Antimicrobial Resistance and strategies to combat AMR

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***Abstract*— Antimicrobial resistance [AMR]is global health problem with 1.27 million deaths in 2019 and trillions of dollars in potential economics losses by 2030, antimicrobial resistance (AMR) is a serious global health concern. The initiative is spearheaded by World Health Organization's (WHO) Global Action Plan (GAP), which advocates for a "One Health" approach that acknowledges the interdependence of environmental, animal and human health. Antimicrobial stewardship is essential, emphasizing, patient education, accurate diagnostic profiling, appropriate antibiotic prescription, and stringent hospital hygiene standards. Light based treatments like antimicrobial blue light, Photodynamic inactivation, and Cold atmospheric Plasma, as well as bacteriocin-natural, non-toxic antimicrobial peptides- are promising new research directions. These novel methods employ a multi- target mechanism that reduces resistance by harming the genetic material lipids, cells of bacteria, protein. To combat AMR, international cooperation is crucial. Global commitments are intended to be strengthen high-level ministerial conferences and consistent investment is essential to the creation an application of successful plans. Governments, healthcare systems, research organization, and the global general public must work together to guarantee that life- saving drugs continue to be effective for upcoming generation. We can lessen the effects of AMR and safeguard public health by fusing traditional tactics with creative fixes and international collaboration.**

I. INTRODUCTION

When bacteria, virus, fungi, and parasites stop responding to antimicrobial medications, it's known as antimicrobial resistance, or AMR. Drug resistance raises the risk of disease transmission, serious illness disability and death by making antibiotics and other antimicrobial medications ineffective and making it harder or impossible to treat infections.

Antimicrobial resistance (AMR), which allows bacteria and other microorganisms to undergo genetic changes and withstand the drugs meant to eradicate them, is caused by overuse and misuse of antimicrobial drugs in both humans and animals. Following the adoption of the global action plan (GAP) on AMR at the 2015 world health assembly, nations pledged to create and carryout multisectoral national action plans utilizing a one health approach to address AMR. The GAP was later approved by the food and agriculture Organization (FAO), the world Organization for animal health and the governing bodies of united nations environment program.

The AMR Multi-partner trust function Global Action Plan, and the ground breaking multisectoral AMR targets were the result of three Global level Ministerial conferences on AMR, held in Oman in 2022 and the Netherlands in 2014 and 2019. In 2024, the kingdom of Saudi Arabia will host a fourth high level ministerial conference. One of the biggest threats to global health and public health is antimicrobial resistance (AMR). Bacterial AMR is thought to have contributed to 4.95 million deaths worldwide in 2019 and been directly responsible for 1.27 deaths. In addition to health and disability, AMR has significant economic costs. The World Bank estimate that AMR could result in US$ 1 trillion additional healthcare costs by 2050, and US$ 1 trillion to US$ 3.4 trillion gross domestic product (GDP) losses per year by 2030.

AMR affects nations across all geographic locations and income brackets. The United States, Kuwait, China have the highest rate of antibiotic resistance.

According to a 1991 and 2001 study on resistance patterns some of the most common bacteria in China, hospital acquired infections were highly prevalent. Additionally, resistance is growing at fastest rate in China. The US had the lowest resistance growth between 1999 and 2003, while Kuwait had the second

largest growth between 1999 and 2003. A tiny dose of penicillin miraculous cured the first streptococcal infection in patient in US in 1942. Streptococcus that is resistant to penicillin is common 60 years later. Sine both old and new infectious diseases continue to pose a serious threat to public health, such antimicrobial resistance puts the health of many people worldwide at risk. Methicillin-resistant Staphylococci infections were treated with the glycopeptide vancomycin in 1958. However, vancomycin-resistant strains of coagulase-negative Staphylococci (CoNS) were discovered in 1979, two decades later, and vancomycin-resistant strains were discovered ten years later.[1]

In 1996, the third-generation fluoroquinolone levofloxacin was added to the list of antibiotics, and that same year, levofloxacin-resistant Pneumococcus was discovered [2]. Introduced in 1980, carbapenem is a β-lactam that has been kept as a backup medication to treat infections brought on by Enterobacterales, particularly those that are resistant to cephalosporins. Since 2006, reports of carbapenem-resistant Enterobacterales (CRE) have come from various nations due to its increased use in the 1990s and 2000s [3]. Since they have prevented infectious diseases from killing millions of people, antibiotics are one of the most significant discoveries of the 20th century. Due to strong selection pressure brought on by the growing use and abuse of antibiotics over time, microbes have developed acquired antimicrobial resistance (AMR) to numerous medications. Through a variety of drug-resistance mechanisms, a vast array of interrelated healthcare and agricultural factors control the development of AMR.

