

Understanding and Combating Antimicrobial Resistance

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I. INTRODUCTION

Definition and Overview of Antimicrobial Resistance (AMR)

AMR, or antimicrobial resistance, is a big health problem all over the world. It happens when drugs that used to kill bacteria, viruses, fungi, and parasites stop working [1]. There are a lot of complicated biological processes that cause this resistance to happen. For instance, enzymes break down antibiotics, drug targets change, efflux pumps become more active, and biofilms form. All of these things make antimicrobial drugs less effective [2]. The main reasons for the spread and rise of AMR are the overuse and misuse of antibiotics in both human medicine and agriculture, bad methods for controlling infections, and the rise of bacteria that are resistant to more than one drug [3]. Because of these things, healthcare is much more expensive, hospital stays are longer, and health systems in other countries are under more stress. They are very bad for the health of people all over the world [2]. To fight AMR, we need a big plan that covers a lot of ground. Setting up antimicrobial stewardship programs, improving surveillance systems, and enforcing strict infection prevention and control measures are all important steps [4]. Researchers are also looking into new treatments that could take the place of regular antibiotics. These include photodynamic therapy, vaccines, and nano antibiotics [1]. We need a One Health approach to make AMR treatments that work for a long time. This method looks at how the health of people, animals, and the environment are all connected [4]. To stop the spread of resistance around the world and control the use of antibiotics, it is also important to have strong legal systems and work with other countries [3].

Historical Background and Emergence of Antimicrobial Resistance (AMR)

AMR comes from both human-made and natural evolutionary processes. Resistance is a normal thing,

but the reality that antibiotics are utilized extensively in farming, healthcare, and the environment has made it happen much faster [5]. The discovery of antibiotics, starting with penicillin in the early 1900s, changed medicine for good. But antibiotics didn't work for long because bacteria promptly figured out how to deal with the selective pressures these drugs put on them. For a long time, scientists have been looking for new antibiotics, and bacteria have been getting better at fighting them. We now call this the "post-antibiotic era," referring to a time when widespread illnesses and minor accidents could kill people again because there are still no good treatments. [6]. AMR has spread around the world because of more people and products moving around because of international travel, not having enough clean water and good antibiotics, and not using good infection control methods [5]. If nothing is done about it, AMR could kill up to 10 million people every year by 2050, which is more than many other diseases [7]. This crisis that is about to happen needs a response from many fields. This includes finding new antimicrobial agents, making strong antimicrobial stewardship programs, and coming up with new treatments like CRISPR-Cas9 gene-editing tools and antimicrobials based on nanomaterials [7,6]. To keep current treatments effective and protect public health, it is important to know where current and future policies came from in the past. [5]

Global Burden and Relevance in Public Health

AMR, or antimicrobial resistance, is a major public health issue in the 21st century. This is mostly because people use antimicrobial agents too much and in the wrong way in farming, veterinary care, human medicine, and the environment [8]. This abuse is causing bacteria that are resistant to many drugs to appear and spread quickly, which makes medicines that used to work less effective. You might not think that AMR has effects that go beyond what you think. As resistance rates go up, so do the rates of illness and

death, hospital stays, and the cost of healthcare around the world. AMR also makes modern medical procedures like organ transplants, cancer chemotherapy, and surgeries less effective because they depend on antibiotics to prevent and treat infections [9]. Microbes can make drugs less effective by breaking them down with enzymes, changing their targets, and using efflux pumps. These are all ways that pathogens change when they are exposed to antimicrobial pressure [10]. There has been a lot of talk about using a "One Health" approach that looks at how animal, human, and environmental health are all connected. For this plan to work, everyone in the world needs to work together to make sure that infection prevention is better, everyone can get medical care, and all businesses use antimicrobials in a responsible way. To stop the AMR epidemic from getting worse, public health plans need to include strong antimicrobial stewardship programs, stricter infection control procedures, and less use of antibiotics in farming [11,9]. Science also needs to stay ahead of new types of resistance. This means finding new ways to treat infections and making new drugs that kill bacteria [9]. Finally, for the sake of global health and the effectiveness of antibiotics, all governments, businesses, universities, and international organizations must work together [8, 10].

II. MECHANISMS OF ANTIMICROBIAL RESISTANCE

Genetic Mutations

Antibiotics (AMR) don't work on bacteria anymore because they change the DNA of the bacteria. These random changes can change the shape of proteins or how they work. This means they aren't as helpful and are less likely to stick to [12]. Bacteria can become much less resistant to common antibiotics when genes that code for DNA gyrase, ribosomal proteins, or penicillin-binding proteins change [13]. A useful mutation can quickly spread through groups of bacteria when antibiotics are used a lot in a clinical, agricultural, or environmental setting [5]. The microorganism can change their genes, which makes them more likely to respond to new drugs that are still being made. We must have to learn more about the events that occur at the molecular level when those modifications happen so that we can make better tools for identifying and managing infections. They can

change their genes, which makes it more likely that they will respond to new drugs that are still being made. This helps them manage the stress of taking antibiotics. Targeted drug development, combination therapy, and genetic tests that can find specific mutations that make bacteria resistant are all promising ways to fight AMR [14]. To effectively deal with the effects of mutation-driven resistance across all health sectors, we need a comprehensive, multidisciplinary approach that takes into account host factors, environmental factors, antimicrobial medications, and microbial genetics [5].

