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Review Article

Antimicrobial Resistance: An Emerging Concern for Humans

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Abstract: Most of the pathogens have developed the ability to combat advanced antimicrobial agents due to which bacterial infections have become complicated to treat. It may occur when microorganisms such as fungi, parasites, and bacteria change their behavior against conventional antimicrobial agents. Some bacteria are intrinsically resistant to some of the antimicrobial agents, if not, they may become resistant by de novo mutations or acquiring some resistant genes. Antimicrobial resistance (AMR) has become a global issue because it may spread worldwide through trade, travel, migration, and healthcare facilities. Antimicrobial resistance has been associated with adverse consequences in the context of invasive infections, including escalated hospital costs, heightened mortality rates, and prolonged hospital stays. In the case of the disturbing normal flora of the intestine, serious and incurable health problems and sometimes death also occur. To combat this rising havoc many emerging approaches are being considered to combat AMR. Some of these include one health approach, phage therapy, nanoparticles, medicinal plants and metals. This review article discusses the leading causes of antimicrobial resistance, its economic impact, and employing emerging approaches as an effective way to treat antimicrobial resistance.

Keywords: Antimicrobial Resistance, One Health Approach, Pathogens, Phage Therapy, Public Health, Vaccines.

1. INTRODUCTION

Antimicrobial resistance (AMR) is a major worldwide health threat [1]. AMR caused 4.95 million deaths worldwide in 2019, according to estimates [2]. The predominant etiological agents responsible for this condition primarily include six pathogens, namely *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [3]. AMR results when microorganisms including bacteria, fungi, parasites and viruses evolve to the extent that they eventually become resistant to antimicrobial medications, such as antibiotics, which are used to treat such conditions [4]. Most of the pathogens have developed the ability to combat advanced antimicrobial agents due to which bacterial infections have become complicated to treat [1]. In history, humans become reconciled to many bacterial outbreaks. With the unearthing of penicillin midway through the 20th century, scientists found a way out by developing agents against pathogens to fight these maladies [2]. During the era (1930-1960) a vast variety of antimicrobials were discovered and made available [5]. Globally the death rate increased due to resistance in pathogens against traditional medications and treatments, the leading cause of which was overuse/misuse of antimicrobials [2]. Multi-drug resistance was spotted initially in the late 1950s and early 1960s in some members of the family *Enterobacteriaceae* [5]. According to the facts given by United States Pharmacopeia (USP), it is evaluated that 0.7 million deaths per year are the result of antimicrobial resistance and if this issue is not properly addressed and resolved death rate can increase up to 10 million per annum till the year 2050 [6].

2. DATA COLLECTION STRATEGY

Through an extensive examination of relevant scholarly works, essential data was gathered, evaluated, and employed to comprehend the

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ramifications and financial burdens associated with antimicrobial resistance on a global scale. Information was obtained by utilizing various search engines and databases such as Google, Google Scholar, PubMed, Microsoft Academic, and Scopus. Additionally, searches were conducted within reputable health organizations and websites including the CDC, WHO and other comparable sources. The review exclusively encompassed published articles authored in the English language. The present study employed a range of search terms, namely "AMR and global burden," "Antimicrobial resistance implications," and "AMR and disease burden," to collect pertinent information.

3. GLOBAL BURDEN OF ANTIMICROBIAL RESISTANCE

The emergence of antimicrobial resistance (AMR) has become a huge concern, prompting the constant monitoring of infection and mortality rates associated with this phenomenon. According to data from the United Kingdom, the estimated incidence of antimicrobial resistance (AMR) infections was 65,162 individuals diagnosed in 2019, representing an increase from the 61,946 patients recorded in the previous year. In contrast, the European Centre for Disease Prevention and Control (ECDC) has documented that within the European Union (EU) exclusively, the incidence of AMR has escalated to exceed 670,000 cases on an annual basis. Based on the findings of a previous investigation [7], it has been determined that in the year 2019, a total of 4.95 million fatalities across the globe were associated with bacterial antimicrobial resistance. Furthermore, it was observed that 1.27 million of these deaths were directly attributable to bacterial AMR. It has been previously documented that the yearly mortality rate attributable to AMR is anticipated to escalate to 10 million by the year 2050. Asia and Africa have been identified as the regions with the highest estimated mortality rates attributed to antimicrobial resistance. This can be primarily attributed to their large populations and the lack of regulatory measures in place for AMR prevention. Based on prior scholarly investigations, it has been established that Sub-Saharan Africa exhibits the most elevated all-age mortality rate within the Global Burden of Diseases (GBD) region. It has been specifically associated with or connected to AMR. In stark contrast, Australasia recorded the lowest rate of mortality attributed to AMR in the year 2019 [7].