II. DOMAINS OF AMR RISK FACTORS ARE

1) Sociodemographic characteristics such as living in urban area, being a migrant, and having a low income.
2) Clinical data about the patient, such as the state of illness and specific test findings.
3) Admission to medical facilities including duration of hospital stay and invasive procedures.
4) Drug exposure including the use of antibiotics in the past or present.

The development and spread of AMR are linked with inadequate oversight and regulation, poor patient adherence to antibiotic therapy and inappropriate medical prescribing practices. [4]

The risk of previous and current medications (particularly antibiotics), monotherapy, combination therapy and drug exposure were among the risk factors for drug exposure. Because resistance is linked to high level of antibiotic use, drug exposure is significant factor in AMR.

III.HIDDEN MECHANISM OF AMR

Antibiotics are typically modified or degraded by enzymes, their entry into cells is restricted to prevent accumulation, metabolic pathways are altered, binding sites such as ribosomes are modified to decrease drug efficacy, and efflux pumps are activated to remove antibiotics from cells before their levels can reach sufficient levels [5], [6].Biofilms, which are surface-bound communities with variable nutrition levels and restricted antibiotic penetration, can also be formed by bacteria. The bacteria are further protected by these biofilms. Furthermore, bacteria are adept at horizontal gene transfer, which is made possible by plasmids and other mobile genetic elements, to acquire resistance genes from neighboring cells or even different species. [7]

These acquired genes allow MDR to spread quickly across microbial populations because they often contain multiple complex resistance mechanisms in a single unit. Microorganisms possess a diverse range of resistance strategies due to their ability to transfer genetic information efficiently horizontally. These strategies can be modified as needed to ensure survival against ongoing advancements and the use of antimicrobial treatments by the medical field.

When a drug loses its ability to inhibit or regulate the activity of a previously susceptible microorganisms (bacteria, virus, fungi or parasites), AMR develops. Because of this, the standard treatment regimen is not longer effective, which makes it harder to control infections, increases the chance that the infection will spread to other people, and in certain situations increases the risk of death for some patients in comparison to those infected by non resistant pathogens. Bacterial infections are treated with antibiotics which are antimicrobials.[8]. For bacteria,

virus and parasites among other microorganisms, AMR arises naturally as part of their evolutionary process. [9]

In the absence of antibiotic- induced selection, spontaneous gene mutations can lead to intrinsic development of antibiotic resistance. When at least one bacterium in a diverse colony of bacteria carries the genetic determinant capable of expressing antibiotic resistance, the bacteria acquire antibiotic resistance. The kind and degree of resistance that the bacterial cell ultimately expresses are characterized by the genetic determinants. No matter how a gene is introduced into bacterium, resistance arise from its efficient expression, which can be passed onto other bacteria and cause them to produce a noticeable biological effect that prevents antibiotic from working.

All organisms exhibit AMR throughout their development which is an inevitable evolutionary phenomenon. The World Health Organization (WHO) has recognized AMR as one of the top three threats to public health. To protect against the deadly selection pressure, antibiotic resistance infections have been identified as the third most common cause of genetic mutations that result in death.

IV.MAJOR DRUG-RESISTANT BACTERIA

Antibiotic resistance and its effect on human health with an emphasis on how resistance affects species that are frequently linked to infections. The most common bacteria that are resistant to antibiotics include *non-typhoid Salmonella, Klebsiella Pneumoniae,* and *Staphylococcus Aureus.* These bacteria are life threatening challenges all over the world.

According a significant study released in January 2022, AMR infections were estimated to have caused 1.27 million deaths in 2019 alone, while drug resistant infections were somehow linked almost 5 million deaths. Methicillin-resistant *Staphylococcus aureus* (MRSA), a well-known example of first “superbug”, is linked to high number of deaths worldwide from infections that are resistant to antibiotics [10]. Currently, MDR-TB (multiprogramming resistant tuberculosis) accounts for 3.5% of active TB cases globally. Concern over XDR-TB (extensively drug-resistant tuberculosis) among many MDR-TB cases in is growing.[11] Despite being crucial in the fight against bacterial infections, antibiotics have been misused and abused for decades at inappropriate dosages and Times, which has led to selection pressure and the emergence of resistant bacteria.

Tuberculosis: Major cause of antimicrobial resistance Multidrug resistant TB, which is drug-caused by bacteria and does not respond to isoniazid and rifampicin, is treated with second line extensively drugs, but in certain cases, drug resistance may develop. IN terms of MDR-TB public health., approximately 2 out of 5 patients with drug resistant TB treatment in 2022.