Horizontal Gene Transfer (Conjugation, Transformation, Transduction)

Horizontal gene transfer (HGT), which lets bacteria get resistance genes from other organisms, even ones from different species and genera, is a big reason why antimicrobial resistance (AMR) happens [15]. Vertical transmission happens when cells divide, but horizontal gene transfer (HGT) lets microbial populations quickly develop resistance to antibiotics, even when they aren't exposed to them. Conjugation is one of the most important types of HGT. During this process, bacterial cells touch each other directly to pass on plasmids, which are DNA pieces that can make copies of themselves. Conjugative plasmids have developed advanced methods to stay alive and spread so that they can outcompete other plasmids and avoid host defences. They often have a lot of AMR genes in them [16]. Recent research has shown that AMR gene mobility is more widespread than previously thought. It has also shown that integrative and conjugative elements (ICEs) and insertion sequence common region (ISCR) elements help resistance genes move from one organism to another [17]. The advent of antibiotic resistance on such a rapid scale is a public-health crisis of an historical scale. Measures to limit the impact of resistance: Clinical and public-policy based mitigation strategies will require a proper understanding of the molecular basis of resistance. This is why the intellectual investigation of these processes is still needed [15].

Enzymatic Degradation (e.g., Beta-lactamases)

The major mechanisms through which microbial communities become resistant to antibiotics entail the synthesis of β -lactamases as they are the enzymes that degrade the penicillin related substances and other

analogues. These enzymes break down the β -lactam ring in cephalosporins and Penicillins thus the drugs don't work. [19]. Resistance has been growing for billions of years, starting with β -lactamase. It is one of many enzymes in a bigger network called the "enzystome." This network has thousands of enzymes that work together to make things resistant [20]. It's important to break down enzymes, but there are other ways to stop them as well. These include changes to the proteins that antibiotics attack, changes to the membranes that make it harder for drugs to get into cells, and the active removal of antibiotics through efflux pumps [19,21]. Plasmids and other mobile genetic elements often have the genes that make this resistance mechanisms work. These things help genes move from one bacterium to another, which speeds up the spread of resistance among a population of bacteria [21]. We need to acquire as much as we can about these enzymatic activities, especially β -lactamase activity and how to control it, so that antibiotic resistance doesn't spread around the world and present antibiotics keep working.

Efflux Pumps and Reduced Permeability

AMR, or antimicrobial resistance, is a big problem for public health. It happens when bacteria use different methods to make antibiotics work less well [13]. Two of the most important of these are efflux pumps and decreased membrane permeability. Efflux pumps push antibiotics out of bacterial cells. This lowers the number of drugs inside the cells, which makes them less effective as medicines [23]. These pumps can get rid of a wide range of antimicrobial drugs. They can be drug-specific or multidrug efflux pumps. Beyond drug resistance, many chromosomally encoded multidrug systems may play essential physiological functions, such as maintaining cellular homeostasis.[24]. Bacteria can also keep antibiotics out by making the membrane less permeable. This is usually done by changing the porin proteins in the outer membrane. This lowers the quantity of drugs that enter the body, especially in species that are Gram-negative [13]. Reduced permeability and efflux mechanisms may cooperate to produce high levels of resistance. Most of the time, these strategies come with extra ways to resist, like changing the target sites of antibiotics, inactivating drugs with enzymes, and avoiding important metabolic processes that antibiotics target [24]. A thorough understanding of

these mechanisms is necessary for the development of next-generation antibiotics. Promising approaches to increase the effectiveness of antibiotics include developing drugs that prevent efflux, developing inhibitors that halt pump activity, and concentrating on auxiliary resistance routes [23, 24].

III. TYPES OF RESISTANT PATHOGENS

ESKAPE Pathogens

The ESKAPE group is composed of up of six germs: *Enterobacter fecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species. They are some of the most dangerous things which can cause infections in health care facilities (nosocomial) around the world. These organisms are becoming more well-known because they can "escape" the effects of antimicrobial drugs. Because they are resistant to many drugs, they are now seen as a major threat to global health [38, 39]. ESKAPE infections use a variety of strategies to resist treatment, such as changing the target sites of antibiotics, changing or dissolving drug structures with enzymes, and lowering the levels of antimicrobial drugs inside cells by actively pumping them out or making the cell walls less permeable. Genetic adaptation makes them even more resistant, and resistance genes can spread through vertical and horizontal gene transfer channels, which are often mobile genetic elements like plasmids and transposons. There are a number of reasons why these resistant organisms have appeared and spread. Some of these reasons are industrialization, rapid population growth, and the widespread use and misuse of antibiotics in hospitals and farms [40]. There are serious clinical effects: infections caused by ESKAPE bacteria are getting harder to treat, which means longer hospital stays, higher medical costs, and a much higher rate of morbidity and mortality due to treatment failure. ESKAPE diseases need a coordinated international effort because they have such a big effect. This effort should focus on strict infection control protocols, better surveillance, and antibiotics.

Multidrug- Resistant Tuberculosis (MDR-TB)

Multidrug-resistant tuberculosis, or MDR is one of the primary causes why antimicrobial resistance (AMR) has become prevalent around the world. It is still an important concern for public health, especially in

places where there are a lot of cases. Every year, MDR-TB kills approximately 150 thousand people. MDR-TB is tuberculosis that doesn't respond to no fewer than isoniazid and rifampicin, which are two of the most effective first-line drugs for managing TB [42]. MDR-TB infection is one of the most common causes of infections in hospitals and in the community around the world, along with the well-known pathogens known as ESKAPE [39]. The excessive use and misuse of antibiotics in cultivating and for human health are now the main causes of MDR-TB and AMR in general [43, 42]. Not planning treatments, not going to therapy, and giving people antibiotics without a prescription are all things that make bacteria that don't react to antibiotics spread. India is experiencing more and more cases of multidrug-resistant, or MDR, and thoroughly drug-resistant (XDR) pneumonia (TB), which is a big public health problem [43]. It is harder to treat infectious diseases when bacteria become resistant to common treatments. Some examples of this are non-typhoidal Salmonella, Klebsiella pneumoniae, and Staphylococcus aureus among others [44]. To create novel antimicrobial medications and treatment plans, we need to know how resistance works at the level of the molecular. For instance, it may modify the drug's the desired level, turn on the discharge pump, or use enzymes that prevent the drug from working. Everyone, which includes healthcare professionals, scientists, politicians, and the general public, needs to work together to stop multiple sclerosis (and other big AMR threats. Antimicrobial resistance should be tackled in a multi-dimensional way: (1) reinforced investment in research and development, (2) systems of incentives promoting considered usage of antibiotics, and (3) mechanisms of support promoting compliance with the antibiotics prescriptive treatment [45].

