

The Global Threat of Antimicrobial Resistance: A Microbiological Review

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Abstract
Antimicrobial resistance (AMR) is a growing global health threat that compromises the effectiveness of current antimicrobial therapies. This review outlines key microbiological mechanisms of resistance, including enzymatic degradation of antibiotics, efflux pump activity, and genetic mutations that enhance bacterial survival. These adaptations contribute to treatment failures and increase patient mortality and healthcare costs. Clinically, AMR limits therapeutic options, prolongs hospital stays, and complicates infections. Environmentally, the spread of resistant bacteria through wastewater, agriculture, and pharmaceutical waste plays a significant role in sustaining resistance in natural ecosystems. A thorough understanding of these mechanisms is essential for developing strategies to monitor, prevent, and manage AMR. Addressing this crisis requires global cooperation, surveillance, and investment in alternative therapies and responsible antibiotic use.

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Introduction

One of the most significant health threats facing humanity today is antibiotic resistance (ABR). Although medical professionals have succeeded in developing novel antibiotics to counter the emergence of sulfonamide and penicillin resistance, the continuous global emergence of multi-drug resistance (MDR) Gram-positive and Gram-negative bacteria remains alarming [1]. This demands a coordinated, multidisciplinary effort based on the One-Health concept that understands the complex interconnections between the health of people, animals and the environment to slow and mitigate the ABR threat, which represents a serious danger to modern healthcare that may render many of today's medications useless and jeopardize many successful medical procedures [2]. Antibiotics are the single most important pharmaceutical innovation that revolutionized modern medicine. However, there is growing awareness that their misuse and overuse in human healthcare and as growth promoters in veterinary medicine has led to the emergence of ABR in bacteria. Bacterial ABR occurs when bacteria develop the ability to survive treatment. This is a natural phenomenon occurring constantly as a result of the fierce Darwinian selection pressure imposed by man-made antibiotics. After decades during which medicine's armed forces grew considerably to combat the existing and continually evolving resistance mechanisms, many of the targets have unfortunately started to send out distress signals [3].

Now, despite continuously discovering novel antibiotics, bacteria strain variants arise steadily that are resistant to them, and their virulence factors have hardened significantly. It has been estimated that currently around 700.000 people worldwide die every year as a consequence of drug-resistant infections, and the prevalence of these pathogens is increasing alarmingly. Consequently, this causes in excess of 23.000 deaths, which outnumber deaths from drug-resistant infections by some threefold. In Germany alone, hundreds of thousands of patients (400.000–600.000) develop a hospital-acquired infection each year, of which 30.000 to 35.000 infections are attributable to a MDR organism, resulting in 1.000-4.000 deaths [4, 5]. The advent of antibiotics revolutionized the treatment of infectious diseases. Penicillin, as the first naturally occurring antibiotic, saved countless lives.

Today, antibiotics remain one of the most important drug classes as they significantly reduce morbidity and mortality. Inappropriately used antibiotics can also have serious side effects, which can be attenuated by using new antibiotics or growing pharmaceutical companies developing antibiotics. However, several factors have led to a significantly increased susceptibility to these drugs over the last 70 years. The emergence of multi-drug resistant organisms (MDRO) threatens the effectiveness of the antibiotics currently in clinical use, leading to diseases that were previously treatable becoming again a major clinical challenge [2].

In humans, the road to successful treatment is not only determined by host factors. The virulence of the pathogen and its ability to resist treatment by the host defense and antimicrobial drugs plays the major role. Born since the inception of life, bacteria have qualified for their great ecological success owing to their exceptional versatility. This required bacteria to evolve the ability to use all currently available niches. In doing so, soil and water become contaminated by anthropogenic waste, leading to the emergence and transmission of possibly new pathogens contaminating both humans, and animal-free and food [6].

In livestock and pet animals, antibiotics are a major tool for both prophylactic treatment and growth promotion. Their high usage has led to a concomitant increase in antibiotic resistance (ABR), especially to methicillin resistance in *Staphylococcus* (MRSA), vancomycin resistance in *Enterococci* (VRE), and the emergence of resistant *Escherichia coli* strains resistant to 3rd-generation cephalosporins, and carbapenem-resistant Enterobacteriaceae (CRE). In this review, the global threat presented by AMDRO, the definition and classification of AMR, as well as mechanisms of resistance are presented. The major players in resistance acquisition and transmission are discussed globally, in the human community, and the environment and food chain. Consequences of resistance acquisition and infection for humans are the increased morbidity and length of hospital stay, as well as the increased cost and mortality [7, 8].

Understanding Antimicrobial Resistance

Antimicrobials are natural or synthetic substances that inhibit the multiplication of micro-organisms. The term “antimicrobial” is often interchangeable with antibiotic, which refers specifically to substances of microbial origin that inhibit or kill either bacterial or fungal cells. Some antibiotics with minor structure alteration are also marketed. Synthetic antimicrobial agents such as sulphonamides that are not of microbial origin but exhibit antimicrobial property are also included under the term antibiotic. The World Health Organization recognizes AMR as one of the top ten global public health threats, leading to 1.27 million deaths globally. Therefore, this review emphasizes the global threat posed by AMR bacteria, the fundamental principles of AMR in Enterobacteriaceae, and the consequence of AMR dissemination in the framework of One Health based platform [2]. Additionally, this review focuses on some mitigation strategies to overcome or control the AMR threat in human, animal, and environmental settings.

AMR is the ability of a micro-organism to resist the effect of a drug. Bacteria can be commensal and can colonize the human body without causing any infection; however, opportunistic bacteria can cause infections under benign conditions. Imbalance between infection causing bacteria and commensal bacteria can lead to infection. AMR gives a distinct advantage for survival and basic biological property by modulating its genes or genome. AMR bacteria can survive in the presence of clinically used antibiotics. In the absence of antibiotics, AMR bacteria do not have any advantage over commensal/sensitive bacteria for survival. AMR bacteria may lose the plugin during evolutionary process and revert back into susceptible form [9].

Microbiological Mechanisms of Resistance

The emergence of antimicrobial resistance (AMR) remains a major long-term threat to global health, significantly impacting morbidity, mortality, and economic costs. Harnessing the rich data generated through multiplexed pathogen sequencing improves resolutions of typing genomes for AMR profiling AMR surveillance and target start legislation to lower infection rates, puts direct pressure on those most responsible for the burden, and targets industrial scale meat production, ceasing overuse of prophylactic antibiotics [10]. Additionally, sewage surveillance provides an early warning signal for new virulence factors circulating in genetic reservoirs, while the assessment of bioengineered treatments to enable innovative precision-photonic smart antibiotics are employed and efficacious [11]. However, increased investments in R&D by pharmaceutical companies targeting the wider microbiome or with novel formulations such as phagogenics are still critically lacking.

The microbiome is the second human genome and hosts innumerable microbial taxa that form methagenomic ecosystem networks. These are resilient and maintain health via metabolic homeostasis under a wider range of conditions. However, microbial dysbiosis can manifest within increasing diversity with loss of metabolic homeostasis, rendering it amagenomic and producing an emergent pathogen that becomes the focal point for disease - a post-biotic. Conversely, the shedding of commensal pathobionts provides an adaptive advantage for opportunistic infection and inflammation diseases to arise, whose potential is contained by biotic factors in a healthy microbiome. However, under pressor factors, those mechanisms of containment are insufficient and organisms become over-represented in a post-biotic. It is considered that this representation is polyantigenic, generating false serological specificity and undetectable serotag. In the absence of correct ID as a pathogenic avatar, it is not feasible to implement effective pathogen-ending treatments [12, 13].

