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Review Article

Antimicrobial Resistance: A Growing Serious Threat for Global Public Health

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Abstract: Antibiotics are the most magnificent discovery of 20th century that have saved millions of lives from infectious diseases. Microbes have developed acquired antimicrobial resistance (AMR) to many drugs due to high selection pressure from increasing use and misuse of antibiotics over the years. The transmission and acquisition of AMR occur primarily via human–human interface both within and outside of the healthcare facilities. A huge number of interdependent factors related to healthcare and agriculture govern the development of AMR through various drug resistance mechanisms. The emergence and spread of AMR from the unrestricted use of antimicrobials in livestock feed has been a major contributing factor. The prevalence of AMR bacteria has attained its incongruous level worldwide and threatening global public health as silent pandemic, necessitating urgent intervention. Therapeutic options of AMR bacterial infections are limited resulting in significant morbidity and mortality with high financial impact. The paucity in discovery and supply of new novel antimicrobials to treat life-threatening AMR infections stands in sharp contrast to demand. Immediate interventions to contain AMR include surveillance and monitoring, minimizing over the counter antibiotics and antibiotics in food animals, access to quality and affordable medicines, vaccines and diagnostics, and enforcement of legislation. An orchestral collaborative action within and between multiple national and international organizations are required urgently, otherwise, a post-antibiotic era can be a real possibility than an apocalyptic fantasy for the 21st century. This narrative review highlights on the basis, mechanisms and factors in microbial resistance and key strategies to combat antimicrobial resistance.

Keywords: antibiotics; antimicrobial resistance; mechanisms of resistance; drivers of resistance; measures to combat resistance

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1. Introduction

Antibiotics are the "magic bullets" for fighting against bacteria and considered as the most remarkable medical discovery of 20th century. The introduction of antibiotics has changed the therapeutic paradigm saving millions of lives from bacterial infections. Antibiotics have absolutely been a godsend to mankind, not just for medicinal uses but have also been exploited in a diverse purpose including animal husbandry and agriculture as preventative measure for decades. With its ever-increasing use and misuse, bacteria have developed antimicrobial resistance (AMR), which is a logical inherent characteristic trait for bacteria. AMR is referred to the potential of microorganism including bacteria, viruses, fungi and parasites to thrive and continue to grow in the midst of drugs designed to kill them. Infections caused by AMR organisms are difficult to treat and there is increased chance of severe illness and even death. There are several types of antimicrobial agents including antibiotics, antifungal, antiviral, disinfectants, and food preservatives that either suppress the growth and multiplication of microbes or kill them. Antibiotics are class of antimicrobials specifically used to combat bacterial infections and antibiotic resistance is much more frequent than any other classes of antimicrobials. AMR is an unavoidable evolutionary phenomenon shown by all organisms through development of genetic mutations in order to safeguard the lethal selection pressure. To withstand the environmental selection pressure, bacteria strive to develop resistance against antibacterial drugs rendering them ineffective. With the ever-increasing use of antibiotics around the world, bacteria have the ample opportunity for developing AMR with profound consequences including much higher morbidity and mortality [1–3]. The incidence and prevalence of AMR bacterial infections has attained its incongruous levels during 21st century and threatening global public health as silent pandemic, necessitating urgent intervention [4]. Antibiotic resistance can happen to any country and can affect anyone irrespective of age and gender. With its current scenario, AMR is one of the unsurpassed threats not only to global health but also to food security today. Evolution and dissemination of AMR is concurrently affected by a huge number of interdependent factors related to healthcare and agriculture. Besides, it can also be affected by factors contributing from pharmaceuticals, inappropriate waste management, trade and finance, creating AMR as one of the most intricate public health concerns worldwide. With the rapid global spread of "superbugs", which are resistant to most known antimicrobials, the situation of drug-resistant pathogens has attained a real alarming status. AMR infection has been ranked to third as the leading cause of death after cardiovascular diseases. An estimated 1.27 million deaths were attributable to AMR infections in 2019 alone, while nearly 5 million deaths were somehow associated with drug-resistant infections, according to a major study published in January 2022. This number is estimated to increase to 10,000,000 per year by 2050, greatly exceeding deaths from cancer [5]. AMR has been acknowledged to be one among the top three major public health threats by the World Health Organization (WHO). As a well-known example of first "superbug", Methicillin resistant Staphylococcus aureus (MRSA) is associated with high death toll from AMR infections across the globe [6]. Currently, 3.5% of active TB and 18% of previously treated TB cases belong to MDR-TB (multidrug-resistant tuberculosis) worldwide and there is a growing concern for XDR-TB (extensively drug-resistant tuberculosis), developing among many MDR-TB cases. Although antibiotics are invaluable in combating bacterial infections, their misuse and abuse with inappropriate dose and duration over decades have resulted in selection pressure with the emergence of resistant bacteria. Apart from human health, the emergence and spread of AMR from the unrestricted use of antimicrobials in livestock feed has been a major contributing factor. It necessitates increased surveillance on the impact of excessive and unregulated use of antibiotics in animal feeds to downturn the incidence of drug-resistant bacteria. An increase in antibiotic resistance can have impact on human health with both therapeutic and preventive consequences. Therapeutic implication is direct and seen through treatment failure and complications, while preventive implications are seen through compromise of treatment options for immunosuppressive situations like anticancer chemotherapy, advanced surgical procedures, transplantation, invasive procedures like intubation or catheterization [7,8].

The current investment in the development of new synthetic small and natural-product-derived molecules stands in sharp contrast with an ever-growing demand for novel antimicrobials to treat

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life-threatening AMR infections. Pharmaceutical giants have relinquished their interest from antibiotic discovery for their own ratiocination that has ceased significant antibiotics inventory since 1980s. Fluoroquinolone was added in the group of last broad-spectrum antibiotics discovered in the 1980s and was brought to market in 1987. Since then, there has been a paucity in the development and only a few new antibiotic groups are in the pipeline that can be used to combat current AMR. Use of antibiotics is intertwined with the development of resistance, implying that resistance can be substantially reduced by avoiding unnecessary consumption of antibiotics. Given the facts that antimicrobials are indispensable tools to treat and prevent diseases, it is now crucial to preserve the efficacy of currently available antimicrobials since there is no significant discovery of new molecules during recent decades [9]. This narrative review spotlights on the basis, mechanisms and factors in microbial resistance and key strategies to combat the antimicrobial resistance.

