicillin-resistant *S. aureus* (MRSA) is mainly conferred by the *mecA* or *mecC* genes, which encode the alternative penicillin-binding protein PBP2a. This protein has markedly reduced affinity for most β -lactam antibiotics, allowing cell-wall synthesis to continue in their presence. Vancomycin-resistant *S. aureus* (VRSA) may acquire the *vanA* operon from vancomycin-resistant *Enterococcus* spp., usually through mobile genetic elements related to Tn1546, resulting in modification of the peptidoglycan precursor and reduced susceptibility to vancomycin [29].

Additional resistance mechanisms include mutations and target alterations, particularly in genes associated with fluoroquinolone susceptibility such as *gyrA* and *parC*, which alter DNA gyrase and topoisomerase IV. Overexpression of efflux systems, including the NorA pump, can further reduce intracellular concentrations of antimicrobial agents. Resistance to macrolide-lincosamide-streptogramin (MLS) antibiotics may arise through modification of antimicrobial targets, enzymatic inactivation, and active efflux, collectively contributing to multidrug-resistant phenotypes [30].

4.4 *Klebsiella pneumoniae*

Klebsiella pneumoniae is a Gram-negative, facultatively anaerobic, non-motile bacterium associated with a variety of infections, including pneumonia, bloodstream infections, wound infections, and meningitis. Its increasing antimicrobial resistance is primarily driven by the acquisition of genes

encoding extended-spectrum β -lactamases (ESBLs) and carbapenemases. ESBL production confers resistance to many penicillins, cephalosporins, and aztreonam, whereas carbapenemases hydrolyze carbapenems and are associated with limited therapeutic options [31].

Additional resistance may arise through reduced outer-membrane permeability, porin alterations, and increased expression of efflux pumps, which can further enhance resistance to multiple antimicrobial classes. The combination of β -lactamase production and permeability-associated mechanisms contributes to the emergence and dissemination of multidrug-resistant *K. pneumoniae* strains, particularly in healthcare settings [32].

4.5 *Enterobacter* species

Enterobacter species are Gram-negative, facultatively anaerobic bacilli that commonly form part of the human gastrointestinal microbiota but can cause opportunistic infections, particularly in hospitalized or immunocompromised individuals. Their antimicrobial resistance is mediated by multiple β -lactam resistance mechanisms, including the production of extended-spectrum β -lactamases (ESBLs) and carbapenemases such as Verona integron-encoded metallo- β -lactamase (VIM), OXA-type carbapenemases, metallo- β -lactamase enzymes, and *Klebsiella pneumoniae* carbapenemase (KPC) [33]. In addition, constitutive or derepressed expression of chromosomal AmpC β -lactamase contributes to resistance to several β -lactam antibiotics. The combined presence of these mechanisms can result in multidrug-resistant strains with greatly reduced susceptibility to multiple antimicrobial classes, thereby limiting effective therapeutic options and complicating the management of severe healthcare-associated infections [34].

4.6 *Enterococci*

Enterococcus species are Gram-positive, facultatively anaerobic cocci that are important causes of nosocomial and healthcare-associated infections. More than 50 species of enterococci have been identified, although *E. faecalis* and *E. faecium* are the two principal species responsible for human infections. Their antimicrobial resistance is facilitated by both intrinsic and acquired mechanisms. Extensive hospital use of broad-spectrum antibiotics, particularly penicillins and cephalosporins, can disrupt the normal intestinal microbiota and promote intestinal colonization by *E. faecium*. Enterococci possess intrinsic resistance to several commonly used antimicrobial agents, while alterations in penicillin-binding proteins can reduce susceptibility to β -lactam antibiotics [35]. Acquisition and expression of additional resistance determinants can further

increase resistance, and these organisms have a notable capacity to acquire, exchange, and disseminate antimicrobial-resistance genes through mobile genetic elements. Collectively, these characteristics contribute to the emergence of multidrug-resistant enterococcal strains and complicate the treatment of healthcare-associated infections [36]. Table 1 summarizes the major bacterial pathogens associated with antimicrobial resistance, highlighting their principal resistance mechanisms, resistant phenotypes, affected antimicrobial classes, and clinical significance. The listed pathogens demonstrate diverse mechanisms,

including β -lactamase production, target modification, altered membrane permeability, efflux-pump overexpression, and acquisition of resistance determinants. These mechanisms contribute to multidrug-resistant phenotypes and significantly limit therapeutic options. Gram-negative pathogens such as *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, and *Enterobacter* spp. are particularly important in healthcare-associated infections, whereas *S. aureus* and *Enterococcus* spp. represent major resistant Gram-positive pathogens. Collectively, these organisms contribute substantially to difficult-to-treat infections and increased clinical burden [37].