1. Enzymatic Degradation

Bacterial resistance against β-lactam antibiotics via hydrolysis was first reported in the 1940s, less than a decade after the invention of penicillin. Ever since, these β-lactamases remain one of the most widespread drug resistance mechanisms in bacteria [14]. Generally, they can be classified as serine- and metallo-β-lactamases according to their active site architecture or by sequence similarity into Ambler class A to D β-lactamases, or as metallo-β-lactamases of class B. There are at least 323 crystal structures determined for β-lactamases, resulting into a well-defined knowledge of their enzyme mechanism with the clear identification of the catalytic residues and the binding sites for the antibiotic and a crucial water mediator molecule. Still in this research field, the medically relevant OXA β-lactamases and novel forms of metallo-β-lactamases continue

to be investigated to understand their evolutionary adaptation. Over such time scale, biotechnological applications were developed using these enzymes and much is known on how these apply to antibiotic monitoring, biodegradation, and biosensors. [15]

Resistance against other class of antibiotics was reported, however the knowledge on the biodegradation mechanisms and structure–function relation is surprisingly limited, with the notable exceptions of the glycopeptide antibiotics and some aminoglycoside antibiotics degrading enzymes. The next generation knowledge and expertise in the biotransformation of these antibiotics and production of derivative antibiotics deserves high attention due to the cellegant biology and chemistry involved and its broad applications [16].

2. Efflux Pumps

The first studies investigating the involvement of efflux pumps in antibiotic resistance in bacteria began in the 1980s. They showed that energy-dependent efflux pumps plasmid-transferred by R-factors in *Escherichia coli* could lead to a rise in tetracycline resistance. Since those early studies, an increasing number of independent investigations have documented the importance of efflux systems in both pathogenic and nonpathogenic bacteria. These systems can be divided into five superfamilies based on their energy-coupling mechanism: ATP Binding Cassette (ABC), Major Facilitator Superfamily (MFS), MATE (Multidrug and Toxic Compound Extrusion), and the Resistance-nodulation-cell division (RND) superfamily, which is the most studied [17] [18]. Efflux pumps are found in all bacteria and play a role in a variety of processes, including normal physiological processes, resistance to biocides, bile salts, and antimicrobial agents. These systems contribute to low-level resistance, providing bacteria with protection from toxic substances, as well as time to develop additional resistance mechanisms.

Unlike most acquisition events, efflux pumps could provide selective advantage prior to antibiotic exposure, as they are likely to confer survival at low concentrations of aminoglycosides, the emergence of which would allow rapid acquisition and dissemination of resistance. The combination of efflux pumps with outer membrane barriers provides a formidable barrier to many different compounds, and some efflux systems in Gram-negative bacteria have been shown to play a significant role in the protection against the harmful effects of a variety of toxic compounds, including several known to inhibit important cellular functions. Meanwhile, the presence of multiple efflux pump genes along with selection pressure might promote the emergence of multidrug-resistant (MDR) bacteria [19]. In its full definition, poly-locus multidrug resistance may be a bacterial condition comprising a set of genes that can limit resistance to any antimicrobial compound. Genes involved in classical efflux pumps could also be involved in multidrug resistance, increasing resistance to a larger variety of drugs through redundancy and cooperative mechanisms. Gene duplications occupying different positions may provide the plasticity required to accommodate new variations of transporters, and selection pressures would favor polymorphisms that are genetically fit. [20, 17]

3. Genetic Mutations

Antimicrobial resistance (AMR) is defined as a microbial population's ability to withstand a dosage of an antimicrobial agent which is lethal to other population of the same species [10]. When resistance refers to a microorganism, it implies that that microorganism is an AMR microorganism. Completely resistant microorganisms are referred to as resistant, but those that are resistant to only a few antimicrobials are referred to as less resistant or non-susceptible. An antimicrobial (or simply drug) is a chemical substance that kills or inhibits a microorganism's growth. A drug which is only inhibitory against microorganisms is referred to as a biostatic agent; example of biostatic drugs is tetracyclines [21]. Resistance mechanisms are factors that enable a microorganism to withstand antimicrobials. Microorganisms capable of AMR often respond to exposure to an antimicrobial drug by developing AMR. Exposure occurs during antimicrobial therapy (prophylactic or curative) or when microorganisms are natural or contaminated reservoirs of drugs used in man or animals. Individual AMR enzymes which ensure non-susceptibility to drugs have been well documented and are listed in online databases. For rapid spread of AMR, a pathogen must be able to sustain a resistant phenotype. This occurs either via stable integration of a resistance determinant into the microorganism's main chromosome or wide distribution of a resistant determinant via a horizontal gene transfer (HGT) mechanism. The HGT mechanism which operates depend on the nature of donor and recipient. For example, transformation occurs between environmentally competent bacteria: streptococci of the genera *Enterococcus* and Streptococcus and gram-negative bacteria of the genera Neisseria and Haemophilus; transduction occurs between normal or pathological plasmids or transmitted viruses; and conjugation occurs among bacteria of different genera, families, and even king, such as streptococci of the genera *Enterococcus* and Streptococcus, and gram-negative bacteria of the genera Neisseria and Haemophilus. Transduction occurs between normal or pathological plasmids or transmitted viruses. Conjugation occurs among bacteria of different genera, families, and even kingdoms [22, 23].

4. Horizontal Gene Transfer Precipitation Method

Horizontal gene transfer (HGT), classified as transformation (the uptake of naked DNA), transduction (the transfer of DNA via a bacteriophage), and conjugation (the cell-to-cell transfer of DNA), can arise from natural or anthropogenic sources. Although transformation and transduction appear to be relatively rare in the acquisition of resistance genes, the importance of conjugative systems in the dissemination of resistome will be the emphasis of this review [24, 25].

Multiple lines of evidence indicate that HGT drives the rapid spread of antimicrobial resistance (AMR). These data demonstrate HGT events that correlate with and can explain their paradoxical epidemiology. In many cases, strain emergence is not the result of the number of mobile genetic elements (MGEs) acquired, but of the increase in their transferability, and consequently their ability to persist and spread. Indeed, clades that acquired a major AMR determinant often elucidate other subsequently acquired elements that look like they co-evolved in time and space with it. Through characterization of whole genomes, phylogenomic frameworks can yield sufficient resolution to demonstrate recent horizontal transfer within localized epidemics. Shiga toxin-producing *Escherichia coli* (STEC) O157:H7 in England, for example, acquired its principal's virulence factor on an MGE, and the subsequent local persistence and spread was partly due to the clonal expansion

of a single transferred element [26].

The clonal expansion of the various MGEs will be discussed first. This time frame does not include the raw recombinogenic potential of the HGT events themselves, which can occur immediately after the acquisition of a new mobile element. For example, strain A acquired the 100 kb plasmid P1 3 years before strain B. P1 has undergone multiple intra-species transfers since and appears imperfectly conserved, with low N-55% identity with the original hybrid [27]. In addition to the capacity to generate novel compatibility types associated with a different gene context, HGT can provide selection stress by enabling both rapid evolution and horizontal gene transfer to co-exist. Horizontal transfer events may also explain partial gene loss, despite existing co-residing elements that can maintain it. After having been supposed, Shiga toxins are usually maintained long term in human-derived STEC. Nevertheless, one strain failed to maintain them for 1,600 generations under laboratory conditions without selection, and still later in vivo [28].

Types of Antimicrobial Agents

Bacteria from a variety of biotopes can produce a wide range of secondary metabolites, which serve various purposes like defense, competition for nutrients, and contact with the environment. This ability, evolutionarily advantageous to bacteria, poses a threat to both public health and food safety due to widespread resistance. It is currently recognized that AMR is a major modern health problem, causing at least 700,000 deaths annually worldwide from drug-resistant bacterial infections. AMR threatens to make many vital medicines ineffective, compromising surgery, chemotherapy, transplantations, and elderly health. Since the onset of the "golden era" of antibiotic drugs in the mid-20th century, the emergence and dissemination of resistance to one or several groups of antibiotics was primarily due to their over-use in human health and livestock farming among other factors. Based on clinical and epidemiological evidence, it is assumed that these benefits, however, came at hidden costs: Inappropriate use (often over- or under-use) of antibiotics in humans and food animals have heighten the resistance risks for the Global North and the Global South [29]. Microorganisms released into the environment, together with resistance genes, could spread into humans and other biota. Such a transfer could take place through direct contact or indirect contact, i.e. via food chain or ecosystem through human water, air, and soil or livestock transport [30].

