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Review Article

Antimicrobial Resistance: The Unfolding Pandemic

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Abstract

In 1928, Alexander Fleming accidentally discovered penicillin, which was followed by the subsequent work of Sir Howard Florey and Ernst Chain in the early 1940s. The golden age of infectious disease management had just begun, or so it was taught. However, this triumph was short-lived; within a few years, the first resistant organism was isolated. That initial resistance has snowballed, leading to an annual record of 35,000 deaths in the USA and a global death toll of 1.27 million in 2019. By 2050, the world may face an additional US$1 trillion in healthcare costs. Microbial organisms seem to be outpacing researchers; their intrinsic and acquired ability to evade drugs that once killed or inactivated them is alarming, placing global health institutions and scientists under immense pressure. The way forward requires a shift in approach. Timely and accurate diagnosis of AMR organisms is a critical component. Developing rapid diagnostic test kits will enable real-time infection control decisions to prevent community spread, while the continuous advancement of vaccines will foster herd immunity. Stricter policies to eliminate over-the-counter and unauthorized purchases of antimicrobial agents are necessary to mitigate this "unfolding pandemic." Furthermore, as antimicrobial use in agriculture rises globally, concerted efforts must be made to control this practice, as AMR organisms are evidently transferred from animals to humans. In conclusion, combining the social determinants of health with a biomedical approach is the best path forward; until all nations are protected, no nation is truly safe. Sustained advocacy regarding the dangers of antimicrobial abuse, alongside research into rapid diagnostic kits and vaccines, is essential to mitigate these growing threats.

1. Introduction

Over the years, several scientists have attempted to define antimicrobial resistance. In 2023, for example, the World Health Organization defined antimicrobial resistance (AMR) as the ability of microorganisms—including viruses, parasites, bacteria, and fungi—to resist the effects of antimicrobial agents that were once effective against them [1]. Furthermore, the United States Centers for Disease Control and Prevention asserted that AMR occurs when microorganisms acquire or develop mechanisms that allow them to survive exposure to antimicrobial agents intended to inhibit or destroy them, thereby rendering standard treatments ineffective and allowing infections to thrive [2]. This phenomenon makes standard treatments such as antibiotics, antivirals, antifungals, and antiparasitics ineffective, leading to recurrent infections that are often difficult or impossible to treat. The persistence of drug-resistant pathogens significantly intensifies the risk of transmission, increases morbidity and mortality rates, and contributes to a prolonged disease burden and disability [3].

The discovery of antibiotics is legendary; it emerged in 1928 from a laboratory at St. Mary's Hospital in London, operated by Alexander Fleming, a Scottish biologist and pharmacologist. His discovery was accidental yet revolutionary. While working with certain Staphylococcus variants, Fleming unintentionally left several culture media plates exposed on his workstation before going on vacation. These plates became contaminated with airborne microorganisms. Upon his return, he noticed that certain Staphylococcus colonies near a large mold contaminant

had turned transparent, suggesting bacterial cell death. Fascinated, Fleming isolated and cultured the mold due to its ability to produce a substance capable of inhibiting bacterial growth. The contaminant was eventually identified as a member of the genus Penicillium; the discovery was formally reported a year later. This fortuitous event marked the beginning of a golden age in microbiology and medicine, ultimately leading to the development of penicillin and ushering in an era of antibiotic therapy that continues to this day [4].

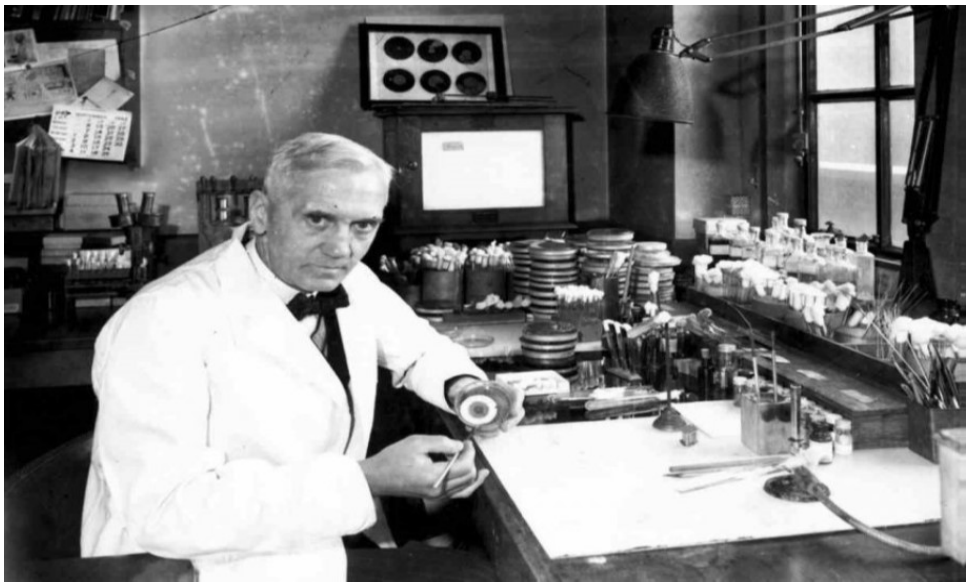

Figure 1: Alexander Fleming, shown working in his laboratory at St. Mary's Hospital in London, (https://www.britannica.com/biography/Alexander-Fleming) [5]