Table 1: Major bacterial pathogens associated with antimicrobial resistance, principal resistance mechanisms, and clinical significance.

S. No.	Pathogen	Major resistance mechanisms described in the manuscript	Important resistant phenotypes/ antimicrobial groups affected	Clinical significance	References
1.	<i>Acinetobacter baumannii</i>	β -lactamase production; efflux pumps (MFS, RND, MATE, SMR); aminoglycoside-modifying enzymes; altered porins	β -lactam and carbapenem resistance; multidrug-resistant phenotypes	Predominantly hospital-acquired infections; important pathogens in healthcare settings	[38]
2.	<i>Pseudomonas aeruginosa</i>	Efflux-pump overexpression; reduced outer-membrane permeability; mutations affecting antibiotic uptake	Multidrug resistance involving multiple antimicrobial classes	Infections in both immunocompetent and immunocompromised patients; important healthcare-associated pathogen	[39]
3.	<i>Staphylococcus aureus</i>	β -lactamase production; mecA/mecC–PBP2a; target modification; efflux; VanA-mediated resistance in VRSA	Penicillin resistance; MRSA; VRSA; fluoroquinolone and MLS resistance	Community- and hospital-acquired infections; major Gram-positive resistant pathogen	[40]
4.	<i>Klebsiella pneumoniae</i>	ESBL production; carbapenemase production	Third-generation cephalosporin resistance; carbapenem resistance	Pneumonia, bloodstream, wound and other serious infections	[41]

5.	<i>Enterobacter</i> spp.	ESBLs; carbapenemases; chromosomal AmpC derepression/overexpression	β -lactam and carbapenem resistance; multidrug-resistant phenotypes	Opportunistic, predominantly healthcare-associated infections	[42]
6.	<i>Enterococcus faecium</i> / <i>E. faecalis</i>	Intrinsic resistance; altered penicillin-binding proteins; β -lactam resistance mechanisms; acquisition/dissemination of resistance determinants	β -lactam resistance; vancomycin resistance in relevant strains	Important healthcare-associated/nosocomial infections	[43]

5. General Mechanism

Bacteria belonging to the same species are not uniformly susceptible to antimicrobial agents, and resistance may vary substantially among genetically related strains. Antimicrobial resistance can broadly be classified as intrinsic or acquired. Intrinsic resistance is a naturally occurring characteristic of a bacterial species that is present independently of previous antimicrobial exposure and is not necessarily associated with horizontal acquisition of resistance genes. It may result from restricted antimicrobial uptake, enzymatic inactivation, or active efflux of the drug. In contrast, acquired resistance develops when bacteria obtain new resistance determinants through horizontal gene transfer mechanisms, including transformation, transduction, conjugation, and transposition, or through spontaneous or selected mutations in their own genetic material [44].

Acquired resistance may involve modification of antimicrobial targets, enzymatic drug inactivation, altered permeability, and active efflux. Major mechanisms of antimicrobial resistance include limiting drug uptake, modification of drug targets, antimicrobial inactivation, active drug efflux, reduced membrane permeability, and biofilm-mediated tolerance. Modification of drug targets occurs when genetic alterations change the structure or expression of the antimicrobial binding site, thereby reducing drug affinity; examples include modifications of ribosomal targets and alterations in proteins involved in DNA replication. Drug inactivation commonly involves bacterial enzymes that chemically modify or hydrolyze antimicrobial agents, such as β -lactamases that degrade β -lactam antibiotics and aminoglycoside-modifying enzymes that alter aminoglycosides [45].

Active efflux systems use membrane transporters to remove antimicrobial agents from bacterial cells, reducing their intracellular concentrations and contributing to resistance in organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Reduced permeability, particularly in Gram-negative bacteria, may result from loss, alteration, or decreased expression of outer-membrane porins, thereby restricting antibiotic entry into the cell. Biofilm-mediated antimicrobial resistance represents an additional multifactorial form of protection in which bacterial cells are embedded within a self-produced extracellular polymeric substance matrix composed primarily of polysaccharides, proteins, and extracellular DNA [46]. The biofilm environment can substantially increase antimicrobial tolerance through restricted drug penetration, reduced metabolic activity and growth rates, altered physiological states, enhanced horizontal transfer of resistance determinants, and increased efflux-pump activity. Collectively, these mechanisms can act individually or synergistically, enabling bacterial populations to survive antimicrobial exposure and contributing to the persistence and dissemination of resistant infections [47].