Between 1995 and 2005, more than 130 million kg of antibiotics were produced in the USA, 60% for human health, 30% for food animals, and 10% for plants. The World Health Organisation (WHO) characterized antimicrobials as "critically important", indicating that some of them must be preserved from inappropriate use in veterinary medicine. In 2010, a new European regulation on veterinary medicines was enacted, prohibiting the use of antibiotics critical for human and veterinary medicine in livestock farming for growth promotion. Nevertheless, in some countries, β-lactams, tetracyclines, and macrolides can still be used as growth promoters. Recent investigations estimated that in India two million kg enrofloxacin were annually used to increase farm yield, and in Vietnam in 2010, 619 tons of oxytetracycline were used in fish farms [31, 32].

1.Beta-Lactams

Antibiotic resistance is an increasingly global problem. The World Health Organization estimates that hospital deaths globally due to antimicrobial resistance number over 700,000 every year, with this toll projected to increase to 10 million by the year 2050 [33]. In regards to Gram-positive organisms, the emergence of resistance to glycopeptides and β-lactams is driven by the horizontally-acquired mecA, mecB, and mecC genes. Gram-negative resistance mechanisms have emerged to virtually all antibiotics, including β-lactams, aminoglycosides, and fluoroquinolones. These mechanisms include the production of class A, C, D, and a growing number of class B β-lactamases, efflux pumps, and porin loss, which have drastically limited antibiotic options [34]. Unfortunately, in the past fifteen years, the antibiotic pipeline has slowed significantly, with few new agents being developed for treatment of Gram-positive and -negative organisms. As such, the focus has turned towards optimizing the use of existing agents, maximizing their potential pharmacologically and clinically. The updated guidelines acknowledged the need for combination therapy when organisms are resistant to other antipseudomonal agents, with β-lactams or β-lactam/β-lactamase inhibitor combinations recommended against organisms with AmpC production, ESBL production, or lack of a porin. Nevertheless, traditional combinations of aminoglycosides and β-lactams, or glycopeptides and β-lactams have had mixed outcomes in clinical use. Additionally, β-lactams have a favorable safety profile. This combination of safety, bactericidal activity, and the fast emergence of resistance has incentivized exploration of enhanced β-lactam dosing strategies.

Dual β-lactam therapy was abandoned due to the development of resistance to specific narrow-spectrum agents, collateral damage, and a lack of clinical efficacy data. However, a growing body of evidence supports its use against resistant infections, offering a means to overcome resistance on multiple levels: the drug itself, the target, and the infection. Nonetheless, any combination therapy increases the risk of collateral damage and resistance development. Further understanding of the mechanisms and evidence base for dual β-lactam therapy and its future direction is warranted [35].

2. Macrolides

Macrolides are bacteriostatic antibiotics with broad spectrum activity, mainly against Gram-positive bacteria, including Gram-negative bacteria like Legionella or Chlamydia. Their core component is a macrolactone ring with a 14- and/or 16-membered atom, linked to one or more saccharides. Older drugs include erythromycin, which are more hydrophobic and unstable against acids. Due to significant side effects, subsequent generations of macrolides were developed, such as clarithromycin and azithromycin (AZM) belonging to the second generation, thus being semi-synthetic derivatives of erythromycin. Newer macrolides, like telithromycin and solithromycin, improved compound structure and pharmacokinetics. Macrolides are effective against bacteria that are resistant to other antibiotics, and due to their ability to penetrate host cells, they may exert activity against intracellular pathogens [36].

Macrolides exert their bactericidal activity mainly against the domains of 23S and 16S rRNA in active and decoding sites, respectively. By covering the protein synthesis peptidyl transferase sites or blocking phosphorus–sulfur bonds, they inhibit chain elongation. While examining antibiotic-resistant strains, a universal phenomenon was observed: the

emergence of mobile genetic elements responsible for horizontal transfer and accumulation of resistance genes in clinical strains as a consequence of antibiotic overuse. Resistance to macrolides can occur through several mechanisms. Commonly, resistance genes augment the rRNA structure or its methylation site, reducing contact with unchanged antibiotics. *Escherichia coli* and S. aureus can develop resistance independently through the additional protein to ribosomal tunnel, lowering macrolide–ribosome structure affinity and double–helix destruction activity [37].

3. Tetracyclines

Tetracyclines are naturally occurring and semisynthetic broad-spectrum antibiotics that are widely used, and their overuse has caused the emergence of resistant strains of bacteria. Noncompliance and improper control measures are factors in the emergence of resistant strains. Antibiotic-resistant bacteria are increasingly found in urban and rural halos across the globe, and their widespread dissemination is concerning. Antibiotic control measures in animal husbandry are desirable to reduce resistant bacteria in the environment and food chain. Marketed antibiotics should be tested for their microbiological effects in order to reduce the unintended consequences of their use [38].

The appropriate use or the withdrawal of certain antibiotics in veterinary medicine is recognized to affect the level of circulating residues in the environment. Enroloxacene, oxytetracycline, and sulfamonomethoxine are among the frequently and widely marketed drugs shown to stain the zebra fish equilibrium and induce direct hematological changes, and tetracycline is among the antibiotics widely used in aquaculture and found in high concentrations in the aquatic environment. Tetracycline and its degradation products can induce bioaccumulation of other antibiotics. Its uncontrolled use inhibits zooplankton reproduction and can induce physiological effects in aquatic organisms. Bacteria resistant to tetracycline result in the dangers of salmonellosis and salmonellosis outbreaks from contaminated fishery products [39].

The unwanted effects of some marketed drugs on nontarget bacteria in aquaculture water can result in the resistance and virulence of these species, and the mechanisms of such noncompliance with the pharmacological view can be discussed. Some marketed drugs are better alternatives for prophylaxis, and vaccines may be a desirable method to control some fish bacterial diseases. Better control measures in animal husbandry are desirable to reduce the occurrence of antibiotic-resistant bacteria in the environment and food chain. In this context, the need for public awareness and education is presented, and antibiotic residue control measures in the aquatic environment should be implemented [40].

4. Glycopeptides

The early 1950s marked the start of the glycopeptide antibiotic era with the discovery of Vancomycin. Both Vancomycin and Teicoplanin are produced by actinobacteria. These antibiotics, known as glycopeptides, are posed as the last line of defense for treating serious infections caused by Methicillin resistant *Staphylococcus aureus* (MRSA) and other drug resistant Gram-positive pathogens. Bacterial resistance against Vancomycin was first reported for Enterococcal infections in 1986, and *Enterococcus* faecium and *Enterococcus* faecalis strains resistant to Vancomycin were isolated later, which were named Vancomycin Resistant *Enterococci* (VRE). The emergence of VRE infections has caused concern resulting in a greater focus on the epidemiology and control of VRE world-wide [41].

The mechanisms of resistance among MRSA and VRE differ from one another. MRSA achieves resistance against β-lactam antibiotics via 5 gene expressions clustered adjacent to each other on the chromosome. In contrast, VRE achieves Vancomycin resistance by chromosomally encoded Van genes which modifies the terminal D-Ala-D-Ala residues in the peptidoglycan precursor to either D-Ala-D-lactate or D-Ala-D-serine. VRE can also acquire conjugably transmissible Van genes by transposon Tn1546. MRSA was thought to pose the greatest threat to public health and bioterrorism agents until recently when a shift in focus to VRE was witnessed. Polyclonal outbreaks of VRE emerged in Flemish hospitals after the introduction of glycopeptide antibiotics in the early 1990s. Islands containing a cluster of 19 Van genes granted Vancomycin resistance to plasmids entered into *Enterococcus* sp. via horizontal gene transfer. The high prevalence of VanA plasmids in hospital settings triggered concerns regarding dissemination, particularly among newly emerged resistant *Enterococcus* germ species and Enterobacteriaceae taxa [42, 43].

