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Review Article

Antimicrobial resistance (AMR): from wonder drugs to worrisome bugs – a review

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ABSTRACT

Antimicrobial resistance (AMR) represents a significant and escalating global health challenge, threatening the efficacy of treatments for infectious diseases. This review explores the complex dynamics underlying the emergence and proliferation of AMR, emphasizing the mechanisms by which microbes evade antimicrobial agents. Key contributors include the misuse and overuse of antibiotics in clinical, agricultural, and community settings, compounded by insufficient development of novel antimicrobial drugs. Particular attention is paid to the ESKAPE pathogens, *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. as critical drivers of nosocomial infections. Resistance mechanisms such as altered drug targets, efflux pumps, and enzymatic deactivation are discussed in detail, alongside the diminishing efficacy of frontline antibiotics like methicillin, vancomycin, and carbapenems. The review also highlights the urgent need for multifaceted strategies to curb AMR. These include antimicrobial stewardship programs, enhanced surveillance, periodic antibiotic rotation, and the integration of advanced diagnostic technologies like artificial intelligence for resistance detection and drug design. Non-prescription antibiotic regulation, improved hygiene practices, and innovations in vaccination and alternative therapies are underscored as pivotal interventions. The document concludes with a call to action for collaborative global efforts involving policymakers, healthcare providers, and the public to mitigate the AMR crisis effectively. This comprehensive examination offers valuable insights into the challenges and potential solutions for safeguarding the future of antimicrobial therapy.

KEYWORDS: Antimicrobial resistance (AMR); ESKAPE pathogens; Antibiotics; Antimicrobial stewardship

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1. INTRODUCTION

Antimicrobials are medications that are utilized to prevent and control infectious diseases in humans, animals, and plants. Examples include antibiotics, antivirals, antifungals, and anti-parasitic agents. When microbes such as bacteria, viruses, fungi, and parasites become resistant to antimicrobial medications, it is referred to as antimicrobial resistance (AMR). Drug resistance thereby renders effective antimicrobial medications such as antibiotics irrelevant and hinders the treatment of infections. This increases the vulnerability of the spread of infections, severe disease, disabilities, and death to individuals [1]. Modern medicine has triumphed over countless infectious diseases that once ravaged humanity. Antibiotics, the cornerstone of this victory, have

become an indispensable tool in our fight against bacterial infections. However, this success story is facing a grave challenge: the rise of antimicrobial resistance (AMR). In hospital wards, where immunocompromised patients and those with severe infections are concentrated, AMR presents a particularly critical threat.

Here's why this topic is so important:

- Public health crisis: AMR, or the antimicrobial resistance crisis, describes the rising prevalence of infections that affect people worldwide and cannot be cured by any known antimicrobial medication. Consequently, the rising incidences and severity of both fatal and crippling diseases in human society will have a disastrous impact as a result of this problem [2].
- Unique challenges in hospitals: Hospitals and clinical environments are thought to be AMR hotspots because they consume the most antibiotics. Hospital effluents are predicted to include a significant number of genes and bacteria that are resistant [3]. It was discovered that the antibiotic concentrations in the wastewater from Indian hospitals were high enough to alter bacterial strains' DNA [4].
- Rapid escalation: The Indian Council of Medical Research (ICMR) annual report of 2021 found that E. Coli's imipenem susceptibility decreased gradually from 86% in 2016 to 64% in 2021, whereas *Klebsiella pneumoniae's* susceptibility decreased gradually from 65% in 2016 to 45% in 2020 and 43% in 2021.
- In 2021, it was shown that *Pseudomonas aeruginosa* exhibited over 60% susceptibility to several aminoglycosides and fluoroquinolones [5], to 45% in 2020 and 43% in 2021.

By delving into this topic, we can gain insights into:

- The specific types of bacteria exhibiting resistance.
- The most commonly used antibiotics that are becoming less effective.
- Factors contributing to the rise of AMR.
- Strategies for mitigating the spread of resistant bacteria and optimizing antibiotic use.

2. SPECIFIC TYPES OF BACTERIA EXHIBITING RESISTANCE

The group recognized as ESKAPE pathogens, which comprises *Enterobacter faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species, are one of the most associated contributors to nosocomial infections across the global setup [6].

2.1. ENTEROCOCCUS FAECIUM

Enterococcus is important in human health as it is widely distributed and is better known for its major involvement in infections related to healthcare. The enterococci are a very hardy and adaptable species that exist in difficult conditions, and therefore are well-suited to fit within the medical environment [7]. The most common enterococcal species encountered in humans are *Enterococcus faecalis* and *E. faecium*. *Enterococcus* spp. are resident organisms of the gut and are also involved in immune system activities as commensals in the host organisms [8]. Because all enterococci are constantly producing low-affinity penicillin-binding proteins, they are relatively resistant, not only to ampicillin and penicillin but also to most cephalosporins and all semi-synthetic penicillins [9]. MDR enterococci display a range of ways to resist antibiotics. These include altering drug targets and deactivating agents, increasing the expression of efflux pumps, have an adaptive response in their cell envelope that helps them survive in both human hosts and hospital settings. All these mechanisms allow MDR enterococci to acquire antibiotic resistance traits [10]. Three of the historically most effective anti-enterococcal antibiotics: ampicillin, aminoglycosides, and vancomycin- now show high-level resistance in the majority of *E. faecium* isolates. Modern antibiotics like tigecycline, daptomycin, and linezolid have good in vitro activity against isolates of enterococci, but their clinical use may be restricted in some clinical scenarios due to low serum levels, underdosing for enterococci,

and reduced success rates. Resistance may also develop (Figure 1). Although there are currently insufficient clinical data, the investigational drug oritavancin may provide some hope for the treatment of vancomycin-resistant enterococci (VRE) [11]. Treatment should be restricted if vancomycin-resistant *Enterococcus* is identified and found to be highly susceptible. Intravenous (IV) high-dose ampicillin (18 to 30 g/day) should be begun as a monotherapy for UTIs. The recommended treatments are nitrofurantoin 100 mg PO twice a day or fosfomycin 3 g PO in a single dosage if the UTI is simple but resistant to ampicillin [12].

