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Increasing Danger of Antimicrobial Resistant Organisms to Human Health Around the World

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Abstract:
Antibiotics, one of the 20th century's greatest discoveries, protected millions from infectious illnesses. High selection pressure from antibiotic usage and abuse has caused microbes to develop AMR to numerous medicines. AMR is mostly spread via human-to-human contact in and out of hospitals. Many interrelated healthcare and agricultural variables drive AMR via drug-resistance mechanisms. The widespread use of antimicrobials in cattle feed has contributed to AMR. Antimicrobial-resistant bacteria are already widespread and endanger global public health as a hidden epidemic, requiring immediate action. Antimicrobial-resistant bacteria infections have few treatment choices, causing high morbidity and death and high costs. In contrast to need, newer antimicrobials to treat life-threatening illnesses by resistant microorganisms are hardly discovered and supplied. Surveillance and monitoring, reducing over-the-counter and food animal antibiotics, access to quality and inexpensive medications, vaccinations, and diagnostics, and law enforcement are immediate AMR measures. A postantibiotic future may become a reality in the 21st century without immediate coordinated effort by numerous national and international organizations. Microbial resistance processes, variables, and antibiotic resistance methods are covered in this narrative overview.

Keywords: *Drivers of resistance; measures to combat resistance; antibiotics; antimicrobial resistance; mechanisms of resistance.*

Introduction

The most significant medical discovery of the 20th century, antibiotics are bacteria-fighting “magic bullets”. Antibiotics have revolutionized treatment and saved millions of lives. For decades, antibiotics have been used in animal husbandry and manufacturing as prophylactic measures in many impoverished and developing nations [1]. Due to overuse and abuse, bacteria have acquired antimicrobial resistance. Antimicrobial resistance occurs when bacteria, viruses, fungi, and parasites multiply in the presence of medications meant to destroy them. Antimicrobial-resistant infections are difficult to treat and raise the risk of serious disease or death. Antimicrobial agents include antibiotics, antifungals, antivirals, disinfectants, and food preservatives kill or inhibit bacteria. Antibiotics are the most often used class of antimicrobials for treating bacterial infections and antibiotic resistance. AMR occurs in all organisms via genetic alterations to protect against deadly selection pressure. To survive environmental selection pressure, microorganisms acquire antibacterial medication resistance, making them useless [2]. As antibiotic usage rises, particularly in developing nations, bacteria have more chances to acquire AMR, which increases morbidity and death [3–5]. Antimicrobial-resistant bacterial infections have reached alarming proportions in the 21st century, threatening worldwide public health as a hidden epidemic that requires immediate action [6].

In every nation, antibiotic resistance may impact anybody, regardless of age or gender. AMR is one of the biggest challenges to global health and food security [7]. Many interrelated healthcare and agricultural variables impact AMR evolution and spread. Pharmaceuticals, improper waste management, commerce, and finance may all contribute to AMR, making it one of the most complex public health issues [8]. The fast worldwide spread of “superbugs” (microorganisms’ resistant to most antimicrobials) has made drug-resistant diseases a serious threat. AMR is one of the top three public health risks, according to the WHO. The third largest cause of mortality after cardiovascular disease is antimicrobial-resistant illness [9]. A large research released in January 2022 found that antimicrobial-resistant illnesses caused 1.27 million fatalities in 2019 and drug-resistant infections

approximately 5 million. The figure is expected to reach 10,000,000 per year by 2050, surpassing cancer deaths [10]. Antimicrobial-resistant infections caused by methicillin-resistant Staphylococcus aureus (MRSA), the first "superbug," kill many people worldwide [11]. MDR-TB accounts for 3.5% of current TB and 18% of previously treated TB patients globally, and many MDR-TB cases are emerging as XDR-TB [12]. Antibiotics are crucial for treating bacterial illnesses, however their overuse and abuse with incorrect dosage and duration over decades have caused selection pressure and resistant microorganisms. Apart from human healthcare, improper use of antimicrobials in animal feed in many underdeveloped nations has contributed to AMR. To reduce drug-resistant microorganisms, excessive and uncontrolled antibiotic usage in animal diets must be monitored [13]. Antibiotic resistance affects human health therapeutically and preventatively. Treatment failure and complications are therapeutic consequences, while compromised treatment options for immunosuppressive conditions like cancer chemotherapy, advanced surgical procedures like transplantation, and invasive procedures like intubation or catheterization are preventive [14,15]. Recent investments in synthetic small and natural-product-derived compounds contrast with the rising need for innovative antimicrobials to treat life-threatening antimicrobial-resistant illnesses. Since the 1980s, pharmaceutical firms have stopped developing antibiotics for their own reasons. Last broad-spectrum antibiotic discovered in the 1980s, fluoroquinolone was introduced in 1987. Since then, progress has slowed, and few new antibiotic families are under development [16]. Antibiotic use is linked to resistance, hence minimizing needless use may minimize resistance. Antimicrobials are essential for treating and preventing infectious illnesses, thus it's important to retain their potency as no new compounds have been discovered in recent decades [17]. This narrative review discusses microbial resistance's causes, mechanisms, and prevention techniques.