Factors Contributing to AMR

Antimicrobials, including antibiotics, are agents used to inactivate or kill microbes. Antibiotic resistance is defined as microbes resistant to inhibition and inactivation by an antibiotic [44]. AMR is a global threat facing humanity. Some observed causes for AMR are described herein.

The antibiotics, metal ions, and RPCs used to treat infections are important causes for the emergence, spread, and persistence of AMR. Rapid increases in the concentration and use of antibiotics and antimicrobial agents may significantly accelerate the emergence and spread of AMR. A detailed assessment of the inputs of antibiotics, metal ions, and RPCs accompanying aquaculture is essential to inform epidemiological modeling to predict the risk of AMR emergence and spread [22].

Increased human activities, input routes, and concentrations of antibiotics, metal ions, and RPCs can accelerate AMR emergence. Following the emergence of AMR in aquaculture environments and the application of management practices to reduce inputs, the spectrums of resistance can shift or return to feral patterns. Such findings not only highlight the links among anthropogenic activities, concentrations of antibiotics, metal ions, and RPCs, and AMR but also provide a warning on the downriver amplification of AMR. Thus, actions, such as reducing inputs, may effectively mitigate environmental AMR. The use of antibiotics, metal ions, and RPCs accompanying aquaculture activities is an important cause for the emergence of AMR in aquaculture environments. Such AMR may spread to drinking water, irrigation water, and feral environments through hydrological dispersal [45, 46].

AMR is due to the development of genetic, enzymatic or physiological characteristics that neutralize the efficacy of these antibiotics in the treated bacterial cells. Such resistance mechanisms can be transferred between members of a population, causing one sensitive organism's demise to aid the proliferation of resistant species. The global emergence of AMR bacteria is now a serious threat to public health due to the emergence of NDM-1, KPC-2, VIM-1 and OXA-48

carbapenemases and the expansion of the opportunistic pathogens carbapenem resistant *Klebsiella pneumoniae* and *Acinetobacter baumanni*. Targeting the resistance mechanisms in the bacteria using small molecule inhibitors has been considered to complement existing antibiotics [44].

The Food and Drug Administration (FDA) approved new antibiotics over the past decade, but their clinical values are limited due to the rapid emergence of resistance. Therefore, alternative approaches to treat bacterial infections by targeting virulence have drawn great interest because they are less likely to develop resistance. The irrigated crop production covers 223 million hectares globally and accounts for 40% of the world's food. However, it is hampered by saline-alkali stress and salinity affects about 830 million hectares of land worldwide. To combat salinity in irrigated agriculture, a large number of antibiotics are applied to inhibit the generation of toxic reactive oxygen species by pathogenic bacteria, and their residues in soil and river systems are thought to be of major concern for human health [47].

1. Overuse of Antibiotics

Antimicrobials are substances that inhibit the growth of or destroy microorganisms. Antimicrobial resistance (AMR) refers to the ability of a microorganism such as bacteria, viruses, and some parasites to stop an antimicrobial agent from working against it. Microorganisms that develop antimicrobial resistance are often referred to as 'superbugs' [29]. More specifically, antibiotic resistance is the ability of bacteria to resist the effects of an antibiotic. These resistant bacteria grow and multiply in the presence of the antibiotic, while other sensitive strains are inhibited or killed.

AMR is a global health problem for which the World Health Organization has called a "silent pandemic". AMR has recently been recognized as a global threat, and its reemergence is attributed to a combination of factors. These include the emergence of resistant strains of bacteria, the lack of new classes of antibiotics, the presence of large pools of antibiotics in the community, and their use in agriculture. As more and more bacteria become resistant to antibiotics, "a world without antibiotics" may be on the horizon where common surgical procedures or treatments of common infections may become fatal again. As AMR spreads, it brings with it dire economic consequences as well, because millions of people may die from non-treatable infections, and health care costs may continually rise [48].

Studies of the prevalence of antibiotic resistance in human pathogens and environmental isolates through time have shown that bacteria became faster to evolve resistance after antibiotics were introduced in the clinic. AMR has thus been called an "anticipated surprise". There are both rapid and slow mechanisms of AMR development, and there is an interaction between the two. Inadequate biodistribution of the antibiotic in the body produces a variety of concentrations in a given bacterial population, which leads to a strong selection for the development of fully resistant mutants. In addition, rapid evolvability of resistance genes is given by gene duplications or horizontal gene transfer in consequence of selection pressure [49].

Antibiotics are the wonder drugs of modern civilization. They are believed to be one of the most important achievements in medicine. The discovery of penicillin opened the era of antibiotics that has saved millions of lives and produced compounds that have reached the market as antibiotics. Beginning in the mid-1940s, pioneer scientists launched the modern antibiotic era. Few other discoveries have been more all-encompassing in their implementation and have roused greater enthusiasm than antibiotics. Such is the complexity, diversity, and intrinsic beauty of the antibiotics produced by bacteria, fungi, and more recently a few plants, that there is no pharmaceutical class that comes close to them [29]. The astounding greed for antibiotics is irrepressible. The incomprehensible attempts to discover every conceivable antibiotics as it is thought to cure the multiply causative diseases, together with the reckless misuse of what reaches the clinics, produced an explosion of resistant strains. Physicians are now left without weaponry to treat common diseases thus increasing the morbidity and mortality of chronic infectious diseases.

Antibiotic resistance is happening worldwide, but it is not happening uniformly. In most developing countries, either the misuse of existing antibiotics was rapid in comparison to developed countries or they are still out of reach for a majority of the people. In developing countries, irrational prescription is rampant, moreover many self-medicate and purchase antibiotics freely without a doctor's prescription. Most importantly, they can get antibiotics "over-the-counter", any time of the day, for a price as low as two cents, particularly for veterinary usage. Curbing the misuse of antibiotics requires raising public awareness and broad-based science education. People have to be aware of the "superbug" situation and dangers associated with antibiotic resistance. In addition, rules and regulations should be enacted and enforced to prevent the abuse of antibiotics, especially for animal husbandry, agriculture, and human consumption. Nonetheless, to learn a lesson from the past is far more effective than curbing the process of discovery. Efforts are ongoing to create phage-based therapies for the treatment of infections. Unbeknownst to many, some modifications of the existing antibiotics are possible and these have proven useful against the resistant pathogen [50].

2. Inappropriate Prescribing Practices

Antimicrobial agents are unique medicines in that their use can affect entire populations. While wide efficacy and safety margins make these agents an essential part of modern medicine, any inappropriate use can harm not only the individual but potentially millions in the community, driving a global rise in resistance [51]. Prescribers need to be aware not only of the immediate consequences of their actions, but of the broader ramifications. Clinicians, both veterinarians and the medical profession, need to consider how each individual prescription will affect the resistance rates in their community, country, and across the globe. Poor prescribing practices are justifiably under attack, as is the term "inappropriate prescribing".

By definition it encompasses a huge range of opined and objectively faulty prescribing practices and is not restricted to situations in which antimicrobials are wrongly prescribed given the clinical context. The complexity of the term limits its utility. Nevertheless, the term "inappropriate prescribing" is widely used and therefore a suitable container term to hang the many unacceptable prescribing practices currently prevalent in human and veterinary medicine. Just as pilferage is another form of theft, the term "inappropriate prescribing" is used in this paper to encompass the socially unacceptable practice of prescribing deemed inappropriate by doctors themselves, for example, use contrary to guidelines or

standard operating procedures. It has been estimated that up to 50% of prescribing in human medicine and even 80% of prescribing in veterinary medicine is inappropriate. However, in their discussions with doctors during consultations, doctors worldwide volunteered that most prescribing practices were inappropriate [52].