Methicillin-resistant Staphylococcus aureus (MRSA) Are unable you control methicillin? Staphylococcus aureus, more commonly known as (MRSA) is a major hospital-acquired bacteria that makes the outbreaks of antibiotic resistance worse around the globe. MRSA, also known is known to cause several kinds of illnesses, particularly in hospitals. These include pneumonia, toxic shock, and infections of the skin and soft tissue. These bacteria have grown resistant to other different kinds of antibiotics, like tetracyclines, macrolides, chloramphenicol, and methicillin [45],

resulting in it harder to choose a treatment. A study in India found that 24 percent of S. aureus isolates were extremely resistant to the antibiotic methicillin and other antibiotics. But vancomycin, which is now used as a last resort to treat MRSA infections, was still effective against all of the isolates that were looked at in the study [46]. MRSA makes persister cells and small colony changes that make it last longer in the environment. This leads to treatment failures and infections that don't go away. The strength and misuse of antimicrobial drugs in hospitals and communities are closely linked to the rise of MRSA and other antibiotic-resistant organisms [47]. MRSA and other drug-resistant infections are big problems for public health around the world that have big effects on healthcare and the economy, in addition to the problems they cause for individual patients. To stop the spread of MRSA, we need to use strict infection control measures, carefully give antibiotics, clean up the environment, and keep an eye on things all the time [44].

Carbapenem resistant Enterobacteriaceae (CRE) Never found in carbapenem It's very worrying that some Enterobacteriaceae (CRE) bacteria are resistant to more than one drug. Escherichia coli and Klebsiella pneumoniae are two important species in this family that are important in medicine. People used to think that carbapenems were the last resort for infections that didn't respond to other drugs, but they don't work on these kinds anymore [48]. The CDC says that "CRE is an imminent public health concern." In addition, there have been reports of in-patient cases in all 50 states, with approximately 9,300 cases indicated each year in the United States of America alone [49]. Infections with CRE are more likely to make people with weakened immune systems and babies sick to kill them [51]. CRE becomes resistant by making the enzymes like New Delhi metallo-beta-lactamase (NDM) and Klebsiella pneumoniae carbapenemase (KPC). These enzymes break down the antimicrobial agents These enzymes make treatment harder because they make bacteria resistant to carbapenems and other antibiotics as well [49]. Two important things that need to be done to stop this growing threat are stopping the spread of CRE in hospitals and keeping antibiotics working. We need strong infection control measures, better diagnostic skills, and new antimicrobial

medicines right away because CRE is spreading and starting to spread [50]. Global And Regional Trends AMR prevalence worldwide (WHO reports, CDC data)

The rise of multidrug-resistant illnesses around the world, which has gone up by 43% in recent years [52], shows that antimicrobial resistance (AMR) is quickly becoming a global health emergency. The rise of carbapenem-resistant Gram-negative bacteria is one of the most worrying things that has happened. It has made treatments less effective and made clinical outcomes worse [53]. Methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant Enterobacteriaceae (CRE), and Enterobacteriaceae that make extended-spectrum β -lactamase (ESBL) have been making people sick and killing themselves all over the world [52]. Those illnesses that don't respond to treatment are easier to spread across borders due to globalization and international travel. This makes it even harder to maintain them from spreading [53]. There are many ways that AMR can happen, including different types of bacteria, genetic factors, and resistance phenotypes. These ways are very different in different parts of the world and in different healthcare settings [54]. The economic effects of antimicrobial resistance (AMR) are huge. It is estimated that the cost of treating resistant illnesses around the world will be more than \$100 billion a year. Surveillance is very important, especially in low- and middle-income countries where the infrastructure and reporting systems aren't good enough to keep track of resistance trends. We need to work together across fields to fight the threat that AMR poses to the world. Putting in place strong antimicrobial stewardship programs, giving money to develop new ways to diagnose and treat infections, and making it easier to get accurate and timely surveillance data are all important strategies [52,55]. Public education campaigns and ongoing training for healthcare workers are both important for raising awareness of resistance trends and encouraging the safe use of antibiotics [53].

Resistance Trends in Developing vs. Developed Countries

Antimicrobial resistance (AMR) is a major and growing danger to health around the world. Rich and poor countries have very different patterns of resistance. *Escherichia coli* and *Klebsiella*

pneumoniae are common diseases in many poor countries, and the rates of resistance are worryingly high up to 60% in some places [56]. There are a lot of reasons for this high burden. For example, there is a lot of clinical abuse, bad or fake antibiotics are easy to get, there aren't many good ways to keep an eye on things, and people can buy antimicrobials without a prescription. Some of these are the common use of antibiotics in animals raised for food and the wrong use of them in hospitals, which makes them resistant in both medicine and farming. [57]. Countries alongside a lot of revenue usually have stricter legislation and regulations, but there are always gaps in them. This is especially true when it comes to making sure that the rules are followed and that people from various industries work together. The number of AMR cases in different countries also depends on how often citizens use antibiotics, how easy it is to get clean water and bathrooms, how good the public health system is, and how good the healthcare services are in general. High-risk clones can also spread quickly across borders when people travel internationally. This shows how important it is for people to be able to move around to spread organisms that are resistant [58]. To fix these problems, the world needs to work together. We need to work together more with other countries, promote antimicrobial stewardship everywhere, and improve surveillance in places where resources are limited in order to slow the spread of AMR around the world. [56,57].