Despite Alexander Fleming's accidental discovery, it was not until the 1940s when two distinguished University of Oxford Scientists called, Ernst Boris Chain and Howard Florey, finally succeeded in the purification of penicillin, thereby transforming the 1928 discovery into an effective treatment therapy. This audacious milestone ushered in the "golden age" of antibiotic therapy, revolutionizing the practice of medicine and the management of infectious diseases, which, before then, were as simple as would infectious, often led to death. The use of antibiotic therapy has saved an immeasurable number of lives and has proven indispensable in many diseases that affects humans and animal existence at every given period of time [6].

The eventful discovery of the wonder drug "penicillin" got Alexander Fleming and the two University of Oxford scientists, Ernst Boris Chain and Howard Florey, the distinguished Nobel Prize in physiology or medicine. The acceptance speech of Fleming highlighted a rather scary future of the discovery of antibiotic therapy if not properly managed. He predicted that due to the ability of bacteria to evolve and adapt, in a few years, it could make this discovery ineffective if the penicillin is used arbitrarily. Unfortunately, after this prediction, the first case of antibiotic resistance was confirmed and documented in 1947. From then till date, antimicrobial resistance is more than a pandemic and has made the control of infectious disease nightmares to scientists and physicians alike [7].

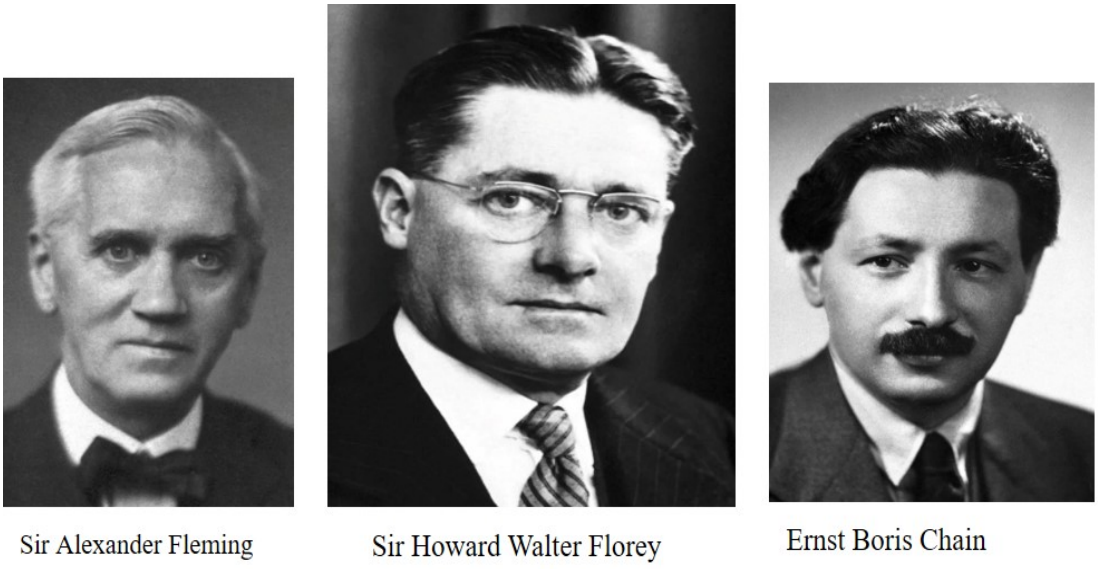

Figure 2: The Nobel Prize in Physiology or Medicine 1945 recipient. (https://www.nobelprize.org/prizes/medicine/1945/summary/) [8]

The unguarded usage of antibiotics is the primary driver of today's scientific dilemma, and this has led to the proliferation of antibiotic-resistant pathogens in both hospital and community settings [9]. Antimicrobial resistance (AMR) impacts nations of the world irrespective of economic stability; however, research has shown that countries with huge poverty deprivation are at greater risk due to a lack of effective

legislation, research, or implementation strategies on the use and distribution of antimicrobial substances. The greatest undoing caused by AMR is its ability to undermine years of medical progress by increasing mortality rate in post medical interventions, as seen in caesarean sections, general surgeries, transplant, cancer therapy, to name a few due to secondary infections without effective antibiotics to treat or manage them. The continuous proliferation of resistant microbes has created both an antibiotics pipeline and an access crisis, characterized by insufficient or a lack of research and development efforts in the face of ever-increasing resistance, which is juxtaposed with a lack of equity in access to novel and existing vaccines, diagnosis, and antimicrobial treatment [10].