The extraordinary utility of antimicrobial agents is now being undermined by the nemesis of their success, the emergence of resistance, which threatens treatments for infection. Overuse and misprescribing of these drugs are key causes of resistance in common pathogens, a problem exacerbated by their application in the rearing of foodstuffs. Rapid resistance emergence is particularly concerning given the limited development pipeline of new agents, many of which have limited activity and undesirable side effects. Continuous surveillance of prescription against independence guidelines aids efforts to control resistance. Doctors' expectations of immediate examination and treatment create pressure for broad-spectrum agents as a compromise against uncertainty. As knowledge about infecting organisms and their drug sensitivities and resourcing of microbiology and pharmacy facilities improve, such expedients should be curtailed. Targeted prescribing, particularly narrower spectrum drugs, should result, and resources currently applied to broad-spectrum agents would in part be freed to finance such developments. However, without global management, resistance to these agents and possible emergence of resistance to their successors will result. Resolution will require cultural change analogous to current attitudes towards smoking, and regulation of nutritional additives and environmental pollution [51].

The Widespread Use of Antibacterials in the Community and Issues of Prescription. Despite data from recent years that directly correlate the inappropriate use of antibacterials with the emergence of resistance, by 1995 consumption of these agents was still steadily growing in Europe and North America. In the United Kingdom alone, prescriptions had reached 26 million per year prior to foothold attempts at abatement. The main reasons for the extensive community use of antibacterials can be summarized thus: (i) The dynamics of bacterial infections, severity of diseases, and community treatment of bacterial infections where actual patient examination and lower resource input lead to the prescription of broad-spectrum, inappropriate antibacterials. Most prescriptions for community-acquired infections in adults such as respiratory tract infections are inappropriate and result in failure of treatment (70%) [53].

3. Agricultural Use of Antimicrobials

Antimicrobials are used in agriculture for growth promotion, feed efficiency, prophylaxis and treatment of infectious diseases [54]. The use of antimicrobials in animal husbandry and aquaculture not only improves health of farm animals in a broad sense, but also improve farming hygiene. In the United States, nearly 80% of all antibiotics produced are used in animal husbandry. Each year 170,000–200,000 kg of advanced antimicrobials are used, and each kilogram of meat from cattle, chickens, and pigs consumes 6.7 g, 73 mg, and 102 mg of advanced antimicrobials, respectively. The total amounts of antimicrobials used in livestock food production globally are projected to increase by 67% by the year 2030. The overuse and misuse of antimicrobials in agriculture raise the public health concern especially for the development of antimicrobial resistant bacteria that limits therapeutic options [55]

In the food production environments, improper use of antimicrobials has led to the emergence and dissemination of antimicrobial resistance (AMR). The first mechanism of resistance is the protection against exposure to naturally occurring antimicrobials. Bacteria can develop resistance through long-term exposure to antibiotics or other antimicrobial compounds in the environments, such as heavy metals. Another important resistance mechanism is horizontal gene transfer, the transfer of DNA fragments from one bacteria to another, which can readily occur between commensal and pathogenic species. Recent evidence suggests co-selection of AMR by non-antibiotic compounds. Non-antibiotic compounds have wide applications in agriculture. The use of these compounds affects AMR development in bacteria that can enter the food chain. A growing public concern on the effects of agricultural antimicrobials on AMR is due to the emergence of multi-drug resistant bacteria (MDR) that has caused finding infections and human deaths. Consequently, there is an increased pressure on the agricultural industry, especially along the livestock food chain from the farm to the retail in view of the increasing public concern [22].

The global population is increasing, and food security is a big concern. As one of the basic food sources, animal protein has attracted more attention from both consumers and suppliers, resulting in the large-scale establishment of intensive animal husbandry. In the past, due to the imperfect environmental sanitation and bio-security conditions, livestock and poultry were often infected with various pathogens. Thus, the use of antimicrobials (AMs), including antibiotics and related drugs, became widespread in animal husbandry for growth promotion, feed efficiency, prophylaxis, and treatment of infectious diseases [54]. It is estimated that in 2015, 131 thousand tons of antibiotics were used in animal husbandry globally, accounting for nearly 80% of the total antibiotics consumed in the United States. Each KG of meat from cattle, chickens, and pigs leads to the consumption of 45 mg, 148 mg, and 172 mg of antimicrobials respectively. It is projected that this consumption will increase by 67% globally by 2030 as the demand for animal protein increases.

Antimicrobial resistance (AMR) limits the therapeutic options of antibiotics for treatment of infectious diseases in humans and animals, and has already posed a significant public health concern. Improper use of antimicrobials, including overuse, underuse, or misuse of medicines, has driven the development of AMR either directly or indirectly in the food production environments. The former is by exposing microbes to the sub-inhibitory antibiotic levels, which acted as stressors that could trigger the expression of resistance genes. The latter is through the horizontal gene transfer among bacteria, which are mediated by mobile genetic elements, such as plasmid, transposons, and bacteriophages. Emergence of co-selection for AMR from non-antibiotic compounds, such as biocides, disinfectants, preservatives, and heavy metals, which are routinely used in agriculture and aquaculture was recently reported. The use of antimicrobials and other biocides down the food chain can impact bacteria in ways that promote entry of AMR into the food chain. There is growing public unrest concerning AMR, and the emergence of multi-drug resistant bacteria (MDR) is increasing the pressure on the industry to address the issue, especially along the livestock food chain from farms to retail agility concerns [56, 57].

4. Global Travel and Trade

There is a significant change in patterns of human mobility worldwide due to globalization, international trade, and world events. In addition to travel for business and pleasure, the rise in global travel heightens the need for the detection of infectious disease and surveillance of pathogens. The risk of international transmission of AMR also increases, and this is further exacerbated by the fact that so many pathogens can cause disease in both humans and animals and have reservoirs in both worlds. Animal populations are seen as a reservoir for both zoonotic AMR pathogens and gene transfer elements that can potentially be transmitted to other microbes when in contact with humans, but the mechanism through which they are transmitted is poorly defined. Model systems that can mimic that interaction would shed light on what bacteria and how gene transfer occurs [58].

Triplaikota focuses on three in vitro methods that could be used to develop the conditions in which humans, animal, and environmental microbes are in contact and the resultant gene transfer studied. The first of these tests antibiotic transfer through membranes of agar making diffusion and plating onto selective media relatively easy to carry out and interpret, but there are questions as to how well it mimics in vivo situations. The second, a double droplet digital platform, uses membrane-encased droplets to separate cells, with agitation providing mixing and the ability to analyze each droplet individually. This system needs further development for real applications with environmental bacteria. Finally, a HCT approach to treat soil with plasmid-laden microorganisms under well-defined conditions could inform this aspect of AMR transmission [59].

Among bacteria, genetic determinants of AMR can be transferred via horizontal gene transfer (HGT) to other strains or species of bacteria. HGT via DNA-associated particles can occur between the same or different genera of bacteria and confer the ability to resist antibiotics to the recipient bacteria. HGT among commensal bacteria in humans is a possible initial step for the emergence of AMR pathogens. Mobile genetic elements encoding AMR genes have been detected more frequently in the gut microbiota of travelers returning from countries with high levels of antibiotic use, indicating that travel can facilitate the acquisition of AMR genes [58].

Colonization or infection with AMR bacteria is a risk issue linked with travel to some regions. This is particularly true for previous travel to South or South-east Asia, which is associated with detection of quinolone resistance genes in enteric bacteria. Although the underlying mechanisms remain to be explained, it has been hypothesized that tourism travel may increase the dissemination of drug-resistant bacteria through alterations of the microbial ecology, antibiotics and lax hygiene practices.