Klebsiella Pneumoniae: Common intestinal bacteria which exhibit increased resistance to antibiotics such as carbapenems, which is causing resistance in various areas. According to Organization for Economic Cooperation and Development projections, antibiotic resistance is expected to increase more than it is now.

Chlamydia trachomatis: Sexually transmitted infections are caused the bacteria *Chlamydia trachomatis*. Point mutations in the gyrA quinolone resistance determining region are a major mechanism of fluoroquinolone resistance, while tetracycline resistance is typically associated with the presence of foreign genome islands integrated in the chlamydia chromosome. Azithromycin resistance in this bacteria is frequently caused by mutations in the peptidyl transferase region of 23S rRNA genes. Rifampicin resistance is caused by a nucleotide substitution in the rpoB gene, and resistance to aminoglycosides, lincomycin, and sulphonamide/trimethoprim combinations has been developed through a variety of mechanisms.

Staphylococcus aureus: Significantly adaptive, Staphylococcus aureus is a dangerous human pathogen. Clones that are resistant to antibiotics quickly arise primarily through the acquisition of antibiotic-resistant genes from other strains of S. aureus or even from other genera.[18] Both conjugation and bacteriophage transduction are the main methods of transfer, with the latter being thought of as the main pathway.[20] Transfer is mediated by a wide variety of mobile genetic elements. terms of the variety of plasmids that can be transferred by

conjugation and the efficiency of transduction, recent research on these processes indicates that transfer by these mechanisms may be more widespread than previously believed.[19] In light of S. aureus's biology as a human commensal and a potentially fatal pathogen, we go over the primary pathways of antibiotic resistance gene transfer.[12]

Salmonella Typhi: By the late 1980s and early 1990s, reports of multidrug-resistant (MDR) Salmonella Typhi—which is resistant to the three first-line [22] medications (ampicillin, trimethoprim and chloramphenicol) —were coming from several southern and Southeast Asian nations, including Pakistan and India. [13] The preferred medication after that was ciprofloxacin, but resistance quickly developed, initially showing up in 1991 as well as during a 1997 outbreak.[21] Typhoid fever has been treated with third-generation cephalosporins [25] macrolides, and carbapenems more frequently since the advent of MDR Salmonella Typhi and MDR with fluoroquinolone resistance. In Hyderabad, Pakistan, in 2016, reports of Salmonella Typhi that was extensively drug resistant (XDR), which is defined as resistant to first-line antibiotics, a fluoroquinolone, and a third-generation cephalosporin, were made.[13] Since then, travel-associated infections have been reported in Canada[23], Denmark[24], Australia[27] and the United States[26], and the WHO has been informed of over 10,365 XDR Salmonella Typhi infections in Pakistan. Salmonella Typhi's antimicrobial resistance (AMR) is therefore a worldwide concern.

Pseudomonas Aeruginosa:
Resistant to antibiotics Because of the development of biofilms, efflux pumps, and the quick acquisition of resistance genes, Pseudomonas aeruginosa is a pathogen that is well-known for its adaptability in clinical settings. Efflux pumps are essential for *P. aeruginosa* development of intrinsic antibiotic resistance. Under antibiotic choice stress, P. aeruginosa has an increased chance of surviving thanks to its capacity to export the antibiotics. Efflux pumps can use ATP or proton motive force [14] to pump particular substrates across the cell membrane and out of the bacterial cells, including different classes of antibiotics (e.g., fluoroquinolones, beta-lactams, and tetracyclines) and other toxic molecules [15].

V.CURRENT APPROACHES TO COMBAT AMR

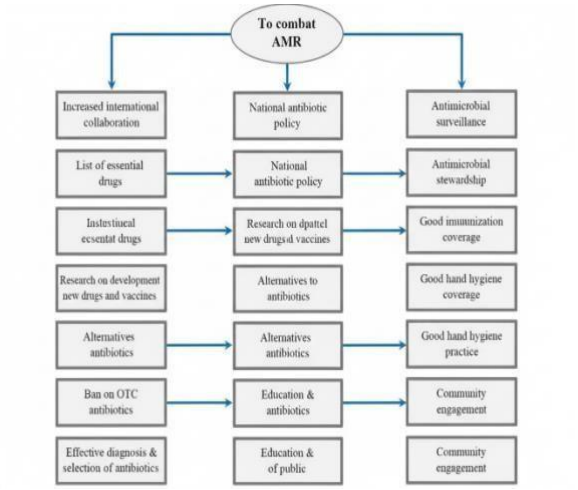

Figure (1): -Current approaches to combat AMR.