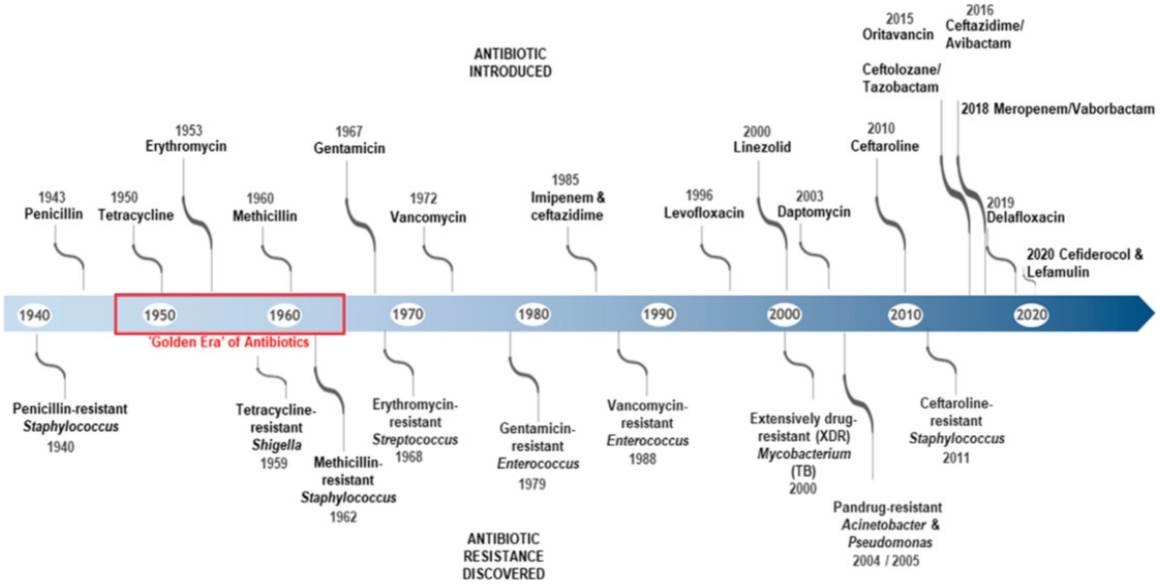

Figure 3: A chronological overview highlighting major milestones in antibiotic discovery (CDC, 2013)

2. Epidemiology and Global Burden

Fletcher asserted that the ever-growing application of antibiotics in agricultural practices, as evident in both plant and meat production, has further exacerbated the global burden of AMR [11]. Documented evidence has proven that many nations, including the United States, have introduced over the years more than 69% of approved antibiotics for humans to veterinary care [12]. Several international bodies mandated to fight this rising treat such as the World Health Organization (WHO), the United Nations (UN), and the European Union (EU), on the overwhelming application of antibiotics in food production, have succeeded in putting control measures in place. The policies emanated from these international bodies are aimed at restricting certain usage of antimicrobial therapy in livestock production and pet care. Even though much progress has been made in developed countries, more needs to be done in terms of awareness and implementation in developing countries to achieve the intended level of antimicrobial stewardship. The ability for organizations and individuals alike to implement these restrictions will do much good in the fight against AMR, as researchers have traced resistant pathogens to be transferred from animals to humans [13].

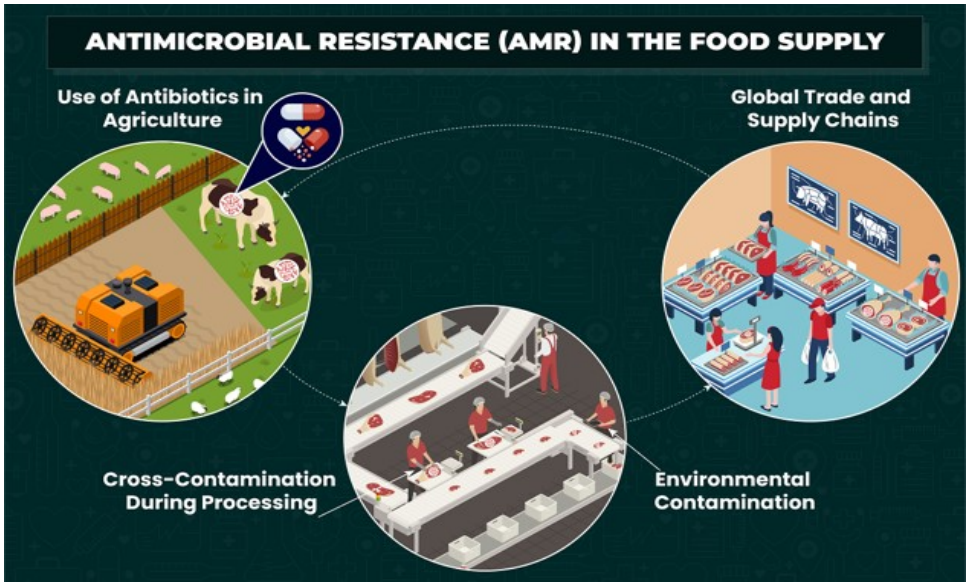

Figure 4: AMR resistance in Food and Supply Chain (https://smartfoodsafe.com/combatting-antimicrobial-resistance-in-food-supply) [14]

AMR has transcended clinical impacts; it has now affected the global economy and social expenses on a large scale. In 2019 alone, the WHO asserted that approximately 1.27 million deaths have been directly linked to AMR, while nearly 4.95 million deaths have been somewhat linked with the AMR pandemic [1]. In the United States, the Centers for Disease Control and Prevention (CDC) reports more than 2.8 million antimicrobial-resistant infections annually, resulting in over 35,000 deaths and placing a heavy burden on the healthcare system [15]. The World Bank projections are rather alarming; it has been estimated that by 2050, AMR may cost the world an additional US$1 trillion in overall healthcare costs. Furthermore, the World Bank in its wisdom has also predicted that between US$1 trillion and US$3.4 trillion will be lost in annual global GDP BY 2030. The predicted impact of AMR in the United States is worth paying attention to, as it has been estimated that AMR infections may cost over US$4.6 billion in direct medical costs annually, while the Council of Economic Advisers pitched the overall national cost as approximately $55 billion, including US$20 billion in healthcare expenditures and US$35 billion in productivity losses due to illness and sudden deaths [16].