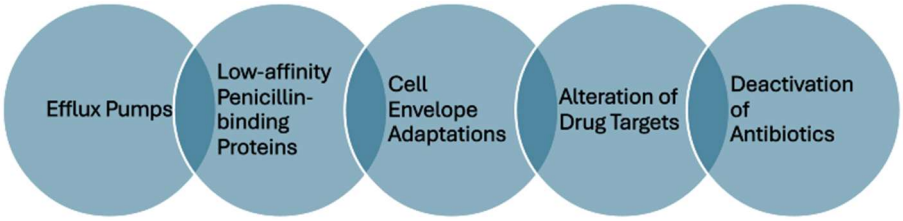


Figure 1. Antibiotic resistance mechanisms of *Enterococcus faecium*.

2.2. STAPHYLOCOCCUS AUREUS

Gram-positive *Staphylococcus aureus* is a type of bacterium that forms clusters resembling grapes and is capable of both anaerobic and aerobic respiration. This significant commensal bacterium is also a human pathogen that can lead to a variety of clinical diseases, such as pneumonia, osteomyelitis, endocarditis, sepsis, and abscesses of different organs [13]. It is well understood that *S. aureus* has ways of developing resistance against beta-lactam medications, which consist of producing beta-lactamase enzymes, changing PBP genes, and forming a new PBP called PBP2A (PBP2a, PBP2') [14]. Methicillin-resistant *S. aureus* (MRSA) first appeared in the 1960s, spread around the world, and is now a major cause of bacterial infections in both community and healthcare settings [15]. One of the most effective pathogens in the modern era is MRSA. The epidemiology of MRSA is characterised by genetic diversity, but the main feature is the recurring appearance of epidemic strains. With its high rates of illness and death, MRSA remains a significant clinical threat even with recent reductions in some regions [16]. Vancomycin, classified as a glycopeptide antibiotic, has traditionally been considered the last option for treating severe infections caused by Gram-positive bacteria [17]. But in recent times, isolates of *S. aureus* that are totally resistant to vancomycin have surfaced [18] (Figure 2). In vitro studies have shown that several novel anti-staphylococcal antibiotics have superior antibacterial efficacy, favourable pharmacokinetic characteristics, and increased safety and tolerability when compared to the anti-staphylococcal medications that are currently on the market [19]. For the treatment of MRSA-related multidrug resistance, the FDA has approved five anti-infective medications: ceftaroline, tigecycline, telavancin, daptomycin, and linezolid [20].

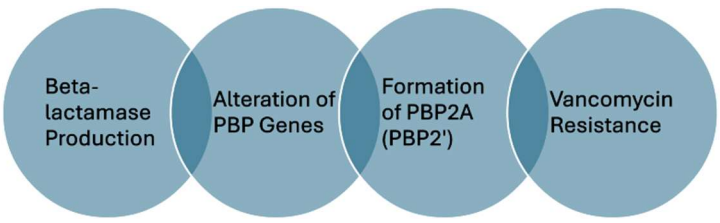


Figure 2. Antibiotic resistance mechanisms of *Staphylococcus aureus*.

2.3. KLEBSIELLA PNEUMONIAE

Klebsiella pneumoniae, found in the environment, a Gram-negative, encapsulated, non-motile bacteria is associated with pneumonia in diabetic and alcoholic patients. The bacterium typically colonizes the oro-pharynx mucosal surfaces and GI tract in humans [21]. The rise of hypervirulent pathotypes, its capacity to

elude the immune system, and rising antibiotic resistance have made it a significant challenge in the field of medicine [22]. It is possible for *K. pneumoniae* to acquire antibiotic resistance elements, such as transposons and plasmids that encode different β-lactamases and efflux pumps. Antibiotic resistance is also caused by mutations in several proteins, including but not limited to efflux proteins, β-lactamases, protein synthesis complexes, gene replication enzymes, outer membrane proteins and transcription enzymes. Antibiotic resistance can also be facilitated by the production of biofilms [23]. Researches has shown the rise of multidrug-resistant *K. pneumoniae* strains that exhibit resistance to the last-resort antibiotic colistin. This resistance is caused by mutational inactivation of the mgrB regulatory gene [24]. The most significant virulence factor of Kp, capsule polysaccharide, is involved in many aspects of the pathogenesis; yet, due to its great variability, finding a therapy or preventative measure that works for everyone is extremely difficult. In the struggle against Kp infections, less changeable virulence factors such the O-Antigen, outer membrane proteins like fimbriae, and siderophores may also be crucial [25]. For clinicians, managing antibiotic resistance in multidrug-resistant *Klebsiella pneumoniae* (MDR-KP) is a significant problem (Figure 3). It's still uncertain which course of action is best for treating MDR-KP infections. The use of combination therapy, which include high-dose meropenem, colistin, fosfomycin, tigecycline, and aminoglycosides, is common although the outcomes are not optimal [26]. Zhu W et. al, in their study, reported a patient with multidrug-resistant *K. pneumoniae* infection who showed improvement after receiving carrimycin treatment following unsuccessful attempts with other antibiotics like meropenem, tigecycline, and polymyxin. Carrimycin proved effective, leading to the patient's discharge from the hospital. This suggests carrimycin as a viable option for such infections when conventional treatments fail [27].

