Next Generation Antibiotics for Combating Antimicrobial Resistance

P. Sowmya[1], P. Ruchitha[2], P. Ashwini [3], P. Varshini[4], P. Satish[5], Dr. S. Sridhar [6]
[1,2,3,4,5] *B Pharmacy, Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, Secunderabad, Medchal District, Hyderabad 500100.*
[6] *Professor, Department of Chemistry, Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, Secunderabad, Medchal District, Hyderabad 500100.*

Abstract—**A major global health concern, antimicrobial resistance (AMR) is caused by the overuse and abuse of antibiotics in numerous fields, which results in the growth of resistant microorganisms. This serious public health concern jeopardizes our capacity to treat common infections. Current antibiotics are ineffective against many diseases due to antimicrobial resistance, which is a serious danger to world health. It is especially common in underdeveloped nations where infectious diseases are still prominent, antibiotic usage is widespread in both humans and animals, and switching from older to newer antibiotics is difficult because of their high cost. The pressing demand for new antibiotics has not been met by conventional bioactivity-guided natural product discovery, mostly because of high rediscovery rates and scarce resources. By the year 2050, antimicrobial resistance (AMR) is expected to cause 10 million deaths annually worldwide, making it a chronic public health concern. AMR happens when bacteria, fungi, viruses, and parasites do not react to antimicrobial treatments in both humans and animals, allowing the microorganism to survive inside the host. The overuse and misuse of antibiotics, especially their improper use, is still the key factor causing the current crisis and adding to the worldwide burden of antimicrobial resistance. The developments in next-generation antibiotics, their modes of action, and their potential to fight AMR are highlighted in this research. Developmental problems and new therapeutic approaches are also covered.**

Index Terms—**Antibiotic, Anti-microbial Resistance, Drug, Enzymes, Treatment, WHO.**

I. INTRODUCTION

The ability of microorganisms such as bacteria, fungi, and viruses to resist antimicrobial agents is known as antimicrobial resistance (AMR). AMR has led to illnesses that are more difficult to treat, resulting in longer hospital stays, greater medical expenses, and higher mortality rates. Among the greatest medical advances of the 20th century are antibiotics. Several lives are suffering from pathogenic illnesses have been saved thanks to their improvement in the clinical field, which has entirely altered the way infectious diseases are treated. High rates of morbidity and mortality from mild illnesses were noted in the pre-antibiotic era [1]. The discovery of antimicrobials, which let humanity survive the devastating impact of microbial illnesses, was then made conceivable by the brilliant brains of Sir Alexander Fleming and Paul Ehrlich [2].

A comprehensive examination of 23 microorganisms and 88 pathogen–drug combinations across 204 countries and territories was conducted in 2019. The analysis covered 471 million individual isolates or records and 7585 study–location–year combinations. According to the data, bacterial antibiotic resistance was directly responsible for 1.27 million (0.911–1.71 million) of the 4.95 million (95% CI 3.62–6.57 million) deaths that occurred in 2019 [3]. Due to antimicrobial-resistant bacteria, the World Health Organization (WHO) has already predicted that yearly healthcare expenditures will increase by 1.2 trillion USD by 2050, reducing the global GDP by 1.1% to 3.8% (CDC, 2020) [4]. According to a two-year study that the UK government commissioned and finished in 2016, 7,00,000 deaths occur in every year [5].

II. EPIDEMIOLOGY of AMR:

Alexander Fleming has been concerned about the possibility of resistance developing if therapy is administered for insufficiently long since the 1950s, when the "golden era" of antibiotics started [6]. It is estimated that 70% of the antibiotics used in human

medicine in the United States can also be used in veterinary medicine [7]. A number of organizations, including the World Health Organization (WHO), the United Nations (UN), and the European Union (EU), have taken action to reduce and restrict the use of antibiotics in animals in recognition of their high usage in global agriculture. These actions include enacting laws that prohibit the use of specific antibiotics in agrifood systems for the purpose of promoting growth and encouraging antimicrobial stewardship initiatives in the treatment of food animals and small domestic companion animals. Implementing such rules could be challenging, especially in emerging nations where the demand for animals for food keeps growing yearly [8]. 35% of participants thought that antibiotics might be used to treat viral infections, while 83% of people acknowledged that they could be used to treat bacteria. Since the 2014 poll, these findings have improved, demonstrating that the UK public is now better informed and educated about antibiotics [9]. In contrast, 49% of respondents to a survey conducted in India stated that antibiotics may be used to treat viral diseases, and 45% stated that they use them to treat colds [10]. India was consequently said to have one of the highest rates of infectious diseases, especially those brought on by viruses that are resistant to several drugs [11].

III. ORIGIN OF RESISTANCE:

It is frequently the case that bacteria as a species or group are equally susceptible as well as resistant to any given antimicrobial agent. Even among related bacterial families, the degree of resistance might differ significantly. The minimum inhibitory concentration (MIC), or the lowest concentration of a medicine that will stop the growth of bacteria, is typically used to test susceptibility and resistance. In reality, the susceptibility is a range of the average minimum inhibitory concentrations (MICs) for a particular medicine within the same species of bacteria. A species is deemed to have intrinsic resistance to a medicine if its average MIC falls within the resistant portion of the range. The degree of resistance will differ based on the species and the genes gained, and bacteria may also pick up resistance genes from other related organisms [12,13].

1.Natural resistance

There are two types of natural resistance: induced (the genes are naturally present in the bacterium but only express to resistant levels after exposure to an antibiotic) and intrinsic (always expressed in the species). A characteristic that is common to all members of a bacterial species, unrelated to horizontal gene transfer, and unaffected by prior antibiotic exposure is known as intrinsic resistance. [13,14]. Reduced permeability of the outer membrane (most especially, the lipopolysaccharide, or LPS, in gram negative bacteria) and the spontaneous functioning of efflux pumps are the most prevalent bacterial mechanisms underlying intrinsic resistance. Another typical method of induced resistance is multidrug-efflux pumps [14,15].