2. Timeline of Major Antibiotics Discovery and Antibiotic Resistance

The dawn of the modern antibiotic era can be marked by the discovery of salvarsan and neosalvarsan, a synthetic prodrug by Paul Ehrlich in 1910 to treat syphilis *caused by Treponema pallidum.* Later on, prontosil, a sulfonamide prodrug discovered by bacteriologist Gerhard Domagk gradually replaced salvarsan. Selman Waksman, an American microbiologist and biochemist is credited with the first systematic evaluation of microbes in the soil and their ability to generate compounds with antimicrobial action in the 1930s. He unearthed multiple antibiotics from filamentous actinomycetes living in the soil including streptomycin, the widely used antibiotic against tuberculosis and defined an antibiotic as "*a compound made by a microbe to destroy other microbes*". Penicillin *was discovered* from a mould called *Penicillium rubens* by *Sir* Alexander Fleming, a Scottish physician and microbiologist in 1928 which glaring the golden era of antibiotic discovery that peaked until mid-1950s. With regards to antibiotic discovery, the period between 1940s to 1960s is regarded as the 'Golden Age' and most of the antibiotics still in current use were discovered during that period. Since then, there is a gradual decline in antibiotic discovery with concomitant evolution of drug resistant pathogens. Bacterial resistance to antibiotics has been recognized almost since the dawn of the antibiotic era [10]. Several years before the introduction of penicillin as a therapeutic agent in 1940, the first penicillin-resistant staphylococcus strain was described. Methicillin was introduced in 1959 as the first semisynthetic penicillinase-resistant penicillin and surprisingly a methicillin-resistant staphylococcus strain was reported in 1960, just a year later [11]. In 1958, vancomycin, a glycopeptide was introduced as a rescue drug for treating infections caused by methicillin-resistant staphylococci but unfortunately in 1979, a couple of decades later, vancomycin-resistant strains of coagulase-negative staphylococci (CNS) were reported and ten years later vancomycin resistant enterococcus (VRE) was also described. Decrease efficacy of vancomycin was subsequently noted for *S. aureus* with vancomycin-intermediate S. aureus (VISA) and vancomycin-resistant S. aureus (VRSA) were reported in 1997 and 2002 respectively [12]. Cephalosporin, a β-lactam antibiotic was discovered in 1945 and introduced in clinical practice in 1964 to treat penicillin resistant cases and since then several generations of cephalosporins have been launched with 5th generation being currently available. It was excellent in efficacy to start with especially against extended beta-lactamases (ESBLs) producing gram-negative bacteria. Until recently all previous generations of cephalosporin up to 4th generation have developed significant resistance. Tetracycline is another important antibiotic, discovered in 1950 and was successfully used for many common infections including gastrointestinal diseases. Within a decade of its discovery, tetracycline was reported to be inefficacious to shigella strains in 1959. Levofloxacin, a member of the third-generation fluoroquinolone was added to the antibiotics list in 1996 and levofloxacin-resistant pneumococcus was reported in the same year [13]. Carbapenem is a type of ß-lactam was introduced in 1980 and preserved to be a reserve drug to treat infections caused by members of Enterobacteriaceae especially cephalosporin resistant cases. With its increased use during 1990s to 2000s, Carbapenem-resistant Enterobacteriaceae (CRE) have emerged from different countries since 2006 [14]. From the timeline it is evident that new classes of antibiotics were produced by the pharmaceutical industries only for two decades, from 1960 to 1980 and afterwards there is dramatic decrease in the speed of discovery

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until recently [9]. This disproportionate ratio between drug-resistant pathogens and number of available antibiotics has given sufficient reasons to critics for their prediction of an eminent post-antibiotic era. Timeline of major antibiotics discovery and their resistance is depicted below (Figure 1).

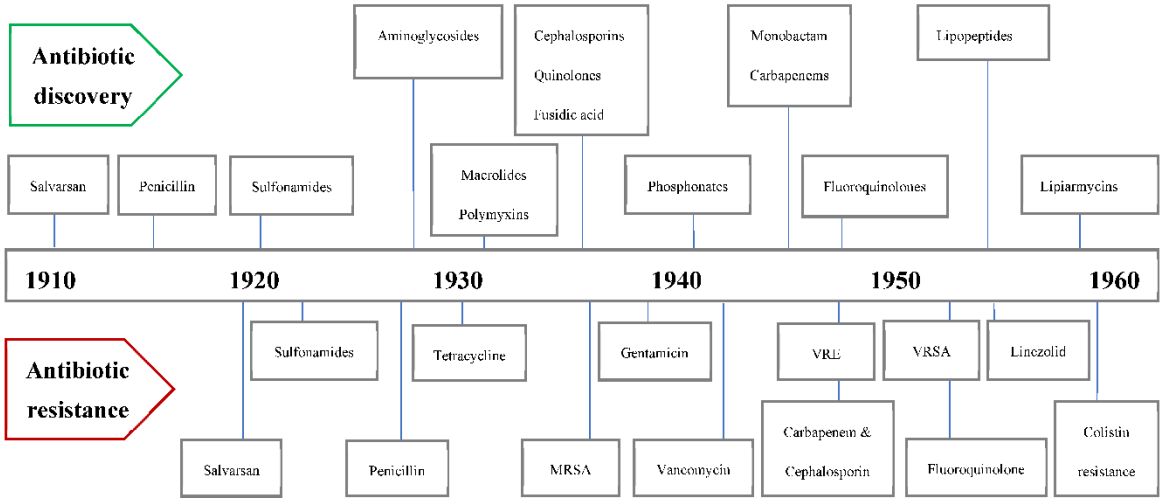

Figure 1. Timeline of discovery of major antibiotics and antibiotic resistance.

3. Superbugs

Superbugs refer to germs that have shown resistance to antimicrobial agents used to treat them and include multidrug or pan drug-resistant bacteria and fungi. In reality, there is scarce or no treatment at all available for superbugs. The term *"ESKAPE"* is the acronym for six highly drug-resistant bacteria (*Enterobacteriaceae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter*) and at present, Carbapenem-resistant Enterobacteriaceae (CRE) and Carbapenem-resistant Klebsiella pneumoniae (CRKP), Methicillin-resistant Staphylococcus aureus (MRSA), ESBL-producing Enterobacteriaceae, Vancomycin-resistant Enterococcus (VRE), multidrug-resistant *Pseudomonas aeruginosa*, and multidrug-resistant *Acinetobacter* are among the topmost encountered superbugs worldwide. Multidrug-resistant bacteria have emerged only after long-continued and widespread use of antibiotics to treat infections caused by them. For example, *M. tuberculosis* has turned out as MDR-TB after decades of treatment with antitubercular drugs, now found as a major superbug prevalent in both underdeveloped and developing countries. Hospital acquired or healthcare associated infections (HAIs) caused by both gram-positive (e.g., *Staphylococcus epidermidis, Clostridium difficile*, and *Streptococcus pneumoniae*) and gram-negative (e.g., *Burkholderia cepacia*, *Stenotrophomonas maltophilia, Campylobacter jejuni, Citrobacter freundii, Enterobacter spp., Haemophilus influenzae, Proteus mirabilis, Salmonella spp., Serratia spp.*,) bacteria are considered as superbugs because most of the available antibiotics have been proven ineffective to treat them [15]. Infections with superbugs enhance the rate of morbidity and mortality as therapeutic options for these bacteria are seriously jeopardized and also there is high treatment cost and extended periods of hospital stay associated with these infections [16].