In terms of trade, special concerns have been raised with regard to imported food and food ingredients. Frequently, the gut reservoirs of foodborne bacteria are colonized by AMR phenotypes, including Salmonella. Risk assessments based on travel histories have indicated that travelers returning from South or South-east Asia present a higher risk of AMR acquisition. Antimicrobial residues have been detected in wild-caught shrimp and livestock in these regions [60].

Travel (particularly by air and ship), tourism and trade (in food and humans) have greatly increased since the second half of the 20th century and played a major role in globalization. Before the rampant use of antibiotics, travel and trade contributed only on a minor scale to the spread of AMR. Enhanced travel during the pandemic has provided unprecedented opportunities for AMR dissemination, and especially of pandemic lineages.

Surveillance and Monitoring of AMR

Antimicrobial resistance (AMR), or the ability of some bacteria to survive despite antimicrobial pressures, is posing one of the major threats to human health, animal health, and food safety. The issue of AMR is not limited to any geographical location rather a global threat. Over the last few decades, AMR has garnered much attention from both the scientific community and global organizations due to its emergence and spread, which has mainly been attributed to the continuous use of antibiotics in human healthcare, veterinary medicine, and food animal production. Consequently, AMR has become a serious worldwide concern and the World Health Organization (WHO) has initiated a global action plan to contain AMR that is supported by national strategies. Such initiatives require information on the AMR situation from all countries, and this necessitates robust AMR surveillance programs [61].

Mandatory AMR surveillance of human infections is pre-requisite for successful AMR containment efforts. It is essential to understand the disease burden caused by resistant pathogens, the impact of resistance on the successful treatment of infections, and for the development of effective protocols. Moreover, it is necessary to implement a surveillance system that captures both human and animal data to detect and control the emergence and spread of new resistances and to capture possible new routes through which resistant bacteria may enter human reservoirs [62]. Laboratory-based surveillance of AMR entails the collection of clinical specimens from humans, isolation of clinically important bacteria within a few controlled and defined conditions in the laboratory, and performance of antimicrobial susceptibility tests (ASTs) on isolated bacteria. AMR surveillance data reflecting antibiotic resistance trends is critical information for estimating the disease burden caused by resistant pathogens. AMR surveillance data is also important for AMR containment efforts to assess the effectiveness of earlier implementation measures and to monitor the emergence of new resistances. A prerequisite for taking appropriate measures is timely and accurate information on the emergence of new resistances [63].

Antimicrobials act to prevent growth or kill microorganisms leading to infections in humans, animals, and plants. The World Health Organization has identified antimicrobial resistance (AMR) as a major global health threat to sustainable development and public health. The situation has been worsening even in the early 2030s and has been aggravated by a lack of governmental focus, funding, and efficient public health system in many nations. The emergence and spread of AMR have drastically narrowed the options of antibiotics and become a challenge to public health worldwide. As a result of the misuse and abuse of antibiotics in healthcare and food production, public health systems have been putting extensive efforts to monitor the distribution and spread of AMR. Surveillance is crucial for estimating the prevalence and impact of AMR and informing treatment protocols of infectious diseases. Surveillance tools and methods must consider the epidemiology of AMR and should integrate approaches with different scales to understand the distribution patterns and risk factors of resistance [64].

Surveillance programs are essential for the effective

management and mitigation of AMR in both humans and animals. Antimicrobial use in humans and animals is proposed to be one of the risk factors for the emergence, development, and dissemination of AMR and resistant bacteria. Therefore, AMR surveillance should involve both humans and animals. The use of antimicrobials in animals is generally much more intensive than in humans. Moreover, resistant bacteria can be transmitted to humans from food or directly from animal carriers. Laboratory-based AMR surveillance is the detection of AMR from laboratories, which involves isolation of bacteria from samples, antimicrobial susceptibility tests (ASTs) using phenotypic detection and newer techniques, and typing and characterization of resistant mechanisms. Conventional phenotypic methods, most commonly disc diffusion and agar dilution, are suitable to conduct ASTs. Newer techniques include molecular diagnostics, whole-genome sequencing (WGS), and metagenomics animals. However, many of the techniques have practical limitations in the field, such as poor diagnostic ability, failure to differentiate viable bacteria, inability in quantitative detection, and inability to conduct typing. Conventional culture-based methods are labor-intensive and time-consuming, especially for fastidious organisms and strict anaerobes [62].

Laboratories in which AMR surveillance is implemented respond to these limitations by performing their in-house upgrading and co-operating with other institutions for diagnosing the limitations. Each laboratory must carefully select the most relevant species, sampling sites, and sampling seasons considering the financial plan and environment to study the epidemiology of AMR in a country. Scientists should also consider the type of sample and methods of collecting it carefully as it can affect risk factor analysis. Proper documentation of sampling, testing, training, and laboratory maintenance can also facilitate the transparency, reproducibility, and time-use of AMR research and strengthen academic collaboration. Surveillance programs are implemented worldwide in Europe, North America, and East Asia to monitor AMR in different reservoirs including animals [61]. Despite these notable surveillance systems, comprehensive AMR surveillance programs including terrestrial and aquatic food animal species, zoonotic bacteria, and recently announced antibiotics are currently absent in countries of South East Asia including Bangladesh.

Global Initiatives and Collaborations

The rapid emergence of resistance to available antimicrobials, and the consequent threat imposed to the control of infectious diseases, have been recognized as a major public health problem over globally, and as a complex problem requiring coordinated international responses. National strategic frameworks in countries such as the United States and United Kingdom offer sets of activities to address the broad and context-specific problem. Future research primarily needs, not to define the problem or responses, but to evaluate actions on outcomes (social and economic) and to assess the cost implications (efficacy, efficiency and equity) of responses. The threat posed by the rapid spread across health services of organisms resistant to one or more antimicrobials introduces a formidable challenge to the effective treatment of infectious diseases. Resistance develops unhindered on agriculture, and 50% of drugs prescribed to patients are ineffective because of the pre-existence of resistance in infecting strains. Failure to develop new, effective replacements for current antimicrobials means that a very considerable public health challenge is posed by the current strains of Gram-negative organisms and S. aureus; both of which remain extremely virulent in treatment collapse, seen in the 1940s–1960s with staphylococcal bacteremia leading to rates of greater than 60% mortality [65].

A one-health approach is now needed in which acknowledgement is made of the interconnectedness of anthropogenic, livestock, wildlife and medical uses of antibiotics. The issue of AMR (antimicrobial resistance), increasingly linking global health threats to political instability, is something that it may be in self-interest for high-income countries to become involved in in all lower-income settings. The announcement of the training of 1,500 experts on AMR is welcomed, but it is noted that this initiative focuses in low-income and lower-middle income countries (LMICs; China, India, South Africa). Economic interconnections among countries are well-established, as is the idea of contagions in global finance, health and environment. A country's drug consumption in each of these fields is reflected in those elsewhere. There is sometimes denial of the interdependence of countries, and marginalization sets off vicious circles of instability (the public health systems accentuating class inequalities in urban areas). As the unfolding story of the COVID-19 pandemic should illustrate, it is voted political factionalism that tends to stall coordinated responses to these threats [66].

Antimicrobial resistance is a major long-term global threat to human health and development. However, there are many other shorter-term issues that are also globally important and that appear to require concerted action. In particular, there are environmental problems such as climate change and ozone depletion. In understanding and assessing the economics of global public goods, it is important to have a clear and agreed definition of what is meant by the term [67]. Generally, such goods exhibit two key features: first, they are resources or conditions that transcend national borders in that their absence or degradation harms individuals or societies in many countries; second, their absence or degradation is often—although not always—contributed to by actions within several, and often many, nations, and cannot easily be solved through the uncoordinated action of individual nations or other agents [68]

AMR is a truly global problem. Up to now, high-income countries containing most pharmaceutical companies, and therefore the largest medical technology markets, have been less severely affected by AMR. Nonetheless, there are a number of reasons that it may not be wise for these countries to delay action until they are directly impacted. Firstly, as a macroeconomic issue, AMR poses a sizeable and growing burden on any country, reducing GDP and productivity. Secondly, AMR is an issue for national public health, given that a very high percentage of airline journeys will visit at least one AMR hotspot. Even if out of pure self-interest, it may make sense for high-income countries to support efforts in lower income settings [22].