4. CAUSES OF ANTIMICROBIAL RESISTANCE

Those drugs which were formerly called the saviour of life on earth stopped working lately owing to the emergence of bacterial resistance to multiple antimicrobials [8]. Due to the unregulated use of antibiotics and incomplete treatment of bacterial infections it has become a global issue. Overuse of antibiotics closely correlates with the disclosure of the resistance against them. Inappropriate antimicrobials can trigger spontaneous mutations in microbial genes leading to resistance. The use of antibiotics is unregulated as these medicines are available everywhere without prescription [9]. The US Food and Drug Administration (FDA) highlights the major point that majority of the doctors prescribe antibiotics to patients suffering from sore throat and flu [10]. Antimicrobial resistance is also caused by the extensive use of broad-spectrum antibiotics. Most of the time physicians avoid proper testing. Rather than targeting the main pathogen after proper clinical investigations by using narrow-spectrum drugs doctors prescribe broad-spectrum antibiotics to avoid laboratory analysis [8]. Using an old or someone else prescription is also a wrong practice because each prescribed antibiotic is for a specific infection and hence cannot be used for every infection or in any other condition. Using old prescriptions can make the bacteria resist [10]. The resistant bacteria are not killed by antibiotics they multiply rapidly and dominate the entire microbial community. The vigorous use of antibiotics in agriculture and livestock is also a major hub of the production of resistant bacterial strains. Antimicrobials are extensively used in fodder to make sure animals do not get infected. The bacterial strains in livestock become resistant and are passed on to humans after the consumption of meat by them. Resistant strains also merge with the environment as they are part of animal waste and thus resistance continues to spread [11]. The availability of new antimicrobials (which can kill resistant strains) is reduced because pharmaceutical industries are no longer interested in funding for them as they are of no profit value [12]. Secondly, if new antimicrobials become available easily at every pharmacy, then, they will again prescribe repeatedly thus spreading resistance against themselves [13].

5. DRIVERS OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is a complex phenomenon that is influenced by a multitude of factors, including intrinsic characteristics of the microorganisms and a range of environmental factors that are influenced by both prescribers and consumers. In a comprehensive analysis, the factors that contribute to AMR can be classified into four distinct categories. Firstly, environmental factors play a significant role, encompassing aspects such as population density and overcrowding, rapid transmission facilitated by mass travel, inadequate sanitation practices, ineffective infection control programs, and the widespread use of antimicrobials in agriculture. Secondly, drug-related factors contribute to AMR, including the presence of counterfeit or substandard drugs, as well as the unrestricted availability of antimicrobials without prescription. Thirdly, patient-related factors also contribute to the development of AMR, such as poor adherence to prescribed treatment regimens, poverty, limited education, self-medication practices, and misconceptions about the appropriate use of antimicrobials. Lastly, physician-related factors, such as inappropriate prescription practices, inadequate dosing, and a lack of up-to-date knowledge and training, also contribute to the emergence and spread of AMR [14]. The emergence of resistance is a multifaceted phenomenon that not only poses a threat to human health but also has significant implications for the environment. This is particularly evident in the context of global travel and trade, where the movement of food products can serve as a vector for the dissemination of resistant organisms. As depicted in Figure 1, the impact of resistance development extends beyond the realm of human health and underscores the need for a comprehensive approach to address this complex issue [15].

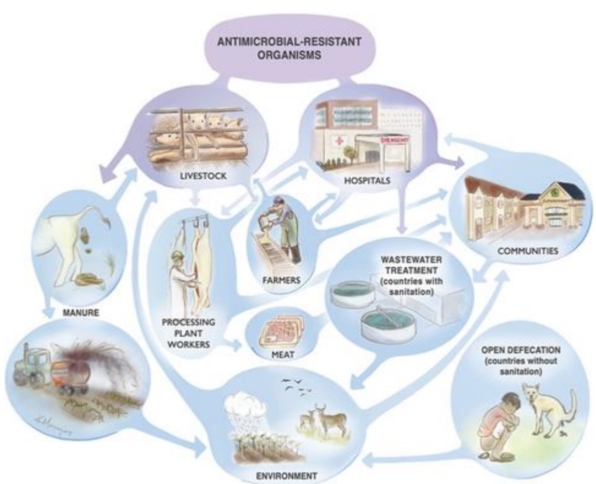

Fig. 1. Dissemination of antimicrobial-resistant organisms [13].

