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Antimicrobial Resistance (AMR): An Evolving Global Threat and Novel Strategies for Combatting It

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ABSTRACT

Antimicrobial resistance (AMR) has emerged as a profound global health crisis, threatening decades of medical progress in infectious disease management. This review provides a comprehensive analysis of AMR as an evolving threat, outlining its historical context, global burden, and underlying molecular mechanisms. We examine the multifactorial drivers fuelling resistance, including inappropriate antimicrobial use in human and veterinary medicine, environmental dissemination, and socioeconomic disparities, alongside the current challenges of weak drug pipelines, diagnostic gaps, and policy shortcomings. Novel strategies for combatting AMR are highlighted, spanning drug-related approaches such as new antibiotics, adjuvants, repurposed drugs, antimicrobial peptides, and bacteriophages; non-drug innovations including vaccines, immunotherapies, probiotics, and microbiome-based therapies; and technological advances such as rapid diagnostics and artificial intelligence-driven discovery platforms. The critical role of stewardship, regulatory reform, and global coordination is emphasized, alongside the One Health approach, which integrates human, animal, and environmental health to address resistance holistically. Looking ahead, sustained interdisciplinary collaboration, expanded surveillance networks, and long-term investment in education, governance, and innovation will be essential to contain AMR and preserve antimicrobial efficacy for future generations.

Keywords: *Antibiotics, Antimicrobial resistance, Bacteriophages, Diagnostics, Global health, One Health, Stewardship, Vaccines*

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INTRODUCTION

Antimicrobial resistance (AMR) refers to the capacity of microorganisms such as bacteria, fungi, viruses, or parasites to resist the effects of drugs that once successfully treated infections caused by them [1-2]. When such resistance occurs, standard treatments become ineffective, infections persist, and spread to others [3]. This includes resistance to antibiotics in bacteria, antivirals, antifungals, and antimalarials [4]. The phenomenon exacerbates morbidity, mortality, and poses serious economic and social burdens globally [5].

The history of antibiotic discovery and resistance is both inspiring and cautionary. The "Golden Age" of antibiotic discovery in the mid-20th century ushered in transformative medical advances: sulfonamides, β-lactams (penicillin and its successors), aminoglycosides, tetracyclines, macrolides, glycopeptides, and

others became core tools in fighting infectious disease [6-7]. With broad adoption of these agents came inevitable resistance. As early as the 1930s, resistance to sulfonamides was documented; by the 1940s, streptomycin-resistant Mycobacterium tuberculosis had emerged [8]. Over subsequent decades, the pace of discovery of new classes slowed, while resistance mechanisms multiplied via mutation, horizontal gene transfer (HGT), efflux pumps, enzymatic inactivation, target modification, and other biochemical strategies [9].

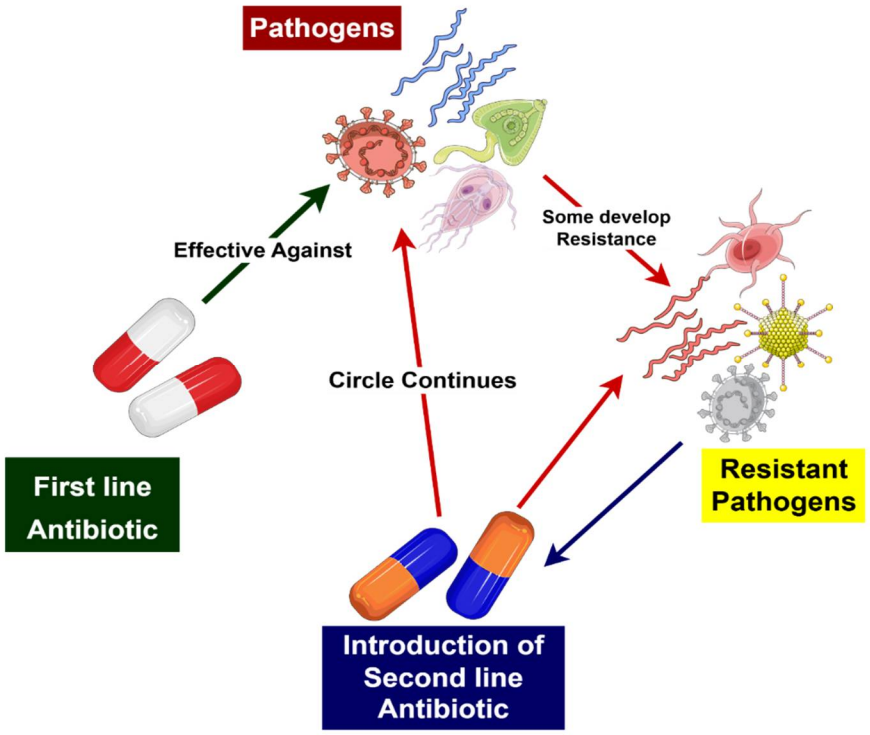

Figure 1: Evolutionary Arms Race in AMR (created by this author)

Figure 1 illustrate the continuous cycle of antimicrobial discovery, widespread use, subsequent microbial evolution leading to resistance mechanisms, and the resulting decline in drug efficacy, emphasizing the dynamic and ongoing nature of the "arms race.

Why is AMR considered one of the major global health threats of the 21st century? First, the scale: recent global analyses estimate that in 2019, bacterial antimicrobial resistance was directly responsible for approximately 1.27 million deaths, and contributed to nearly 5 million deaths overall [10]. Secondly, projections to mid-century are alarming: deaths directly attributable to AMR may rise to ~1.9 million per year by 2050, with many more cases where resistance contributes to mortality. Thirdly, AMR threatens not just treatment of infections, but the viability of many modern healthcare procedures such as surgery, chemotherapy, organ transplantation rely on effective antimicrobials for prophylaxis or treatment of opportunistic infections [11-12]. Fourth, the burden falls disproportionately on low- and middle-income countries, where health infrastructure, diagnostic capacity, antibiotic regulation, sanitation and infection control are often less robust [13].