4. Basis of Antibiotic Resistance

Antibiotic resistance is an evolutionary response of bacteria when they are challenged with therapeutic antibiotics. From a clinical perspective, all targeted pathogens remain susceptible to an antibiotic when it is first launched but with sustained use bacteria develop resistance to it. From an evolutionary perspective, bacteria adapt the action of antibiotic by either the *(i)* chromosomal gene mutations or *(ii)* acquisition of foreign DNA through horizontal gene transfer (HGT) that codes for resistance determinants. Mutations principally involving three different types of genes, viz., gene encoding the targets of the antibiotic, transporters of antibiotic, and regulators that repress the

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expression of transporters (e.g., antibiotic modifying enzymes and multidrug efflux pumps) lead to antibiotic resistance. There is entrancing evidence to support the notion that commensal or environmental bacteria are the source for the antibiotic resistance gene(s) and transmitted to human pathogenic bacteria through HGT [17]. It is well known that there are many antibiotics naturally synthesized by environmental microorganisms and to safeguard them from the action of self-synthesized antibiotics, they must possess antibiotic resistant genes too, otherwise they would have been killed by their own antibiotics [18].

Bacteria exhibiting antibiotic resistance can have gene(s) from intrinsic, acquired, or adaptive sources [19].

Intrinsic resistance: It refers to bacterial inherent natural capacity to show resistance to certain class of antibiotic due to presence of own chromosomal genes without mutation or gain of further genes. The implication of intrinsic resistance is that these bacteria will show inevitable resistance against these antibiotics if used to treat their infections. As far as the drug resistance mechanisms are concerned, both efflux pumps and reduced permeability are involved in intrinsic resistance. It also can affect the multidrug-efflux pumps frequently [20,21].

Acquired resistance: It is defined as an evolutionary process of exhibiting the resistance by a previously sensitive bacterium due to acquisition of chromosomal gene mutation or gaining an exogenous new genetic material via HGT. There are three main mechanisms for HGT, viz., transformation, transposition, and conjugation. The acquired resistance is most often transmitted through plasmid acquired via conjugation and it may be temporary or permanent [22,23].

Adaptive resistance: This phenotype is conditional to environmental changes and depending on the ability and duration of selection pressure, it may be interim or permanent adaptive resistance. When bacterial growth is influenced by sub inhibitory concentrations of antibiotics along with specific environmental signals like growth factors, nutrition, stress, pH, concentrations of ions, bacteria can develop adaptive resistance in both humans and livestock. As opposed to intrinsic and acquired resistance phenotypes, adaptive resistance is usually developed transiently and generally reverts back to the original state upon removal of the inducing signals. Although the exact biological processes involved in the evolution of adaptive resistance are not well understood, several factors including high mutation rates, gene amplification, efflux pumps, biofilm formation, epigenetic inheritance, population structure and heterogeneity have been mentioned as possible explanations for its development [24,25].

5. Sources and Routes of Transmission of AMR

The transmission and acquisition of AMR occur primarily via human–human interface both within and outside of the health-care facilities. Humans, animals, water and environment are found to be reservoirs and antimicrobial resistance genes can be transmitted between and within these reservoirs. As far as the transmission routes are concerned, there is significance difference between bacterial species and resistance elements [26].

Transmission of AMR bacteria is much facilitated by certain hotspot sources like wastewater and sludge from urban wastewater treatment plants, natural fertilizers like pig slurry, cow manure and fertilizer from poultry farming [27]. Animal feeds treated with antibiotics and their subsequent transfer to the humans through consumption of these animals constitute the direct route of acquisition of antimicrobial resistance from animals. Further, ingestion of fecal contaminated food or water and direct contact between animals and humans constitute other common routes [28].

6. Mechanisms of Drug Resistance

Antimicrobials and bacteria coexist in the same ecological niche, and bacteria develop defences against the harmful effects of antibiotic molecules. There are four essential targets in a bacterial cell for antibiotics (e.g., cell wall, cell membrane, protein synthesis and nucleic acid synthesis) and primary mechanisms for antimicrobial resistance include: limiting drug uptake, altering a drug target, inactivating a drug, and increasing active drug efflux (Figure 2).

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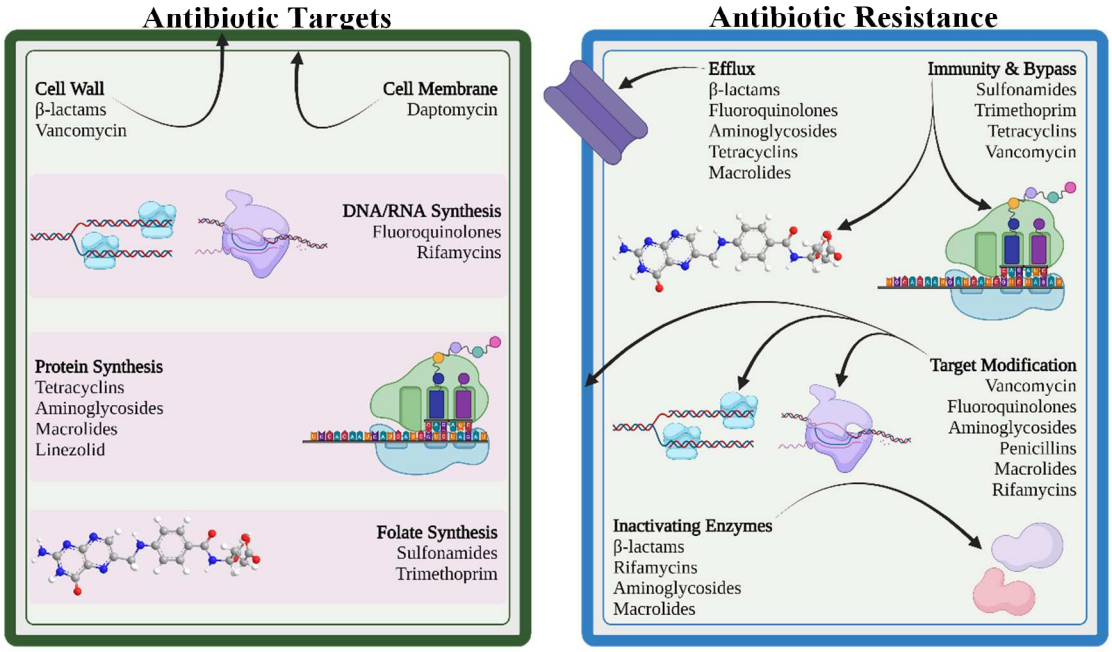