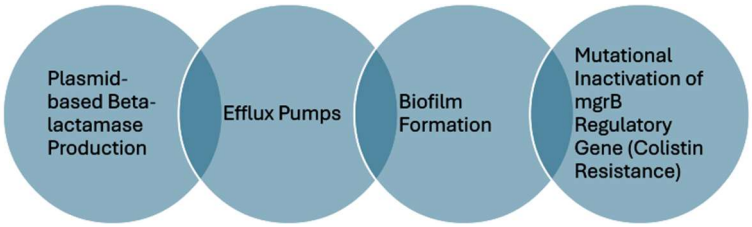


Figure 3. Antibiotic resistance mechanisms of *Klebsiella pneumoniae.*

2.4. ACINETOBACTER BAUMANNII

The opportunistic bacterial pathogen *Acinetobacter baumannii* is mostly linked to infections acquired in hospitals [28]. Its remarkable capacity to either acquire or upregulate factors of antimicrobial drug resistance has rightfully thrust it to the forefront of scientific inquiry [29]. Three primary pathways exist for the conferment of antibiotic resistance in *A. baummannii:* altering the targets of the antibiotics, enzymatically inactivating the medicines, and controlling the drugs' passage through membranes (by decreasing permeability or increasing efflux) [30]. A major source of concern is the emergence and spread of *Acinetobacter* species that are resistant to the majority of antimicrobial drugs currently on the market [31]. In light of the scope and financial implications of hospital-acquired infections as well as the rise in organisms resistant to drugs, it is important to reassess our present methods and search for supplements or substitutes for conventional antibiotic treatments [32] (Figure 4). When treating *A. baumannii* infections in regions where carbapenem resistance is uncommon, carbapenems are the preferred medication. If not, carbapenems shouldn't be used at least not alone for serious infections in regions where the prevalence of antibiotic resistance to this class of drugs is high [33].

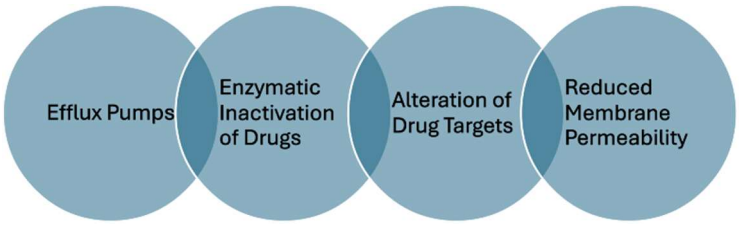


Figure 4. Antibiotic resistance mechanisms of *Acinetobacter baumannii*.

2.5. PSEUDOMONAS AERUGINOSA

Pseudomonas is a common type of bacteria that can be present in the environment (soil, water). In humans, after surgery, it may lead to bloodstream infections, lung infections (pneumonia), or infection in other areas of the body [34]. The third most common nosocomial bacteria leading to bloodstream infections is gram-negative *P. aeruginosa* [35]. In addition to showing intrinsic resistance to a wide range of antibiotics, *P. aeruginosa* is known to actively acquire genetic alterations that increase its resistance [36]. Furthermore, *P. aeruginosa* is the main cause of morbidity and death in individuals suffering from the hereditary condition cystic fibrosis (CF) [37]. The three chromosomally encoded resistance mechanisms in *P. aeruginosa* that have been researched the most are the multidrug efflux pumps, the OprD outer membrane porin, and the AmpC cephalosporinase [38] (Figure 5). Appropriate antipseudomonal therapy with in vitro susceptibility must be started as soon as possible to treat *P. aeruginosa* infections and avoid the negative effects of therapy delay, such as marked increases in morbidity, mortality, surgical intervention need, length of hospital stay, and treatment costs [39]. In cases where there's a high risk of MDR *P. aeruginosa* infections or if local data indicates resistance to common antibiotics, the recommended initial treatment options are ceftolozane-tazobactam or ceftazidime-avibactam. However, if the risk is low and there are no identifiable factors for drug resistance, third or fourth generation cephalosporins can be used, aiming to avoid carbapenem use. It's advised to adjust antibiotic therapy based on susceptibility tests, and if needed, cefiderocol or imipenem-cilastatin-relebactam can be considered for cases resistant to other newly available antibiotics [40].

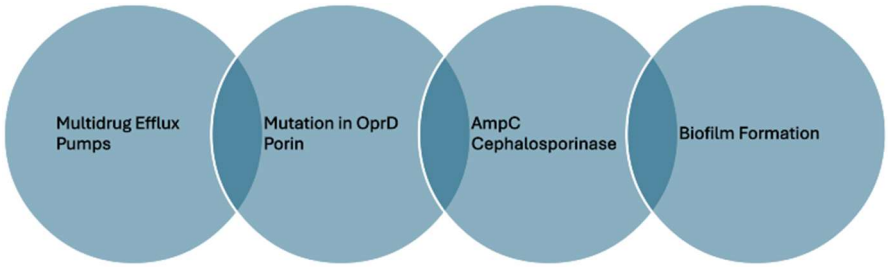


Figure 5. Antibiotic resistance mechanisms of *Pseudomonas aeruginosa*.