Surveillance networks (GLASS, ReAct, etc.)

Antimicrobial resistance (AMR) is a big health problem all over the world, but it's worse in countries with low incomes [56]. The Global Antimicrobial Resistance and Use Surveillance System (GLASS) was set up by the World Health Organization (WHO) to keep an eye on AMR trends around the world in a consistent and coordinated way. This was in response to the growing threat [60]. GLASS has improved national monitoring systems, made doctors better at treating patients, and started programs in Africa, the Americas, and Asia to help people use antibiotics safely. The program caused a 15% rise in the number of countries that regularly share AMR data between 2017 and 2020. This means that more countries are committed to working together on a global scale to fight resistance. Even with these improvements, a lot of low- and middle-income countries still have a hard

time fully implementing GLASS. This is mostly because they don't have enough money, staff, or good infrastructure [61]. Fluoroquinolones and aminoglycosides are two important groups of antibiotics that are often used in clinical treatment. In India, for example, there has been a lot of resistance to them. Carbapenem-resistant *Klebsiella pneumoniae*, on the other hand, is still an exception, and its levels of resistance are still going up [62]. The European Union, on the other hand, has said that the rates of AMR are going down for some diseases. We need surveillance networks like GLASS and programs like ReAct and regional monitoring to keep an eye on resistance trends, guide treatment based on evidence, and change national law. But for these systems to work as well as they can, they need money, help from other countries, and technical help, especially in places where AMR is the worst. Things That Cause It to Happen

IV. CAUSES AND CONTRIBUTING FACTORS

Overuse and Misuse of Antibiotics in Humans.

Overusing and misusing antibiotics in people is one of the main reasons for antimicrobial resistance (AMR), which is a big threat to global health. Experts and regular people often say that the rise in resistant diseases is mostly because people don't follow their treatment plans, take antimicrobial drugs too often, or give them out too often [25,26]. The problem is worse because the rules for healthcare aren't strict enough, it's hard to get diagnostic tools, and antibiotics are easy to get without a prescription. Resistance microorganisms spread because of poor sanitation, throwing away antibiotics the wrong way, and the spread of pharmaceutical residues in the environment [26]. If we fail to do something associated with it, the rising number of AMR cases could undo decades of medical development and take us back to the time before prescription antibiotics, when prevalent ailments couldn't be cured [27]. We need to work together and use many different methods to fight AMR. This means accepting the "One Health" idea, which stresses how human, animal, and environmental health are all connected. [26, 27]. Some important strategies are making sure that there are strict government rules to stop misuse, teaching people how to use antibiotics correctly, and strengthening antibiotic stewardship programs. [26, 28].

Antibiotic Use in Agriculture and Animal Husbandry

The development and prevalence of antibiotic-resistant bacteria (AMR) are one of the acute global problems of population health. One of the principal contributory factors happens to be the large-scale use of antibiotics in the agribusiness especially in raising livestock. In intensive farming systems, giving animals antibiotics is a common way to help them grow and stay healthy [29, 30]. People use this a lot and don't care, which puts selection pressure on bacteria and helps resistant species grow and spread [29, 33]. There are a lot of ways for people to get these viruses that don't respond to drugs. For example, they can eat bad food, be around animals, or touch dirty water and soil [33]. Using important human antibiotics in farming, like fluoroquinolones and third-generation cephalosporins, is especially bad because it makes these drugs less effective and raises the risk of cross-resistance [34]. The One Health paradigm, which emphasizes the connections between human, animal, and environmental health, says that this issue needs a coordinated response from a number of different areas [34]. It would be helpful to make it harder to use antibiotics on farms, keep a closer eye on how antibiotics are used and how resistant they are, encourage veterinarians to be responsible with antibiotics, and help create alternatives to antibiotics like probiotics, vaccines, and better sanitation on farms [30, 34].

Poor Infection Control in Healthcare Settings

The main reason for the rise in antimicrobial resistance (AMR) is that healthcare facilities don't do enough to stop infections from spreading. This is especially true in developing countries [32]. Poor hygiene, not properly sterilizing medical equipment, hospitals that are too full, and not having enough isolation measures all make it easier for resistant bacteria to spread quickly in clinical settings [26, 35]. Systemic problems like limited access to diagnostic tools, poor healthcare infrastructure, and health systems that are too busy can make these problems even worse. Medical staff who don't get enough training in antimicrobial stewardship and don't have enough diagnostic support often prescribe drugs in the wrong way. Even when antibiotics aren't needed for medical reasons, patients' pressure and demand for them change how doctors write prescriptions [36]. Also, the illegal sale of antibiotics and the lack of regulatory

oversight make it possible for people to keep using them incorrectly, both in and out of medical settings [32,26]. Poor infection control and too much antibiotic use can lead to a higher risk of drug-resistant disease transmission, fewer treatment options, longer hospital stays, higher rates of illness and death, and high costs [35]. A One Health approach that focuses on the connections between animal, human, and environmental health is needed to solve these problems [26]. Important treatments include improving training for healthcare workers, making sure that proper hygiene is followed, strengthening infection prevention and control (IPC) protocols, and encouraging strict adherence to clinical guidelines based on evidence [36].