Timeline of Major Antibiotics Discoveries and Antibiotic Resistance

Paul Ehrlich discovered salvarsan and neosalvarsan, a synthetic prodrug, in 1910 to treat Treponema pallidum-induced syphilis, marking the beginning of the modern antibiotic era. Eventually, bacteriologist Gerhard Domagk's sulfonamide prodrug prontosil supplanted salvarsan. In the 1930s, American microbiologist and biochemist Selman Waksman conducted the first systematic study of soil bacteria and their potential to produce antibiotic chemicals. He discovered antibiotics from soil-dwelling filamentous actinomycetes, including streptomycin, a commonly used TB treatment, and described an antibiotic as “a compound made by a microbe to destroy other microbes”. Sir Alexander Fleming, a Scottish physician and microbiologist, developed penicillin from Penicillium rubens in 1928, starting the antibiotic discovery golden age that lasted until the mid-1950s. The 1940s to 1960s are considered the "Golden Age" of antibiotic discovery, when most of the antibiotics now in use were found. Since then, antibiotic development has declined and drug-resistant bacteria have evolved. Since the antibiotic era began, bacteria have developed drug resistance [16]. Penicillin-resistant Staphylococcus strains were initially documented many years before its 1940 launch as a medicinal drug. Methicillin, the first semisynthetic penicillinase-resistant penicillin, was released in 1959, and a methicillin-resistant Staphylococcus strain was described in 1960 [18]. Vancomycin, a glycopeptide, was introduced in 1958 as a rescue drug for methicillin-resistant Staphylococci infections, but in 1979, coagulase-negative Staphylococci (CoNS) and vancomycin-resistant Enterococcus (VRE) were reported. VISA and VRSA were reported in 1997 and 2002, respectively, indicating decreased vancomycin efficacy for S. aureus [19]. Since its discovery in 1945, cephalosporin, a β-lactam antibiotic, has been used in clinical practice to treat penicillin-resistant illnesses. The fifth generation is now available. Initial effectiveness was high, notably against ESBL-producing gram-negative bacteria. Before recently, all cephalosporin generations up to the fourth had gained significant resistance. Tetracycline, developed in 1950, proved effective for numerous infections, including gastrointestinal disorders. Tetracycline proved ineffective against Shigella strains in 1959, a decade after its discovery. In 1996, third-generation fluoroquinolone levofloxacin was added to the antibiotic list, and levofloxacin-resistant Pneumococcus was reported [20].

Introduced in 1980, carbapenem is a β-lactam used as a reserve medicine for treating enterobacterales infections, particularly cephalosporin-resistant instances. Since 2006, carbapenem-resistant enterobacterales (CRE) have been discovered from several nations due to its growing usage in the 1990s and 2000s [21]. The pharmaceutical industry developed new antibiotic classes just for two decades, from 1960 to 1980, after which innovation slowed until recently [17]. The high ratio of drug-resistant microorganisms to antibiotics has led detractors to anticipate a postantibiotic future. Figure 1 shows significant antibiotic development and resistance timelines.