This review aims to map the evolving landscape of AMR, tracing its past and current burden, elucidating mechanisms and drivers behind resistance, and highlighting novel strategies for counteracting the threat. Specifically, we will survey recent epidemiological data to quantify morbidity, mortality, and economic impacts; examine biological, environmental, and socio-political drivers of resistance; assess gaps in drug discovery, diagnostics, and policy; and review cutting-edge strategies including non-conventional therapeutics, stewardship, surveillance innovations, and regulatory approaches that show promise in curbing the rising tide of AMR. Through this scope, we hope to provide a framework for research, public health action, and policy needed to avert a post-antibiotic era.

THE GLOBAL BURDEN OF AMR

Antimicrobial resistance (AMR) has become one of the foremost global health crises of the 21st century. Recent epidemiological estimates quantify its enormous morbidity, mortality, and economic burden. A landmark analysis reported that in 2021, approximately 4.71 million deaths were associated with bacterial AMR, of which 1.14 million were directly attributable [14]. Age-stratified data reveal stark disparities: while deaths in children under five have declined, mortality among adults over 70 years has increased by more than 80% over the past three decades [14].

The economic burden is equally daunting. A modeling study estimated that the global cost of hospitalizations linked to antibiotic resistance exceeded US$693 billion, while productivity losses added nearly US$194 billion [15]. National data illustrate similar patterns: in Spain alone, resistant infections accounted for 6,199 premature deaths, 426,495 additional hospital days, and EUR 338.6 million in annual costs [16].

Pathogens of Concern

A major driver of the AMR crisis is a group of highly resistant organisms collectively known as the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp.), sometimes expanded to include *Escherichia coli* [17]. These organisms are notorious for causing hospital-acquired infections and for their ability to "escape" standard treatments. For example, a South African study found that more than 90% of bloodstream ESKAPEEc isolates were multidrug resistant, particularly in intensive care units [18].

Tuberculosis remains another major concern. Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) continues to threaten progress in TB control. Treatment is costly, prolonged, and associated with high failure rates [19]. The World Health Organization has repeatedly emphasized MDR-TB and XDR-TB as top priorities in its global AMR action plan [20].

Respiratory pathogens such as *Streptococcus pneumoniae*, *K. pneumoniae*, *E. coli*, and *S. aureus* also account for substantial mortality, particularly in low- and middle-income countries. A regional review by Okeke et al [21] highlighted that in sub-Saharan Africa, AMR is a leading cause of deaths associated with lower respiratory infections.

Regional Variations and Disparities

The burden of AMR is distributed unequally across the globe. In the WHO African region, infection-related mortality reached 3.83 million in 2019, with over 1 million deaths associated with AMR and 250,000 directly attributable to it. Limited access to diagnostics, poor infection prevention, and weak health systems exacerbate the crisis [21].

In contrast, high-income countries benefit from stronger stewardship programs and diagnostic capacity, yet still face rising resistance. For example, carbapenem-resistant Gram-negative bacteria and methicillin-resistant *S. aureus* (MRSA) remain persistent threats.

Forecasts suggest that by 2050, deaths directly attributable to AMR could rise to nearly 1.9 million per year, with associated deaths surpassing 8 million annually if no action is taken [14]. This burden will fall most heavily on South Asia, Latin America, and sub-Saharan Africa.

MECHANISMS OF ANTIMICROBIAL RESISTANCE

Understanding mechanisms is critical both for anticipating emergent resistance and designing interventions. Mechanisms fall into genetic, biochemical, and sometimes structural / phenotypic categories.

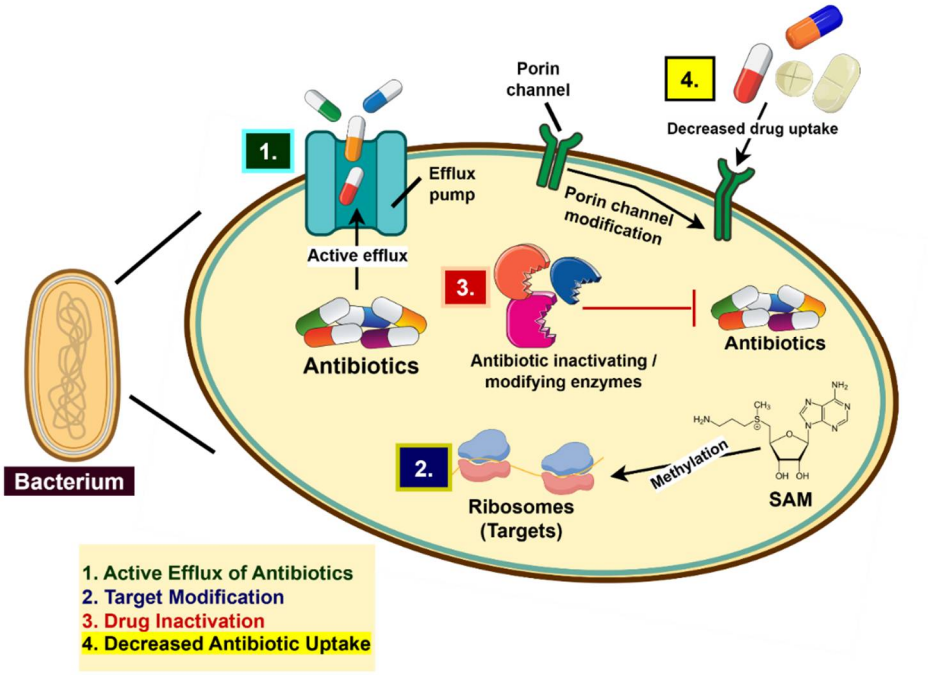

Figure 2: Diagram of Key Molecular Mechanisms of Antimicrobial Resistance (created by this author)
Figure 2 illustrates four primary resistance mechanisms employed by bacteria to evade antibiotic action: (1) Active efflux of antibiotics – efflux pumps actively transport antibiotics out of the bacterial cell, reducing intracellular drug concentration; (2) Target modification – ribosomes (antibiotic targets) undergo structural modifications through methylation by S-adenosylmethionine (SAM), preventing antibiotic binding; (3) Drug inactivation – antibiotic-inactivating or modifying enzymes chemically alter antibiotics, rendering them ineffective; (4) Decreased antibiotic uptake – porin channel modifications reduce drug permeability across the bacterial cell membrane, limiting antibiotic entry. These concurrent mechanisms enable bacteria to develop multidrug resistance, posing significant challenges to antimicrobial therapy.