3. Clinical Interpretation of AMR

In an attempt to improve a unanimous pattern for the interpretation of AMR, it has become imperative for medical laboratories globally to adopt a standardize reporting metrics of antimicrobial susceptibility testing. Global organizations such as the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the Clinical and Laboratory Standards Institute (CLSI) are taking the lead [17, 18]. As part of global surveillance, countries are mandated to report AMR to WHO and an Approximately, 94% of reporting countries adopt these guidelines from EUCAST and CLSI. EUCAST standards are primarily adopted across Europe, whereas CLSI guidelines serve as the prevailing reference standard in laboratories in the United States. Both EUCAST and CLSI methodologies are officially recognized and adopted within the WHO's Global Antimicrobial Resistance Surveillance System [1].

According to EUCAST (2019), the standard of reporting antimicrobial susceptibility testing is classified as follows:

- **R – Resistant:** A high probability exists that treatment will fail.
- **S – Susceptible, standard dosing regimen:** Treatment is likely to be successful when the drug is administered using the usual dosage criteria.
- **I – Susceptible, increased exposure:** Successful treatment is expected, but only if the drug exposure is enhanced, for example, by increasing the dose or achieving higher concentrations at the infection site through the route of drug administration.

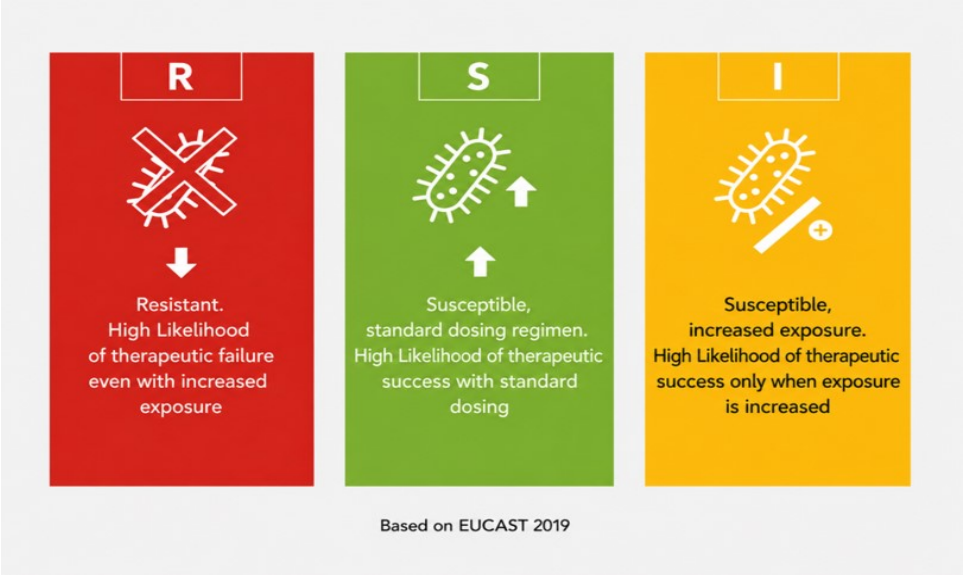

Figure 5: Diagrammatic representation of antibiotic Susceptibility Interpretations [17]

Before 2019, antimicrobial susceptibility testing was broadly categorized into two groups: resistant (R) and susceptible (S). Then, EUCAST, after much research, introduced the third prong of antibiotic reporting "I," which is another form of susceptibility, thereby redefining the S, R method (EUCAST, 2019). This new framework redefined the antibiotic reporting method that once had two resistance-associated categories (I and R) and one susceptible category (S), to the current metrics that have two susceptibility categories (I, S) and one resistant category (R). This updated context has its basis on the correlation of antimicrobial bioavailability to actualizing therapeutic outcomes through certain criteria, such as the drug dosage, route of administration, dosing intervals, infusion time, and the distribution and elimination of the antimicrobial agent at the localized infection point [19].

4. Emergence of Bacterial Resistance

Research has shown variations in bacteria of the same species. This greatly impacts the pharmacodynamics and pharmacokinetics of drugs on bacteria cell, making treatment relatively difficult, because not one bacteria management has same prescription or dosage, which poses challenges in the treatment and management of infectious diseases [20]. The EUCAST and CLSI standard of susceptibility evaluation is based on the principle of minimum inhibitory concentration (MIC). MIC is defined as the minimum or lowest concentration of antimicrobial agents that will impede or annihilate bacterial growth. Furthermore, to calculate the MIC of any given bacterial strain, a distribution of the

average MIC values of each species is collected. When this average MIC falls within the resistant range, it is concluded that an intrinsic resistance to the drug is present. Intrinsic resistance of bacteria to a drug is achieved by the inherent capabilities of the bacteria to evade the pharmacokinetics of any given drug without external influences. These intrinsic components are usually achieved from the structural makeup, or inherent characteristics of the overall lifestyle of the bacterial species [21].