6. CLINICAL OUTCOMES AND ANTIMICROBIAL RESISTANCE

Antimicrobial resistance has been linked to negative outcomes in invasive infections, such as increased hospital expenditures, mortality, and stay duration. This finding has been attributed to a variety of factors, including a delay in implementing effective treatments, less effective definitive therapy compared to that available for susceptible bacteria, and the virulence of some resistant species (Table 1) [16]. Lambert *et al.* [17] investigated in a study between January 1, 2005, and December 31, 2008, they gathered information on 119 699 patients who had spent more than two days in 537 intensive care units across 10 different nations. The higher risk of death (hazard ratio) for pneumonia is present in the completely modified model ranging from 17 (95 percent CI 14–19) for S aureus is drug-sensitive to 35 (29–42) for *P. aeruginosa* is drug-resistant. The excess risk for bloodstream illnesses varied from 21 (16–26) for *S. aureus* which was drug-sensitive to 40 (27–58) for *P. aeruginosa* which was drug-resistant. For a combination of pneumonia and bloodstream infections, antimicrobial resistance increased the probability of death from infections by 12 (111–14) in the case of pneumonia and by 12 (09–15) in the case of septicemia. They concluded that pneumonia dramatically lengthens hospital stays in intensive care units, and increases mortality from healthcare-associated bloodstream infections, and death overall; however, the most prevalent antimicrobial resistance patterns have only a small additional impact [17]. So, antimicrobial resistance can affect the fitness of microorganisms as it can boost their strength to survive in critical conditions and enhance their pathogenicity. One of the most important elements that can cause proper medication to be delayed is a discrepancy between the analytical therapeutic agent and subsequent susceptibility results for a specific organism [18].

Table 1. Representative reports of attributable costs, excess lengths of stay, and risks of mortality associated with various anti-microbial resistance pathogens.

Type of antimicrobial-resistant infection	Increased risk of death	Attributable (days)	Attributable costs
MRSA bacteremia	1.9	2.2	US$6,916
MRSA surgical infection	3.4	2.6	US$13,901
VRE infection	2.1	6.2	US$12,766
Resistant *Pseudomonas*	1.8–5.4	5.7–6.5	US$11,981–32,949
Resistant *Enterobacter* infection	5.0	9	US$29,379
Resistant *Acinetobacter* infection	2.4–6.2	5–13	US$3,758
ESBL or KPC-producing *Escherichia coli* or *Klebsiella* infection	3.6	1.6-fold increase	1.7-fold increase

* ESBL: Extended-spectrum β lactamase; KPC: *Klebsiella pneumonia carbapenemase*;
VRE: Vancomycin-resistant *enterococci*; MRSA: Methicillin-resistant *staphylococcus aureus*

7. EVALUATION OF THE FINANCIAL IMPACT OF ANTIMICROBIAL RESISTANCE

Poverty and the gap in knowledge between developed and developing countries are going to increase due to antimicrobial resistance. Due to an increase in the resistance of livestock, treatments become ineffective and increase people's death rate due to the severity of infection [19]. This may result in a decrease in livestock trade and an increased price rate of protein, milk, eggs, and meat; all this exerts pressure on the economy [20]. Even in the greatest institutions around the world, the rising incidence of resistant infections is raising healthcare costs, making infection management more challenging, and harming patient outcomes. Therapy becomes more challenging, requiring less tried-and-true procedures and therapies as well as more awareness among healthcare professionals. Reduced income can cause families to experience financial losses as long-term illness and premature death wreak havoc. In addition, using antibiotics inappropriately, such as taking them for a cold, results in needless out-of-pocket expenses for a medication. Instead, this money may be applied to the cost of necessary medications or the cost of education. AMR has a major influence on healthcare prices; an estimated $700 will be added to the cost of treatment for a resistant bacterial illness [21].