Figure 2 illustrates the major mechanisms by which bacteria develop or express antimicrobial resistance. These include reduced antimicrobial uptake due to altered membrane permeability, modification of drug targets, enzymatic inactivation of antimicrobial agents, active efflux of drugs, acquisition of resistance determinants through horizontal gene transfer, and biofilm-mediated tolerance. Collectively, these mechanisms reduce intracellular drug activity and enhance bacterial survival during antimicrobial exposure [48].

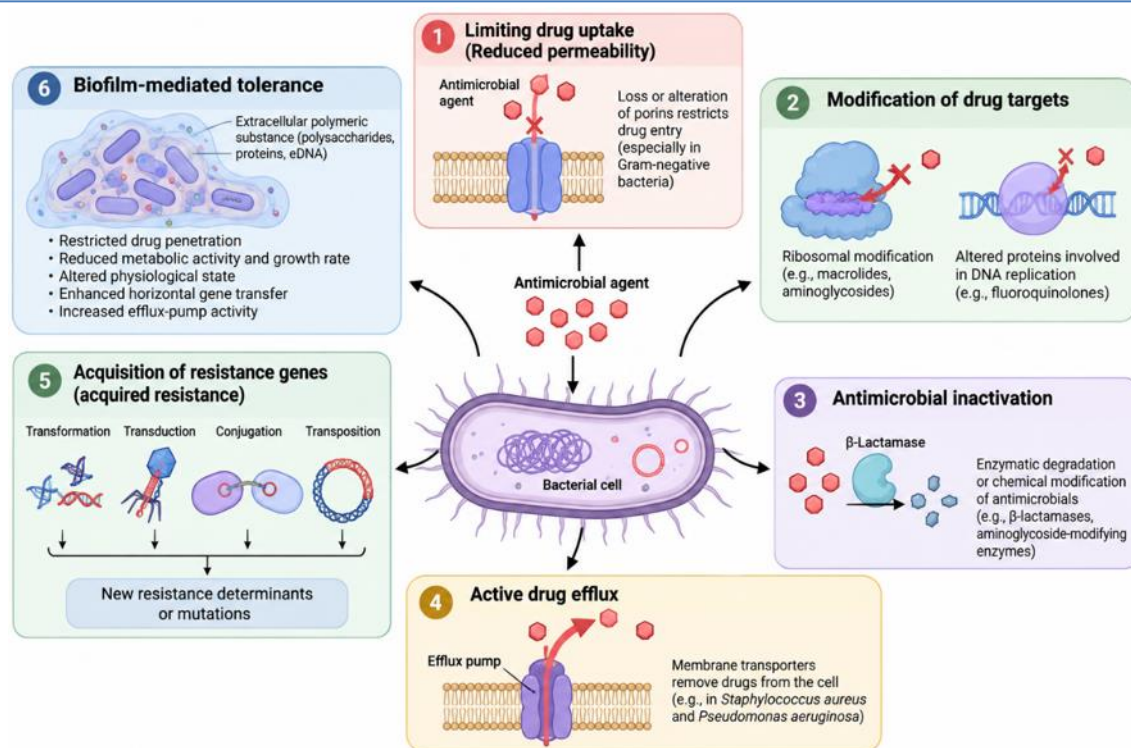


Figure 2: Major mechanisms of antimicrobial resistance in bacteria.

6. Clinical Implications of AMR

The clinical implications of antimicrobial resistance (AMR) are extensive and multifaceted, with major consequences for patient outcomes and healthcare systems. One of the most significant concerns is increased morbidity and mortality, as infections caused by resistant organisms are often more difficult to manage and may require prolonged hospitalization, intensive medical care, and alternative antimicrobial therapies. In some cases, alternative agents may be less effective, more toxic, or associated with greater risks of adverse effects. The increasing difficulty of treating resistant infections also contributes substantially to healthcare costs through longer hospital stays, increased use of expensive antimicrobial agents, additional diagnostic investigations, and enhanced infection-prevention and control measures [49].

AMR also threatens the safety and effectiveness of several essential medical interventions that depend on reliable antimicrobial therapy. Procedures such as organ transplantation, cancer chemotherapy, major surgery, and other invasive interventions frequently require effective antibiotics for the prevention and treatment of infections. The increasing prevalence of resistant pathogens may therefore complicate these procedures and increase the risk of treatment-related infections and adverse outcomes [50].

Furthermore, AMR can substantially restrict therapeutic options, particularly when pathogens exhibit multidrug resistance. In severe cases,

clinicians may have very few effective antimicrobial agents available, while some infections may become extremely difficult or, in certain circumstances, impossible to treat with currently available therapies. Collectively, these effects make AMR an important threat to modern clinical practice and emphasize the need for effective antimicrobial stewardship, infection prevention, surveillance, and development of novel therapeutic strategies [51].