Lambert and Pearson asserted that while intrinsic resistance is well known, bacteria can also evade antimicrobial agents through an acquired resistance mechanism. Transfer of genes from one bacterium to another, or mutation of the genetic components of bacteria, is the pathway through which acquired resistance is achieved. Furthermore, the degree of acquired resistance is directly proportional to the number of resistant genes involved and the strain of the bacteria [22, 23]. Altogether, the resistance of bacteria to antimicrobial agents may be naturally occurring (Intrinsic) or acquired due to mutations in endogenous genes or an exogenous gene incorporation.

5. Natural Resistance

Cox & Wright (2013) asserted that microbial organisms may exhibit intrinsic (natural) resistance to certain antibiotics, that is, they can grow and multiply even at the highest concentrations that are therapeutically achievable in the human body [24]. This type of resistance characteristic is not impacted by prior exposure to the drug and is typically determined by inherent structural or functional characteristics of the organism. For example, anaerobic bacteria lack the transport systems required for aminoglycoside uptake, while mycoplasmas, which lack a cell wall, are naturally resistant to β-lactam antibiotics that target cell wall synthesis [25]. Furthermore, the outer membrane of a Gram-negative bacterium is structurally designed to act as a selective barrier to antimicrobial penetration; therefore, glycopeptides (e.g., vancomycin, teicoplanin), which are relatively large molecules, cannot pass through this membrane, rendering these organisms intrinsically resistant. Similarly, penicillin G, rifampicin, macrolides, and several other antimicrobial agents have limited ability to penetrate the outer membrane of enteric Gram-negative bacteria like Escherichia coli [26, 27]. The combination of structural Impenetrability and the acquisition of efflux pump mechanisms and β-lactamase production contributes immensely to the inherent resistance documented in organisms such as *Pseudomonas aeruginosa, Enterobacter cloacae*, and *Klebsiella* species [25].

In addition, natural resistance is encoded in the genetic components of bacteria cell. For example, Gram-negative bacteria possess a chromosomal β-lactamases, which renders the antimicrobial agent inactive. Some bacteria, including *Streptomyces*, are inherently resistant to the antibiotics they produce, serving as a self-protection mechanism. Additionally, resistance genes are rather an ancient evolution, as it has been documented even before the 1928 discovery of penicillin by Alexander Fleming [28–30]. Furthermore, it is imperative to note that not one single resistant mechanism is responsible for microbial resistance, but a combination of factors such as the structural makeup with certain adaptive genes, which makes microbial resistance not universal. It is also well documented that several bacteria, such as enterococci, are usually easily identified based on their resistance to a specific antimicrobial drug [21, 31].

Table 1: Intrinsic antimicrobial resistance patterns among clinically important bacterial pathogens and major taxonomic groups [32–34].

ORGANISM / GROUP	INTRINSIC RESISTANCE PHENOTYPE (TYPICAL AGENTS INEFFECTIVE)	KEY BASIS OF RESISTANCE
KLEBSIELLA PNEUMONIAE	Aminopenicillins (ampicillin)	Chromosomal β-lactamase production
ENTEROCOCCUS SPP.	Cephalosporins; low-level aminoglycoside activity; lincosamides	Low-affinity PBPs; reduced drug uptake
BACTEROIDES SPP. (ANAEROBES)	Aminoglycosides; reduced susceptibility to many β-lactams and quinolones	Anaerobic metabolism limits drug uptake; enzymatic inactivation; permeability barriers
LISTERIA MONOCYTOGENES	Cephalosporins	Altered penicillin-binding proteins
ESCHERICHIA COL I (ENTEROBACTERALES)	Macrolides	Outer membrane permeability restriction
SERRATIA MARCESCENS	Aminopenicillins; macrolides	Inducible β-lactamases; permeability barriers
PSEUDOMONAS AERUGINOSA	Aminopenicillins, early-generation cephalosporins, tetracyclines, chloramphenicol, sulfonamides	Efflux pumps; low outer membrane permeability
STENOTROPHOMONAS MALTOPHILIA	Carbapenems, most β-lactams, aminoglycosides, fluoroquinolones	Intrinsic β-lactamases; efflux mechanisms
ACINETOBACTER SPP.	Aminopenicillins; reduced susceptibility to multiple classes	Outer membrane impermeability; efflux systems
GRAM-NEGATIVE BACTERIA (GENERAL)	Glycopeptides (e.g., vancomycin), lipopeptides	Outer membrane barrier prevents entry
GRAM-POSITIVE BACTERIA (GENERAL)	Aztreonam	Lack of effective target penetration