Genetic Mechanisms

Mutation

Spontaneous point mutations in genes encoding drug targets or regulators can reduce drug binding. For example, in *Plasmodium falciparum*, mutations in the Kelch13 (K13) propeller domain are implicated in artemisinin resistance; similarly, PfCRT and PfMDR1 mutations affect resistance to partner drugs [22].

Horizontal Gene Transfer (HGT)

Many resistance genes reside on mobile genetic elements (plasmids, transposons, integrative conjugative elements), enabling transfer across strains and species. In bacterial pathogens, plasmid-mediated resistance is a major driver especially of β-lactamases, ESBLs (extended-spectrum β-lactamases), carbapenemases, and mobile quinolone resistance determinants. Efflux gene cassettes frequently move via plasmids [23].

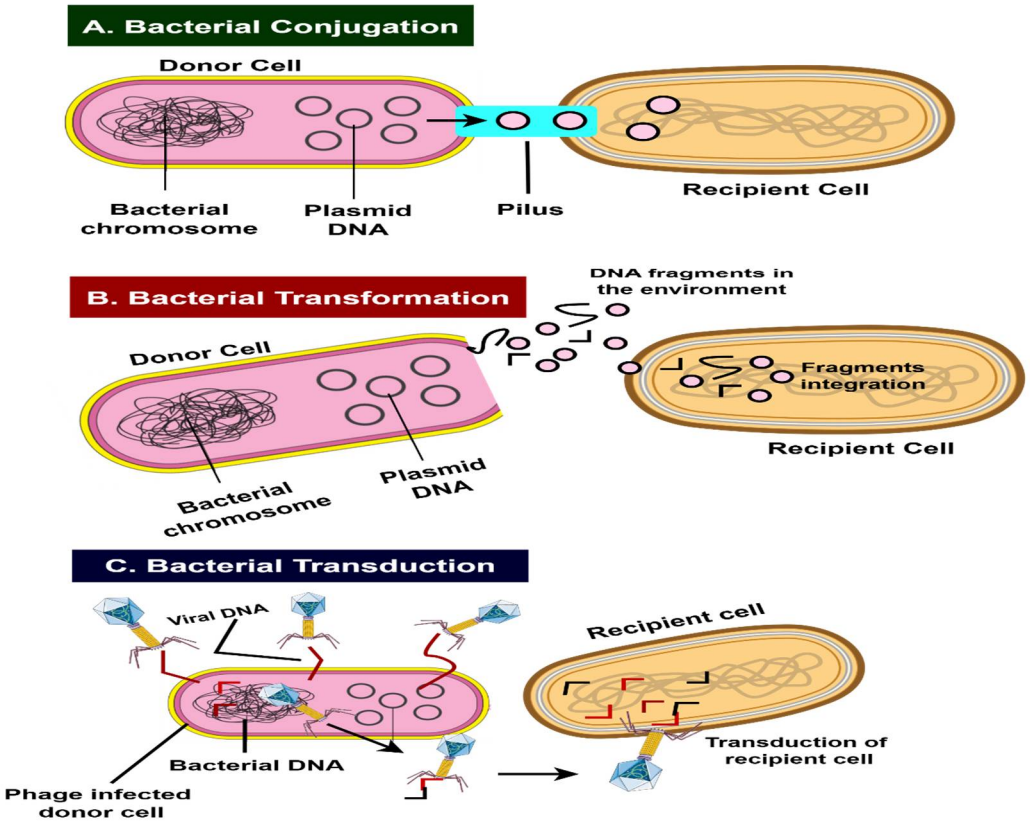

Figure 3: Mechanisms of Horizontal Gene Transfer (HGT) (created by this author)

Figure 3 illustrate the three main mechanisms of HGT: Conjugation (direct cell-to-cell contact via pilus), Transformation (uptake of free DNA from the environment), and Transduction (phage-mediated transfer of DNA). It would show how these processes facilitate the spread of antimicrobial resistance genes (ARGs) between bacteria.

Gene amplification - duplication and regulatory changes

Overexpression of resistance genes via promoter mutations, gene amplification, or regulatory factor modifications is also key, especially in fungal pathogens (see below) or when dosage sensitivity is involved [24].

Biochemical Strategies

Enzyme production / drug inactivation

Bacteria produce enzymes that degrade or modify antibiotics, e.g. β-lactamases (including ESBLs and carbapenemases), aminoglycoside-modifying enzymes. These render drugs ineffective before they reach their target.

Efflux pumps

Pumps that expel antibiotic molecules from microbial cells, reducing intracellular concentrations. This is observed in bacteria (e.g. Gram-negative RND family pumps) and in fungi (efflux transporters like CDRs, MDR1 etc.). Reviews show many bacteria are resistant due in part to overexpressed efflux, and inhibitors of efflux pumps are being explored [25].

Reduced permeability / target site modification

Alterations in cell walls or membrane porins reduce antibiotic uptake in bacteria; modification of target sites (mutations in binding proteins or ribosomal RNAs, etc.) reduce binding affinity. In fungi, mutations in genes like *ERG11*, *UPC2* (azole target pathway), *FKS1 / FKS2* (echinocandins) etc [24].

Biofilm formation

Microbial communities embedded in extracellular polymeric substance matrices (biofilms) can have physical barriers to drug penetration, altered metabolic states (slow growth), high numbers of persister cells, enhanced efflux, etc., making cells in biofilms much more tolerant/resistant than planktonic cells. Efflux pumps also play roles in biofilm formation and quorum sensing [26].