8. EMERGING APPROACHES TO LIMIT ANTIMICROBIAL RESISTANCE

8.1 One Health Approach

Antimicrobial resistance (AMR) is a burgeoning concern that necessitates a cohesive global strategy. “One Health” embraces the concept that there is a clear connection between the health of both humans and animals and the shared surrounding environment. After careful consideration of all relevant factors, it is evident that AMR has emerged as a highly significant concern within the framework of the “One Health” approach. This is primarily due to its capacity to rapidly disseminate throughout populations, as well as infiltrate the food chain, healthcare facilities, and the environment; consequently, the management of numerous infectious diseases in both human and animal populations becomes considerably more complex. The “One Health Concept” (Figure 2) embodies a multidisciplinary approach that necessitates the collaborative involvement of all relevant stakeholders to effectively participate in this initiative. The World Health Organization (WHO) has engaged in a close partnership with the Food and Agriculture Organization of the United Nations (FAO) and the World Organization of Animal Health (OIE) to ensure that comprehensive measures are implemented across all sectors to mitigate the risks of AMR stemming from this approach [22]. One of the approaches employed to enhance recognition of the issue of AMR was the initiation of the “Global Antimicrobial Awareness Week”. Since the year 2020, the designated term “World Antimicrobial Awareness Week” has been employed to encompass a comprehensive range of antimicrobial agents, including antibiotics, antifungals, antiparasitic, and antivirals. This global initiative endeavors to enhance global consciousness regarding AMR and promote optimal approaches among the general populace, healthcare professionals, and policymakers to mitigate the

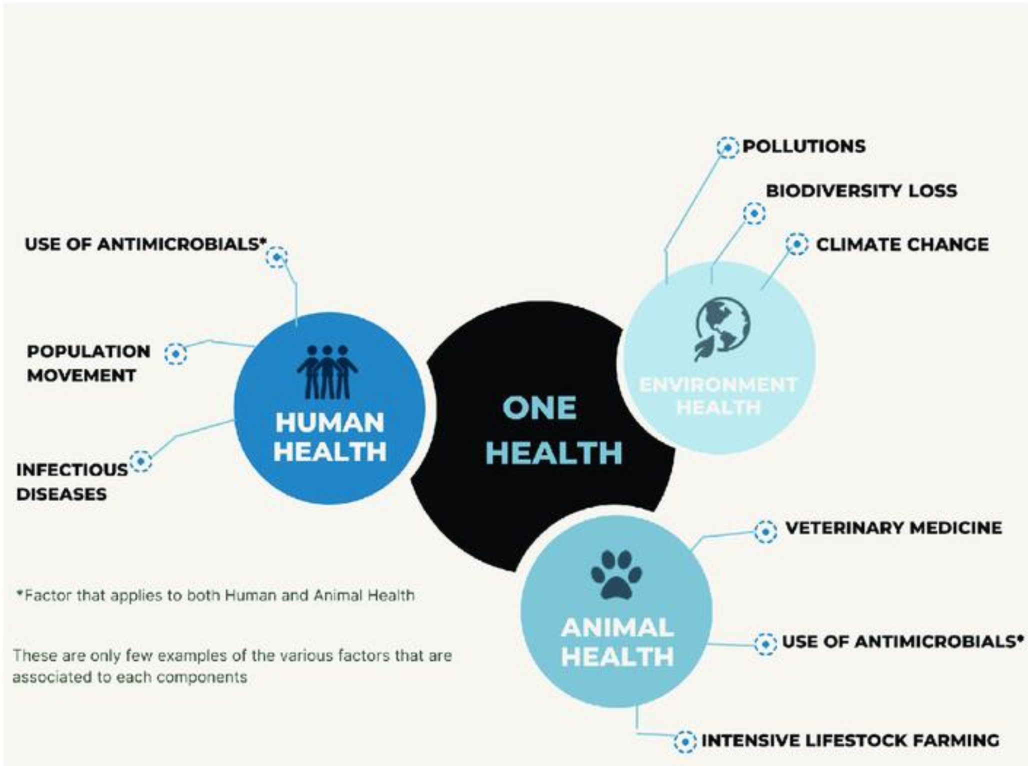

Fig. 2. Illustration representing the concept of One Health Approach [7].

progression and dissemination of drug-resistant infections [23].