Figure 2. Antibiotic targets and mechanisms of drug resistance (created with BioRender.com).

In general, for acquired resistance, bacteria use mechanisms like drug target modification, drug inactivation, and drug efflux, whereas intrinsic resistance mostly results from the use of restricting uptake, drug inactivation, and drug efflux. Gram-positive and gram-negative bacteria differ in their structural makeup, which causes variance in their drug resistance mechanisms. Gram positive bacteria less frequently utilize the method of restricting the uptake of a drug because they lack the lipopolysaccharide (LPS) outer membrane and have limited capacity for efflux mechanism to certain types of drugs [29,30]. Meanwhile, gram negative bacteria have been shown to use all four main mechanisms.

6.1. Limiting Drug Uptake

Lipopolysaccharide, a highly acylated glycolipid forms the major component of the outer membrane of gram-negative bacteria and serves as a permeability barrier for a variety of chemicals, including antibiotics. This intrinsic resistance of gram-negative bacteria lowers permeability of specific antibiotic agents leading to resistance. Additionally, modifications in the permeability of outer membrane proteins, in particular porin protein, can lead to acquired resistance. Porins serve as the primary entry point for hydrophilic antibiotics like β-lactams, fluoroquinolones, tetracyclines, and chloramphenicol. The quantity and type of porin proteins have an impact on the entry of these antibiotics into the bacterial cell and consequently, the bacterial susceptibility to these antibiotics [31]. Furthermore, acquired antibiotic resistance may result from mutations that impair expression of porin or its function. Mutations affecting expression of porin lead to high levels of resistance when combined with other co-existing mechanisms such efflux pumps or enzymatic degradation of antibiotics [32]. Development of biofilms by some bacteria is another method of antimicrobial resistance shown by these bacteria (e.g., *Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus viridans, E. coli, Klebsiella pneumoniae, Proteus mirabilis* and *Pseudomonas aeruginosa*). A biofilm is *an assemblage of microbial cells* embedded in self-produced exopolysaccharide and attached to abiotic or biotic surfaces. It is known to confer bacterial tolerance and resistance to antibiotics through a variety of processes including obstruction in antibiotic penetration and may stop building of bactericidal concentrations over the entire biofilm [33,34].

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6.2. Modification of Targets for Drug

Bacteria can modify the targets required for drug binding so that the drug cannot bind or binds poorly to the modified target. This modification results from spontaneous mutations of the gene or genes that encode the drug target. For instance, when mutations impact the quinolone-resistance-determining region (QRDR) in the DNA gyrase (topoisomerase II and topoisomerase IV), fluoroquinolone resistance develops in both gram-positive and gram-negative bacteria [35]. Another way of target modification is methylation, which is considered to be very efficient method in developing resistance. Examples of methylation include *erm* methylases against macrolides, lincosamides, and streptogramin B antibiotics in both gram-positive and gram-negative bacteria. Similarly, methylation of the *cfr* gene has been linked to the development of resistance in a variety of bacteria, including *Proteus vulgaris, Staphylococcus spp., Enterococcus spp., Bacillus spp.,* and *E. coli* [36]. *Staphylococcus spp.* exhibit a significant reduction in their affinity to β-lactam antibiotics due to an alternative penicillin-binding protein encoded by *mecA* and *mecC* genes [37,38].

6.3. Inactivation of Drug

Drug resistance may result from the inactivation of antibiotics by certain bacterial species and follow two ways: either the antibiotic is really degraded, or a chemical group is transferred to the antibiotic. The hydrolysing enzymes known as β-lactamases, produced by members of the Enterobacteriaceae family are particularly effective at inactivating β-lactam antibiotics. The β-lactamases originally known as penicillinases and cephalosporinases inactivate β-lactam ring structure by opening at a specific point rendering it ineffective to bind with the target called penicillin binding proteins. Several members of Enterobacteriaceae family as well as many species of gram-positive bacteria like *Staphylococcus aureus, Enterococcus faecalis,* and *Enterococcus faecium,* are known to harbor β-lactamase genes that are transmitted by HGT. Additionally, tetracycline is hydrolysed by an enzyme, expressed by the *tetX* gene present in certain bacteria [39]. The transfer of acetyl, phosphoryl, and adenyl groups is the most frequently seen chemical groups for inactivation of drugs. Phosphorylation and adenylation are known to be utilized predominantly against aminoglycosides, while acetylation is the most diversely used mechanism against aminoglycosides, chloramphenicol, streptogramins, and fluoroquinolones [30].

6.4. Efflux of Drug

By using an energy-dependent efflux pump located on the cytoplasmic membrane, bacteria are able to control the accumulation of antibacterial chemicals, including antibiotics inside the bacterial cells. By expelling harmful compounds such as antibiotics, metabolites, and quorum sensing signal molecules from the cell, efflux pumps enable bacteria to control their internal environment. In 1980, researchers described the first plasmid-encoded efflux pump in *Escherichia coli*, which pushed tetracycline out of the bacterial cell. Since then, numerous gram-positive and gram-negative bacteria with diverse efflux mechanisms implicated in their resistant phenotypes have been found. It is interesting to note that the majority of efflux systems engage in multidrug efflux mechanisms that are always chromosomally encoded and ensure bacterial intrinsic drug resistance [40]. Instead, genes for substrate-specific efflux pumps (for example those for chloramphenicol, tetracyclines and macrolides) are more likely to be found on mobile genetic elements [30,41].