2.6. ENTEROBACTER SPECIES

The *Enterobacter* genus is a member of the *Enterobacteriaceae* family and is mainly linked to illnesses related to healthcare. *Enterobacter* currently includes 22 species. But not every species is recognised to be harmful to humans [41]. Many serious, potentially fatal infections are caused by *Enterobacteriaceae*, and an increasing global public health concern is the germs' resistance to numerous antibiotics. Antibiotic resistance is partly caused by chromosomal gene mutations, but *Enterobacteriaceae* are suited to exchange genetic material, so 'mobile' resistance genes play a major role in resistance [42]. The emergence of plasmid-borne extended-spectrum beta-lactamases (ESBL), particularly those from the CTX-M family, is the primary cause of the sharp rise in resistance rates to third-generation cephalosporins observed in *Enterobacteriaceae*. In critically ill patients, the effectiveness of beta-lactam/beta-lactamase inhibitor combinations for severe infections caused

by ESBL-producing *Enterobacteriaceae* has not been sufficiently assessed; carbapenems remain the preferred treatment in this scenario. But during the past decade, strains that produce carbapenemase have appeared all throughout the world [43]. Carbapenems (used in a double carbapenem regimen), tigecycline, fosfomycin, and polymyxins are among the possible treatments for carbapenem-resistant *Enterobacter* (CRE) [44].

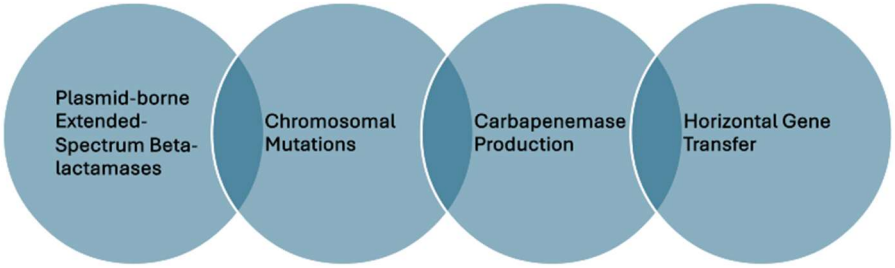


Figure 6. Antibiotic resistance mechanisms of *Enterobacter* species.

3. THE MOST COMMONLY USED ANTIBIOTICS THAT ARE BECOMING LESS EFFECTIVE

The fast growth of resistant bacteria has made bacterial illnesses a worry again, decades after the first patients were treated with antibiotics. This issue is linked to antibiotic overuse and a dearth of new treatment development [45]. Alarming rates of resistance among common bacterial infections are highlighted in the 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report. A significant worry is the median reported rates of 35% for methicillin-resistant *S. aureus* and 42% for third-generation cephalosporin-resistant *E. coli* across 76 nations. One in five cases of *E. coli* urinary tract infections had reduced susceptibility to common antibiotics, to ampicillin, co-trimoxazole, and fluoroquinolones (in 2020). As a result, common infections are becoming difficult to treat [46].

3.1. METHICILLIN

The β-lactam antibiotic methicillin works by preventing penicillin-binding proteins (PBPs) from synthesising peptidoglycan, a necessary mesh-like polymer that envelops the cell [47]. Resistant to methicillin, one of the most significant multidrug-resistant infections in the world is *S. aureus*. The methicillin resistance gene, mecA, carried by the mobile genetic element staphylococcal cassette chromosome mec (SCCmec), which is thought to be transmissible between staphylococcal species, is acquired exogenously by methicillin-susceptible *S. aureus* (MSSA). This results in the formation of methicillin-resistant *S. aureus* (MRSA) [48].

3.2. VANCOMYCIN

Glycopeptide antibiotic vancomycin is active against gram-positive bacteria such as *streptococci* and *staphylococci*. When treating infections caused by *Corynebacterium jeikeium*, methicillin-resistant *staphylococci*, and multiply-resistant strains of *Streptococcus pneumoniae*, this is the drug of choice [49]. Vancomycin-resistant bacteria (VRB) are a significant medical and public health concern because they can cause infections that are potentially fatal, show no signs of healing, and continue to exist in the body even after treatment. The evolution of the most common van genes in the VRB genome indicates extensive gene flow and a wide range of antimicrobial resistance traits, as well as different environmental and animal conditions [50].

3.3. CARBAPENEMS

They are distinct from other β-lactams now on the market because they target penicillin-binding proteins while also acting as "slow substrates" or inhibitors of β-lactamases, making them comparatively resistant to hydrolysis by the majority of β-lactamases [51]. Carbapenem resistance is a persistent global public health issue that mostly affects Gram-negative bacteria. This kind of antibiotic resistance is spreading quickly, leading

to significant outbreaks and severely reducing the number of available treatments, particularly when it is mediated by genes expressing transferable carbapenemase [52].

3.4. ERYTHROMYCIN

Erythromycin has long been used to treat a variety of respiratory diseases, including community-acquired pneumonia and Legionnaires disease; chlamydia and neonatal conjunctivitis prevention. Additionally, the FDA has approved it for the treatment of rheumatic fever, syphilis, intestinal amebiasis, prophylaxis, skin infections, and pelvic inflammatory disease (PID) [55]. Erythromycin resistance has increased as a result of increased usage of this antibiotic in the treatment of infections caused by bacteria other than Group A *Streptococcus* (GAS) in recent years [56]. The cause of erythromycin resistance in *streptococci* can be either an efflux mechanism or target-site alteration by a rRNA-methylating enzyme [57].