Inadequate Diagnostic Tools and Treatment Guidelines

There are two main reasons why antimicrobial resistance (AMR) is spreading around the world: treatment guidelines are unclear, and people can't easily get the tools they need to find it. These problems happen a lot in countries with low or middle incomes, but they can also happen in places with a lot of resources. A lot of people don't always follow the directions for taking antibiotics because of them [32]. Healthcare providers often give patients wide-spectrum antibiotics to treat possible illnesses, even when they shouldn't require them because there aren't any accurate methods for diagnosing them. This makes it easier for resistance to spread. The problem gets worse because there aren't any treatment guidelines that are based on facts and take the situation into account. Doctors who don't know how to properly prescribe antibiotics and there aren't any professional guidelines [36] make them less likely to work as well as they should. It's even worse when doctors and nurses don't always follow the rules and don't know how to use antibiotics the right way. There are fewer and fewer treatments that work because drug companies don't have enough money to research and develop new antimicrobials [37]. People all over the world are scared of AMR for this reason. It makes antibiotics work less well, raises the cost of medical care, and makes more people sick and die [35]. You need a plan that is well thought out and has a lot of moving parts to get around this. We need to make tests for diagnosis faster and cheaper, enhance the infrastructure of labs, and set and enforce standard

treatment protocols. This public health crisis is getting worse, and everyone, irrespective of where they choose to live, needs to help fix it. This includes making it easier for people to get good medicines, helping surveillance systems [26, 35], and keeping an eye on how antibiotics are spread.

V. IMPACTS OF AMR

Clinical consequences (prolonged illness, treatment failure)

Antimicrobial resistance (AMR) is a big and growing problem for public health around the world that makes it harder to treat diseases. AMR increases the acute condition, leading to lower responses to treatment and subsequent patient deaths, especially those who are already sick, ageing, or have low immunity [63,64]. Thus, clinicians are faced with growing challenges of treating common and severe infections as they become ineffective to drugs previously used successfully. This leads to the subsequent clinical performance of worse outcomes of patients involved, longer hospital stays, and reliance on more toxic or expensive medication. AMR makes it harder to treat bacterial infections in the clinic. This causes resistant strains to appear and spread, and traditional empirical treatments to fail. For this reason, treatment plans need to be updated often to take into account how resistance patterns change [65]. Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), carbapenem-resistant Gram-negative bacilli are some of the infectious diseases which have proved persistent, despite conventional antibiotics. These bacteria are becoming more and more connected to diseases that could kill you [66]. The main clinical issues are the overuse and misuse of antibiotics, a lack of enforcement, and healthcare systems that are not unified and do not follow the same rules for infection control and stewardship [63,64]. We need a comprehensive approach to fix these issues that includes better surveillance systems, ethical antibiotic prescribing practices, effective infection control methods, and ongoing funding for the development of new antimicrobial drugs [63]. A lot of people also need to learn about AMR, and countries need to work together to slow its spread. If people don't act quickly and work together, the world could go back to a time before antibiotics, when even small illnesses could kill people [64].

Economic Burden on Healthcare Systems

Antimicrobial resistance (AMR) is a big and growing cost for healthcare systems all over the world. Estimates say that AMR costs over €9 billion a year in Europe alone and about \$20 billion in direct medical costs in the US [67]. The main reasons for these costs are longer hospital stays, the need for more expensive and complicated treatments, and the money lost because of lower productivity and higher death rates. A thorough study done in France looked at the financial effects in more detail and came up with a total national cost of €109.3 million for AMR. The study found that patients with resistant infections stayed in the hospital for an extra 1.6 days and spent an average of €1,103 more on each hospital stay [68]. These numbers show that AMR not only raises the cost of healthcare in the US, but it also puts a strain on hospitals' resources and infrastructure. There are many things that affect AMR's global economic cost, such as poorly treated wastewater, wrong empirical prescription methods, and the fast movement of people and goods through international trade and travel [69]. Also, the cost of antibiotic resistance is very different depending on the type of medicine and the country's income level. For example, research shows that the average cost of an antibiotic in the US and Thailand is between \$0.1 and \$0.7 per unit [70]. These rising costs make it clear that we need to take action right away to stop AMR in a big way and for a long time. Some important solutions are to give more money to research and develop new antibiotics, encourage responsible drug use, strengthen initiatives for antimicrobial stewardship, and improve global surveillance systems so that diseases can be diagnosed and treated more quickly [67].

Threat to Surgeries and Immunocompromised Patients

Patients who are having surgery or have weakened immune systems, especially transplant patients, are more likely to have antimicrobial resistance (AMR). The spread of resistant diseases around the world has led to more illness and death, which makes it harder to treat these vulnerable groups [71,72]. Infections caused by multidrug-resistant organisms are especially bad for transplant recipients, and the lack of effective antimicrobial medications often leads to bad clinical outcomes [72]. It is especially concerning that resistant Gram-negative bacteria are showing up in intensive care units (ICUs) and among patients with

weakened immune systems. These germs are known to be hard to treat and can sometimes make patients' conditions worse very quickly [73]. Resistance makes preventative antibiotics less effective. The use of antibiotics is very important for stopping infections that can happen after surgical procedures. Infections like these can cause difficulties and make people stay in the hospital longer. Antimicrobial quality assurance programs have value due to the help people with weakened immune systems get better, lower resistance, and and make sure that antibiotics are used correctly. For these initiatives to work, surgery teams, transplant specialists, as well as individuals who know a lot about infectious illnesses need to work together. [71]. AMR is a major global public health issue that could undo decades of medical progress. If countries don't work together to take action, antibiotics may stop working in critical care and surgery, which could put future generations at risk. This growing threat needs a full approach that includes behavioral, social, economic, and animal health [74].