2.Acquired resistance

All three of the primary ways that bacteria can acquire genetic material that confers resistance—transposition, conjugation, and transformation—collectively referred to as horizontal gene transfer, or HGT. In addition, the bacteria may undergo mutations to its own chromosomal DNA. The purchase could be either short-term or long-term. The most frequent method of acquiring external genetic material is by plasmid-mediated transmission of resistance genes; bacteriophage-borne transmission is rather uncommon. Because they are natively competent, some bacteria, like Acinetobacter species, can directly absorb genetic material from their surroundings. Genetic material may be moved internally by integrins and insertion sequences, while genetic changes (substitutions, deletions, etc.) are frequently brought on by stresses like as chemicals, UV light, and hunger. An average of one mutation occurs in bacteria for every 106 to 109 cell divisions, and the majority of these alterations are harmful to the cell [12,16].

IV. MECHANISM OF ANTIMICROBIAL RESISTANCE:

The four primary categories of antimicrobial resistance mechanisms are: (1) restricting medication uptake; (2) altering a drug target; (3) rendering a drug inactive; and (4) active drug efflux. Limiting uptake, drug inactivation, and drug efflux are examples of intrinsic resistance mechanisms; drug target alteration, drug inactivation, and drug efflux are examples of acquired resistance mechanisms. Gram negative and

gram-positive bacteria employ different kinds of processes due to structural variations, among other factors. Gram positive bacteria lack the ability to use some drug efflux mechanisms and are less likely to limit drug uptake due to their lack of an outer membrane made of LPS, while gram negative bacteria use all four major mechanisms [17,18].

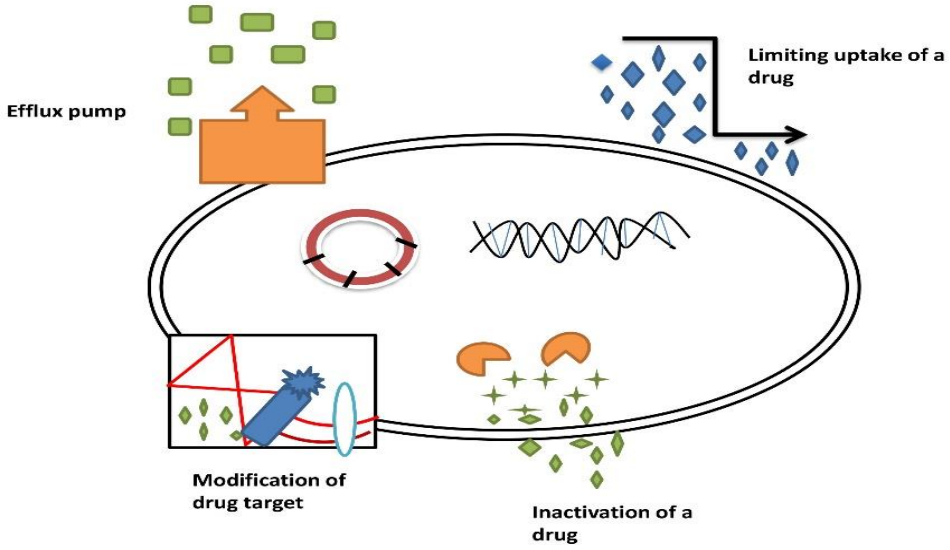

Figure:1 General Anti-Microbial Resistance Mechanism

1.Limiting drug uptake:

Bacteria differ naturally in their capacity to restrict the absorption of antimicrobial drugs. Gram-negative bacteria's LPS layer's composition and properties operate as a barrier to specific kinds of chemicals [19]. As a result, certain bacteria are naturally resistant to specific classes of potent antimicrobial medicines. Because of the high lipid content of the mycobacteria's outer membrane, hydrophobic medications—like rifampicin and fluoroquinolones—had better access to the cell, but hydrophilic medications have less [20,21].

2.Modification of drug targets:

Many parts of the bacterial cell might be targets for antimicrobial treatments, and the bacteria could alter many of those targets to make them resistant to the medications. Changes in the number and/or structure of PBPs (penicillin-binding proteins) are one way that gram-positive bacteria can develop resistance to the β-lactam antibiotics that they almost exclusively employ. PBPs are transpeptidases that aid in the cell wall's peptidoglycan synthesis. The amount of drug that can bind to that target is affected by changes in the number of PBPs (either a drop in PBPs with normal drug binding or an increase in PBPs with a decrease in drug binding ability). A structural alteration (such as PBP2a in S. aureus due to the acquisition of the mecA gene) may reduce or completely prevent drug binding [22,23].

3.Drug inactivation:

Bacteria can inactivate medications in two major ways: either by physically breaking down the drug or by adding a chemical group to it. The β-lactamases are a broad class of enzymes that hydrolyze drugs. Tetracycline is another medication that can be hydrolyzed to inactivate it through the TetX gene [24,25].

4.Drug efflux:

Genes encoding efflux pumps are chromosomally encoded in bacteria. The main purpose of the efflux pumps is to remove harmful substances from the bacterial cell; several of these pumps can move a wide range of substances (multi-drug [MDR] efflux pumps). The available carbon source has an impact on several of these pumps' resistance capabilities [26,27]. Gram-

positive bacteria's efflux pumps, which are encoded on their chromosomes, may provide inherent resistance. These pumps include efflux fluoroquinolones and members of the MATE and MFS families. It is also known that plasmids have gram-positive efflux pumps. At the moment, the MFS family comprises the described pumps in gram-positive bacteria [28].