Thirdly, there is increasing interconnectivity between countries and economies, particularly as regards trade. On the other hand, the experience of the global COVID-19 pandemic has opened many eyes to the complexity and extent of global interconnectivity. Such mechanisms work in reverse in terms of interconnectivity: human behaviour and antibiotic consumption practices in lower and middle income countries immediately impact public health in higher income countries

[69]. Fourthly, historically and in the present, there is an ethical dimension to this problem, and hence a normative concern by international organisations such as the United Nations and World Health Organisation. Such concerns are partly based on ethical commitments to the principle of regional equality.

World Health Organization Efforts

The first governing bodies of the World Health Organization (WHO) in public health started to formulate policy options and strategies to contain AMR in 2004, which culminated in the publication of the Global Strategy in 2001. This strategy contained several recommendations to member states and other stakeholders for the development of national policies and actions on AMR control. Since then, the problem of AMR has been elevated in prominence in global public health. Resolutions have been put forward and adopted in the World Health Assembly and regional committees urging governments to take action against AMR. However, the actions taken so far by states have been inadequate and the strategies contained in the 2001 Global Strategy have not been widely or effectively implemented [70].

In support of the theme of the 2011 World Health Day, WHO has been working to tackle AMR and its impacts by promoting six complementary policy actions. Collectively, they are intended to engage member states to take action on AMR. The six-point policy package includes a commitment to the development of national plans for the containment of AMR, and then to develop, strengthen, or maintain, within the national health systems, national surveillance of antimicrobial resistance. Ensuring the quality of antimicrobials that are marketed is needed to improve regulatory capacity. Rational use of antimicrobials is promoted through public awareness campaigns, training healthcare professionals in generally acceptable practices in prescription and dispense, and using alternative medicines or disease control methods which obviate the need for antimicrobials. Efforts are increased to improve infection prevention and control in hospitals and in the community. Finally, research and development for both new antimicrobials and new methods to manage disease effectively are promoted [71]. Gaps in knowledge and awareness about the AMR problem and its health impacts, and awareness-raising strategies undertaken in the countries have been identified. Dialogue about how to best respond to this challenge is continued.

As mentioned earlier, [70]. To achieve these, WHO has emphasized the importance of multisectoral collaboration beyond the health sector, engaging healthcare, agriculture, veterinary, and environment sectors.

While a number of countries have successfully responded to some recommended policies (largely focusing on the health aspects), WHO's Western Pacific Regional Office has been conducting interviews with key informants, with a focus on policy makers, to assess the relevance of the recommendations and to cultivate awareness of AMR. The past decade has seen a dramatic increase in the publication of scholarly articles regarding AMR. The geographic reach of AMR publications has spread globally over time, although there has tended to be an unevenly developing shortage of research and publications in relation to AMR among least developed countries, particularly in Africa. A significant rise in the number of articles addressing AMR has been noted since 2012, with the U.S., the U.K., and Australia producing the highest number of AMR articles [22].

Global Antimicrobial Resistance Research and Development Hub

The Global Coalescing effort to prepare and implement an Action Plan against Antimicrobial Resistance began under the auspices of the G7 and now has engagement from the G20, the United Nations General Assembly, the World Bank and other Partners, including industry. This effort coincides with, and responds in part to, the 2030 Sustainable Development Agenda, which argues that 'peace and security, and inclusive development and cooperation are essential to a sustainable world of the future'. Similarly, it recognizes that 'the world is presently the target of many terrorist groups, and… such violence results in instability… inflaming the climate of fear, resulting in the collapse of honest and trustworthy leadership'. Infectious disease, including AMR, which is described as one of the greatest threats facing humanity, is one of these security challenges affecting development. The concept is clearest in the context of the human health threats posed by AMR, y*et al*so applies in the contexts of animal health and agribusiness, environmental protection, global finance, governance, transparency and others [72, 22].

Many of the health issues discussed above also threaten global security. Infectious diseases do not regard national borders, and pathogens can move quickly across the globe in an internationalized world. The rapid spread of HIV/AIDS in the 1980s and 1990s, Severe Acute Respiratory Syndrome in 2002, and the H1N1 influenza pandemic in 2009 are witness to this new environment in which improved health and disease security depend on collective action. Germs concerned with AMR, including infection-causing bacteria associated with various diseases and resistant genes, also spread rapidly by being carried by international travelers and by being transported in foodstuffs. Resistant bacteria are not limited by national borders, and often colonize individuals around the world before being recognized and therefore contained. The large measure of ignorance and blind spots in middle-income countries offers pathways through which new pathogens and resistance genes can be introduced and spread. The new disease can pose an enormous national burden, but there are also transnational effects on investments, growth, trade and finance. Evidence of disease outbreaks, or their exclusion from importation lists by other countries, can lead to sudden loss of markets worth billions of dollars, which further endangers relatively vulnerable countries. Strikingly, evidence of one new disease can often result in countries being dropped from multiple importation lists [73, 74].

On 27 February 2023, the first meeting of the Global Antimicrobial Resistance Research and Development Hub recognised the strategic role of the Hub as a global initiative facilitating Member States, as well as relevant stakeholders, in addressing the global research and development needs, gaps and priorities for antimicrobial compounds (including antibiotics, vaccines, and diagnostics), and to ensure equitable access to the resulting products [69.

In 2021, the World Health Organization initiated the development of a platform to bring together international stakeholders to increase and coordinate investments in antimicrobial resistance R&D, focused on economic SandP research proposals. It was called the Global Antimicrobial Resistance Research and Development Hub, and was launched as a non-profit external entity of WHO in the summer of 2023. The Hub is open to collaboration with partners from multiple sectors, including government,

industry, civil society, and philanthropic organisations [75].
The Hub aims to facilitate investments in R&D for antimicrobial compounds. To achieve this goal, it is necessary to define the research and development needs, gaps, and priorities for antimicrobial compounds at a global level. The first Global Research and Development Needs Assessment identified three priority areas for the R&D of new antibiotics: broad-spectrum oral antibiotics for outpatient settings treating typhoidal salmonella infections; topical antibiotics and adjuvants for the treatment of chronic wounds; and novel systemic beta-lactam antibiotics, with activity against both *Escherichia coli* and K. *pneumoniae* contractible in an outpatient setting [76].