There are six drug efflux pumps based on the structure and energy source namely ATP-binding cassette (ABC) superfamily, the major facilitator superfamily (MFS), the multidrug and toxic compound extrusion (MATE) family, the small multidrug resistance (SMR) family, the resistance-nodulation-division (RND) superfamily, and the drug metabolite transporter (DMT) superfamily. The majority of the efflux pumps that are present in gram-positive bacteria belong to the ABC and MFS families and are either carried on plasmids or encoded by chromosomal genes. While the main clinically significant efflux systems in gram-negative bacteria are members of the RND superfamily, which is typically made up of an outer membrane protein channel, a periplasmic protein, and a cytoplasmic membrane pump [42].

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7. Drivers to AMR

Antimicrobial resistance is driven by multifaceted drivers including inherent traits of the microbes and many environmental factors that involve both prescribers and consumers. Broadly, factors contributing AMR can be of 4 categories; environmental factors (e.g., population and overcrowding, rapid spread through mass travelling, poor sanitation, ineffective infection control program, widespread agricultural use), drug related (e.g., fake drugs, substandard drugs, over the counter availability), patient related (poor compliance, poverty, lack of education, self-medication, misconception) and physician related (inappropriate use, inadequate dosing, lack of updated knowledge and training) [30,43]. Some of the recognized factors are elaborated below:

7.1. Misuse and Overuse of Antibiotics

The process of development of antibiotic resistance occurs as a natural phenomenon, but it has been accelerated by the misuse of antibiotics both in humans and animals over the years. There is a causal relationship between overuse and development of microbial resistance to antibiotics as revealed by epidemiological studies [44]. Despite being warned repeatedly by the health organizations, unfortunately, misuse and overuse of antibiotics continue to be any disproportionate level worldwide with the current scenario seems to be at the point of no return.

Surveys have revealed that people across the globe especially non-educated section do have misconception and believe about the antibiotics that it would help to recover from viral diseases like the common cold or flu, which are most common among illnesses. Moreover, it has been observed that antibiotics are frequently prescribed medicine for patient management particularly practiced in many developing countries where there is lack of adequate diagnostic facilities [45]. Administering antibiotics without a clear indication is a good example of common misuse and emergence and spread of drug-resistant pathogens are facilitated further when antibiotics can be bought for human as well as animal use as over the counter (OTC) drugs. Antibiotic abuse is also contributed by lack of antibiotic policy and standard treatment guidelines, frequently reported from developing countries where antibiotics are often over-prescribed by health workers, pharmacy dealers and veterinarians. Substandard or poor quality of antibiotics in the supply chain has made the situation of AMR worst in many developing countries. Further, antibacterial resistance can also be contributed by the physicians unnecessarily prescribing lengthy course of antibiotics. Unethical though but sometimes to gain financial incentives from pharma companies and to satisfy patient's expectations, many physicians especially in the developing countries prescribe antibiotics without indication [45,46].

7.2. Increase in Gross Domestic Product (GDP)

The significant rise in antibiotic use globally is predominantly accredited to rise in the GDP especially in many developing countries. With the rise in GDP, there has been substantial improvement in the quality of life of people from low and middle-income countries (LMICs) that positively correlated with increased antibiotic consumption. It is estimated that between 2000 and 2015, the global antibiotic use has been elevated by 65% according to Klein et al. [47] Further, with rise in GDP, consumption of animal protein has also been risen which added further in the transmission of AMR from animal sources in these countries [48].

7.3. Inappropriate Prescribing Patterns

Inappropriately prescribed antibiotics contributes significantly to promoting AMR [49]. Inappropriate antibiotic prescribing refers to prescription of antibiotics where it is not necessary or selection of inappropriate antibiotics or the wrong dose and duration of an antibiotic [50]. It has been shown in a study that at least one antibiotic was received by 50% of the patients without compelling reasons during their stay at the hospital. Introduction of antibiotics should ideally be guided by prior isolation and antimicrobial susceptibility testing of bacteria but according to the CDC (centers for disease control and prevention) report in 2017, antibiotic prescriptions were made for about one third of hospital patients without adequate testing and continued for longer durations [51]. Situation in

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nursing homes is even worst, where about 75% of the antibiotic prescriptions are incorrect or inappropriate with wrong doses and durations [52].

7.4. Paucity in Futuristic Antibiotics

The looming problem of antibiotic resistance demands urgent response by the pharma companies with new novel antibiotics [53]. Unfortunately, there is a dearth of developments in new antibiotics despite having repeated calls from the World Health Organization. Surprisingly, only 8 out of the 51 newly developed antibiotics can be catalogued as innovative drugs to treat AMR, overwhelming majority are just the reformations of previous drugs. As a consequence, it is speculated that these new drugs are likely to show resistance shortly. Current scenario states that management of drug-resistant TB, urinary tract infections, pneumonia and other gram-negative infections have been seriously jeopardized because of lack of available treatment options. Paucity in new drugs has made patients of extreme of age much vulnerable with life-threatening infections [54]. Regulatory restrictions and economic liability are major hindrance to production of new antibiotics according to pharmaceutical companies. On that account, many organizations have reduced their investment on research and innovation category substantially and surprisingly 18 major companies have abandoned their antibiotics production. Considering profit, pharma companies have shifted their priority and now interested in producing drugs for chronic diseases than infectious diseases.

7.5. Agricultural Use of Antibiotics

Use of antibiotics in livestock farming has been markedly increased in most developing countries for various purposes including increase demand of animal protein in the recent years which contributing to AMR due to presence of antibiotic residues in animal-derived products (e.g., muscles, kidney, liver, fat, milk, and egg). Antibiotics are being used randomly for different purposes including treating animal diseases, preparation of animal feed for growth promotion, improved feed conversion efficiency, and for disease prevention [55]. This practice is more prevalent in the developing countries to gain more incomes from the food animal farms and due to lack of regulatory government policies, it has been a major contributor to human AMR [56]. Approximately 70% of all medically important antibiotics are sold for use in animals in the United States [57]. It is a matter of great concern that the uses, types, and mode of actions of antibiotics employed in agriculture and veterinary practice are closely related or the same to those prescribed to humans.

7.6. Easy Travel Routes

There is growing evidence that emergence and global spread of AMR bacteria are much facilitated by human movement. Dissemination of AMR across the globe are contributed significantly by easy and modern travelling routes available not only for human but also for animals and goods [58]. Human travellers are highly plausible to return to their own countries with colonisation or infection by AMR organisms from countries of visit unknowingly. It has been shown that the AMR bacteria may persisted for up to 12 months as carriage after travelling to highly endemic AMR regions, amplifying the risk of transmission among susceptible populations [59].