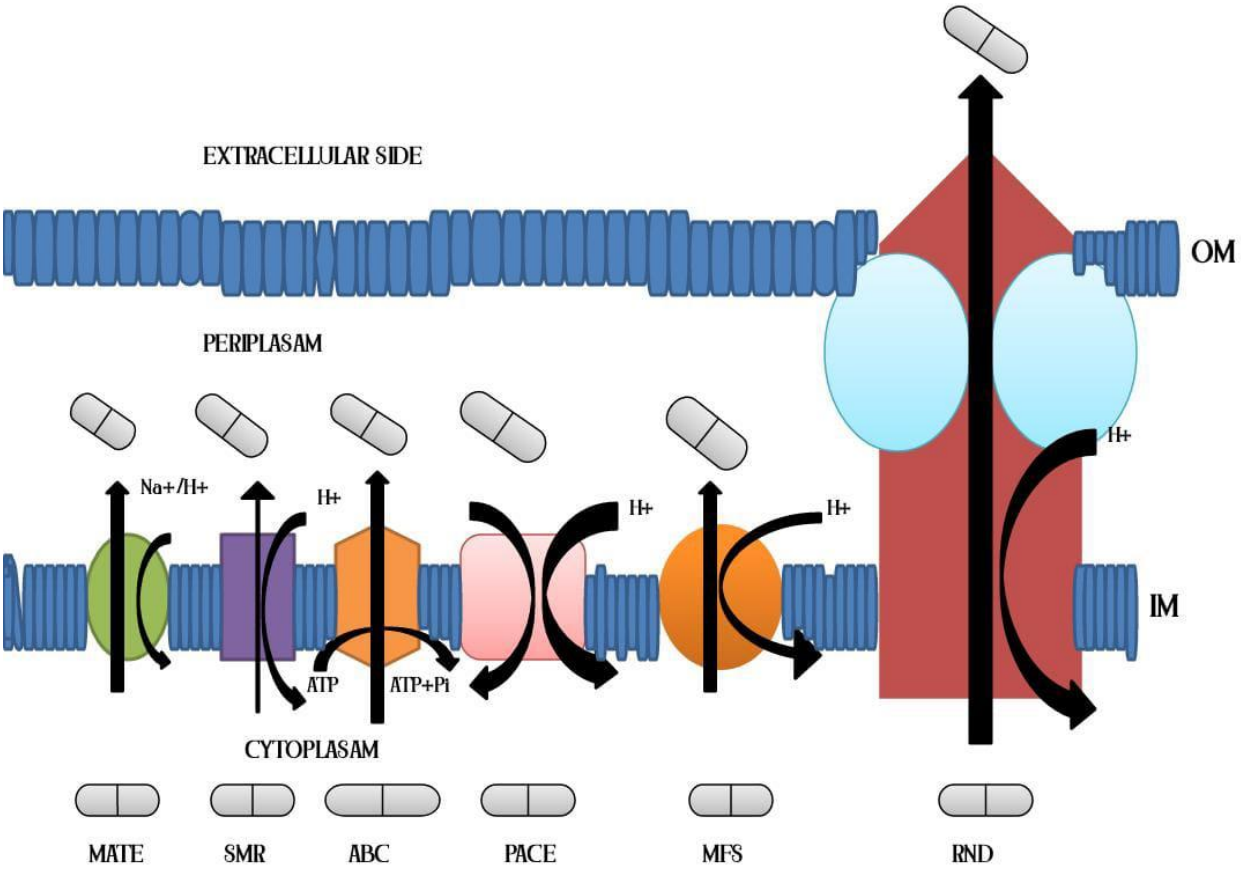

Figure2: General structure of main efflux Pump Famlies

5.Beta-lactamases:

By hydrolyzing a particular location in the β-lactam ring structure, the β-lactamases (formerly known as penicillinases and cephalosporinases) render β-lactam medications inactive by opening the ring. The target PBP proteins cannot be bound by the open-ring medications. There are several known β-lactamases, and the group includes enzymes that can render any of the available β-lactam medications inactive. The most significant resistance mechanism against penicillin and cephalosporin medications, as well as the most prevalent resistance mechanism employed by gram-negative bacteria against β-lactam medications, is the synthesis of β-lactamases [29].

The molecular structure and/or functional properties of the β-lactamase enzymes are used to classify them. They fall into one of four major structural groupings (A, B, C, or D). Based on substrate specificity, the three functional groups are Metallo (zinc-dependent) β-lactamases, serine β-lactamases, and cephalosporinases. These enzymes may also be referred to by their family of enzymes, such as the CTX (preferentially hydrolyze cefotaxime) family, the SHV (sulfhydryl variable) family, and the TEM (named after the first patient) family. All four structural categories can manufacture β-lactamases in gram-negative bacteria. Gram-positive bacteria primarily contain β-lactamases from group A, while some are also found in group B [30].

V. INNOVATIONS OF ANTIMICROBIAL RESISTANCE:

Evolvability:

The evolutionary processes of microbes and viruses differ from those of other higher organisms because they undergo high selection pressures and drastic population fluctuations, which may be exacerbated if they have within-host and between-host life cycles. Microbes are the most abundant and diverse life forms on Earth, dating back 4 billion years [31]. Only an estimated 1% of bacterial and archaeal species have been sequenced and cultured, and the remaining microbial genomes are still unknown as Microbial Dark Matter [32].

Specificity:

The variety of microorganisms that small-molecule antibiotics can inhibit varies. They are categorized as either narrow-spectrum antibiotics, which can only target a small number of bacterial species, or broad-spectrum antibiotics, which can target a broad range of bacteria, according to the spectrum of antimicrobial action. Only certain Gram-negative bacteria are susceptible to the effects of extended-spectrum antibiotics. Since both pathogenic and non-pathogenic bacteria are subject to the selective pressure for resistance, broad-spectrum antibiotics are generally more likely to cause antimicrobial resistance. Antimicrobial resistance genes that can be passed on to pathogenic bacteria are persistently stored in microbiomes' non-pathogenic commensal bacteria during this process [33].

Non-Immunogenicity:

The immunological and digestive systems are the most frequently affected by antibiotic side effects, according to the Centers for Disease Control and Prevention (CDC). Antibiotics have a negative impact on microbial homeostasis, which can lead to indigestion, diarrhea, and nausea. Antibiotic side effects also include allergic reactions, which can cause redness, coughing, wheezing, and breathing problems. Antibiotics can occasionally result in medical emergencies like anaphylaxis, a severe and potentially fatal allergic reaction. Severe allergic responses account for the majority of ED visits involving antibiotic side effects. Babies are frequently treated with preventative or therapeutic antibiotics because they are susceptible to bacterial infections, particularly if they are born prematurely and/or underweight [34].