3.5. CLINDAMYCIN

Numerous infections, amongst them septicaemia, intra-abdominal infections, lower respiratory infections, gynaecological infections, infections of the bones and joints, and infections of the skin and skin structure, can be treated with the medicine clindamycin. Additionally, streptococcal pharyngitis, acne vulgaris, bacterial vaginosis, and severe pelvic inflammatory disease are treated with clindamycin [58]. Because erm genes can cause therapy failure when in vitro conventional tests for clindamycin susceptibility fail to detect inducible clindamycin resistance, it is necessary to regularly detect this resistance using a simple D test [59].

3.6. COLISTIN

Since the middle of the last century, colistin has been widely utilised in animal sespecially swine, to treat enteric illnesses. Colistin is currently thought to be the final line of defence against infections in humans brought on by multidrug-resistant Gram-negative bacteria including *P. aeruginosa*, *A. baumannii*, and *Enterobacterales*, which produce carbapenemase [60]. The product of the mobilised colistin resistance (mcr) gene and its variations circulates among the bacterial community and is one of the major sources of colistin resistance, which is emerging due to the widespread use of colistin in veterinary medicine. Colistin resistance is also mediated by a few more intrinsic genes and proteins besides mcr genes [61]. Summary of above in-depth discussed commonly used antibiotic is portrayed in Table 1.

Table 1. Overview of commonly used antibiotics.

Antibiotic	Mechanism of action	Common uses in treatment	Resistance mechanisms	Clinical significance of resistance
Methicillin	Inhibits penicillin-binding proteins (PBPs), disrupting peptidoglycan synthesis in bacterial cell walls.	Effective against infections caused by Staphylococcus aureus and other susceptible bacteria.	Resistance occurs due to the mecA gene on the SCCmec element, leading to the PBP2A production, which methicillin cannot effectively inhibit.	Methicillin-resistant *S. aureus* (MRSA) is a major multidrug-resistant pathogen and a significant global health concern.
Vancomycin	A glycopeptide that targets Gram-positive bacteria by preventing cell wall synthesis.	Used to treat infections caused by MRSA, *Streptococcus pneumoniae*, and *Corynebacterium* spp.	Resistance involves van genes, which alter cell wall precursors, reducing vancomycin binding and efficacy.	Vancomycin-resistant strains are associated with severe, difficult-to-treat infections that may persist despite therapy.
Carbapenems	Broad-spectrum β-lactams that inhibit PBPs and act as slow substrates for β-lactamases, resisting enzymatic hydrolysis.	Treats Gram-negative infections, including those caused by multidrug-resistant bacteria.	Resistance is primarily due to carbapenem-ase production or efflux pump activity, reducing drug effectiveness.	Resistance severely limits treatment options, leading to outbreaks and posing global public health challenges.

Antibiotic	Mechanism of action	Common uses in treatment	Resistance mechanisms	Clinical significance of resistance
Erythromycin	A macrolide that binds to the 50S ribosomal subunit, blocking bacterial protein synthesis.	Used to manage respiratory infections, syphilis, rheumatic fever, and pelvic inflammatory disease (PID), among others.	Resistance mechanisms include the use of efflux pumps or target modification via methylation of rRNA, reducing drug binding.	Rising resistance reduces the drug's effectiveness in treating bacterial infections, particularly those caused by *Streptococcus* spp.
Clindamycin	A lincosamide that interferes with bacterial protein synthesis by binding to the 50S ribosomal subunit.	Treats a variety of infections, including septicemia, respiratory infections, skin infections, and bacterial vaginosis.	Resistance often involves erm genes, which can lead to therapy failures when inducible resistance is undetected by routine tests.	Inducible resistance can cause treatment failures, highlighting the need for appropriate susceptibility testing.
Colistin	A polymyxin that damages bacterial membranes by interacting with lipopolysaccharides.	Considered a last-resort antibiotic for multidrug-resistant Gram-negative bacteria, including *Pseudomonas* and *Acinetobacter* spp.	Resistance is caused by the mcr gene or other intrinsic genetic changes, reducing membrane affinity for the drug.	Resistance to colistin jeopardizes the treatment of infections caused by multidrug-resistant Gram-negative bacteria, making it a critical public health issue.

4. FACTORS CONTRIBUTING TO THE RISE OF AMR

One of the most significant medical advances of the 20th century has been the creation of antibiotic therapy; yet, the tremendous progress made by the availability of antibiotic therapy is in jeopardy due to the emergence of resistance in healthcare facilities and the general population [62].

Antimicrobial resistance is the result of using and abusing antibiotics. It is the state in which an organism loses its susceptibility to an antimicrobial treatment that it was previously susceptible to, usually through mutation or the acquisition of a resistance gene. After then, conventional therapies stop working, which can result in chronic infections that could infect other people [63]. When compared to identical infections produced by susceptible strains, infections caused by resistant bacteria can result in up to two times higher likelihood of unfavourable consequences. The failure or postponement of antibiotic treatment is the primary cause of these unfavourable consequences, which might be either clinical or financial [62]. In addition to being crucial for patients and healthcare professionals, ensuring safe, effective treatments for infections is also necessary for sustainable health systems [64].