VI. STRATEGIES TO COMBAT AMR IN TREATMENT BASED MANNER

Development of New Antimicrobials

Research on novel antibiotics is crucial to addressing the waning efficacy of existing drugs. Innovation in this area remains the foundation for long-term AMR management.[75].

Research and Development of New Antibiotics and Vaccines

Antimicrobial resistance (AMR) is a global health problem that is getting worse and needs both short-term and long-term solutions [85,86]. Developing new antibiotics is still an important short-term strategy for fighting resistant species that are changing, but long-term solutions need to focus on evolutionary and preventive strategies [87]. Vaccines help fight antimicrobial resistance (AMR) by lowering the demand for antibiotics and the selection pressure that makes resistant strains appear. This is because they lower the number of diseases that people get [85,88]. One of the best things about AMR mitigation strategies is that they can stop primary infections and lower the number of secondary bacterial illnesses [86]. Researchers are looking into new ways to treat diseases. These include phage therapy, which uses

bacteriophages to kill bacteria that are resistant to antibiotics; microbiological cleaning, which keeps beneficial microbial habitats healthy; and microbiome transplants, which bring back healthy microbial communities [87]. There are, however, a number of things that make it hard to research and develop vaccines. Some of these are the complicated biology of viruses, the technical problems with making vaccines, and the difficulty in finding reliable correlates of protection, or biomarkers that show effective immune responses [86]. Current research is trying to solve these problems by learning more about how the immune system works and using the latest technology to make vaccines that are more accurate and delivery systems that are better [88]. Vaccines are a possible and preventive way to lower the need for antibiotics and stop the spread of disease, even though they are hard to make. This makes them an important part of long-term strategies for controlling AMR [86].

Plasmid Curing and Anti-Plasmid Strategies

The spread of resistance genes is being slowed by new techniques for eliminating or blocking bacterial plasmids that confer resistance. [76]

Genomics and CRISPR-Based Technologies

New genomic technologies, specifically, precision-targeted interceptive tools on the basis of CRISPR can be used currently. This has given rise to the achievement of gene-editing tools with the ability to prohibit resistance genes, high-throughput platforms that can diagnose pathogens rapidly, and personalised regimens with respect to the individual patient.. [77]

Phage Therapy

The growing problem of antimicrobial resistance (AMR) has made the search for new treatments that work better than antibiotics go faster. Even though it still takes a lot of time and money to make new medicines, scientists are finding more and more ways to fight diseases that don't respond to drugs [98]. One of the most promising methods is phage therapy, which uses bacteriophages viruses that only attack and kill bacteria as targeted therapeutic agents. This drug has a clear advantage in keeping the microbiota healthy and reducing unwanted side effects because it targets resistant bacteria directly [99]. Researchers are also looking into combination treatments that make existing antimicrobials work better. This is in addition

to phage therapy. One of these is using natural substances that kill bacteria, like propolis and essential oils. When used together, they may make medications work better. Nanotechnology is also making it easier to get medicine to patients and into their bodies, especially in places where infections are hard to reach [100]. Pathogen-Oriented Therapy (POT) is another new breakthrough that improves the effectiveness and specificity of treatments while lowering the risk of resistance development. It does this with precise, targeted treatments like CRISPR-Cas systems, antimicrobial peptides, and antibiotic-antibiotic conjugates [101]. Researchers are also looking into probiotics, monoclonal antibodies, vaccines, and phytochemicals. All of these things help the immune system fight off bacteria or stay healthy [98]. The way we combat AMR has advanced significantly with these new treatments. The findings provide new hope in the current fight against infections that are resistant to the traditional antibiotics.

CRISPR and gene editing

The rise of antimicrobial resistance (AMR) around the world has shown that we need better treatments than the ones we already have [102,105]. Scientists have learnt a lot of new and interesting things, like gene editing and CRISPR. Designing infection control agents that operate in a different mode of inhibition against bacterial growth compared with the classical antibiotics is an acute goal in modern microbiology. These would minimize the need of antibiotic treatment, and offer clinicians backup treatment against resistant microbes. On-going research in this field aims at utilizing gene-editing technology to determine and kill the genetic factors of antibiotic-resistance through the use of gene-editing systems CRISPR-Cas systems specifically. Through its genetical reduction of the systems that enable resistance to the commercially bought antibiotics, those investigators are hoping to normalize the sensitivity of the bacteria to those kinds of drugs and maintain their functionality [103]. Some CR drift-based antimicrob telomereslicaners can kill bad bacteria without hurting good ones. This makes the treatment more focused and less likely to cause problems. Gene-editing/genomic technologies are central technologies both in understanding pathogenhost interplay, resistance isolate determinants, and ensuring that antimicrobial

regimens can remain effective even in the face of populations. Their use improves diagnosis, increases surveillance, and allows coming up with unique treatment plans hence decreasing the rate of relapse and preventing resistance development [104]. More and more researchers are coming up with ways to treat AMR. Some of these are probiotics, aptamers, peptide therapies, phage therapy, and RNA-based drugs [103]. There needs to be more research on how to change the host's immune system and kill pathogens [105]. Selective breeding, microbiome manipulation, and gene editing in cattle are also new ways to use fewer antibiotics in farming and veterinary care [104]. These new technologies have a lot of good things about them, but there are also some things that make it hard for a lot of people to use them. For instance, they don't have enough money, they have to follow strict rules, and some people don't want them to be used [103]. These problems need to be fixed before gene editing and CRISPR-based technologies can be used successfully to fight AMR around the world.