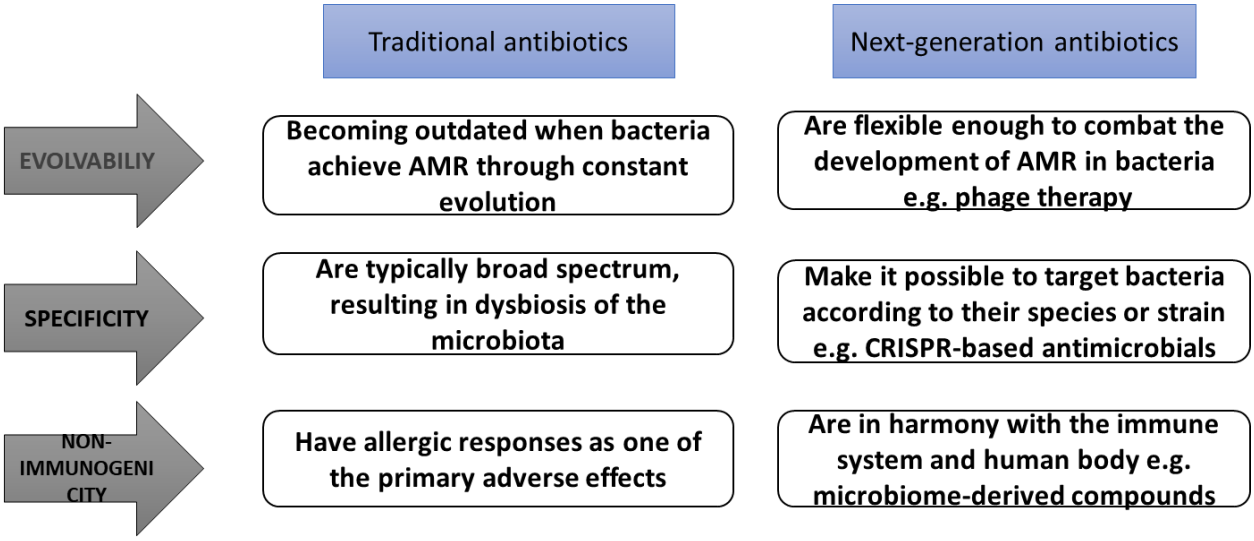

Figure 3: Traditional Anti-biotics vs Next Generation Antibiotics

VI. EMERGING STRATEGIES IN ANTIBIOTIC DEVELOPMENT:

1.Novel chemical scaffold

A novel chemical scaffold is a special molecular backbone or framework that serves as the foundation for developing new therapeutic agents, particularly in drug development. Because they provide new ways to target resistant organisms by evading known resistance pathways, these scaffolds are crucial for the next generation of antibiotics.

In order to produce new pyridazine compounds, the effort concentrates on coupling reactions with various amino esters (7a, 7b, 7c, and 7d). The structures of these materials have been investigated using spectroscopic techniques like 1H, 13C NMR, IR, and

mass spectroscopy. The chemicals were effective against two bacterial strains: Staphylococcus aureus strain CIP543154 and Escherichia coli strain ATCC25922. Molecular docking data revealed that the protein 7AZ5 had a considerable affinity for these chemicals through hydrogen bonding. The compounds 7a and 7d demonstrated the highest binding energies and the best antibacterial activity, suggesting that they could serve as a model for the creation of potent new antimicrobial compounds [35].

2.Bacteriophage therapy

Viruses known as bacteriophages specifically infect and destroy bacteria. They present a viable treatment option for infections that are resistant to antibiotics. Clinical trials have demonstrated the effectiveness of bacteriophage therapy, especially for illnesses brought on by multidrug-resistant bacteria such as Klebsiella pneumoniae and Staphylococcus aureus. To target certain bacterial strains, phages are either obtained from the environment or created in a lab. While the remainder of the body's microbiome remains intact, they can be quite selective to the target microorganism. Standardization, regulatory approval, and the creation of phage cocktails that are capable of efficiently targeting a variety of bacterial species are still issues that must be resolved.

3.CRISPR-Cas System

The genome-editing technology known as CRISPR, or Clustered Regularly Interspaced Short Palindromic Repeats, has revolutionized molecular biology. The CRISPR system, especially the CRISPR-Cas9 variant, is derived from a natural defense mechanism that bacteria use to fight off viral infections [37]. Bacteria in this method seize DNA fragments from invasive viruses and store them in their own genome. If the same viruses attack again, the bacteria can identify and fight them thanks to these stored sequences, also referred to as CRISPR arrays. The CRISPR system converts the stored DNA sequences into RNA molecules when a virus infiltrates. The complementary DNA of the invasive virus is subsequently bound by these guide RNAs. These RNA molecules direct the endonuclease Cas9 protein to the precise spot on the viral DNA. Cas9 disables the virus by cleaving the DNA. This exact targeting technique has been used by scientists to edit genes in a variety of organisms, allowing for highly accurate targeted alterations [38].

4.Adjuvants and Resistance Breakers

Class I type of adjuvants works with antibiotics on bacterial sites that cause resistance is a direct resistance breaker. These adjuvants directly block antibiotic resistance mechanisms, such as enzymes, efflux pumps, or other targets that make up for the initial targets. β-lactamase inhibitors are the only currently used therapeutically approved adjuvants because they inactivate β-lactamases. It is theoretically possible to achieve multiple target engagement by "physically combining" various compounds. Combination treatments for HIV, cancer, cardiac conditions, and antimicrobial methods have all shown therapeutic efficacy. Soon after antibiotics were discovered, combination therapy was created with little understanding of their molecular mechanisms of action. More than 60 combinations (two-component or higher order) were recognized by the middle period of the 1950s. The effectiveness of early antibiotic combinations was enhanced. Sulfonamides, trimethoprim, and streptomycin and penicillin are a few examples. In the 1950s and 1960s, respectively, the value of combination therapy for the treatment of leprosy and tuberculosis was recognized [39].