7. Risk Factors

Antimicrobial resistance (AMR) is a global challenge that affects countries across all income levels. Its emergence and dissemination are influenced by multiple interconnected factors involving antimicrobial use, environmental conditions, patient characteristics, healthcare practices, and agricultural activities. Understanding these risk factors is essential for developing effective prevention and control strategies [52].

7.1 Antibiotic Misuse and Overuse

Inappropriate and excessive use of antibiotics is one of the major drivers of AMR. Common contributing practices include prescribing antibiotics for viral infections, unnecessary use of broad-spectrum antibiotics, self-medication, incorrect dosing, and poor adherence to prescribed treatment regimens. These practices create selective pressure that favors the survival and proliferation of resistant bacterial populations [53].

7.2 Poor Sanitation, Environmental

Contamination, and Inadequate Infrastructure

Inadequate sanitation, poor infection-control infrastructure, and improper management of hospital and pharmaceutical waste can facilitate the persistence and dissemination of resistant microorganisms. Pharmaceutical and healthcare waste may contain antimicrobial residues and resistant bacteria, creating environmental reservoirs that contribute to the transmission of resistance through wastewater, soil, and water systems [54].

7.3 Sociodemographic Risk Factors

Certain sociodemographic characteristics have been associated with an increased risk of antimicrobial-resistant infections. These include older age, socioeconomic disadvantage, limited access to appropriate healthcare, and migration or displacement. Such factors may increase exposure to healthcare environments, infectious diseases, inadequate sanitation, or inappropriate antimicrobial use [55].

7.4 Patient-Related and Clinical Risk Factors

Underlying clinical conditions and disease severity can influence the likelihood of infection with resistant organisms. Higher clinical severity scores, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II), as well as abnormal laboratory findings, including anemia and positive tuberculosis sputum-smear results, have been associated with increased AMR risk in specific patient populations. Both infectious diseases, including pneumonia and tuberculosis, and noncommunicable diseases, such as diabetes, cancer, and cardiovascular disorders, may increase susceptibility to resistant infections. Trauma and other underlying conditions may further contribute to this risk [56].

7.5 Healthcare-Associated Risk Factors

Healthcare settings provide important opportunities for the emergence and transmission of resistant

organisms. Prolonged hospitalization, previous antimicrobial exposure, surgical procedures, intensive-care admission, and invasive interventions such as mechanical ventilation and catheterization can increase the risk of acquiring resistant infections. Frequent exposure to healthcare environments may also facilitate transmission between patients, healthcare workers, and contaminated equipment [57].

7.6 Agricultural and Livestock Practices

Extensive antimicrobial use in livestock and agricultural systems can exert selective pressure that promotes the emergence of resistant microorganisms. Antibiotics may be used for disease prevention, treatment, and, in some settings, growth promotion. Resistant bacteria and resistance determinants can subsequently spread through animals, manure, food products, soil, and water, highlighting the importance of integrating agricultural practices into AMR control programs [58].

7.7 Substandard and Falsified Antimicrobials

The use of substandard or falsified antimicrobial products can contribute to the development of resistance. Medicines containing inadequate or inconsistent quantities of active pharmaceutical ingredients may result in subtherapeutic antimicrobial exposure, allowing susceptible organisms to be suppressed incompletely while favoring the survival and selection of resistant populations. Ensuring the quality, safety, authenticity, and appropriate distribution of antimicrobial medicines is therefore an important component of AMR prevention [59]. Several interconnected factors, including inappropriate antimicrobial use, healthcare exposure, environmental contamination, agricultural practices, and poor-quality medicines, contribute to the emergence and dissemination of antimicrobial resistance (**Table 2**) [60]

Table 2: Key risk factors contributing to antimicrobial resistance.

S. No.	Risk Factor	Major Contributing Factors	Mechanism/Role in AMR	Potential Consequences	Prevention/Control Measures	References
1.	Antibiotic misuse	Inappropriate prescribing, use without clear indication	Creates selective pressure favoring resistant organisms	Treatment failure and persistence of resistant infections	Antimicrobial stewardship and prescription monitoring	[61]
2.	Antibiotic overuse	Excessive, prolonged, or repeated antimicrobial therapy	Accelerates selection and expansion of resistant populations	Increased prevalence of multidrug-resistant organisms	Rational prescribing and restriction of unnecessary use	[62]
3.	Broad-spectrum	Unnecessary	Causes extensive	Emergence of	Prefer targeted	[63]