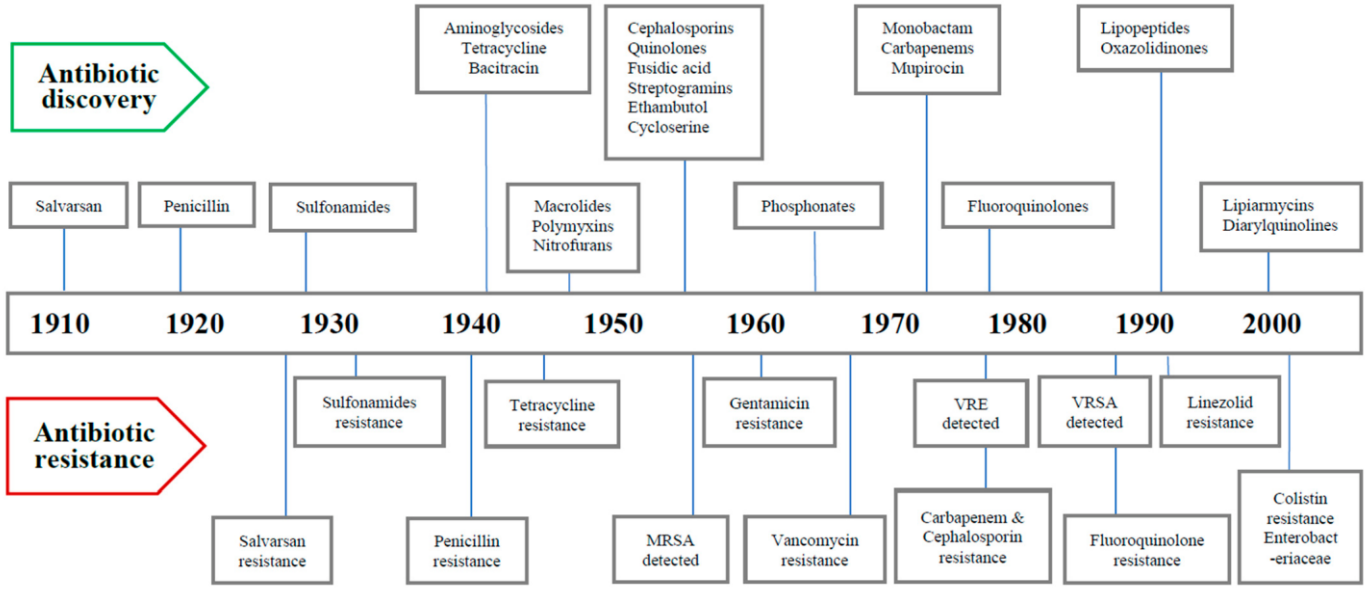

Figure 1. Timeline of discovery of major antibiotics and antibiotic resistance.

Superbugs

Superbugs are multidrug- or pan-drug-resistant bacteria and fungi. In actuality, superbug infections have little or no therapy. The acronym "ES- KAPE" stands for six highly drug-resistant bacteria (Enterobacterales, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enter-obacter) and currently, carbapenem-resistant enterobacterales (CRE), CRKP, MRSA, ESBL-producing enterobacterales, VRE, multi-resistant Enterobacter Multidrug-resistant microorganisms have evolved following extensive antibiotic usage to treat illnesses. After decades of anti-tituberculer medication therapy, M. tuberculosis became MDR-TB, a superbug widespread in both industrialized and poor nations. Haemophilus influenzae, Proteus mirabilis, Salmonella spp., and Serratia spp. are gram-positive and gram-negative bacteria that cause hospital-acquired infections (HAIs). Superbug infections increase morbidity and mortality due to their high treatment costs, limited therapeutic choices, and long hospital stays [23].

Basis of Antibiotic Resistance

Bacteria evolve to resist therapeutic antibiotics. Clinically, all targeted pathogens are susceptible to an antibiotic at first, but bacteria acquire resistance with usage. Bacteria evolve antibiotic resistance by chromosomal gene mutations or horizontal gene transfer (HGT) of resistance-coding foreign DNA. Mutations mostly involve genes encoding antibiotic targets, transporters, and regulators that repress transporters (e.g., antibiotic-modifying enzymes and multidrug efflux pumps) to cause antibiotic resistance. HGT transmits antibiotic-resistance genes from commensal or ambient bacteria to human pathogenic bacteria, according to fascinating data [24]. Environmental bacteria manufacture numerous antibiotics, as is widely known. They need antibiotic-resistant genes to avoid being destroyed by self-synthesized antibiotics [25]. Bacteria with antibiotic resistance may contain inherent, acquired, or adaptive genes [26]. Bacteria having their own chromosomal genes may withstand specific antibiotic classes without mutation or gain of genes. Due to inherent resistance, these bacteria will resist some antibiotics if employed to treat illnesses. Intrinsic drug resistance involves efflux pumps and decreased permeability. The multidrug efflux pumps are also often affected [27,28]. Some previously sensitive bacteria acquire resistance by chromosomal gene mutation or HGT. Three processes drive HGT: transformation, transposition, and conjugation. Resistance is usually transferred by a conjugated plasmid and may be transitory or permanent [29,30].

Adaptive resistance is contingent on environmental changes and may be temporary or permanent depending on selection pressure. Bacteria may acquire adaptive resistance in people and cattle when subinhibitory antibiotic concentrations and environmental cues like growth hormones, nutrition, stress, pH, ion concentrations, etc. affect bacterial development. Unlike intrinsic and acquired resistance phenotypes, adaptive resistance is typically temporary and reverts to the original condition when inciting cues are removed. High mutation rates, gene amplification, efflux pumps, biofilm formation, epigenetic inheritance, population structure, and

heterogeneity may explain adaptive resistance evolution [31,32].