VII. CHALLENGES IN ADDRESSING AMR:

Addressing the advent of AMR poses difficult problems that cannot be easily solved. Antimicrobials are widely used in medicine and the economics of food animal production, which makes it difficult to minimize humanity's enormous use of them [40]. Modern farming systems rely on the routine administration of antimicrobials to animals for infection prevention and growth promotion, while doctors frequently rely on empirical antibiotic prescribing to protect against bacterial infections due to the lack of rapid point-of-care diagnostics. Despite awareness of the hazards of antibiotic resistance linked to overuse, antimicrobial stewardship programs in healthcare and updated animal husbandry rules are still not widely implemented. These problems are exacerbated by the antibiotic drug development pipeline's inability to keep up with MDR bacteria' ongoing evolution. Costly antimicrobial research with few financial incentives is being abandoned by pharmaceutical companies more and more. Furthermore, although legislative changes that fund

the development of antibiotics represent advancements, given the length of phase trials, it appears doubtful that any immediate fixes will be found.

Despite agencies like the WHO, CDC, and UN acknowledging the cross-border hazards of AMR, international coordination on surveillance and stewardship protocols is still fragmented, which further impedes containment efforts. Novel resistance variables can evolve locally and spread globally due to differences in access to high-quality diagnostics and antibiotic supervision between nations. Localized success may be continuously undermined and negated by patches of poor care. In the end, the distinct "tragedy of the commons" character of antibiotic resistance necessitates shared accountability and fair, coordinated international action. But geopolitical issues still prevent agreement on legally enforceable international regulations and financing avenues that are required to improve antimicrobial innovation and stewardship globally [41].

VIII. WORLD ORGANIZATION WORKING TOGETHER TO ADDRESS AMR:

AMR is being actively addressed by a number of international organizations that fund research, surveillance, public health campaigns, and policy formulation at various levels. Of them, WHO is a specialized United Nations agency that oversees global public health. By bringing attention to the urgent need to address AMR and preserve the lives of future generations, WHO has been at the forefront of global efforts to battle AMR. By exercising global leadership, establishing standards and norms, and offering financial and technical assistance to nations worldwide, it is significantly contributing to the fight against AMR. In May 2015, the World Health Assembly adopted resolution WHA67.25, endorsing WHO's Global Action Plan on Antimicrobial Resistance.

The global action plan has five objectives:

1. Increase knowledge and comprehension of antibiotic resistance.
2. Increase knowledge by doing study and surveillance.
3. lower the rate of infection.
4. Use antibacterial agents as efficiently as possible.
5. Assure long-term funding for the fight against antibiotic resistance.

A non-profit organization called GARDP (Global Antibiotic Research & Development Partnership) was founded by WHO and DNDi (Drugs for Neglected Diseases initiative) with the goal of creating novel antibiotic treatments for priority bacterial infections, especially those that affect susceptible groups like infants and people with STDs. In order to guarantee the accessibility, affordability, and availability of novel antibiotics, GARDP also works with the public and private sectors. To fight AMR worldwide, WHO collaborates with organizations such as the Food and Agricultural Organization (FAO), Organization for Animal Health (OAH), and World Bank under the framework of the UN system [42].

IX. THE IMPACT OF ANTIMICROBIAL RESISTANCE ON HUMAN AND ANIMAL POPULATIONS:

AMR has emerged as a complex problem that affects both human and animal health. Drug-resistant strains of bacteria have emerged more quickly as a result of the overuse and misuse of antibiotics in a variety of fields, including veterinary medicine, agriculture, and healthcare facilities. Antibiotic-resistant bacteria, or "superbugs," have emerged as a result of an over-reliance on antibiotics. These germs can cause serious infections and provide serious obstacles to the effectiveness of therapy. Additionally, the problem is made worse by the lack of advancement in the creation of new antimicrobial drugs, since resistance is emerging faster than effective treatments are being discovered [43].

One of the biggest risks to human health in the twenty-first century is AMR. Significant clinical concerns are presented by the growing intractable nature of previously curable infections. A growing dependence on second and third-line treatments, which are frequently more costly, hazardous, and necessitate longer treatment durations, has resulted from the loss of effective first-line antimicrobials [44]. Due to

prolonged hospital stays, chronic illnesses deplete the resources of both the patient and the healthcare system. Economic productivity is also impacted by longer recoveries, which provide more quality time off. Similar to this, AMR infections call for further isolation measures, laboratory testing, and outpatient clinic visits. Over a million lives are lost each year as a direct result of AMR pathogens [45].

X. FUTURE PROJECTIONS OF AMR BURDEN AND ASSOCIATED ISSUES:

According to studies commissioned by the UK government, the picture for the future is not promising. Approximately 10 million fatalities per year could be related to antibiotic-resistant infections by 2050, according to this study. While big surgeries like organ transplants, chemotherapy, or hip replacements may become excessively dangerous, simple illnesses and small injuries could once again become life-threatening. By 2050, AMR-related economic losses will total $100 trillion USD [46]. As bacterial resistance increases faster than new antibiotic choices are developed, low- and middle-income nations are predicted to bear the brunt of this burden. At the same time, access to currently available, high-priced medicines is hindered by resource limitations. Piecemeal containment measures cannot keep up with the evolutionary potential of harmful bacteria that are constantly exposed to humanity's widespread use of antibiotics in healthcare, agriculture, and the environment due to a severe lack of global coordination.

The growing ineffectiveness of antimicrobials could seriously impair contemporary medicine and allow the recurrence of bacterial infections that had previously been uncommon due to antibiotic treatments, in addition to the direct mortality and cost effects. Individuals who are immunocompromised, have cancer, or need surgery are more susceptible to newly developing bacterial strains that are resistant to many drugs [47].