	antibiotic misuse	use of broad-spectrum agents	microbiome disruption and selection pressure	multidrug resistance and superinfections	therapy based on diagnosis and susceptibility testing	
4.	Self-medication	Over-the-counter use, use of leftover antibiotics	Promotes inappropriate drug, dose, and duration selection	Delayed effective treatment and increased resistance	Public education and regulated antimicrobial dispensing	[64]
5.	Incorrect dosing and poor adherence	Underdosing, missed doses, premature discontinuation	Produces inadequate drug exposure and permits survival of resistant bacteria	Relapse, treatment failure, and resistance selection	Patient counselling and adherence monitoring	[65]
6.	Poor sanitation and hygiene	Inadequate sanitation, unsafe water, poor hand hygiene	Facilitates persistence and transmission of resistant microorganisms	Community and healthcare-associated spread	Improved sanitation, hygiene, and infection prevention	[66]
7.	Environmental contamination	Contaminated wastewater, soil, and water systems	Provides reservoirs for resistant bacteria and resistance genes	Environmental dissemination and potential human exposure	Wastewater treatment and environmental surveillance	[67]
8.	Improper healthcare and pharmaceutical waste management	Discharge of antimicrobial residues and contaminated materials	Introduces antimicrobials and resistant organisms into the environment	Selection and persistence of environmental resistance	Proper waste segregation, treatment, and disposal	[68]
9.	Sociodemographic factors	Older age, socioeconomic disadvantage, limited healthcare access, displacement	Increases exposure to infection, inadequate sanitation, and inappropriate antimicrobial use	Higher susceptibility and delayed access to appropriate therapy	Improved healthcare accessibility and targeted public-health interventions	[69]
10.	Patient-related clinical conditions	Diabetes, cancer, cardiovascular disorders, trauma	Compromise host defenses or increase healthcare exposure	Greater risk of severe and resistant infections	Early diagnosis, management of comorbidities, and infection prevention	[70]
11.	Severe or complicated infections	Pneumonia, tuberculosis, high disease severity	Increase antimicrobial exposure and facilitate prolonged infection	Greater probability of treatment failure and resistant infection	Timely diagnosis and evidence-based antimicrobial therapy	[71]
12.	Prolonged hospitalization and ICU admission	Extended hospital stay, critical illness, repeated healthcare exposure	Increases contact with resistant pathogens and contaminated environments	Healthcare-associated multidrug-resistant infections	Infection-control programs, screening, and antimicrobial stewardship	[72]
13.	Invasive medical procedures	Mechanical ventilation, catheterization, surgery	Disrupt natural barriers and provide routes for pathogen entry	Device-associated and postoperative resistant	Aseptic techniques and minimizing unnecessary device use	[73]

				infections		
14.	Agricultural and livestock practices	Antimicrobial use in animals, manure application, food-chain contamination	Selects resistant bacteria and facilitates environmental and foodborne dissemination	Transfer of resistance determinants between animals, environment, and humans	Responsible veterinary antimicrobial use and One Health surveillance	[74]
15.	Substandard and falsified antimicrobials	Inadequate active ingredient, poor-quality or counterfeit medicines	Causes subtherapeutic antimicrobial exposure and incomplete suppression of pathogens	Treatment failure and selection of resistant populations	Quality assurance, regulatory surveillance, and authenticated drug supply chains	[75]

8. Strategies to Combat AMR

The global challenge posed by antimicrobial resistance (AMR) requires coordinated, multisectoral, and sustained action involving governments, healthcare institutions, healthcare professionals, communities, patients, agricultural sectors, and international organizations. Effective AMR control requires interventions that address inappropriate antimicrobial use, infection transmission, inadequate surveillance, environmental contamination, and the limited availability of effective therapeutic options. In healthcare settings, the Centers for Disease Control and Prevention (CDC) has developed a structured framework for preventing antimicrobial resistance. Different strategies for combating AMR [76].

8.1 International Measures

International collaboration is essential for addressing the cross-border emergence and dissemination of antimicrobial-resistant organisms. Key measures include strengthening collaboration among governmental and nongovernmental organizations, international agencies, professional bodies, and other relevant stakeholders. Establishing and expanding surveillance networks can facilitate monitoring of antimicrobial consumption, resistance patterns, and emerging threats across regions [77]. International initiatives should also be developed and existing AMR-control programs strengthened to improve coordinated action. Global mechanisms for detecting, regulating, and controlling counterfeit and substandard antimicrobial medicines are important for protecting treatment effectiveness. In addition, appropriate incentives should be established to stimulate research and development of novel antibiotics, alternative antimicrobial therapies, vaccines, diagnostics, and other technologies addressing resistant infections [78].