Plant-based antimicrobials

Antimicrobial resistance (AMR) is still a big threat to health around the world, but plant-derived antimicrobials (PDAMs) are new and interesting ways to fight it [106]. Plants have a lot of chemicals that kill germs on their own. Some of these are quinones, alkaloids, flavonoids, and essential oils. They can kill viruses, fungi, bacteria, and parasites, and they don't usually have any bad side effects. These phytochemicals help microbes fight off infection in a number of ways, including breaking down their membranes, stopping the production of DNA and RNA, and messing up the formation of quorum sensing and efflux pumps [106]. You can also mix PDAMs with regular antibiotics to make them work better and maybe get around resistance mechanisms that are already in place [108,106]. This ability to work together shows how important it is to add plant-based compounds to modern antibacterial drugs. PDAMs are a promising way to treat drug-resistant infections because there aren't many other options and resistance to standard treatments is still growing [108,109]. They are a good choice for making new, safe, and effective antimicrobial drugs because they are not very toxic, work in many ways, and come from nature [106].

Immunotherapies and probiotics

People are becoming more and more worried about antimicrobial resistance (AMR), which has made it clear that we need to look into alternatives to regular antibiotics right away [103, 98]. Some of the retirees' most promising new ways to loot infections are immunotherapies, probiotics, bacteriophages, and antimicrobial peptides [110, n98]. Probiotics, in particular, have shown a lot of promise in preventing and treating infections. These living bacteria are important for keeping the immune system in check, stopping pathogens from spreading, and keeping the gut microbiota in balance [111]. New technologies like aptamers, phage therapy, and RNA-based drugs also help us find new ways to attack bacteria that are hard to kill. Even though these alternatives have a lot of promise, there are some issues with making and using them. These problems include not having enough money, having complicated rules, and worrying about how the public will react [103]. These new methods, however, are useful weapons in the fight against the AMR pandemic and could help us rely less on antibiotics that have been around for a long time [98,110].

VII. STRATEGIES TO COMBAT AMR IN PROGRAM BASED MANNER

Antimicrobial stewardship programs

The current global challenge of antimicrobial resistance (AMR) requires a very wide-ranging and diverse response in order to deal with it successfully. It has been empirically shown that the following interventions are vital to this cause.

Antimicrobial Stewardship Programs (ASPs):

ASPs provide a way of choosing the right antimicrobials, optimizing dosing regimens, reducing unnecessary duration of inappropriate therapy, and simultaneously decreasing ineffective prescriptions through judicious use of antibiotics, thus improving the outcomes of patients [75].

Enhanced Surveillance Systems

Prompt public health responses are made possible by expanding national and international monitoring systems, which improve the tracking of resistance patterns and outbreaks.[75]

Alternative Therapeutics

Analysing non-traditional treatment modalities such as bacteriophage therapy and antimicrobial peptides offers strategies to circumvent typical resistance mechanisms and boost the therapeutic pipeline. [77]

One Health Approach

To tackle AMR, an integrated approach that considers human health, agriculture, veterinary care, and environmental concerns is required. These sectors need to work together to prevent opposition from growing.[75]. There are still a lot of challenges to be solved despite these motivating strategies. These include a lack of funding for AMR research, low public awareness, and, in many places, subpar laboratory infrastructure [75]. To overcome these challenges, substantial investment in R&D, worldwide collaboration, and robust legal frameworks are required [77].

Infection Prevention and Control (IPC)

AMR is a big health problem in every country. To fix it, people, animals, and the environment all need to work together. One of the best ways to stop antimicrobial resistance is to use all of the infection prevention and control (IPC) methods. A few of these things tell people to wash their hands often, keep things clean, and get more people to get shots. These things all help stop the spread of infections, which means that not as many people need antibiotics. [75,78]. To cut down on the wrong use and overuse of antibiotics, we also need antimicrobial stewardship programs and national action plans. To make good decisions and set the right course of action, it is important to better track how antimicrobials are used and how resistance is growing [75,79]. Low- and middle-income countries (LMICs), on the other hand, often have a hard time successfully adopting IPC policies because they don't have the right infrastructure, money, or public awareness [78]. To get past these problems, agencies that carry out policies need to have better technical skills, better governance, and make sure that all sectors are committed to the same policies [79]. In addition, working together on a global scale is important for making sure that laws and rules are the same everywhere, especially in places like the Asia Pacific. The global campaign to get rid of AMR [80] needs to raise awareness and encourage cooperation between countries.

Public Awareness and Education

AMR is a global health crisis that is getting worse and needs a wide range of solutions to be managed properly. It is very important to change how people use antibiotics through public awareness and education programs. To design powerful tools to change mass opinion about the antimicrobial agents and promote adequate use pattern, one must implement the well-planned communications programs. These efforts must start with an identified key audience such as healthcare professionals, chemists, agricultural experts, etc. so that it reaches the audience during the time of need, and it would be measurable [81]. Application of multidisciplinary approach which combines behavioural science, psychology, and education helps significantly reduce the impact of cognitive biases, fixed behaviours, and the spread of misinformed data that help promote antibiotics misuse through the application of antibiotic stewardship measures.[82]. Other important educational goals are to limit the sale of over-the-counter drugs, encourage the responsible use of antibiotics, and improve infection control practices, such as hand hygiene.[83]. To make the best use of antibiotics, these efforts must be in line with bigger goals like the WHO's Aware classification system, antimicrobial stewardship programs, and the National and Global Action objectives. But these efforts do have some problems. It can be hard to run successful AMR awareness campaigns because not many people know about them, there isn't enough money, and changing people's behaviour is hard. To get rid of these problems, governments and other interested parties need to support education programs, encourage cooperation between sectors, and push for policies that are based on behaviour. In the end, community education is very important for controlling AMR and should be given the same level of importance as medicine research, regulation, and surveillance [84].