XI. AI IN COMBATING ANTIMICROBIAL RESISTANCE:

Artificial intelligence is widely applied in contemporary medical operations, as evidenced by its application in a variety of healthcare domains. Numerous published research on artificial intelligence shows how successful it is at preventing antibiotic resistance by quickly spotting trends in bacterial behavior and adjusting treatment plans accordingly. These developments have enormous potential for creating more individualized and efficient strategies to combat the threat that antibiotic-resistant organisms represent to global health. Promising chances to improve antimicrobial stewardship and precision medicine tactics tackling the urgent AMR epidemic are presented by the development of artificial intelligence (AI) and machine learning techniques.

AI solutions that may improve diagnostics, optimize prescribing patterns, and replenish depleted drug pipelines will become important as AMR undermines the effectiveness of current antibiotic regimens against increasingly prevalent "superbugs." AI integration in healthcare delivery is a step forward from traditional antibiotic stewardship systems that depend on formulary restriction restrictions and specialist staff control. Based on clinical presentations, advanced neural networks and predictive analytics may be able to detect high-probability infections or positive cultures early, enabling more rapid focused therapy. To suggest the best antibiotic choice, AI prescription helpers can also use hospital metadata on local microbiology, patient characteristics, and treatment protocols. The empirical overuse of broad agents is limited by such AI antibiotic advisors. In the absence of conclusive diagnosis, human practitioners frequently overprescribe antibiotics, thus clever precautions that balance the risks of infection with the development of resistance can be extremely helpful. The ability of stewardship programs to continuously monitor patients on appropriate antibiotic withdrawal post-cultures may also be enhanced by AI integration. Dynamic formulary strategies can be better informed by AI-powered epidemiological surveillance that identifies local resistance outbreaks outside of direct treatment. Pharmaceutical corporations are progressively abandoning antibiotic development workflows, and computational methods that mine omics databases, published literature, and molecular libraries may also uncover new therapeutic targets or chemical scaffolds. All things considered, a crucial evolutionary step toward maintaining antibiotic efficacy is the addition of AI stewardship to

conventional antimicrobial governance and precision medicine initiatives.

The potential of modern artificial intelligence to prevent AMR is currently limited by a variety of issues, primarily related to algorithmic biases, data quality, and practical implementation challenges. The majority of AI in healthcare is still restricted artificial neural networks that are susceptible to biases because they were trained on small clinical samples. If poor projections undermine physician confidence or create new usage motivations, careless application could exacerbate antibiotic overuse and toxicities. Additionally, most antibiotic prescription data comes from wealthy countries, which could limit the generalizability of the methodology. Additionally, the underlying logic of the majority of AI antibiotic advisors is currently not transparent enough for physician users to understand. Explainable models are necessary to gain user trust so that suggestions can be clinically confirmed using the metadata that is currently accessible. Despite advancements in scaffold prediction and mechanism elucidation, there is still a dearth of experimental validation in the drug development field. Beyond technical limitations, the majority of AI antimicrobial tools still remain confined to academic research without clear translation pathways toward clinical and policy integration. Still, with prudent development and application, AI constitutes a promising avenue amidst the pressing AMR crisis [48].

XII. GLOBAL BURDEN OF AMR:

Since AMR is developing quickly, infection and mortality rates are constantly being closely watched. The anticipated number of AMR infections in the UK grew from 61,946 patients in 2018 to 65,162 newly diagnosed cases in 2019. In contrast, the European Centre for Disease Prevention and Control (ECDC) has estimated that the annual infection rate of antimicrobial resistance (AMR) has surpassed 670,000 cases in the EU alone. Data analysis from a previous study indicates that bacterial AMR was directly responsible for 1.27 million of the 4.95 million deaths that were attributed to the disease globally in 2019. According to a well-known assessment, by 2050, the number of deaths directly attributable to AMR is expected to increase to 10 million annually. Asia and Africa have the greatest predicted fatality rates from this, primarily as a result of their sizable populations and lax AMR prevention regulations. In contrast to Australasia, which had the lowest rate of AMR-associated mortality in 2019, Sub-Saharan Africa has the highest all-age death rate in the Global Burden of Diseases (GBD) region that is directly linked to or related to AMR, per prior study [49].

XIII. THE ROLE OF BIOMEDICAL SCIENCE IN HELPING TO COMBAT AMR:

Biomedical experts and the clinical microbiology lab play a crucial part in the fight against AMR on a national and worldwide scale. Diagnostics are essential for adding value in the form of 1) laboratory surveillance of AMR epidemiology through monitoring; 2) providing antimicrobial susceptibility results for clinically significant pathogens to help avoid empirical antibiotic prescribing; 3) assisting in determining whether the aetiology of clinical infections is bacterial or viral, thereby assisting in determining the potential value of intervening with antibiotics; 4) offering innovative techniques to robustly allow more rapid turnaround times for reporting antimicrobial susceptibility results to antibiotic prescribers, so that good antimicrobial stewardship practices are encouraged; and 5) enabling the elucidation of novel mechanisms of antimicrobial resistance through whole genome sequencing techniques [50].

XIV. CONCLUSION:

Though their development and responsible use are urgently needed to address the growing global health threat posed by antibiotic resistance, next-generation antibiotics are essential for fighting antimicrobial resistance because they target novel bacterial pathways, disrupt virulence factors, and may delay the development of further resistance. This makes them an essential tool to combat multidrug-resistant pathogens and preserve effective healthcare treatments. By using creative strategies to target pathogens, such as breaking up biofilms, blocking enzymes that mediate resistance, or employing bacteriophage therapy, these revolutionary medications seek to circumvent

resistance mechanisms. Furthermore, the creation of synthetic molecules and customized antibiotics is being made possible by developments in genomic and computational technology. To ensure fair access and stewardship, these alternatives must, however, be supported by ongoing research funding, a decrease in the overuse and abuse of currently available antibiotics, and international cooperation. Together, these initiatives could combat the growing threat of AMR and maintain the effectiveness of antibiotics.

XV. ACKNOWLEDGEMENT:

We sincerely express our deep sense of gratitude to the management of Malla Reddy College of Pharmacy. We are highly in depth of Dr. M Sudhakar Principal of Malla Reddy College of Pharmacy we are also obliged to our mentor and Colleagues. This work would not have been possible without their help.