Sources and routes of AMR transmission

AMR is mostly spread via human–human contact in and out of hospitals. Antimicrobial-resistance genes may spread across and among reservoirs including humans, animals, water, and the environment. Bacterial species and resistance elements vary in transmission pathways [33]. Hotspot sources include urban wastewater treatment plant effluent and sludge and natural fertilizers like pig slurry, cow dung, and poultry fertilizer help spread antimicrobial-resistant bacteria [34]. Direct acquisition of antimicrobial resistance from animals occurs via antibiotic-treated animal feeds and human intake [35]. Ingestion of feces-contaminated food or drink and direct animal-human contact are alternative transmission vectors [36].

Drug Resistance Mechanisms

Antimicrobials and bacteria share an ecological niche, and bacteria acquire antibiotic resistance. Antibiotics attack the cell wall, membrane, protein synthesis, and nucleic acid synthesis of bacteria. Limiting drug uptake, changing a drug target, inactivating a drug, and boosting active drug efflux are main antimicrobial resistance mechanisms (Figure 2).

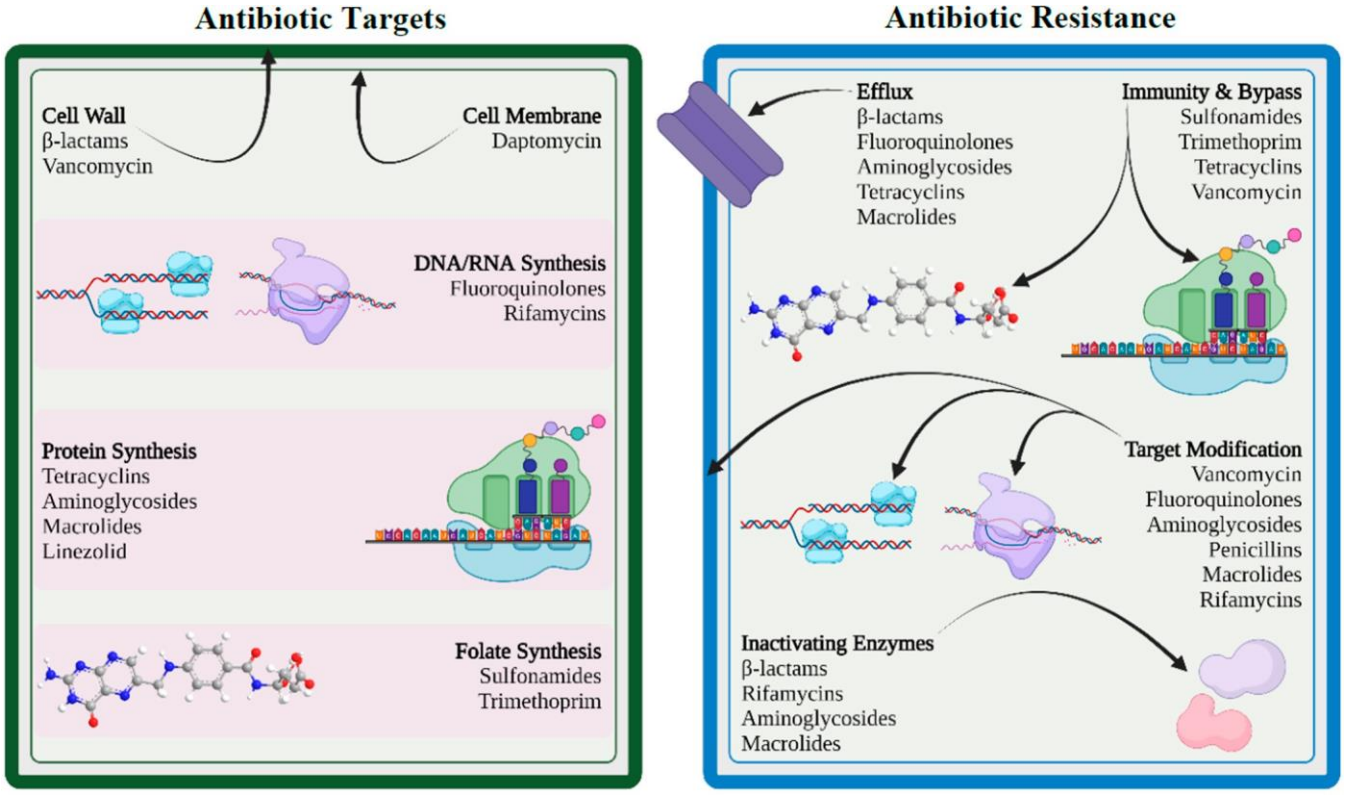

Figure 2. Antibiotic targets and mechanisms of drug resistance (created with BioRender.com (accessed on 12 November 2022)).