7.7. Knowledge Gap

There is substantial evidence that both healthcare workers (HCWs) and members of public have knowledge gaps about appropriate use of antibiotics and mechanisms of antibiotic resistance [60]. Surveillance is a pre-requisite to estimate the magnitude of AMR burden and to establish any intervention strategies like antimicrobial stewardship. Unfortunately, actual statistical data regarding use of antibiotics and status of AMR in both health care and agriculture sectors are yet to gather worldwide [61]. Surveillance data provide critical information and help in identifying areas for strategic interventions to maximize the outcomes. In order to launch successful intervention approaches through cooperative efforts from different stakeholders (e.g., international agencies,

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human and veterinary medicine sectors, agriculture and animal production industries and consumers), the existing knowledge gap needs to be addressed first.

8. Clinical Implications of AMR

- Successful treatment of microbial infections including bacterial, fungal, and viral infections is hindered by the antimicrobial resistance.
- Emergence and dissemination of new resistant mechanisms threaten the scope of treatment for many common illnesses like urinary tract infections, upper respiratory tract infections, typhoid and flu resulting in treatment failure, permanent disability or even death.
- The success of cancer chemotherapy, transplantation surgery, and even minor dental procedures would be seriously jeopardized by virtue of AMR unless the novel drugs are available.
- AMR infections impose mandatory prolonged treatment with higher health care cost and may need expensive alternate drugs [62].

9. How to Combat AMR

Antimicrobial resistance is a serious concern affecting not only people, but animals, plants, and the environment at large. Like humans, animals sometimes can be a potential source of MDR germs, that can be transmitted through close contact or consumption of animal foods. No single government department or independent organization in any country can tackle the problem of ever-growing AMR alone. To contain and control AMR, it demands an orchestral coordination and collaboration within and between multiple sectors like healthcare industries including pharmacy, agriculture, finance, trade, education, non-government organizations at national and international levels. Multisectoral collaboration can be both horizontal as well as vertical. Horizontal collaboration is across sectors and departments within the country i.e., multistakeholder forums and the vertical collaboration involves different levels within country, region and international.

The trend of physicians prescribing broad-spectrum antibiotics for trivial conditions needs to be checked immediately and the usage of antimicrobials for animals by veterinarians also needs close monitoring. In order to combat AMR, rational antibiotic prescription, limited use of prophylactic antimicrobials, patient's education and compliance with antibiotic therapy and appropriate hospital hygiene through antimicrobial stewardship are among the main focuses. Furthermore, development and availability of faster diagnostic tools and accurate antimicrobial profiling for targeted antibiotic therapy are also important.

World health assembly adopted five key strategic action plan to combat AMR which include (i) improve awareness and understanding of antimicrobial resistance; (ii) strengthen knowledge through surveillance and research combating infection through control measures; (iii) effective sanitation, hygiene and infection prevention measures; (iv) optimize the use of antimicrobials in human and animal health; and (v) sustainable investment in new medicines, diagnostic tools and vaccines [63]. Highlights of a few important measures to combat AMR are described below (Figure 3).

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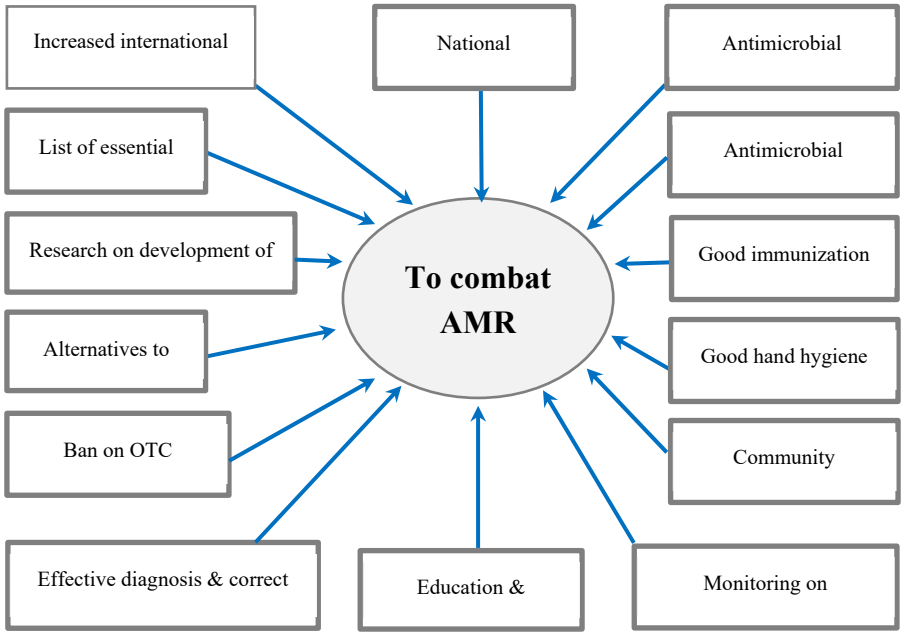

Figure 3. Major interventions to combat AMR.

9.1. International Measures

- Establishing and strengthening collaboration among international agencies, governments, nongovernmental organizations and professional groups.
- Establishment of surveillance networks for antimicrobial use and AMR globally.
- Building laboratory capacity for the detection and reporting of AMR pathogens that have global health impacts.
- Establishing and strengthening international tracking systems for quick identification and mitigation of emerging pathogens.
- International monitoring to control the counterfeit antimicrobials across the globe.
- Investment on research, new drug discovery and vaccines.

9.2. National Strategies

- Implementation of 'Antibiotic policy' for judicious use in healthcare and agricultural settings.
- Strengthening of national surveillance, monitoring and evaluation efforts by integration of public health and veterinary sectors.
- Development of innovative point-of-care diagnostic tests for pathogen identification and resistance monitoring.
- Investment for basic and applied research on new antibiotics and vaccines.
- Building capacity and strengthening international collaboration to combat AMR.
- Adoption of antimicrobial stewardship at health-care settings with essential drug list.

9.3. Rational Use of Antibiotics

"Rational use of medicine" has been defined by the WHO as using correct medications including antibiotics appropriate for clinical needs of the patients, in exact doses of individual needs, for an adequate period of time and at the lowest cost [62]. The optimal results of treating infections can only be achieved when the selection of pathogens, drug toxicity, and development of resistance are minimized through the rational use of antibiotics. Antibiotic stewardship program (ASP) in health care settings is primarily aimed to maintain a rational use of antibiotics.