6. Acquired Resistance

Horizontal gene transfer (HGT) mechanisms are the pathways through which bacteria acquires resistant, which is usually through transformation, transduction, and conjugation, as well as through spontaneous chromosomal mutations [32, 35]. The modifications of the genetic

component of a microbial organism may be transient or stably incorporated into the bacterial genome. While there are several HGT pathways, plasmid-mediated conjugation is the most frequent mechanism for acquiring external resistance determinants; bacteriophage-mediated transduction occurs less commonly. Researchers have also discovered that Certain organisms, such as *Acinetobacter* spp., have the intrinsic abilities to directly adopt and incorporate extracellular DNA from the environment [35, 36]. Mobile genetic elements, including insertion sequences and integrons, are also incorporated within bacterial genetic makeup, which helps to facilitate rearrangement and dissemination of resistance genes. In addition, natural causes such as nutrient deprivation, exposure to chemical and ultraviolet radiation, can further enhance mutation rates, resulting in substitutions, insertions, or deletions in chromosomal DNA. Researchers and scientists alike have documented that bacteria can spontaneously mutate as fast as 10^{-6} to 10^{-9} per cell division [37].

There are several complex ways bacteria usually evade antimicrobial agents, such as mutations that typically impact the genes encoding antibiotic targets, the use of membrane transport systems (including efflux pumps), the application of regulatory elements controlling expression of resistance mechanisms, or enzymes that modify or degrade antimicrobial agents [37, 38]. However, resistance acquisition is often associated with a biological cost that may include a reduced replication efficiency; *Staphylococcus aureus* that is resistant to methicillin (MRSA) may demonstrate a growth pace that is slow compared to relatively susceptible strains [32]. The major dilemma among researchers and scientists alike is that the more the antimicrobial usage, the faster resistance occurs. Even if the dosage is sub-inhibitory, there is still a greater tendency for resistant subgroups. This further increases the emergence of hypermutator phenotypes, enhances the acquisition of additional resistance traits, and promotes the mobilization of genetic elements that facilitate further dissemination of resistance [39].

Table 2: Acquired antimicrobial resistance patterns among clinically important bacterial pathogens and major taxonomic groups [37, 38] [32, 37, 38]

Organism	Acquired resistance mechanism(s)	Resistant phenotype (examples)
Staphylococcus aureus (MRSA)	mecA gene (PBP2a production via SCCmec element)	Resistance to all β-lactams except ceftaroline/ceftobiprole
Enterococcus faecium (VRE)	vanA/vanB genes (cell wall target alteration)	Vancomycin resistance
Streptococcus pneumoniae	Altered PBPs via recombination	Penicillin and cephalosporin resistance
Escherichia coli	ESBLs (CTX-M, TEM, SHV), carbapenemases (KPC, NDM)	Resistance to penicillins, cephalosporins, carbapenems
Klebsiella pneumoniae	ESBLs, carbapenemases (KPC, OXA-48, NDM)	Multidrug resistance including carbapenem resistance
Pseudomonas aeruginosa	Efflux pump overexpression, AmpC derepression, porin loss	Carbapenem and fluoroquinolone resistance
Acinetobacter baumannii	OXA-type carbapenemases, efflux pumps	Extensive carbapenem resistance
Neisseria gonorrhoeae	β-lactamases, penA mosaic genes	Penicillin and cephalosporin resistance
Salmonella enterica (Typhi/Non-typhi)	Plasmid-mediated resistance genes	Multidrug resistance (ampicillin, TMP-SMX, chloramphenicol)
Mycobacterium tuberculosis	Target gene mutations (rpoB, katG, inhA)	Rifampicin and isoniazid resistance (MDR-TB)
Helicobacter pylori	23S rRNA mutations, gyrA mutations	Clarithromycin and fluoroquinolone resistance

7. Mechanisms of Antimicrobial Resistance

7.1. Reduced intracellular accumulation of antibiotics

The abilities of microbes to reduce uptake of antimicrobial agents into their cells or ejection of antimicrobial drugs through their efflux pumps play a major role in antimicrobial resistance. These changes are usually embedded in the structural makeup of the cellular structure of both Gram-positive and Gram-negative bacteria [40]. Hydrophilic antibiotics, which include β-lactams and fluoroquinolones, usually penetrate Gram-negative bacteria primarily via porin channels located in the outer membrane. The functions of these channels are to facilitate the passive diffusion of small molecules. Therefore, a reduction in porin expression or functional alteration significantly decreases antibiotic entry, resulting in reduced intracellular bioavailability of drugs, leading to a diminished pharmacokinetic ability of antimicrobial agents, as seen in the naturally endowed low outer membrane permeability of *Pseudomonas aeruginosa*. This contributes immensely to the multidrug resistance (MDR) [41].

7.2. Efflux pump–mediated resistance

To actively export antimicrobial agents and ensure sub-inhibitory concentrations are not achieved within its intracellular space, bacteria have a membrane-mediated transport system, structurally located in the cytoplasm, called an efflux pump [38]. Unlike porins, which control influx, efflux pumps directly counteract intracellular drug possessions. The efflux systems are highly efficient and can prevent antimicrobial agents from reaching their target units. Although polymyxins, a last resort antibiotic for treating multidrug resistant organism such as *Pseudomonas aeruginosa*, are relatively unaffected for now, most antibiotic classes are usually susceptible. Efflux pumps exhibit broad substrate specificity and contribute to resistance against structurally diverse agents, such as macrolides, tetracyclines, and fluoroquinolones [40, 42]. In summary, the efflux pump is a major culprit in the multidrug resistance of clinically important pathogens.