Differences among Bacterial, Fungal, Viral, and Parasitic Resistance

Bacteria

As above, resistance is often via mutations or acquisition (e.g. plasmids) of genes encoding drug-inactivating enzymes, modified targets, efflux pumps, reduced uptake. Antibiotic classes have diverse

mechanisms. Because bacteria reproduce rapidly and share genes readily, resistance can spread fast. ESKAPE pathogens are a good example [27].

Fungi

Fewer classes of antifungals, inherently more limited drug targets. Resistance arises via mutations in target enzymes (e.g. ERG11 for azoles, FKS genes for echinocandins), overexpression of efflux transporters (CDR, MDR), biofilm formation, and sometimes chromosomal changes (aneuploidy, gene duplication) [28]. Some fungal species can be intrinsically resistant or acquire resistance in the environment (e.g. *Candida auris*, azole resistance in *Aspergillus fumigatus*) [24].

Parasitic pathogens

notably *Plasmodium falciparum* in malaria. Resistance mechanisms include mutations in drug target or transport proteins (as above: PfCRT, PfMDR1), changes in drug metabolism, stress responses, sometimes in regulation of endocytosis (e.g. Kelch13 mutations affecting hemoglobin uptake and oxidative stress response) and partner drug resistance via variation in proteases or other enzymes [29]. Also, selection pressure from misuse of monotherapy, substandard drugs, pharmacokinetics (drug levels not maintained) play large roles. Recent surveillance in Uganda showed decreased susceptibility over 2019-2024 to artemisinin and lumefantrine, although clinical implications are still being evaluated [30].

Viruses

Although less discussed in the data I gathered, antiviral resistance arises via mutations in viral polymerases, reverse transcriptases, proteases etc. Resistance tends to emerge rapidly when single-agent therapy is used (e.g. HIV, influenza, SARS-CoV-2 antivirals) [31]. Because viruses depend on host machinery, there are fewer drug targets and often narrower therapeutic windows.

DRIVERS OF AMR

Antimicrobial resistance (AMR) does not emerge in isolation but is shaped by complex and interdependent drivers across human, animal, environmental, and policy domains. A One Health perspective, recognizing the interconnection between humans, animals, plants, and the environment is essential to understanding how these drivers perpetuate the global AMR crisis [32].

Misuse and Overuse of Antibiotics in Humans

The misuse and overuse of antibiotics in human health remain the primary forces accelerating resistance. Antibiotics are often prescribed for viral infections, such as influenza or common colds, despite offering no clinical benefit [21]. In many countries, antibiotics are available over the counter, enabling self-medication, which frequently results in incomplete courses, subtherapeutic dosing, and drug selection mismatches. These practices favour survival of partially resistant bacterial populations that evolve into fully resistant strains.

Hospital settings illustrate how prescribing behaviours accelerate resistance. For instance, a study in Ethiopia found that prophylactic antibiotics were routinely administered before, during, and after surgery even when clinical guidelines recommended limited or no prophylaxis [33] . Such practices are driven by clinicians' fear of surgical site infections in under-resourced environments where infection prevention and control (IPC) systems are weak.

The COVID-19 pandemic further amplified antibiotic overuse globally. Despite low bacterial co-infection rates, empirical antibiotic prescribing became widespread to preempt secondary infections [34]. In some settings, more than 70% of hospitalized COVID-19 patients received antibiotics, most commonly azithromycin, ceftriaxone, and fluoroquinolones [34]. This massive and often unnecessary use of antibiotics during the pandemic has left behind a legacy of heightened resistance levels in hospital and community settings.

Veterinary and Agricultural Use

The role of antimicrobials in agriculture and veterinary medicine is equally significant. Antibiotics are used not only to treat animal infections but also for growth promotion and prophylaxis in intensive farming systems. The Food and Agriculture Organization (FAO) estimates that more than half of global antimicrobial use occurs in animals, much of it non-therapeutic [32].

Antibiotic residues and resistant bacteria shed in animal waste enter soil and water systems. These environmental reservoirs promote horizontal gene transfer (HGT) between commensal and pathogenic bacteria [35]. For example, resistant *E. coli* and *Salmonella* strains found in livestock manure have been shown to contaminate vegetables irrigated with untreated wastewater, creating a direct food-chain pathway of resistance to humans [36].

Aquaculture further contributes to AMR by exposing aquatic microorganisms to prolonged antibiotic pressure, fostering multi-resistant strains such as *Aeromonas hydrophila* and *Vibrio* spp. [37]. These bacteria can transfer resistance genes to clinically important pathogens via plasmids and integrons, worsening the clinical burden.

Regional studies confirm the magnitude of the problem. In South Asia, where aquaculture is widespread, multidrug resistance in aquaculture-associated pathogens is now common, with isolates resistant to tetracyclines, sulfonamides, and quinolones [38]. In sub-Saharan Africa, weak veterinary regulation allows over-the-counter sales of veterinary antibiotics, often without prescriptions, compounding the issue [39].

Poor Infection Prevention and Control (IPC) Practices

Weak infection prevention and control (IPC) systems amplify the emergence and spread of AMR in healthcare facilities. In low-resource hospitals, inadequate sanitation, overcrowding, insufficient supplies of gloves and sterilization equipment, and poor hand hygiene compliance contribute to the rapid spread of resistant organisms [40].

For example, a Ghanaian study found significant IPC gaps in maternal units, including inadequate hand hygiene infrastructure and waste disposal, which correlated with high rates of resistant neonatal sepsis [41]. Similarly, Ethiopian hospitals continue to rely on routine prophylactic antibiotic use due to limited IPC capacity, demonstrating the vicious cycle between poor infection control and rising resistance [33].

Healthcare-associated infections (HAIs) often involve multidrug-resistant pathogens such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, which thrive in hospital environments. Without robust IPC, resistant HAIs not only prolong hospital stays and increase costs but also contribute substantially to morbidity and mortality, particularly in LMICs where critical care infrastructure is weak [21].