Traditionally, AMR research has focused on specific hospital wards where patient-to-healthcare worker transmission of germs occurs. However, because patients are frequently moved between wards, they cannot be considered separate entities. There's a chance that a patient may introduce new antibiotic-resistant bacteria with them each time they move to a new ward. Because of this, every hospital ward and, by extension, every hospital in a nation, is linked together in a vast network that makes it simple for AMR bacteria to spread [65].

Bacterial selection, which occurs when bacteria resistant to antibiotics outcompete and replace more vulnerable ones, is another factor contributing to the emergence of AMR. Because of the large amount of antibiotics taken, most bacterial communities in hospitals most certainly already contain some resistant germs that have an advantage. Still, little is known about how patient ward transfers and bacterial selection interact to influence the spread of antimicrobial resistance (AMR) in a hospital network [66].

Spagnolo et. al., conducted a study, using an approach called metapopulation biology. The study ran computer simulations to understand how infections spread in hospitals. They found that even after removing the initial infected patient, the germs stick around in small groups within the hospital for a long time. This

increases the chances of infecting other patients. The study also showed that these small groups of germs can remain undetected for a while, making it harder for hospitals to identify and stop the spread of infections. Additionally, the number of surfaces and areas where germs can hide is crucial for their survival and spread. This suggests that hospitals need to be extra vigilant in cleaning and monitoring various surfaces to prevent infections [67].

Zizhong Ji et. al., conducted a study to associate age and antibiotic resistance of *Helicobacter pylori* and found that the age of patients plays a crucial role in the battle against antibiotic resistance. Older patients, especially those above 70 years old, exhibit higher resistance rates, particularly to levofloxacin. This age-related resistance complicates treatment effectiveness globally, especially with commonly used antibiotics like clarithromycin and levofloxacin. Moreover, tailoring treatment strategies based on age-specific resistance patterns is essential to overcome this challenge and achieve successful outcomes [68].

Ventola concludes that the antibiotic resistance crisis stems from several key factors: overuse and inappropriate prescribing of antibiotics, both in healthcare settings and in agriculture; extensive agricultural use of antibiotics as growth supplements in livestock, leading to the spread of resistant bacteria through the food chain and environmental contamination; and the lack of development of new antibiotics due to economic and regulatory challenges, with many pharmaceutical companies abandoning antibiotic research. These factors collectively fuel the evolution and spread of antibiotic-resistant bacteria, posing a significant threat to public health globally [69].

5. STRATEGIES FOR MITIGATING THE SPREAD OF AMR

Antimicrobial resistance is a complicated issue with a wide range of underlying causes. It is a major source of health issues that have a direct or indirect financial impact on the individual as well as the community. The most effective way to stop the spread of infections and, consequently, AMR is still prevention. Not only is it necessary to employ antimicrobial medications in a prudent manner, but new and efficient chemicals as well as new diagnostic equipment must be developed. In order to combat the worldwide spread of antibiotic resistance, collaboration between patients, prescribers, and individuals as well as international regulators and policy makers is required [70] (Figure 7).

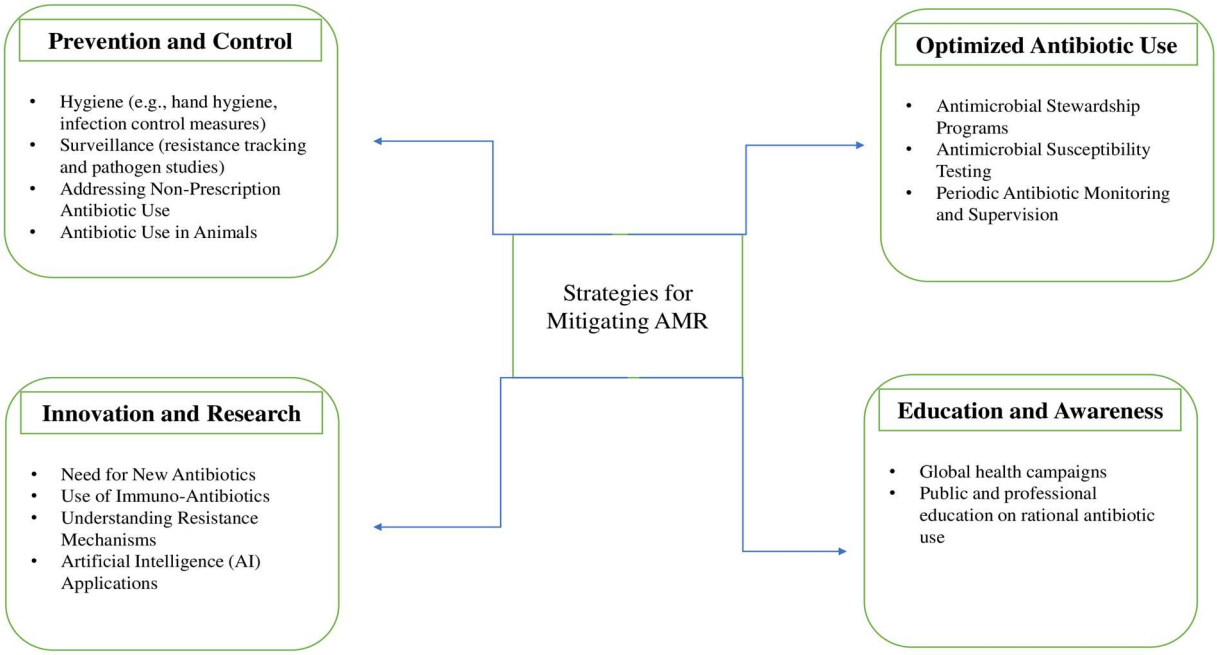


Figure 7. Strategies for mitigating the spread of AMR.