Reasonable antibiotic prescription limited use of prophylactic antibiotics, patient education, antibiotic therapy compliance, and proper hospital hygiene through antimicrobial stewardship are some of the primary strategies to combat Antimicrobial Resistance (AMR). Accurate antimicrobial profilin for targeted antibiotic therapy is also crucial. The following actions are part of the five major strategic action plans that the World Health Assembly adopted to combat AMR:

- Increase knowledge and comprehension of antibiotic resistance
- Increase understanding of infection control strategies through research and surveillance
- Put in place efficient measures for infection prevention, hygiene, and sanitation
- Make the best use of antibiotics for both human and animal health
- Promote long term investments in vaccines, diagnostic equipment and new medications
- Certain bacteria produce natural antimicrobial peptides called bacteriocins, which have bactericidal or bacteriostatic effects on strains of bacteria that are similar or phylogenetically related.

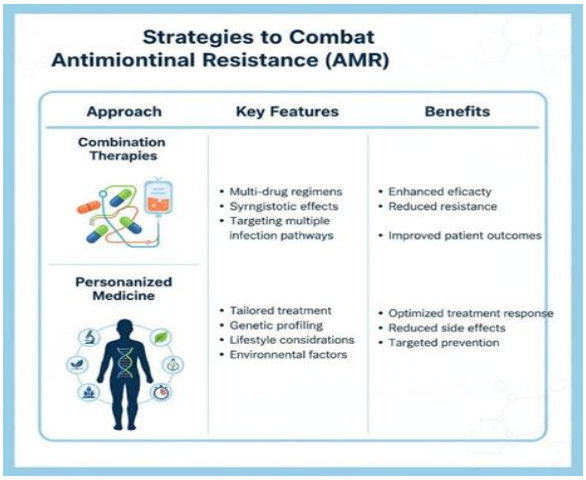

Figure (2): - Strategies to combat AMR

Numerous bacteriocins are currently being investigated for their possible application as antibacterial therapy because of their innocuous nature which would make them perfect agents. A common food preservative, Nisin is an example of a bacteriocin that come from the antibiotic family of antibacterial peptides and is generated by some gram-positive bacteria, including Lactococcus and Streptococcus species.

Additional methods that have been employed to stop AMR. Antimicrobial tolerance----Many light-based techniques show effective killing regardless of drug resistance in microorganism. Studies conducted in vitro and in vivo have shown that the light-based therapies have strong bactericidal activity.

a. Blue light that is antimicrobial (ALB)
b. Photodynamic inactive antimicrobial (aPDI)
c. Light pulses (PL)
d. Plasma in the cold atmosphere (CAP)
e. UV rays (Ultraviolet rays)

Light based treatment considered to have low risk for development of tolerance. This treatment based on multitarget leading to deterious effect (Cell, Protein Lipid, Genetic, etc.).

VI.CONCLUSION

The misuse and overuse of medications has resulted in antimicrobial resistance (AMR), a major threat to global health. By 2030, it is predicted to cause up to cause $3.4 trillion in economic losses and millions of deaths. The WHO's Global Action Plan promotes a multipronged strategy that includes improved antimicrobial stewardship, new diagnostics and treatments, and increased surveillance. New approaches that show promise include light-based therapies and bacteriocin. Since AMR is an unavoidable evolutionary process accelerated by human practices, addressing it also requires an understanding of its mechanism and risk factors, such as past antibiotic use and extended hospital stay. Implementing solutions requires international cooperation. Addressing AMR, an inevitable evolutionary process accelerated by human activity, requires a comprehensive strategy. To create and execute successful strategies, this calls for teamwork. We can prevent the spread of resistance and maintain the effectiveness of antibiotics by adopting a One Health approach. Additional delays run the risk of reversing the pre-antibiotic susceptibility patterns that have historically supported the dominance of infectious disease mortality, which could jeopardize both the security of global health and modern medical capabilities.

VII.FUTURE ASPECTS

A number of innovative tactics have recently been proposed to stop the spread of resistance. These include the CRISPR-Cas9 gene-editing method, lytic bacteriophage particles, biofilm disruption, efflux activity inhibition, closing of the mutant selection window (MSW), nanoantibiotics, and engineered antimicrobial peptides. [16] [17].The application of these tactics, either separately or in combination, has demonstrated promise in reducing resistance and promoting beneficial therapeutic results. In order to reduce AMR, the new personalized medicine paradigm necessitates creative solutions like enhanced and precise point-of-care diagnosis and treatment. One new and extremely promising nucleic acid manipulation and detection technique that may be used to control AMR is the CRISPR-Cas system.

In order to impending "post-antibiotic" era, the specifics of some AMR-mitigating strategies while pointing out their shortcomings. It also discusses the developments in CRISPR-based technology as a crucial point-of-care tool for monitoring and reducing AMR.

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