Environmental Factors

The environment is increasingly recognized as both a reservoir and amplifier of resistance genes. Wastewater treatment plants, pharmaceutical manufacturing effluents, hospital discharges, and agricultural runoff are major conduits for resistance dissemination [35].

For instance, studies in China have found high concentrations of antibiotic residues such as sulfonamides and macrolides in surface waters downstream from pharmaceutical factories, along with elevated levels of resistance genes [42]. In Malawi, resistant bacteria were identified in soils and vegetables fertilized with animal manure, confirming environmental spread along the "farm-to-fork" pathway [43].

Urbanization and changing land-use patterns also contribute. Riverine ecosystems exposed to untreated wastewater in urban areas have been shown to harbor high levels of antimicrobial resistance genes (ARGs) and multidrug-resistant organisms [44]. In Cameroon, urban agriculture irrigated with untreated wastewater facilitated the spread of resistant bacteria to crops, representing a neglected but important transmission pathway [45].

Environmental dissemination is especially problematic because resistant organisms and ARGs can persist for long periods outside clinical settings, increasing opportunities for horizontal gene transfer to human pathogens [35].

Socioeconomic and Policy Gaps

Socioeconomic disparities and policy weaknesses represent systemic drivers of AMR. Poverty, limited healthcare access, and weak governance structures often force individuals to rely on informal providers or purchase antibiotics directly from pharmacies and street vendors [39]. In such contexts, unregulated antibiotic use flourishes.

National AMR action plans exist in most countries, but many lack sustainable financing, enforcement capacity, or integration into broader health system strengthening [36]. In Africa, most countries have launched AMR policies, yet implementation is constrained by resource shortages and competing health priorities [39].

Socioeconomic drivers also interact with cultural perceptions of antibiotics as "strong medicine." In parts of Asia and Africa, patients often expect antibiotics for quick relief, pressuring clinicians to prescribe unnecessarily [21].

Global inequities further compound the challenge. While high-income countries (HICs) have greater capacity for stewardship and surveillance, LMICs shoulder the heaviest burden of AMR but have the least resources to respond [21]. Without global solidarity and equitable investment, policy gaps will continue to fuel resistance in regions least equipped to cope.

CURRENT CHALLENGES IN COMBATTING AMR

While the drivers of antimicrobial resistance (AMR) are increasingly well documented, addressing them is complicated by a series of persistent scientific, economic, and governance challenges. These obstacles are deeply interconnected, and progress in one area is often undermined by shortcomings in another.

Limited Pipeline of New Antibiotics

The global antibiotic pipeline remains alarmingly thin. World Health Organization (WHO) reported that of more than 60 antibacterial agents in development, only a handful target priority multidrug-resistant pathogens such as carbapenem-resistant *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter*

baumannii [46]. Furthermore, the majority of drugs in clinical trials are derivatives of existing classes, offering only incremental benefits rather than novel mechanisms of action.

The reasons are largely economic. Antibiotics are less profitable than drugs for chronic conditions because they are typically taken for short courses and stewardship programs limit their widespread use [47]. As a result, pharmaceutical companies face disincentives to invest in antibiotic research and development (R&D). Many small biotech firms now lead antibiotic innovation, but these companies are financially fragile, and several have gone bankrupt after bringing drugs to market [48].

Novel financial mechanisms have been proposed, including subscription-based models where governments pay companies for access to new drugs regardless of use, thus "delinking" profitability from sales volume [49]. However, global adoption of such models has been slow, and most remain limited to pilot programs in high-income countries (HICs). Without systemic changes to R&D incentives, the world risks entering a post-antibiotic era with an inadequate therapeutic arsenal.

Diagnostic Gaps

Rapid and affordable diagnostics are essential for targeted antibiotic prescribing, yet significant gaps persist, especially in low- and middle-income countries (LMICs). In many hospitals, clinicians lack access to culture and sensitivity testing, forcing them to rely on empirical therapy with broad-spectrum antibiotics [50]. This not only drives resistance but also delays appropriate treatment, increasing morbidity and mortality.

The barriers to diagnostic uptake are multifaceted: high costs, lack of laboratory infrastructure, shortages of trained personnel, and limited supply chains for reagents [51]. Even when diagnostic tools are available, results may take days, which is incompatible with the urgency of treating severe infections such as sepsis.

Point-of-care (POC) diagnostics, which deliver results within hours, are a promising solution. However, their rollout has been uneven, and many LMICs lack sustainable financing mechanisms to procure and maintain such technologies [21]. Furthermore, the COVID-19 pandemic demonstrated the importance of scaling diagnostics rapidly, but it also diverted resources away from AMR-related diagnostic development [34].

Regulatory, Financial, and Market Barriers

Even when effective antibiotics exist, weak regulatory environments undermine stewardship. In many countries across Africa, Asia, and Latin America, antibiotics can still be purchased without prescriptions [52]. Informal drug markets and unregulated pharmacies sell antimicrobials of questionable quality, including counterfeit and substandard products that accelerate resistance [39].

Financial barriers also restrict national responses. Most LMICs rely heavily on donor-funded AMR initiatives, which are often project-based and unsustainable [53]. Long-term investment in stewardship, surveillance, and innovation remains inadequate. Meanwhile, market failures discourage pharmaceutical companies from maintaining older but essential antibiotics because they generate little profit [47].

Addressing these barriers requires global financing frameworks similar to those for vaccines and HIV/AIDS programs, where pooled procurement and guaranteed markets incentivized industry participation [54]. Without comparable commitments, antibiotics will continue to be marginalized in global health financing.

Global Coordination Challenges

AMR is inherently a transboundary issue, but global coordination has struggled to keep pace with the scale of the threat. The 2015 WHO Global Action Plan on AMR established a framework for national action plans, yet implementation remains uneven. By 2023, while more than 140 countries had developed plans, fewer than 20% reported full funding and operationalization [46].