8.2 National Measures

At the national level, a dedicated coordinating body or

multidisciplinary committee should oversee AMR prevention and facilitate collaboration among healthcare, veterinary, agricultural, environmental, regulatory, and other relevant sectors. Such bodies should support the development and implementation of national AMR policies, treatment guidelines, regulatory standards, professional training, public awareness programs, and antimicrobial-use monitoring systems. National strategies should also include indicators for evaluating the effectiveness of AMR prevention and control interventions. Additional measures include implementation of standardized treatment guidelines, maintenance of national essential-medicine lists, strengthening antimicrobial-use regulations, improving diagnostic capacity, and expanding vaccination coverage to reduce the incidence of preventable infections and subsequent antimicrobial use [79].

8.3 Community-Level Measures

Community-based interventions are essential for reducing inappropriate antimicrobial use and limiting transmission of resistant organisms. Public education should promote rational antimicrobial use and increase awareness that antibiotics are ineffective against viral infections. Strong regulatory control of non-prescription and over-the-counter antibiotic use is necessary to reduce inappropriate self-medication [80]. When empirical antimicrobial therapy is required, treatment decisions should consider the clinical presentation, likely pathogens, local resistance patterns, and relevant treatment guidelines. Proper hand hygiene, including the appropriate use of alcohol-based hand rubs, should be promoted to reduce the transmission of infectious organisms. Patients infected or colonized with multidrug-resistant organisms should be managed according to established infection-control and treatment guidelines [81].

8.4 Hospital and Healthcare-Setting Measures

Healthcare facilities represent important environments for the emergence and transmission of antimicrobial-resistant pathogens. Effective prevention requires establishment and functioning of infection prevention and control committees, together with strict adherence to hand-hygiene practices. Accurate diagnosis and appropriate antimicrobial treatment should be supported by microbiological testing whenever clinically indicated [82]. Antimicrobial stewardship programs should promote rational selection, dosing, route, and duration of therapy while minimizing unnecessary antimicrobial exposure. Hospitals should maintain robust surveillance systems to monitor antimicrobial use and resistance trends. Good microbiological practices should include standardized laboratory testing, accurate reporting of resistance patterns to infection-control teams, and routine monitoring of sterilization and disinfection procedures. Regular audits and feedback can further improve adherence to antimicrobial-use and infection-control policies [83].

8.5 Healthcare Professional-Level Measures

Physicians, nurses, pharmacists, microbiologists, and other healthcare professionals play an important role in preventing and controlling AMR. Healthcare professionals should adhere to infection prevention and control procedures, institutional antimicrobial-use policies, and evidence-based prescribing practices. Suspected or confirmed antimicrobial-resistant infections should be identified and reported promptly through appropriate surveillance and infection-control systems. Regular education and training of healthcare personnel regarding AMR, antimicrobial stewardship, aseptic procedures, hand hygiene, and appropriate infection-control practices can reduce the risk of transmission and inappropriate antimicrobial use [84].

8.6 Patient-Level Measures

Patients also have an important role in reducing the emergence and spread of antimicrobial resistance. Appropriate aseptic practices should be followed during medical procedures whenever applicable, while simple measures such as covering the mouth and nose during coughing and sneezing can reduce transmission of infectious organisms. Patients should take antimicrobials strictly according to professional instructions and should not initiate antibiotic treatment without appropriate medical advice [85]. Leftover antibiotics should not be reused for subsequent illnesses, and patients should not independently increase, reduce, or discontinue treatment without consulting a healthcare professional. Follow-up should be completed when advised, and treatment failure or adverse effects should be reported promptly rather than managed

through self-modification of therapy. Unused or expired antimicrobial medicines should be disposed of through appropriate medicine take-back or disposal systems where available rather than stored for future self-medication or discarded improperly [86].

8.7 Role of Pharmacists

Pharmacists have a central role in antimicrobial stewardship and can contribute substantially to improving antimicrobial use and reducing resistance. Their responsibilities include reviewing antimicrobial selection, dose, route, frequency, and duration and identifying inappropriate prescribing, unnecessary combination therapy, excessive treatment duration, and dosing errors. Pharmacists should assess potential drug-drug interactions and contraindications and recommend dose adjustments, particularly in patients with renal or hepatic impairment. They can counsel patients regarding the appropriate use of antibiotics and explain that antibacterial agents are not effective against viral infections. Pharmacists should encourage patients to seek medical evaluation when bacterial infection is suspected rather than promoting inappropriate antimicrobial use [87].

Within healthcare institutions, pharmacists can participate in antimicrobial stewardship programs, infection prevention and control committees, antimicrobial prophylaxis planning for surgical procedures, and surveillance of antimicrobial utilization and resistance patterns. They can contribute to the collection, analysis, and interpretation of antimicrobial-use data and support the early identification of emerging resistance trends. Pharmacists should collaborate closely with physicians, microbiologists, nurses, and infection-control professionals to optimize antimicrobial therapy and improve patient outcomes [88]. In addition, pharmacists can contribute to research examining antimicrobial utilization, prescribing practices, resistance trends, stewardship interventions, and healthcare outcomes. Emerging data-driven and artificial intelligence-assisted approaches may further support antimicrobial-use optimization, resistance surveillance, clinical decision support, and prediction of antimicrobial resistance. Patient counseling should remain an integral component of pharmacy practice, with emphasis on correct administration, adherence to the prescribed regimen, recognition of adverse effects, and avoidance of inappropriate self-medication [89].