5.1. ANTIMICROBIAL STEWARDSHIP PROGRAMS (ASPS)

An organisation can optimise the use of antibiotics, enhance patient outcomes, lower the rate of antibiotic-associated illnesses and antimicrobial resistance, and save healthcare expenditures by implementing antimicrobial stewardship programmes [71]. Globally, antimicrobial resistance (AMR) is still spreading at a startling rate. Innovative methods are required to lessen its detrimental effect on the effectiveness of antibiotics. The goal of antibiotic stewardship is to encourage the responsible use of antibiotics by implementing evidence-based practices [72].

5.2. ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST)

One of the biggest health care issues of the new millennium is antimicrobial resistance, and the clinical microbiology laboratory is essential for maximising the therapeutic management of infected patients [73]. When it comes to a quick and accurate assessment of the effectiveness of antibiotics in treating bacterial infections, antimicrobial susceptibility testing (AST) can be a valuable tool. The most widely used techniques measure bacterial growth in the presence of the antibiotic under test in order to identify phenotypic resistance. Many methods have been shown to be effective in identifying resistance in different bacterial species, including mass spectrometry, microarrays, PCR-based techniques, microfluidics, whole-genome sequencing and cell lysis-based methods [74].

5.3. ADDRESSING NON-PRESCRIPTION ANTIBIOTIC USE

Frequent use without a prescription is correlated with the prevalence of microorganisms resistant to antibiotics. There is hope that certain regulatory initiatives can lower the use of antibiotics as well as their resistance. In order to effectively manage antimicrobial resistance, public health programmes must acknowledge and address the use of non-prescription antibiotics [75].

5.4. PERIODIC ANTIBIOTIC MONITORING AND SUPERVISION (PAMS)

It is a real-time strategy based on antibiotic heterogeneity. It adjusts antibiotic classes every three months based on usage and resistance rates, overseen by a multidisciplinary team. PAMS has shown significant success in optimizing antibiotic use, but effective monitoring and supervision are essential. While antibiotic mixing shows promise, more research is needed, and caution is advised due to the risk of inappropriate antibiotic use [76].

5.5. GARP INITIATIVE

To fight antibiotic resistance, we need proactive measures like vaccinations, hospital infection control, and rational antibiotic use. These measures not only benefit individuals but also contribute to reducing antibiotic usage and the spread of resistant bacteria. Sharing knowledge globally through initiatives like Global Antibiotic Resistance Partnership (GARP) is crucial for success [77].

5.6. HYGIENE

Improving antimicrobial usage and enforcing infection control measures, especially hand hygiene, are crucial in combating hospital infections caused by resistant bacteria. Neglecting proper antimicrobial use and hygiene practices contributes to the increasing incidence of these infections [78]. Ramay et. al., conducted a study in Guatemala and found that better hygiene practices significantly reduced the presence of antimicrobial-resistant bacteria in households. The findings emphasize the importance of combining efforts to enhance both antibiotic stewardship and hygiene conditions to combat antimicrobial resistance effectively [79].

5.7. SURVEILLANCE

Tracking resistance helps us fight infections. Studying how much antibiotics are used and how resistant pathogens are can help doctors choose the right treatment and develop new drugs. This kind of research needs to be well-organized to avoid wasting time and resources [80].

5.8. EDUCATION AND AWARENESS

Global health policy's main instruments for influencing public behaviour and combating antibiotic resistance are education and awareness-building [81]. Antibiotic resistance is a serious problem for everyone's health. To tackle it, we need to educate people of all ages about antibiotics and how to use them wisely. This can be done through fun and engaging activities like games, plays, and online learning [82].

5.9. ANTIBIOTICS USE IN ANIMALS

Antimicrobial-resistant bacteria can enter human populations through the environment and through the consumption of animal products [83]. Aquaculture also uses a lot of antibiotics. This can spread antibiotic resistance to other animals and humans because the antibiotics are not always fully metabolized by fish and can also get into the water [84]. New breakthroughs in vaccines and disease understanding offer ways to fight infections without relying heavily on antibiotics [85]. A number of feed products categorised as probiotics, prebiotics, or competitive exclusion cultures have also been used in food animals with varying success for pathogen reduction techniques [86].

5.10. NEED FOR NEW ANTIBIOTICS

Antibiotic resistance is a growing threat, with fewer new antibiotics being developed to replace ineffective ones [87]. Drug companies are doing less research on new antibiotics, even though antibiotic resistance is a growing problem. There are many reasons for this, including the high cost of developing new drugs and the difficulty of making money off them [88].

5.11. USE OF IMMUNO-ANTIBIOTICS

Strong evidence points to the interaction between antimicrobials and host immunity, which can enhance antibacterial activity and produce more rapid and comprehensive bactericidal effects. One emerging strategy to combat antibiotic resistance in bacteria is the use of immuno-antibiotics, a new class of antibiotics that target components of the biochemical resistance pathway, such as hydrogen sulphide and SOS response inhibition, as well as the biochemical underlying networks of bacteria [89]. Islam and Kumar's review suggests that enzymes in the riboflavin pathway, which is important for bacteria but not humans, could be new targets for antibiotics. Researchers are looking at the structure and function of these enzymes to design drugs that block them [90].

5.12. UNDERSTANDING RESISTANCE MECHANISMS FOR BETTER ANTIBIOTIC USE

Knowing both how bacteria resist antibiotics (phenotypes) and the specific genetic mutations behind that resistance will help clinicians regarding how they choose antibiotics in various circumstances [91].