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9.4. Ban on over the Counter (OTC) Antibiotics

Stringent regulatory control should be imposed on OTC selling and dispensing of oral and injectable antibiotics, which is unfortunately still a common practice in many underdeveloped and developing countries. Antibiotics should only be dispensed to serve the prescription from a qualified physician. Continuous awareness program on the use of antibiotic and AMR among patients and pharmacy drug dispensers is strongly recommended along with revisit of existing antibiotic policy with local and regional AMR surveillance.

9.5. Infection Prevention and Control (IPC)

Infection prevention and control (IPC) is an essential and evidence-based practical approach to safeguard both patients and healthcare workers from being vandalised by avoidable infections including drug-resistance pathogens. This is an indispensable measure mitigating the AMR concern in health care settings. The role of physicians, nurses, pharmacists and other health-care providers are very crucial to combat AMR through IPC. The physicians being involved in direct patient care can play a paramount role in combating AMR through complying with hospital infection control and antibiotic policies along with timely notification of resistant cases to IPC team. Besides, nurses and other health care providers need to be educated about the AMR and aseptic practices in controlling the spread of infections since they are also in direct contact with the patients. The role of hospital pharmacist as an important member of the IPC team is to inculcate patients regarding treatment compliance including antimicrobial use, which contribute tremendously to combating AMR [64].

Recommended measures related to IPC in a health-care facility include:

- Formation of 'infection prevention and control committee'.
- Practices of good hand hygiene.
- Proper diagnosis and successful treatment of infection.
- Responsible use of antimicrobial agents.
- Continuous surveillance and monitoring of antibiotic use and antibiotic resistance.
- Establishing quality antimicrobials supply chain.
- Good Microbiological Laboratory Practices.

9.6. Antimicrobial Stewardship Program (ASP)

Antimicrobial stewardship is the coordinated program to educate and persuade prescribers to follow the appropriate selection, dosage, and duration of antimicrobial agents for improved patient outcomes, to reduce microbial resistance and spread of AMR infections. The first goal of antimicrobial stewardship is to make sure that health care practitioners prescribe the most appropriate antimicrobial with the correct dose and duration for each patient. The second goal is pointed towards prevention of overuse, misuse, and abuse of antimicrobials. The third goal is to keep resistance development minimum. There are two major overlapping approaches in achieving the primary goals of antimicrobial stewardship: (a) using antibiotics to optimise healthcare outcomes and (b) using antibiotics to ensure sustainable access for all who need them. In 2014, CDC has released the '*Core Elements' of* antimicrobial stewardship in achieving these goals which are applicable to all hospitals, regardless of size with specific suggestions for small and critical access hospitals in their i*mplementation* [65,66].

9.7. Use of Antibiotics in Animals

WHO specifically called for stricter legislation in using medically important antibiotics in animals to curtail the problems of antimicrobial resistance. Further, it emphasizes on overall reduction and complete restriction of the use of antibiotics for the sake of growth promotion and disease prevention. Antibiotics to prevent disease can be administered if infection has been diagnosed in other animals in the same flock, herd, or fish population. As alternative measures, improved hygiene, provision of probiotics or nutritional supplements in feed, better use of vaccination, and changes in practices of animal husbandry are encouraged [67].

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9.8. Development of New Drugs and Vaccines

Rapid development of resistance to each new class of antibiotic and the challenges in producing new effective drugs, focusing on research into an integrated strategy that includes development of both vaccines and novel antibiotics. To combat AMR, greater investment is required in operational research and innovation of new antimicrobials through collaborative efforts of academia and industries both at the national and international levels. Vaccines have been used as prophylactic measure to prevent infectious diseases for long and considered as an essential tool to decrease demand for antimicrobial drugs and thereby combat AMR. Moreover, they are not blamed with resistance development like that of antibiotics. Thus, innovation and use of vaccines against AMR bacterial infections especially carbapenem-resistant Enterobacteriaceae and *Acinetobacter baumannii are of prime importance and* could be a potential strategy to fight against AMR transmission [63,64].

9.9. Introduction of Checkpoints

Practice of illegal sales and self-medication of antibiotics are still a prevailing trend observed in some countries, especially in underdeveloped and low-income countries where anyone can buy drugs from the pharmacies without prescription of a registered doctor. Sometimes decision of antibiotic prescription by physicians is influenced by patient's desire which is totally irresponsible. Stringent control and checkpoints should be introduced to contain these detrimental practices which escalate the development of AMR. Proper legislation and its implementation could be appropriate step to limit the illegal sale of drugs especially antibiotics. Other checkpoint may include delayed antibiotic prescribing (intake of antibiotic in a prescription is deferred until symptoms appear and the patient is clearly instructed) is a successful strategy to combat AMR [50,52].

9.10. Community Engagement

Development and propagation of AMR is often considered as a biological phenomenon that relates to many everyday practices of people such as home and animal hygiene, food production, health seeking behaviours, and waste disposal in a community. Moreover, this is likely that each community may have their own language and perception with regards to use of antimicrobials and drug resistance that develop through everyday practices. So, community engagement approach towards behavioural change for antimicrobial use could potentially safeguard both existing and future treatment options and offers better strategies to combat AMR at community level. It demands more research engaging people to explore their understanding and experiences with an aim to translate these ideas into applications that could be better ways tackling AMR problem [68].

9.11. Alternatives to Antibiotics

Researchers are trying best to find potential alternatives for antibiotics from natural resources. Plants are being considered as the untapped sources of potential antimicrobial agents according to recent findings on compounds derived from plants such polyphenolics, alkaloids, and other plant extracts [69]. However, the antimicrobial potential of several phytochemical compounds including polyphenolics, alkaloids, and flavonoids has yet to be investigated [70–75]. Moreover, the big challenge is to transfer and translate some of these precious discoveries out of the laboratories into hospital practices. With the advent of advanced technological breakthrough especially in biotechnology, genetic engineering and synthetic chemistry, opportunities of research for innovative alternative therapies have been widen that bring optimism to growing AMR problem. Scientists now know that microbes such as bacteria, viruses and moulds compete for resources living next to each other and are indulged in chemical warfare i.e., to defend themselves from their own secreting chemicals. Manipulating the phenomenon of microbial chemical warfare, discoveries of new alternatives to antibiotics that attack disease-causing bacteria are on the way [76].