REFERENCE

[1] Letao Bo, Haidong Sun and Jonathan Zhu et.al., -Combating antimicrobial resistance, *Experimental Pharmacology and Drug Discovery*, vol.15, pp.1347750, Feb 2024.

[2] V. Bhandari and A. Suresh, -Next-Generation Approaches Needed to Tackle Anti-microbial Resistance for the Development of Novel Therapies Against the Deadly Pathogens, Front Pharmacol, vol.13, pp.838092, June 2022.

[3] **3.**B. Peng, H. Li and X-x peng et al., -Call for next-generation drugs that remove the uptake barrier to combat antibiotic resistance, *Drug Discovery Today*, vol.10, pp.103753, Oct 2023.

[4] CDC (2021). Antibiotic-resistant Germs: New Threats. Atlanta, GA, United States: Centers for Disease Control and Prevention. Available: https://www.cdc.gov/drugresistance/biggest-threats.html (Accessed June 12, 2021). [Google Scholar]

[5] M. Woolhouse and J. Farrar, -Policy: An Intergovernmental Panel on Antimicrobial Resistance, National Library of Medicine, vol.509(7502), pp.555–557, May 2014.

[6] S. B. Zaman, M. A. Hussain, R Nye, V. Mehta, K. T. Mamun and N. Hossain, -A Review on Antibiotic Resistance: Alarm bells Are Ringing, National Library of Medicine, vol.9(6): e1403, June 2017.

[7] C. Mc Kernan Benson, S. Farrell and M. Dean, -Antimicrobial Use in Agriculture: Critical Review of the Factors Influencing Behavior, National Library of Medicine, vol.3(4): dlab178 Nov 2021.

[8] S. Pokharel, P. Shrestha and B. Adhikari, -Antimicrobial Use in Food Animals and Human Health: Time to Implement 'One Health' Approach, Antimicrob Resist Infect Control vol.9(1), pp.181, Nov 2020, 10.1186/s13756-020-00847-x [DOI] [PMC free article] [PubMed] [Google Scholar].

[9] Public Health England. Antibiotic Use and Resistance: What the Public Know (2020). Available from: https://www.gov.uk/government/publications/antibiotic-use-and-resistance-what-the-public-know (Accessed March 21, 2023). [Google Scholar]

[10] K. Bhardwaj, M. S. Shenoy, S. Baliga, B. Unnikrishnan and B. S. Baliga, -Knowledge, Attitude, and Practices Related to Antibiotic Use and Resistance Among the General Public of Coastal South Karnataka, India – A Cross-Sectional Survey, Clin Epidemiol Glob Health vol.11, pp.100717, July-Sep 2021, 10.1016/j.cegh.2021.100717.

[11] D. Torumkuney, A Poojary, B Shenoy, P Nijhara, K Dalal and Manenzhe R, -Country Data on AMR in India in the Context of Community-Acquired Respiratory Tract Infections: Links between Antibiotic Susceptibility, Local and International Antibiotic Prescribing Guidelines, Access to Medicine and Clinical Outcome, J Antimicrobial Chemo vol.77(1), i10–7, Sep 2022, 10.1093/jac/dkac212 [DOI].

[12] B. I. Coculescu, -Antimicrobial resistance induced by genetic changes, J Med Life, vol.2(2), pp.114–123 Apr 2009.

[13] J. L. Martinez, -General principles of antibiotic resistance in bacteria, Drug Discov Today, vol.11, pp.33-39, Mar 2014.

[14] G. Cox, and G. D. Wright, -Intrinsic antibiotic resistance: mechanisms, origins, challenges and solutions, Int J Med Microbial, vol.303, pp.287–292, Aug 2013.

[15] A. Fajardo, N. Martinez-Martin, and M Mercadillo et al, -The neglected intrinsic resistome of bacterial pathogens, PLoS One, vol.3, e1619, Feb 2008.

[16] J. Davies, and D. Davies D, -Origins and evolution of antibiotic resistance, Microbial Mol Biol Rev, vol.74, pp.417–433, Sep 2010.

[17] S. T Chancey, D. Zahner, and D. S Stephens, -Acquired inducible antimicrobial resistance in Gram-positive bacteria, Future Microbiol, vol.7, pp.959–9, Aug 2012.

[18] C. R Mohon, D. C Lehman, and G. Manuselis, -Antimicrobial agent mechanisms of action and