9. Novel Antimicrobial Development

The increasing prevalence of multidrug-resistant bacterial infections has created an urgent need for innovative antimicrobial strategies capable of addressing infections that are difficult to treat with

conventional antibiotics. The traditional antimicrobial discovery pipeline has encountered several challenges, including the emergence of resistance, limited discovery of new antibiotic classes, and lengthy and costly development processes [90]. Consequently, multiple complementary approaches are being explored to overcome antimicrobial resistance (AMR), including nanotechnology-based antimicrobial systems, computational drug discovery, fragment-based drug design, drug repurposing, and the development of novel antibiotics and prodrugs. These approaches aim to improve antimicrobial efficacy, overcome established resistance mechanisms, enhance drug delivery, and identify new therapeutic candidates [91].

9.1 Nanotechnology

Nanotechnology has emerged as a promising approach for developing alternative and enhanced antimicrobial therapies. Nanomaterials, including metallic nanoparticles, metal oxide nanoparticles, polymeric nanoparticles, lipid-based systems, and nanocomposites, possess physicochemical properties that can facilitate their interaction with microbial cells and improve antimicrobial activity. Their high surface-area-to-volume ratio provides extensive interaction with bacterial surfaces, while their small size can facilitate penetration into bacterial cells and biofilms. The surface charge of nanoparticles also influences their interaction with microorganisms; positively charged nanomaterials can interact electrostatically with negatively charged bacterial cell envelopes, potentially causing membrane disruption, leakage of intracellular components, oxidative stress, and ultimately bacterial cell death [92].

Metallic nanoparticles, particularly silver nanoparticles, have demonstrated broad-spectrum antibacterial activity through multiple mechanisms, including disruption of bacterial membranes, generation of reactive oxygen species, interaction with proteins and nucleic acids, and interference with essential cellular processes. Nanotechnology can also be used as a drug-delivery platform rather than solely as a direct antimicrobial agent. For example, poly(lactic-co-glycolic acid) (PLGA) nanoparticles can encapsulate antibiotics such as rifampicin, potentially improving drug stability, cellular uptake, sustained release, and intracellular delivery. The multimodal activity of nanomaterials and their ability to transport antimicrobial agents may help overcome some conventional resistance mechanisms and provide opportunities for targeted antimicrobial therapy [93].

9.2 Computational Methods

Computational approaches have become increasingly important in antimicrobial drug discovery because

they can accelerate the identification and optimization of potential candidates while reducing dependence on extensive experimental screening. Structure-based drug design (SBDD), ligand-based drug design (LBDD), molecular docking, molecular dynamics simulations, artificial intelligence (AI), and machine-learning techniques can be used to identify molecular targets, predict ligand-target interactions, optimize lead structures, and estimate pharmacological and toxicological properties. These approaches enable the rapid screening of large chemical libraries and can help identify compounds with potential activity against resistant pathogens [94].

Fragment-based drug design (FBDD) is another important computational and medicinal chemistry strategy in which small molecular fragments are screened for binding to a selected biological target and subsequently optimized into higher-affinity lead compounds. This approach can explore chemical space efficiently and facilitate the development of structurally novel antimicrobial agents. Computational workflows integrating AI, molecular modeling, and experimental validation may further improve target identification and lead optimization, thereby supporting a more efficient antimicrobial discovery pipeline [95].

9.3 Drug Repurposing

Drug repurposing involves identifying new antimicrobial applications for previously approved or clinically investigated drugs and offers a potentially faster and more economical approach to addressing AMR. Because many repurposed compounds already possess established pharmacokinetic, safety, and manufacturing information, their development may require fewer early-stage investigations than completely novel chemical entities. Several non-antibiotic drugs have demonstrated antimicrobial or antibiofilm properties, suggesting their potential use as adjunctive therapies. For example, statins such as simvastatin and selected nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated for activity against bacterial biofilms, including those formed by *Staphylococcus aureus* [96]. Nanotechnology can further enhance this strategy by combining repurposed drugs with nanoscale delivery systems. Ibuprofen incorporated into silver-nanoparticle-loaded microspheres, for instance, has demonstrated enhanced antibacterial activity against *Escherichia coli* and *S. aureus*. Such combination approaches may improve drug delivery and antimicrobial performance while providing alternative strategies for managing resistant bacterial infections [97].