Surveillance is a particular weak point. The Global Antimicrobial Resistance and Use Surveillance System (GLASS) has improved data collection, but participation remains heavily skewed toward high-income regions, leaving major blind spots in Africa and South Asia [55]. The absence of standardized reporting frameworks further hampers comparability across regions.

Policy misalignment is also evident. Many national AMR strategies are not integrated into broader Sustainable Development Goal (SDG) frameworks, weakening intersectoral collaboration [54]. For example, food security programs often neglect AMR risks from agricultural antibiotic use, while water and sanitation initiatives rarely incorporate surveillance for resistance genes in wastewater [35].

The COVID-19 pandemic further disrupted global AMR coordination by diverting resources and political attention. Although it highlighted the critical importance of diagnostics, surveillance, and resilient health systems, progress on AMR initiatives slowed as governments prioritized immediate pandemic response.

Intersecting Challenges

These challenges are mutually reinforcing. Limited diagnostics drive empirical prescribing, which fuels resistance, while weak regulatory oversight allows over-the-counter sales, undermining stewardship. The lack of new antibiotics exacerbates the consequences of poor infection prevention and weak surveillance, while insufficient global coordination prevents scaling of successful interventions.

Addressing AMR thus requires systemic approaches that simultaneously tackle scientific innovation, regulatory governance, financial incentives, and cross-sectoral collaboration. Piecemeal efforts will not suffice in the face of an escalating crisis projected to cause nearly 10 million deaths annually by 2050 and trillions of dollars in economic losses [56].

NOVEL STRATEGIES FOR COMBATTING AMR

The complex, multifactorial nature of antimicrobial resistance (AMR) demands a portfolio approach that combines improved drugs, non-drug interventions, technological innovation, and policy levers. Below we summarize contemporary and emerging strategies across those domains.

Drug-related strategies

Development of novel antibiotics and antibiotic adjuvants

Renewing the antibiotic armamentarium remains essential. Recent efforts include discovery of new scaffolds via traditional medicinal chemistry as well as adjunctive molecules that restore the activity of existing antibiotics (antibiotic adjuvants) by inhibiting resistance mechanisms (e.g., β-lactamase inhibitors, efflux pump blockers, membrane-permeabilizing agents) [57]. Adjuvants can "rescue" legacy antibiotics, extend their clinical lifespan, and reduce selection pressure for novel agents [58-59]. However, translating adjuvants to the clinic requires careful pharmacology and safety profiling because potentiators often act on host–microbe interfaces [57].

Repurposing existing drugs

Drug repurposing screening approved drugs or clinical candidates for antibacterial activity or synergy offers a faster, lower-cost path to new therapies because toxicology and pharmacokinetics are often already characterized [60-61]. Repurposed agents may act as direct antibacterials, virulence inhibitors, or adjuvants that sensitize bacteria to antibiotics. Nonetheless, clinical efficacy against specific resistant pathogens must be proven in rigorous trials; repurposing is not a panacea and faces challenges including intellectual property and appropriate dosing for antibacterial indications [60].

Antimicrobial peptides and bacteriophages

Antimicrobial peptides (AMPs) are innate immune effectors with broad activity and unique mechanisms (membrane disruption, immune modulation). Advances in peptide engineering, stabilization, and delivery systems have revived clinical interest in AMPs as therapeutics and as antibiotic adjuvants [62]. Peptides can be optimized to reduce host toxicity and proteolysis, and to target resistant pathogens. However, cost of manufacture, potential immunogenicity, and pharmacokinetics are barriers to widespread adoption [62].

Bacteriophage therapy has made substantive strides: modern safety studies and compassionate-use case series report promising outcomes against multidrug-resistant infections, and several controlled trials and compassionate programs are underway internationally [63]. These offer high specificity, self-amplifying killing at infection sites, and the ability to evolve alongside bacterial hosts, but regulatory frameworks, standardized production, and avoidance of phage resistance remain active challenges [63].

Non-drug approaches

Vaccines and immunotherapies

Preventing infections is one of the most effective means of curbing antibiotic use and thus AMR. Vaccination reduces both disease incidence and antibiotic consumption for vaccine-preventable diseases, and broad modeling suggests sizable reductions in antibiotic doses if vaccine coverage is expanded [36,46]. New vaccine strategies, conjugate and protein vaccines for bacterial pathogens, and vaccines that reduce viral respiratory disease (thereby lowering inappropriate antibiotic prescribing), are central to AMR prevention [46]. Monoclonal antibodies and other immunotherapies targeting critical virulence factors are also under development. Implementation barriers include manufacturing capacity, cost, and prioritization of targets that will yield maximal AMR impact.

Microbiome-based therapies and probiotics

Manipulating the microbiome to restore colonization resistance and displace resistant organisms is a promising non-antibiotic strategy. Fecal microbiota transplantation (FMT) has demonstrated capacity to reduce carriage of multidrug-resistant organisms (MDROs) and to prevent recurrent *Clostridioides difficile* infection, while targeted next-generation probiotics and engineered commensals aim to selectively suppress pathogens or degrade resistance genes [64]. Early randomized controlled feasibility studies (e.g., FERARO) are evaluating whether intentional microbiome modulation can reduce gut reservoirs of ARGs; outcomes to date are encouraging but require larger trials to define durability, safety, and ecological impacts [64].

Technological innovations

Rapid diagnostics and point-of-care testing

Rapid, accurate diagnostics enable targeted therapy, de-escalation, and stewardship. Nucleic acid amplification, multiplex panels, rapid phenotypic susceptibility tests, and host-response biomarkers can shorten time-to-appropriate therapy and reduce broad-spectrum antibiotic exposure [65]. Systematic reviews and meta-analyses indicate that rapid diagnostics bundled with stewardship programs reduce mortality and antibiotic use in sepsis and other severe infections [66]. Key barriers remain: cost, laboratory capacity in LMICs, reimbursement models, and integration with clinical workflows. Implementation science is needed to scale POC diagnostics where they will yield greatest AMR benefit.