5.13. ARTIFICIAL INTELLIGENCE

The field of science and engineering known as artificial intelligence (AI) is devoted to the computational comprehension of intelligent behaviour. Artificial Intelligence has enormous applications in many human professions, such as clinical diagnosis and prognosis [92]. A new paradigm in the fight against AMR is artificial intelligence (AI) [93]. AI may make it possible to accurately anticipate and recognise AMR in bacteria [94].

Machine learning shows promise in fighting antibiotic resistance (AMR) by analyzing large datasets. It can predict how bacteria will respond to antibiotics, design new antibiotics, and optimize treatment [95] (Figure 8).

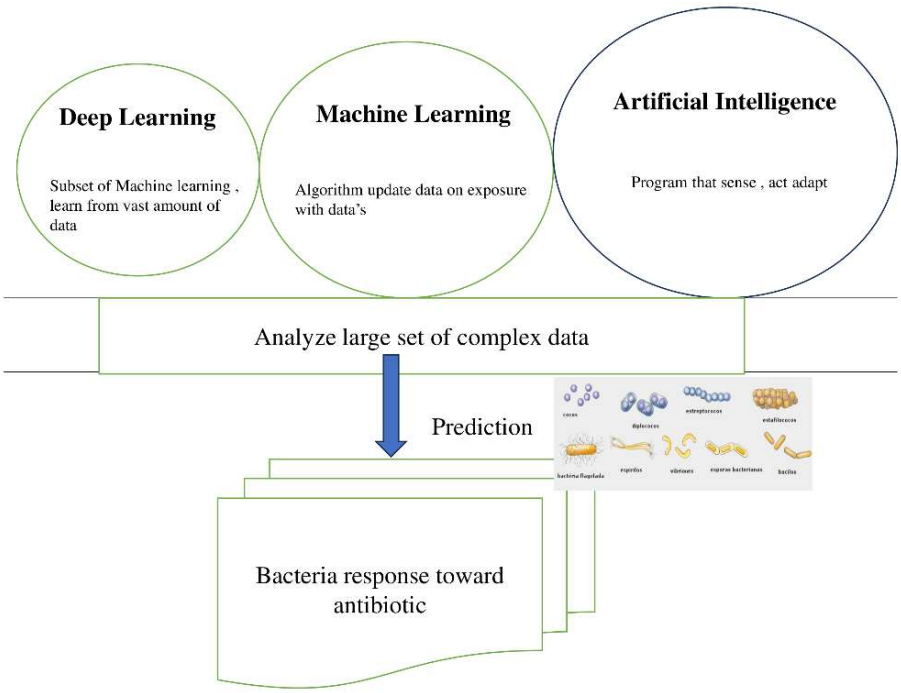


Figure 8. Artificial intelligence and AMR.

6. CONCLUSION

Antibiotics are compounds designed to target bacteria with the goal of treating and preventing bacterial illnesses [96]. Antibiotic-resistant bacteria have emerged as a result of the careless use of antibiotics in both people and animals [97]. Antimicrobial resistance (AMR) has become a persistent global public health issue, with an estimated 10 million deaths annually worldwide by 2050 [98]. Due to their resistance to specific antibiotics, the World Health Organisation (WHO) has designated ESKAPE pathogens *E. faecium, S. aureus, K. pneumoniae, A. baumannii, P. aeruginosa, and Enterobacter* spp. as the highest priority pathogens [99]. Antimicrobial-resistant bacteria infections have few therapeutic choices, leading to severe morbidity and mortality with a large financial cost [100]. In order to maintain the usage of current antibiotics and to gain a deeper understanding of resistance mechanisms, comprehending them is essential [101]. One of the most important strategies for combating AMR is the creation of novel antimicrobial agents. But when it comes to creating new strategies to tackle antimicrobial resistance (AMR), it seems that the scientific community is lagging behind due to the ability of multi-drug resistant (MDR) bacteria to evolve. There are multiple factors that contribute to antibiotic resistance. This review provides insights into those factors, including overuse and misuse of antibiotics, agricultural practices, and a slowdown in the development of new antibiotics; as well as strategies to combat AMR like implementing antimicrobial stewardship programs, conducting regular surveillance, artificial intelligence, and educating healthcare providers and the public about rational antibiotic use.

List of abbreviations

- AMR: Antimicrobial Resistance
- ESKAPE: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter* spp.

- MDR: Multidrug-Resistant
- MRSA: Methicillin-Resistant *Staphylococcus aureus*
- VRB: Vancomycin-Resistant Bacteria
- CRE: Carbapenem-Resistant Enterobacteriaceae
- PBPs: Penicillin-Binding Proteins
- SCCmec: Staphylococcal Cassette Chromosome mec
- UTI: Urinary Tract Infection
- FDA: Food and Drug Administration
- GLASS: Global Antimicrobial Resistance and Use Surveillance System
- GAS: Group A *Streptococcus*
- rRNA: Ribosomal Ribonucleic Acid
- CF: Cystic Fibrosis
- D Test: Disk Diffusion Inducible Resistance Test
- mcr: Mobilized Colistin Resistance
- ICMR: Indian Council of Medical Research
- AI: Artificial Intelligence
- AST: Antimicrobial Susceptibility Testing
- ASPs: Antimicrobial Stewardship Programs
- PAMS: Periodic Antibiotic Monitoring and Supervision
- GARP: Global Antibiotic Resistance Partnership

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