10. Current Challenges in Combating

Antimicrobial Resistance

Despite advances in antimicrobial stewardship, surveillance, infection prevention, and therapeutic development, antimicrobial resistance (AMR) remains a major global challenge. The continuous emergence of multidrug-resistant and extensively drug-resistant pathogens is driven by bacterial mutations and horizontal transfer of resistance determinants. A further concern is the limited discovery of new antibiotic classes, while the development of novel antimicrobials is hindered by high research costs, complex clinical trials, regulatory barriers, and limited commercial incentives [98].

Inadequate surveillance and diagnostic infrastructure, particularly in resource-limited settings, can delay detection of emerging resistance patterns and promote inappropriate empirical treatment. Misuse and overuse of antimicrobials in human healthcare, veterinary medicine, and agriculture continue to exert strong selective pressure. Environmental contamination from healthcare, pharmaceutical, and agricultural sources further facilitates the persistence and dissemination of resistant microorganisms and resistance genes [99].

Biofilm-associated tolerance also reduces treatment effectiveness by restricting antimicrobial penetration and promoting bacterial persistence. Although emerging approaches such as nanotechnology, antimicrobial peptides, phage therapy, drug repurposing, and computational drug discovery offer promising solutions, challenges related to toxicity, clinical validation, scalability, manufacturing, and regulatory approval remain. Effective AMR control therefore requires sustained investment, improved diagnostics and surveillance, antimicrobial stewardship, and coordinated One Health interventions [100].

11. Future Perspectives

The future management of antimicrobial resistance (AMR) will depend on integrating innovative therapeutic technologies with effective prevention, surveillance, and antimicrobial stewardship. Development of novel antibiotics with new molecular targets and mechanisms of action remains an important priority, particularly against multidrug-resistant pathogens. Nanotechnology-based systems, antimicrobial peptides, bacteriophages, engineered nanocomposites, and combination therapies may provide alternative approaches for overcoming established resistance mechanisms and improving antimicrobial delivery [101].

Artificial intelligence (AI), machine learning, molecular modeling, and other computational

approaches are expected to accelerate antimicrobial discovery by enabling rapid identification of potential targets, lead compounds, resistance patterns, and drug combinations. Drug repurposing and fragment-based drug design may further expand the antimicrobial pipeline while reducing development time and costs. Advanced diagnostic technologies capable of rapidly identifying pathogens and their resistance profiles could support earlier, more precise, and pathogen-directed therapy [102].

Future AMR control should also strengthen global surveillance systems using integrated genomic, clinical, and environmental data to detect emerging resistance and transmission pathways. Greater emphasis is required on responsible antimicrobial use in human healthcare, veterinary medicine, agriculture, and aquaculture within a One Health framework. Continued investment in research, interdisciplinary collaboration, regulatory innovation, vaccination, infection prevention, and public education will be essential to preserve antimicrobial effectiveness and address the evolving threat of resistant infections [103].

Conclusion

Antimicrobial resistance has progressed from a minor concern during the pre-antibiotic era to a critical global health concern today, driven by inappropriate use of antimicrobial agents since the early and golden era of antibiotic discovery. Current epidemiological evidence shows a rising burden of resistant infections worldwide, with common pathogens developing complex resistance mechanisms that compromise treatment efficacy. This has resulted in serious clinical consequences, including treatment failure, prolonged hospitalization, increased morbidity, and mortality. This concern is further intensified by multiple risk factors such as irrational prescribing, self-medication, poor infection control practices, and lack of awareness. Addressing AMR necessitates a comprehensive and coordinated approach involving international initiatives, national strategies, policies at the national level, and targeted interventions at the community and patient level. Healthcare professionals, particularly pharmacists, play a crucial role in promoting rational antimicrobial use, ensuring treatment adherence, and providing back-up support to antimicrobial stewardship programs. Besides the conventional strategies, emerging novel approaches such as nanotechnology-driven antimicrobial systems, computational drug design, and drug repurposing serve as promising avenues for addressing the rising antimicrobial resistance. These innovations, when integrated with existing stewardship and policy measures, may enhance the development of effective and sustainable therapeutic options. Key research

gaps in AMR include limited region-specific surveillance, fragmented One Health monitoring, inadequate rapid diagnostics, and insufficient evidence on sustainable antimicrobial stewardship interventions. Further research is needed on novel antimicrobials, alternative therapies, environmental transmission, and the clinical application of AI-based AMR prediction tools. Future priorities should focus on integrated One Health surveillance, affordable rapid diagnostics, context-specific stewardship, development of new therapeutic approaches, and translation of research into effective clinical practice and policy.

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