Future Directions in AMR Research

Antimicrobial resistance (AMR) is not new environmental phenomena, but challenges concerning AMR are mounting. A high level of mortality is associated with AMR infections. To challenge AMR smartly, new ideas, tactics, and techniques are essential. AMR can be confronted by exploring fresh avenues for the synthesis of novel antimicrobials, studying AMR-related toxicity effects, and deciphering the mechanisms of action of new agents. The role of natural compounds in countering AMR is being explored globally. Isolation and characterization of natural products are essential to evaluate their toxicity effects as well as their potential as AMR nature mimics. Determining resistance mechanisms of existing antimicrobial agents is essential to develop more effective agents. Deep mining libraries of existing antimicrobial peptides (AMPs) will aid in the de novo design of new AMPs with enhanced effectiveness. The potential benefits and drawbacks of various AMPs including host defence peptides in mammalian systems should also be explored. Drug combinations are now being studied as a strategy to counter AMR. Synergy between antibiotics and phages blends the specificity of phages with the broad-spectrum nature of antibiotics that target the cell machinery of bacteria, also referred to as combinatorial therapy. Other combinations explored include antibiotics with AMPs, metal nanoparticles, agents to mediate biofilm dispersal and CRISPR-esque agents to inhibit defence systems [77].
Designing inhibitors of bacterial defence systems may be useful in enhancing antibacteriophage therapies and/or the effectiveness of antibiotics. Bacteriophages are being studied as alternatives to antibiotics but resistance development is problematic making the combinatory approach promising. The delivery of antimicrobials with liposomes is a time-honoured approach to reduce toxicity. Gene therapies target DNA, RNA and proteins. New solutions: bacteriophage therapy, drug delivery via nanomaterials. Peptides – alternative to antibiotics. Combinatorial treatment of antibiotics with phages. Phage therapy uses native, harnessed, on the rise. Amplify bacteriophages that aren't restricted by resistance, doling it out like antibiotics. Treatment/bacteriophage pools to glean similar phages. New antibiotic treatments with two or more mechanisms of action. New delivery systems, including nanoparticles and aerosols. Hard drugs with the least chances to side effects. AMR doesn't happen with other treatments: naturally-derived anti-eukaryotes. Many require voice amplification or navigating environments. There's a level of immune stimulation against AMR-maintreatment. Make sure drugs do new things [78, 79].
Funding new antibiotics discovery and development is expensive. Industry generates many antibiotic drug candidates from synthetic series. However, to obtain fully characterized drug candidates, costs, production and application should be monitored up through discovery into development stage. Hand-offs along the production chain should also be managed and documented effectively, using appropriate regulatory and information technologies. Businesses can only feel secure with quantitative risk and extra cost analysis, realistic demands, technology choice, and schedule and resource information transfers before the drug application through feasibility studies, appropriate project planning, and risk management. Clinical trials must be conducted and reported according to Good Clinical Practice and other pharmacovigilance regulations, for valid licensing and continued approval of the drug [80].
Funding new antibiotics discovery and development is expensive. Moreover, on the mammalian model stage, the probability of successful drug regulatory approval is lower than 30%, and the mean cost of drugs that reach early clinical proof-of-concept is expected to rise above USD160 million in the pharmaceutical market. Therefore, production and application of drug candidates before and after the move into the development stage must be managed and monitored up through discovery, so that the first products can be licensed as soon as possible. Otherwise, the numerous drug candidates that can save lives will perish in the production chain unqualified for use [77].
All production to application processes sequentially execute simple tasks based on physics, mathematics or biology. Nevertheless, there are pictorial flow charts and Gantt-style project schedules to show the obligations that each actor must meet throughout the stages, their deadlines, organization, calculations and control measures along with critical path, operating time, slack and floats, utility, information flows and government's roles. In the past 10 years, numerous reviews have been published on new class antibiotics discovery chemistry, mechanism of action, synthesis, improvement, conservation, clinical pharmacology, resistance potential and "squeeze-out" avoidance. However, not a single review encompasses the excellent tracking of fully characterized drug candidates on the overall chain [81].
In summary, to satisfy the unmet medical need for new antibiotics, "swimming upstream" has to be started using computational compound libraries, robotic experiment control and A/B testing on controllable robot devices.

Conclusion

Antimicrobials, the substances that kill microbes that cause disease in humans and animals, have aided the healing process in humans since the discovery of penicillin shortly after the 2nd World War. For decades they have been very effective. Infections with otherwise devastating diseases could be treated, chronic inflammatory conditions could be controlled, organs such as the kidney and heart could be transplanted, and living could proceed with artificial joints and other implants. However, the effectiveness of these substances has been endangered by the development of antimicrobial resistance (AMR) [9].
Antimicrobial resistance can develop at any point of the antibiotic use cycle, affecting human and animal medicine as well as aquaculture or agriculture. With increased understanding of the evolution of AMR, there is a growing awareness that the overuse and inappropriate use of antibiotics in any part of this cycle creates a pressure that leads to resistance that may subsequently transfer between

species, genera, and kingdoms. The use of human antibiotics in animal husbandry for prophylactic purposes and to promote growth is known to lead to extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae in animals and is one example of how AMR can travel along the food chain. However, residues of antibiotics in waste waters from pharmacological industry might also represent a huge risk of developing AMR in bacteria when they come into environmental contact. [82]

Difficult to treat infections, the so-called "hard to treat infections" (HUITs), in humans can arise from a number of resistant bacteria such as the Enterobacteriaceae (e.g. *Escherichia coli*, *K. pneumoniae*, *S. marcescens*, *Enterobacter* spp.), *Acinetobacter baumanni* and *Pseudomonas aeruginosa*. The spreading of those pathogens is enhanced by clinic-to-clinic or country-to-country transfer of patients, leading to difficult to treat infections in the otherwise low prevalence areas. Microbiologists might be of help in pinpointing the origin of an outbreak as each bacterial species has a typical gene pool sharing a set of antibiotic resistance genes. Thus, it is possible to investigate if a certain resistance gene or even a less common strain is showing up in an area where is was not previously found. In recent years, advances in bacterial genomics have increased to a large extent the potential of molecular biology to study the genetic basis of virulence and AMR in any bacterial species [83, 84].

Different aspects of AMR compatibility, challenges, and cross-sectoral approaches, or "One Health," are currently being discussed in several Working Groups of the Coalition. Prior to knowledge transfer to the Working Groups in the Coalition, a review and synthesis of scientific evidence on the key research findings related to AMR compatibility and consistency with different political parameters was conducted globally. The purpose of this paper is to summarize these findings and suggest their validity for consideration by the Working Groups [22].

Antimicrobial resistance (AMR) is a globally emerging concern as it threatens the future efficacy of both human and animal therapeutic agents. The World Health Organization's (WHO) ad hoc and continually updated Global Action Plan on Antimicrobial Resistance comprises five priority objectives. To accommodate and preserve the therapeutic usefulness in interventions on AMR threats in the whole food chain, it would be of utmost importance to ensure the compatibility of predetermined objectives with their progress parameters and challenge situations. The WHO's Global Action Plan, with its wide-ranging objectives, is dissected in this regard. It is suggested that as a general and integrative tool for AMR research and policy actions, "One Health" remains valid for AMR compatibility with different political and scientific angles and is worth investigating in depth. Each of its three sectors can and should approach the challenge independently and with domain-specific contributions. Nevertheless, cross-sectoral approaches are highly recommended as they have crucial managerial and practical advantages over siloed approaches [64, 85].

Unfortunately, until now there has been little success in implementing a globally coordinated approach towards the mitigation of AMR threats. Thus, instead of merely keeping it optional for nations, governmental institutions and international organizations are to coordinate and harmonize governmental and institutional stakeholders across nations worldwide in massively resorting to a tough, inclusive, and internationally binding agreement on AMR, similar to the WHO's FCTC [9]. Afterwards global accountability measures should be set up and respectively enacted for executive agencies such as the World Bank and the World. Antimicrobial resistance (AMR) is a major global health concern that affects not only human medicine but also various sectors, including vulnerable patient populations and environmental reservoirs. For instance, patients undergoing hemodialysis are at increased risk of viral hepatitis infections, particularly hepatitis B and C, which are prevalent due to repeated blood transfusions and prolonged medical interventions, further complicating their clinical outcomes. In parallel, multidrug-resistant bacterial strains have also been identified in non-clinical settings, such as commercial fish tanks, raising concerns about environmental dissemination and potential transmission to humans. In light of the growing threat posed by resistant microorganisms, there has been a growing interest in exploring plant-based alternatives to conventional antibiotics. Our previous experimental research demonstrated that *Nigella sativa* (black seed) and *Zingiber officinale* (ginger) extracts exhibit significant antibacterial activity against multidrug-resistant *Escherichia coli*, highlighting their potential role as natural antimicrobial agents.

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