7.3. Modification of antibiotic target sites

The most frequent ways bacteria confer resistance are the ability to undergo spontaneous structural modification to change their specific targets and reduce the binding affinity, thereby invalidating antimicrobial agents. These modifications are traceable to mutations that occur in the chromosome or acquired genetic variation [21, 43].

7.4. Ribosomal modification

Bacterial alterations in the 30S or 50S ribosomal subunits confer resistance to protein synthesis. For example, Aminoglycosides bind to the 30S subunit, while macrolides, lincosamides, chloramphenicol, and streptogramin B target the 50S subunit, so that once there are modifications in these ribosomal components, the resultant effects will be a reduction in the binding abilities of the antimicrobial agent to the target cells and inhibition of translation [44, 45].

7.5. Penicillin-binding protein modification

While Gram-negative bacteria rely heavily on the production of β-lactamase to evade antimicrobial agents, Gram-positive bacteria such as *Streptococcus pneumoniae* and *Enterococcus faecium* that are resistant to penicillin rely on the alteration of their penicillin-binding protein sites. An alteration in PBP genes reduces binding affinity for β-lactam antibiotics [46]. Methicillin-resistant *Staphylococcus aureus* (MRSA), is mediated by acquisition of the staphylococcal cassette chromosome mec (SCCmec), which carries the mecA gene encoding PBP2a, a low-affinity penicillin-binding protein. This gene is primarily responsible for methicillin resistance and often results in cross-resistance to multiple β-lactams and other antimicrobial classes [47].

7.6. Alteration of cell wall precursors

Vancomycin, a glycopeptide, usually inhibits peptidoglycan synthesis by binding to the D-Ala–D-Ala terminus of cell wall precursors. For resistance to occur, the D-Ala–D-Ala terminus of cell wall precursors is replaced by D-Ala–D-Lac, significantly reducing binding affinity and preventing inhibition of cell wall cross-linking. Vancomycin-resistant enterococci (VRE) use this to prevent lysis. High-level resistance to vancomycin and teicoplanin is conferred by the VanA phenotype, whereas VanB and VanC phenotypes confer resistance to vancomycin while retaining susceptibility to teicoplanin [48].

7.7. Target enzyme mutations

The mutation of DNA gyrase and topoisomerase IV results in the resistance of fluoroquinolone, which is encoded by *gyrA, gyrB, parC,* and *pare* which are enzymes that are essential for DNA replication. When mutations occur, particularly in *gyrA* and *parC*, there is a reduction in the fluoroquinolone binding and an impairment in the inhibition of DNA synthesis. Mutations in RNA polymerase (*rpoB*), conferring rifampicin resistance, and Ribosomal protection proteins conferring tetracycline resistance are also examples of target-based resistance mechanisms [33].

7.8. Enzymatic inactivation of antibiotics

Bacteria can also confer resistance to antimicrobial agents by enzyme modification or degradation of antimicrobial agents. Major enzyme systems include β-lactamases, aminoglycoside-modifying enzymes, and chloramphenicol acetyltransferases [49].

7.9. β-lactamases

The enzyme, β-lactamases, breaks down the β-lactam ring, inactivating penicillin, cephalosporins, monobactams, and carbapenems. These enzymes are classified using the Ambler system of distributing β-lactamase enzymes into four molecular classes (A, B, C, and D):

- **Class A:** Serine β-lactamases (e.g., TEM-1, SHV-1), precursors of ESBLs that break down extended-spectrum cephalosporins but remain inhibitor-sensitive.
- **Class B:** Metallo-β-lactamases (e.g., NDM), zinc-dependent enzymes that hydrolyze nearly all β-lactams, including carbapenems.
- **Class C:** AmpC cephalosporinases with resistance to clavulanate inhibition.
- **Class D:** OXA-type enzymes conferring resistance to penicillin and related agents [42, 50, 51].

7.10. Aminoglycoside-modifying enzymes

Bacteria resistant to aminoglycosides are mediated by acetyltransferases, phosphotransferases, and nucleotidyltransferases, which chemically modify the drug and reduce its affinity to the 30S ribosomal subunit drug target sites. Both Gram-positive and Gram-negative pathogens possess these enzymes, which contribute immensely to multidrug resistance profiles [52].

7.11. Chloramphenicol acetyltransferase

Gram-positive and Gram-negative bacteria, including *Haemophilus influenzae*, that are resistant to Chloramphenicol antimicrobial agents are mediated by chloramphenicol acetyltransferase (CAT). This enzyme acetylates hydroxyl groups on chloramphenicol, which in turn prevents binding to the 50S ribosomal subunit and thereby invalidates its bactericidal activities [53].