AI-driven drug discovery and computational tools

Artificial intelligence (AI) and machine learning (ML) have accelerated discovery pipelines by screening chemical space, predicting antibacterial activity, designing AMPs, and optimizing adjuvant combinations. Notable successes include ML-driven identification of novel scaffolds active against *A. baumannii* and other resistant pathogens [67]. AI also supports diagnostics (pattern recognition, imaging), surveillance (anomaly detection), and stewardship (decision support). Yet challenges include data quality, model interpretability, and the "last-mile" of validating computational hits in vivo [67].

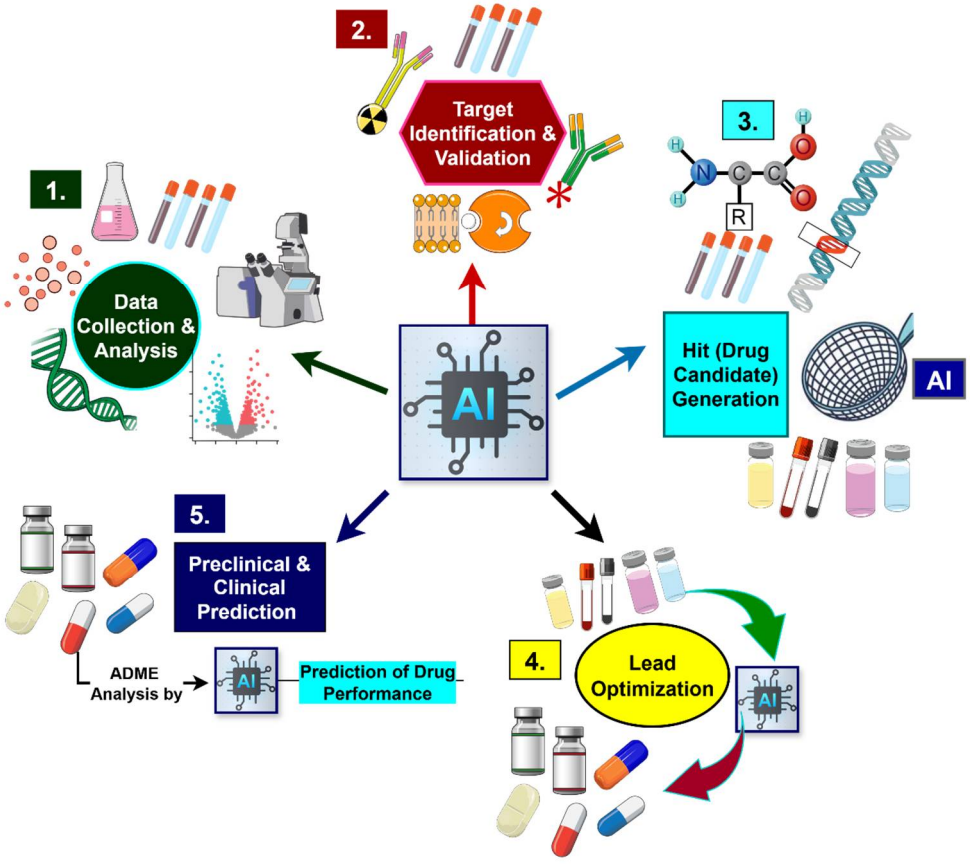

Figure 4: Conceptual Diagram of AI's Role in Drug Discovery and Optimization (created by this author)

Figure 4 illustrate how AI (machine learning, deep learning) integrates into the drug discovery pipeline, from target identification and lead compound generation to optimization and clinical trial acceleration. It would show how AI analyzes vast datasets to predict properties, design novel molecules, and optimize existing ones.

Policy and stewardship strategies

Antimicrobial stewardship programs (ASPs)

ASPs comprising prescriber education, audit and feedback, formulary restriction, and diagnostic stewardship remain the cornerstone of conserving antibiotic efficacy. Evidence shows ASPs lower inappropriate prescribing, reduce length of therapy, and improve clinical outcomes when paired with diagnostics and administrative support [66,68]. Scaling ASPs globally requires workforce training, financing, and embedding stewardship into routine care metrics.

Global action plans and international initiatives

Multilateral initiatives such as WHO Global Action Plan, UN high-level meetings, Gavi's engagement on vaccines for AMR prevention, and push-funding mechanisms such as CARB-X—create enabling environments for R&D, surveillance, and implementation [46]. These frameworks promote One Health integration, standardized surveillance (GLASS), and resource mobilization, but progress varies by region and depends on sustained political will.

Incentivizing antibiotic R&D

To correct market failures, a suite of incentives has been proposed and piloted: "push" funding (grants), "pull" incentives (market entry rewards, subscription payments that delink revenues from sales volume), and public–private partnerships (e.g., CARB-X) [69-70]. Early pilots suggest subscription models increase pipeline sustainability but require global coordination to be equitable and affordable. Robust economic evaluation and international agreement on valuation of novel antibiotics remain urgent priorities.