resistance, In: Textbook of Diagnostic Microbiology, St. Louis: Saunders, pp.254–273, 2015.
[19] J. M. A. Blair, G. E Richmond, and L. J. V. Piddock, -Multidrug efflux pumps in Gram-negative bacteria and their role in antibiotic resistance, Future Microbiol, vol.9(10), pp.1165–1177, 2014.
[20] A. Kumar, and H. P. Schweizer, -Bacterial resistance to antibiotics: active efflux and reduced uptake, Adv Drug Deliv Rev, vol.57, pp.1486-1513, 2005.
[21] P. A Lambert, -Cellular impermeability and uptake of biocides and antibiotics in gram-positive bacteria and mycobacteria, J Appl Microbiol, vol.92, pp.46S–54S, 2002.
[22] W. Reygaert, -Methicillin-resistant Staphylococcus aureus (MRSA): molecular aspects of antimicrobial resistance and virulence, Clin Lab Sci, vol.22 pp.115–119, 2009.
[23] A. Beceiro, M. Tomás, and G. Bou, -Antimicrobial resistance and virulence: a successful or deleterious association in the bacterial world? Clin Microbiol Rev vol.26, pp.185–230, Apr 2013.
[24] S. Kumar, M. M. Mukherjee, and M. F. Varela, -Modulation of bacterial multidrug resistance efflux pumps of the major facilitator superfamily, Int J Bacteriol, 2013.
[25] J. M. Blair, M. A. Webber, A. J. Baylay, et al, -Molecular mechanisms of antibiotic resistance, Nat Rev Microbiol, vol.13, pp.42–51, Jan 2015.
[26] N. A. Villagra, J. A. Fuentes, M. R. Jofré, et al, -The carbon source influences the efflux pump-mediated antimicrobial resistance in clinically important Gram-negative bacteria, J Antimicrob Chemother, vol.67, pp.921–927, Apr 2012.
[27] N. A. Villagra, J. A. Fuentes, M. R. Jofré, et al, -The carbon source influences the efflux pump mediated antimicrobial resistance in clinically important Gram-negative bacteria, J Antimicrob Chemoth, vol. 67, pp. 921–927, Apr 2012.
[28] B. M. Jonas, B. E. Murray, and G. M. Weinstock, -Characterization of emeA, a norA homolog and multidrug resistance efflux pump, in Enterococcus faecalis, Antimicrob Agents Ch, vol.45, pp. 3574- 3579, Dec 2001.
[29] K. Bush and G. A. Jacoby, -Updated functional classification of β-lactamases, Antimicrob Agents Ch, vol.54, pp.969–976, Mar 2010.
[30] C. Schultsz, and S. Geerlings, -Plasmid-mediated resistance in Enterobacteriaceae, Drugs, vol.72, pp 1–16, 2012.
[31] E V Koonin, and Y I Wolf, -Evolution of microbes and viruses: A paradigm shifts in evolutionary biology? Front. Cell Infect. Microbiol, vol.2, pp.119, Sep 2012, doi: 10.3389/fcimb.2012.00119.
[32] J.-Y. Jiao, L Liu, Z.-S. Hua, B.-Z Fang, E.-M., et al., -Microbial dark matter coming to light: Challenges and opportunities, Natl. Sci. Rev, vol.8, nwaa280, 2021, doi: 10.1093/nsr/nwaa280.
[33] R.J. Melander, D.V. Zurawski, and C. Melander, -Narrow-spectrum antibacterial agents, MedChemComm, vol.9, pp.12–21, 2018, doi: 10.1039/C7MD00528H.
[34] S. Shekhar, and F. C. Petersen, -The Dark Side of Antibiotics: Adverse Effects on the Infant Immune Defense Against Infection, Front. Pediatr, vol.8, pp.544460, Oct 2020, doi: 10.3389/fped.2020.544460.
[35] L Mouad, B Khadija, S Riham et al., Development of novel antibiotics from pyridazine, Results in chemistry, vol.10, pp.101699, Aug 2024.
[36] A Kaylor, -Using Next-Generations Antibiotics to Combat Antimicrobial Resistance, Using Next-Generation Antibiotics to Combat Antimicrobial Resistance | TechTarget, Mar 2024.
[37] M.A Hossain, -CRISPR-Cas9: A fascinating journey from bacterial immune system to human gene editing. Progress in Molecular Biology and Translational Science, vol.178, pp.63-83, 2021.
[38] S. Jamehdor, S. Pajouhanfar, S. Saba, G. Uzan, A. Teimoori, and S. Naserian, -Principles and applications of CRISPR toolkit in virus manipulation, diagnosis, and virus-host interactions, Cells, vol.11(6), pp.999, Mar 2022.
[39] G. Dhanda, Y. Acharya, and J. Haldar, -Antibiotic Adjuvants: A Versatile Approach to Combat Antibiotic Resistance, ACS Omega, vol.8, pp.10757−10783, Mar 2023.
[40] M.M. Rahman, M.A. Alam Tumpa, M. Zehravi, et al., -An Overview of Antimicrobial Stewardship Optimization: The Use of Antibiotics in Humans and Animals to Prevent Resistance Antibiotics, vol.11, pp.67, May 2022.
[41] G.M. Du Plessis, Microbial Geopolitics: Living with Danger and the Future of Security., PhD diss, 2017. Google Scholar.
[42] V. H. KrishnaPrasad, and S. Kumar, Antimicrobial Resistance: An Ultimate Challenge for 21st Century Scientists, Healthcare Professionals, and Policymakers to Save Future Generations, J. Med.Chem, vol.67(18), pp.15927-15930, Sep 2024.
[43] K.H. Luepke, K.J. Suda, H. Boucher, R.L. Russo, M.W. Bonney, and T.D. Hunt, J.F, -Mohr III Past, present, and future of antibacterial economics: increasing bacterial resistance, limited antibiotic pipeline, and societal implications, Pharmacother.

J. Hum. Pharmacol, Drug Ther, vol.37, pp.71-84, Jan 2017.

[44] R. Smith, and J. Coast, -The true cost of antimicrobial resistance BMJ, vol.346, Mar 2013, 10.1136/bmj. f1493View at publisher Google Scholar.

[45] D. Tamma, and S.E. Cosgrove, -Antimicrobial stewardship, Infect Dis. Clin, vol.25, pp.245-260, Mar 2011, 10.1016/j.idc.2010.11.011.

[46] J. O'Neill, -Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations, 2014, 〈 https://amr-review.org/sites/default/files/AMR 〉 Review Paper - Tackling a crisis for the health and wealth of nations_1.pdf (accessed October 16, 2023).

[47] D.P. Kofteridis, A.M. Andrianaki, S. Maraki, et al., -Treatment pattern, prognostic factors, and outcome in patients with infection due to pan-drug-resistant gram-negative bacteria, Eur. J. Clin. Microbiol. Infect. Dis, vol.39, pp.965-970, 2020, 10.1007/s10096-019-03784-9.

[48] K. A. Sirwan, H. Safin, Q. Karzan, H. I. Radhwan, F. Abdulmalik, A. M. Kochr, and G. M. Mona, -Antimicrobial resistance: Impacts, challenges, and future prospects. Journal of Medicine, Surgery, and public Health, vol.2, pp.100081, Mar 2024.

[49] Ka K T, C. M. Beverley, E. M. John, -Antimicrobial Resistance. Institute of Biomedical Science, published: 28 June 2023, doi: 10.3389/bjbs.2023.11387.

[50] A Cherkaoui, and J Schrenzel, -Total Laboratory Automation for Rapid Detection and Identification of Microorganisms and Their Antimicrobial Resistance Profiles, Front Cel Infect Microbiol, vol.12, pp.807668, Feb 2022, doi:10.3389/fcimb.2022.807668.