7.12. Impact of Vaccination on Antimicrobial Resistance

Over the years, vaccines have helped with the prevention and mitigation of various infectious and non-infectious diseases. When vaccines, such as those meant to prevent infections from *Streptococcus pneumoniae, Haemophilus influenzae,* and *Neisseria*, to mention but a few, are effective, it means that the likelihood of infection from these organisms is reduced, leading to antibiotics not being administered for these infections. It is already an established fact that the more antibiotics are administered, the greater the likelihood of developing resistance to once-effective antimicrobial agents. Furthermore, researchers have discovered that viral vaccines, such as those meant for the influenza virus, may help to mitigate symptoms and other secondary complications, such as otitis media and pneumonia [54]. When these secondary infections are prevented or their symptoms reduced, vaccination indirectly decreases or prevents the prescription of antimicrobial agents.

Two principal mechanisms explain how even moderately effective seasonal influenza vaccines can reduce antibiotic use. First, when primary infections are prevented, this reduces the likelihood of secondary bacterial infections, thereby leading to a substantial reduction in antibiotic therapy. A major study conducted in Turkey discovered an approximate 50.9% decline in acute otitis media among children, which suggests a corresponding decline in antibiotic administration among vaccinated populations [55]. In addition, another study conducted in North America, specifically Canada, supports this evidence. Following the universal influenza immunization program in Ontario, antibiotic prescriptions to manage influenza and its secondary symptoms were markedly reduced by about 64% compared with provinces in Canada where vaccination was restricted to high-risk groups such as the elderly, immunocompromised patients, and children [56]. Adequate vaccination programs can also reduce the misuse or overuse of antibiotic therapy for viral-related infections, because a significant amount of antibiotics is administered to treat viral diseases such as influenza and respiratory syncytial virus (RSV), against which these drugs are ineffective. Even developed countries suffer from such incorrect prescriptions. For example, in the United States, it is estimated that nearly 50% of antibiotic prescriptions are unnecessary, particularly in the management of respiratory tract infections [57].

8. Role of Clinical Microbiology and Strategies for Reducing Antimicrobial Resistance

The importance of Clinical microbiology laboratories in addressing AMR, both local and international, can never be overemphasized. Diagnosis remains the bedrock of modern medicine. Clinical laboratory scientist, researchers, and pathologist has worked in synergies over the years to collect susceptibility data for surveillance purposes and monitoring trends in resistance patterns, these data helps to drive policies by local and international health organizations such as World Health Organization, Centers for Disease Control, the Nigeria Centers for Disease Control (NCDC), the UK Health Security Agency (UKHSA), EUCAST etc, secondly, the Clinical laboratories provides timely and accurate antibiotics susceptibility testing on clinical samples to assist healthcare providers to make real time informed prescription decisions [19, 58].

Table 3: Antimicrobial resistance (AMR) reduction strategies and associated outcomes [1, 15, 59–61]

AMR Theme	Description	Outcome / Impact
Global and National Action Plans	International frameworks, led by organizations such as WHO, aimed at mitigating the emergence and spread of AMR	Many countries have implemented national AMR strategies, with some progressing to updated multi-phase action plans
AMR Surveillance Systems	Coordinated programs (e.g., GLASS, NARMS, EARS-Net, SMART) that collect antimicrobial susceptibility data from human, animal, and environmental sources	Enables monitoring of resistance trends across time and geography; informs public health policies and intervention strategies
Diagnostic Advancements	Development of phenotypic and molecular diagnostic tools for detecting resistant organisms and resistance genes	Improved clinical management through rapid, accurate detection; supports real-time surveillance and targeted therapy
Public Health Awareness Initiatives	Global and national campaigns (e.g., World Antimicrobial Awareness Week, CDC and BSAC initiatives) to promote responsible antimicrobial use	Increased awareness among healthcare professionals, policymakers, and the public; improved antimicrobial literacy
Antimicrobial Stewardship Programs	Coordinated healthcare strategies promoting appropriate antimicrobial use, including guideline development and multidisciplinary oversight	Optimized antibiotic prescribing, reduced misuse, and preserved antimicrobial efficacy
Veterinary and Agricultural Stewardship	Policies regulating antimicrobial use in animal health and agriculture (e.g., NOAH, RUMA initiatives)	Reduction in non-human antimicrobial misuse contributes to limiting resistance transmission across sectors

9. Conclusion

Addressing this escalating crisis requires a multifaceted approach; all hands must be on deck, as thousands of lives are lost daily to this pandemic. Government and health officials must implement stricter measures to prevent the underuse, misuse, and overuse of antimicrobial agents. There must be a juxtaposition of social determinants of health and a biomedical approach to fight this menace. If social amenities are

improved, especially the provision of clean water, good sewage systems, and proper food processing facilities, the likelihood of microbial infection will be reduced drastically; when people are healthy, there will not be a need for antimicrobial prescriptions. The most disturbing aspect of AMR is that resistant organisms have been isolated in public facilities, such as door handles [62] and currency notes [63]. Proper awareness campaigns to educate the public on how to mitigate possible infection should be implemented. There must be intensified research and development of rapid diagnostic test kits for real-time bedside testing; vaccines and therapeutic agents must also be consistently researched, otherwise, the milestones achieved in modern medicine will be ridiculed.

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