8.2 Phage therapy

Phage therapy employs bacteriophages to (1) specifically target a bacterial population, (2) transport drug molecules to a bacterial target, and (3) introduce enzymes capable of deactivating or reversing resistance genes. Due to their widespread prevalence and remarkable selectivity for bacterial receptors, bacteriophages can be genetically modified to specifically target a particular pathogenic bacterial population, while leaving the surrounding microbiota unharmed [23].

8.3 Nanoparticles

Nanoparticles, consisting of metals or metal oxides, exhibit a multifaceted approach to combating microbes. This is achieved through various simultaneous mechanisms, such as the disruption of the cell membrane, the generation of reactive oxygen species, and the infliction of damage to intracellular contents. Consequently, nanoparticles possess a reduced risk of resistance development, rendering them highly appealing in the fight against multidrug-resistant (MDR) pathogens. Nanoparticles exhibit significant promise as protective coatings, particularly in the context of wound dressings or implants, intending to mitigate the occurrence of biofilm-related infections. Despite the theoretical and initial investigational potential of innovative strategies, the majority of these approaches are still in their nascent stages of development. Further investigations are required to establish their safety, in vivo efficacy, interactions with human immunity, and pharmacokinetics before they can be employed clinically to address antimicrobial resistance [24].

8.4 Vaccines

Vaccines have a very minimal impact on developing resistant microbes because they affect the immune system. Vaccination has long-lasting impacts due to which they are less frequently used. Contrary to vaccination, antimicrobial agents must be used regularly, and they have short-term influence. Vaccines can be produced by using more harmful virulence factors such as a vaccine against Streptococcus pneumoniae has been made by using this technique [25].

8.5 Medicinal Plants and Phytochemicals

Plants have developed distinctive mechanisms to safeguard themselves against microorganisms through the presence of natural phytochemicals, also known as secondary metabolites, which are present in various parts of the plant such as seeds, roots, leaves, stems, flowers, and fruits. Moreover, plants can synthesize a wide array of chemically diverse compounds that play a crucial role in their defense mechanisms against microbial invasion. Hence, the pharmaceutical and scientific communities have shown considerable interest in exploring the potential effectiveness of plant-derived compounds as viable drug candidates. In this pursuit, numerous plant extracts and oils have been thoroughly assessed for their potential as antibacterial agents and agents capable of modifying antibiotic resistance. The novel drug discovery screening programs are comprised of three distinct approaches: random, computational, and ethnopharmacological. The most potent antimicrobial activity is exhibited by a selection of plant-derived substances (PDSs) that hold significant medical relevance. These substances encompass alkaloids, organosulfur compounds, phenolic compounds, coumarin, and terpenes [26].

8.6 Metals

The utilization of unbound metal ions as a means to eradicate bacteria and fungi has a well-established historical background. Bacteria, analogous to the majority of organisms, exhibit a complex association with metals, characterized by a simultaneous dependence and aversion: while a particular metal may be indispensable for their survival. It can also become toxic under specific forms and concentrations. Metal ions have been recognized for their antimicrobial properties for a considerable time and have garnered significant attention in contemporary times due to the emergence of antimicrobial resistance. The host immune system employs various strategies to disrupt the equilibrium of transition metals to counteract the intrusion of pathogens. One example of a host defense mechanism against bacterial infection is the inhibition of bacterial iron acquisition by the host protein lipocalin. This protein binds to siderophores, which are molecules produced by bacteria to sequester iron from their environment. By binding to siderophores, lipocalin prevents bacterial access to iron, thereby limiting their growth and survival. Calprotectin, an additional protein host, exhibits the ability to sequester manganese at locations where infection is present. Zinc plays a crucial role in maintaining the normal immune function of the host. At the cellular level, macrophages possess the ability to employ distinct strategies, namely zinc starvation and zinc toxicity, to effectively eliminate the bacteria, they engulf [27].

9. CONCLUSIONS

The significant morbidity and mortality caused by antimicrobial resistance in bacterial infections is a matter of great concern. Both gram-positive and gram-negative bacteria with multidrug resistance patterns pose challenges in terms of treatment, and may even exhibit resistance to currently available standard medications. Given the lack of successful treatments, effective preventive measures, and new antibiotics, bacterial infections and the associated diseases present formidable challenges that necessitate the development of novel strategies and alternative antimicrobial medicines for a more promising future.

10. CONFLICT OF INTEREST

The authors declare no conflict of interest.

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