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9.11.1. Phage Therapy

Phage therapy refers to application of bacterial viruses to combat populations of pathogenic bacteria. Bacteriophages also called phage are viruses capable of infecting bacteria and loosely known as "bacteria eaters". There are a few unique properties of bacteriophages over antibiotics like easy availability, diversity, auto dosing (increase in number spontaneously), low inherent toxicity, specific host range, lack of cross resistance with antibiotics, and low environmental impact that are quite attractive to consider phages as alternative to antibiotics. However, certain limitations of phage therapy including proper phage selection, narrow host range, effective formulation, probable immune reaction and clinician understanding need to be addressed before its clinical application becomes a reality. While phage therapy is unlikely to be an absolute replacement of antibiotics, its application as an alternative therapy to topical infections has been successful where antibiotics have proved to be ineffective [77].

9.11.2. Antivirulence Drugs

A novel class of drugs called antivirulence that focuses on interfering with bacterial virulence factors instead of growth inhibition or killing of bacteria is an alternative approach to antibiotic therapy. It can disable specific bacterial proteins that are used to attach to host cells for initiation of infection. Thus, disarming the bacteria, antivirulence drugs prevent the establishment of infection and since they utilize different mechanism of action, development of antibiotic resistance to antivirulence drugs is unlikely. Moreover, it has been shown that alike conventional antibiotics, antivirulence drugs do not support drug-resistant bacterial strains to dominate over susceptible ones and there is negligible perturbation of the healthy microbiota. Food and Drug Administration (FDA) has approved the use of antivirulence drugs for bacterial toxin-mediated diseases and recently it has been found effective against MRSA infections in mice. However, due to challenges in development and clinical use, antivirulence drugs would be suitable as adjunct or combination therapy with antibiotics [78].

9.11.3. Bacteriocins

Bacteriocins are natural antimicrobial peptides produced by bacteria that have bactericidal or bacteriostatic effects on similar or phylogenetically related bacterial strains. The harmless nature of bacteriocins would make them ideal agents and a number of bacteriocins are now being studied for their potential use as antibacterial therapy. They are also being increasingly used to prevent the growth of dangerous bacteria in food, extending shelf life of food and delaying food spoilage. Nisin is an example of bacteriocin derived from the lantibiotic family of antibacterial peptides, widely used as food preservative and produced by certain gram-positive bacteria like *Lactococcus* and *Streptococcus* species. Apart from its use in food production, nisin has now been found to have antibacterial activity against both gram-positive and gram-negative disease-associated pathogens including drug-resistant bacterial strains such as methicillin resistant Staphylococcus aureus, Streptococcus pneumoniae, Enterococci and Clostridium difficile [79].

10. Conclusions

Evolution of antimicrobial resistance by bacteria is a continuous phenomenon occurring either by new chromosomal mutations or acquisition of drug-resistance gene through HGT. Incremental development of AMR over the previous two decades has created grave risk for global public health and now appraised to be the highest health danger in the 21st century, seriously limiting treatment options. MDR bacteria are being frequently detected in many common infections like respiratory, urinary, sexually transmitted or tuberculosis globally. Meanwhile, development and supply of new antibiotics has lagged significantly since 1980s and not keeping pace with the speed of development of AMR. The future of successful antimicrobial therapy looks bleak in the context of unprecedented evolution of AMR infections and paucity in the development of new antimicrobials. Unless global

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coordinated actions to stop the on-going trend of AMR is adopted, a post-antibiotic era for the 21st century can be a real possibility than an apocalyptic fantasy.

Multiple drivers are contributing for the development and dissemination of antimicrobial resistance globally creating a major concern for both human and animal health adding higher financial burden. AMR infections are more difficult to treat leading to treatment failure and complications on top of huge financial costs to oneself and to the community. Prudent use of antibiotics with appropriate dosage and duration is among the most important means to reduce the selective pressure required for the emergence of resistant organisms. Strict practice of infection prevention and control measures in all healthcare facilities is another vital step in controlling the spread of MDR organisms [49,50].

Combating AMR requires an improved and coordinated global effort from all international governmental and non-governmental agencies besides strong political momentum. Integration and cooperation of policymakers, researchers, public health practitioners, pharma companies, hospital administrators, agriculture industry leaders and members of public are important in this endeavour. The unified and eventual goal of this collaboration is to decelerate the ongoing trends in AMR to minimize the health and economic burden. Establishing antimicrobial stewardship and rigorous compliance of antibiotic policy in healthcare settings are invaluable strategies to combat antibiotic resistance. Further, good microbiology practice, surveillance and monitoring, minimizing OTC antibiotics and antibiotics in food animals, increase access to quality and affordable medicines, vaccines and diagnostics and enforcement of legislation are among the essential steps mitigating the problem [63–67].

Prevention is still the best strategy to reduce the AMR infections and their spread globally. While restoration of efficacy of existing antibiotics through their rational use is essential, desperate efforts should be exerted towards development of new effective molecules from both antibiotics and alternatives to antibiotics besides new technological breakthrough in diagnosis and vaccines development. Until now, many attempts have been made to address the problems of antibiotic resistance and the interventions required, however, coordinated action is largely absent, especially the political will at national and international levels. The forcible trend of AMR infections indicates that within just a few years, we might face the dire setbacks in medical, social, and economical sectors and all our achievements in modern medicine, such as major surgery, organ transplantation, treatment of preterm babies, and cancer chemotherapy will be vanished, unless a real and robust global coordinated actions are immediately taken [80].

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Author's note: The areas covered in relation to antimicrobial resistance and mitigation measures described herein this manuscript are considered randomly without any prior selection. Information has been aligned based on recent literature on these areas.

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Abbreviations

AMR, Antimicrobial resistance; AST, Antimicrobial susceptibility testing; MDR, Multi drug resistant; XDR, extensively drug resistant; CNS, coagulase-negative staphylococci; MRSA, methicillin resistant staphylococcus aureus; VRE, vancomycin resistant enterococcus; VISA, vancomycin intermediate staphylococcus aureus; VRSA, vancomycin resistant staphylococcus aureus; CRE, carbapenem resistant enterobacteriaceae; ESBLs, extended beta-lactamases; *ESKAPE, Enterobacteriaceae, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter*; HAIs, healthcare associated infections/hospital acquired infections; HGT, horizontal gene transfer; LPS, lipopolysaccharide; QRDR, quinolone resistant determining region; ABC, ATP-binding cassette; MFS, major facilitator superfamily; SMR, small multidrug resistance; RND, resistance-nodulation-division; GDP, gross domestic product; LMICs, low and middle-income countries; CDC, centers for disease control and prevention; FDA, Food and Drug Administration; OTC, over the counter; IPC, infection prevention and control; HCWs, healthcare workers; ASP, antibiotic stewardship program.

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