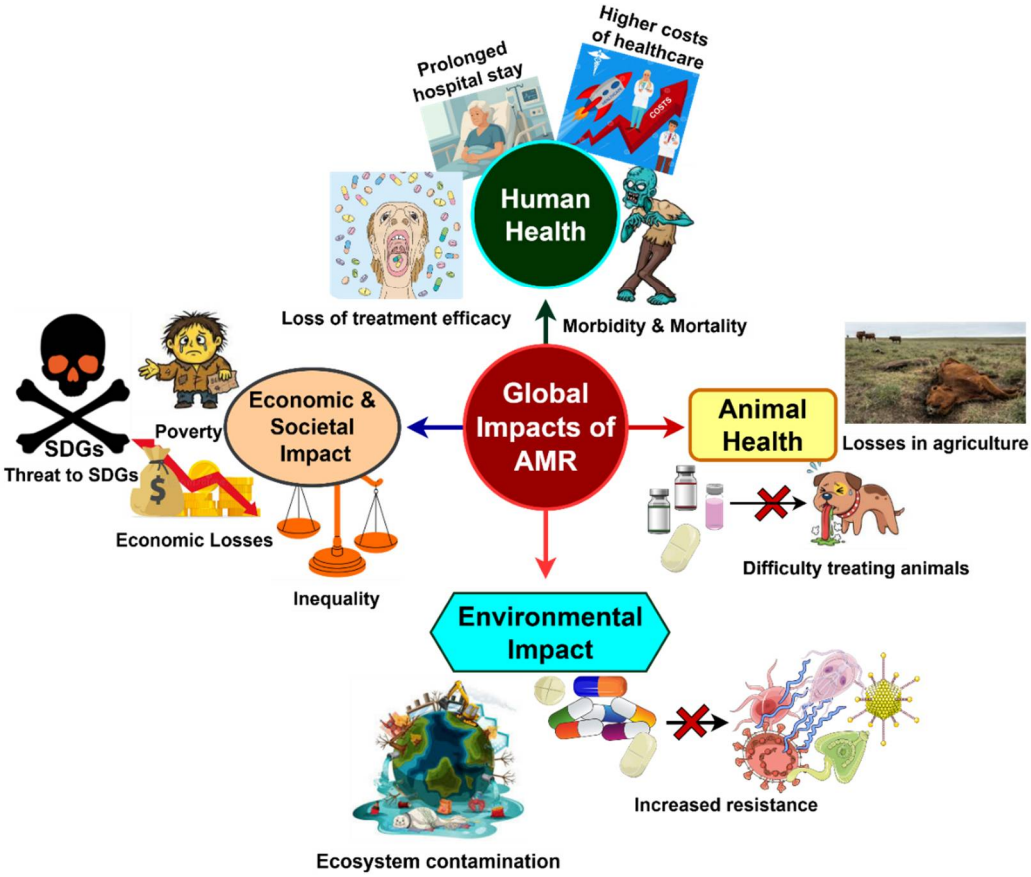

Figure 5. Global Impact of Antimicrobial Resistance (created by this author)

Figure 5 represent the multifaceted impact of AMR, showing its effects on human health (mortality, morbidity, risk to medical procedures), animal health (impact on agriculture), and the economy (healthcare costs, GDP losses, productivity losses). It would use icons or simple graphics to convey these different dimensions.

ONE HEALTH APPROACH

AMR is a quintessential One Health problem: resistance genes and organisms move freely between humans, animals, and the environment, mediated by food systems, waste streams, and human behavior. Integrated interventions that bridge sectors are therefore essential.

Antimicrobial use in agriculture, environmental contamination (wastewater, pharmaceutical effluents), and human clinical use interact to select and disseminate resistance [32,35]. A One Health lens reveals amplification pathways—manure used as fertilizer, untreated hospital effluent entering rivers, and aquaculture runoff—that perpetuate ARGs across ecological boundaries. Interventions limited to a single sector will therefore be less effective than coordinated actions spanning public health, veterinary services, agriculture, and environmental management [70]. Several national and subnational programs illustrate One Health success. For example, integrated surveillance linking human clinical isolates with veterinary and environmental sampling has identified shared resistance plasmids, enabling targeted interventions in

farms and wastewater management [68]. WHO collaborations demonstrate how vaccination campaigns in humans and animals can reduce antibiotic use in primary care and animal husbandry, respectively [68]. These case studies show that coordinated policy, data sharing, and joint financing yield measurable AMR gains.

Timely, high-quality surveillance underpin successful One Health strategies. GLASS and complementary national systems provide baseline data but suffer from geographic and sectoral gaps. Emerging platforms that federate genomic, phenotypic, and environmental data combined with interoperable standards and open-data agreements can speed detection of emergent resistance and inform cross-sectoral responses [71]. Building capacity for genomic surveillance, especially in LMICs, is a priority for equitable AMR control.

FUTURE DIRECTIONS

The path forward requires sustained multidisciplinary effort, new financing models, and societal engagement. Scientific advances must be matched by social science, implementation research, and systems engineering to translate laboratory breakthroughs into affordable, equitable interventions. Collaborations among clinicians, veterinarians, ecologists, engineers, and economists will accelerate pragmatic solutions and reveal unintended consequences of novel interventions [64]. Global governance must prioritize sustainable financing for AMR—blending domestic budgets, multilateral financing, and innovative instruments (subscriptions, advanced market commitments) to underwrite R&D, surveillance, and stewardship in all regions. Equity must be central: financing mechanisms should ensure LMICs gain timely access to new antibiotics, diagnostics, and vaccines while supporting local capacity building.

Public and professional education campaigns tailored to cultural contexts reduce inappropriate antibiotic demand and improve adherence to stewardship practices. Integrating AMR education into medical, veterinary, and agricultural curricula, and leveraging digital platforms for continuous professional development, will sustain behavior change over time [66]. Sustainability requires reducing selection pressure (vaccines, infection prevention, reduced non-therapeutic use in animals), expanding affordable diagnostics, maintaining a well-funded R&D pipeline (including adjuvants and phages), and operationalizing One Health surveillance. Combining technological innovation with governance reform and societal engagement offers the most credible path to avert a future defined by untreatable infections. Continued evaluation through robust trials, economic modeling, and real-world implementation studies will be critical to refine priorities and allocate resources effectively [44,66].

CONCLUSION

Antimicrobial resistance represents one of the most urgent health challenges of the 21st century, demanding innovative, coordinated, and sustainable responses. While scientific advances in drug discovery, diagnostics, vaccines, and microbiome research offer promising solutions, they must be matched with strong stewardship, global policy alignment, and equitable resource distribution. The One Health framework underscores the interconnectedness of human, animal, and environmental health, reminding us that fragmented approaches will fall short. Future progress hinges on interdisciplinary collaboration, robust governance, and sustained investment to safeguard the efficacy of antimicrobials and ensure resilient health systems for generations to come.

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