VIII. ROLE OF REGULATORY AND INTERNATIONAL BODIES

WHO's Global Action Plan on AMR

International efforts to address the growing issue of antibiotic resistance (AMR) have benefited greatly from the World Health Organization's Global Action Plan on AMR. The 'whole of United Nations approach,' which promotes cooperation among

numerous international organisations to combat AMR through coordinated, multisectoral action, is supported by this plan [89]. The main objectives of the Global Action Plan are to ensure access to safe and effective medications, encourage the responsible use of antibiotics, and assist in the creation and execution of National Action Plans in each of the member nations [90]. Antimicrobial stewardship, infection prevention and control, and strong monitoring systems to spot trends in antibiotic resistance and use are the main tactics of the plan [91]. For these projects to be implemented successfully, a robust regulatory framework is required. It promotes a whole-of-system approach that combines governance, policy, and enforcement mechanisms and provides the framework for enabling cross-cutting actions [90]. Singapore's National Strategic Action Plan, which demonstrates alignment with the WHO's global goal, is an example of successful national implementation. The prevention of infections, research, surveillance, education, and antibiotic optimisation are the five main focusses of this national policy [92]. Only a tiny percentage of international organisations still give priority to AMR in spite of these developments. To effectively address this complex issue, more interdisciplinary collaboration, sustained political commitment, and shared global accountability are sorely needed [89,91].

National and Regional AMR Action Plans

Antimicrobial resistance (AMR) is a big problem for the health of people all over the world that needs coordinated action from both national and international groups [93]. National Action Plans (NAPs) are very important for fighting AMR at the national level, but the type and amount of international cooperation they include varies a lot from region to region, especially in Europe [94]. To fix this problem and encourage cooperation between different sectors and agencies, some people have called for a "whole of United Nations strategy." It is interesting to note that 21 international organisations are currently working on AMR-specific projects and 36 organisations are working on AMR-sensitive projects [89]. This shows how important it is for different sectors to work together on a global scale. The National Action Plan for Singapore is a great example because it follows WHO guidelines and has a One Health approach. This plan brings together a lot of government and non-governmental groups to work together on all aspects

of AMR through coordinated efforts in research, education, infection prevention, surveillance, and optimising antibiotic use [92]. Many countries' NAPs don't put much emphasis on working together with other countries, even though some countries want to lead global AMR efforts [94]. To make sure that the world responds to AMR in a coordinated and effective way, we need to make it easier for national efforts to work with regional and international ones and strengthen global governance systems. One of the biggest problems that still needs to be fixed is the gap between the global scope of AMR and the implementation of solutions that are focused on the home country. This often makes it hard for countries to work together on international problems.

Policies from FDA, EMA, ICMR

The overuse and misuse of antibiotics in both healthcare and agriculture is a major cause of antimicrobial resistance (AMR), which is becoming a bigger problem around the world [91,95]. The U.S. Food and Drug Administration (FDA), India's Indian Council of Medical Research (ICMR), and the European Medicines Agency (EMA) are just a few of the international and regulatory groups that have made big rules and frameworks to help lessen the effects of AMR. Two important groups that make rules, help with monitoring systems, and promote the safe use of antibiotics around the world are the World Health Organisation (WHO) and the European Centre for Disease Prevention and Control (ECDC). These groups give governments and health systems technical help, action plans, and suggestions to help them plan and carry out projects in their own countries and around the world. The ICMR set up a statewide AMR surveillance network in India to gather information on antimicrobial resistance in a structured way to help make decisions about policies and treatment based on facts [97]. Because of this, the country is now better able to deal with resistance trends and improve how it handles antimicrobials. To come up with solutions that deal with the many causes of AMR, we need to take a One Health approach that includes the health of the environment, animals, and people [96]. Many national and international organisations that want to work together across sectors use this all-encompassing approach in their plans. Also, new ways of doing things are becoming more popular, such as making new antibiotic alternatives, using artificial intelligence

(AI) for early diagnosis, and using precision medicine to customise antimicrobial treatments [95]. More and more, rules are being put in place to support these new technologies. These rules are meant to make sure they are safe and effective while also encouraging new ideas. To really reduce AMR, there needs to be collaboration between different fields, strict enforcement of rules, better monitoring, and programs to teach the public [91,95]. Regulatory agencies often back and require Antimicrobial Stewardship Programs (ASPs) to improve treatment results, lower resistance, and encourage the responsible use of antibiotics [91].

IX. CONCLUSION

The antimicrobial resistance (AMR) has been labeled a global public health emergency, causing the impairment of life-saving antibiotic efficacy and complicates the control of infectious diseases. Expressed as overuse and misuse in the human, animal and agricultural sectors, AMR is enabled by genetic mutation, horizontal gene transfer, enzyme knockdown (e.g. 8-lactamases), efflux pumps and low membrane permeability. The MRSA, CRE, MDR-TB, and the ESCAPE group of pathogens have become linked to treatment failure, long-term disease durations, and increased death rates. The poor levels of diagnostics, poor infection-control procedures, and restricted regulation of quality have caused this burden to be excessively high in developing nations. The other costs that are incurred through AMR relate to increased length of stay in hospital and dependence on more expensive therapies. Effective methods are needed to combat AMR and are very complex. These strategies are antimicrobial stewardship programs, global surveillance systems (e.g., GLASS) and implementation of one health, education of the population and regulatory change. The potential solutions include the improvement in alternative therapeutics (phage therapy, CRISPR-based gene editing, and vaccines, plant-derived antimicrobials, etc.). A post-antibiotic world can be avoided through continuous financial investment in research, united international governance and robust policy enforcement. Unless immediate and combined action is taken to face the problem of AMR, it will turn the medical achievements of the past into waste and will not enable the future generations to fight infections efficiently.

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