In general, bacteria employ drug target alteration, drug inactivation, and drug efflux for acquired resistance, whereas intrinsic resistance generally occurs from inhibiting uptake. Gram-positive and gram-negative bacteria have different drug-resistance mechanisms due to their structure. Because they lack the lipopolysaccharide (LPS) outer membrane and have restricted efflux mechanisms to some medications, Gram-positive bacteria seldom impede drug absorption [37,38]. Gram-negative bacteria employ all four drug resistance mechanisms.

Minimizing Drug Use

Gram-negative bacteria' outer membranes are mostly composed of lipolysaccharide, a highly acylated glycolipid that blocks substances like antibiotics. This inherent resistance of gram-negative bacteria reduces antibiotic permeability, causing resistance. Acquired drug resistance may also result from outer-membrane protein permeability changes, particularly porin protein. Porins are the main entrance site for hydrophilic antibiotics such β-lactams, fluoroquinolones, tetracyclines, and chloramphenicol. Porin protein amount and type influence antibiotic penetration into the bacterial cell and bacterial sensitivity [39]. Mutations that alter porin expression or function may also cause acquired antibiotic resistance. Porin mutations, along with efflux pumps or enzymatic degradation of medicines, increase resistance [40]. Some bacteria, such as Enterococcus faecalis, Staphylococcus aureus,

Staphylococcus epidermidis, Streptococcus viridans, E. coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa, develop biofilms to resist antimicrobials. Biofilms are microbial cells embedded in self-produced exopolysaccharide on abiotic or biotic surfaces. Several mechanisms, including drug penetration blockage, give bacterial tolerance and resistance to antibiotics. It may also prevent biofilm-wide antibiotic bactericidal concentrations [41,42].

Drug Target Modification

Bacteria may change drug binding targets so the drug cannot or poorly binds. This change is caused by spontaneous mutations in the drug target protein gene(s). Fluoroquinolone resistance occurs in both gram-positive and gram-negative bacteria when mutations affect the DNA gyrase's quinolone-resistance-determining region (QRDR) [43]. Methylation is another effective target modification approach for resistance. Gram-positive and gram-negative bacteria have erm methylases against macrolides, lincosamides, and streptogramin B antibiotics. Methylation of the cfr gene has also been associated to resistance in Proteus vulgaris, Staphylococcus, Enterococcus, Bacillus, and E. coli [44]. Staphylococcus. Lower affinity for β-lactam antibiotics is caused by an alternate penicillin-binding protein produced by mecA and mecC genes [45,46].

Drug Inactivation

Drug resistance may develop from some bacterial species degrading or transferring a chemical group to antibiotics. The β-lactamases generated by enterobacterales are very efficient at inactivating β-lactam antibiotics. Penicillinases and cephalosporinases, also known as β-lactamases, inactivate the β-lactam ring structure by opening a particular location, leaving it inefficient for interacting with targets, known as penicillin-binding proteins Many enterobacterales and gram-positive bacteria, including Staphylococcus aureus, Enterococcus faecalis, and Enterococcus faecium, have β-lactamase genes that are transferred by HGT. Certain bacteria express the tetX gene to hydrolyze tetracycline [47]. Acetyl, phosphoryl, and adenyl groups are the most common drug inactivation chemicals. Acetylation is most often employed against aminoglycosides, chloramphenicol, streptogramins, and fluoro-quinolones [38]. Phosphorylation and adenylation are mostly used against aminoglycosides.

Efflux of drugs

Bacteria regulate antibiotic accumulation in their cells via an energy-dependent efflux pump on the cytoplasmic membrane. Eflux pumps help bacteria regulate their internal environment by removing antibiotics, metabolites, and quorum-sensing signal molecules. The first Escherichia coli plasmid-encoded efflux pump, which removed tetracycline, was discovered in 1980. Since then, several gram-positive and gram-negative resistant bacteria with various efflux mechanisms have been identified. It is notable that most efflux systems use multidrug efflux mechanisms that are invariably chromosomally encoded to guarantee bacterial intrinsic drug resistance [48]. Instead, mobile genetic elements are more likely to include substrate-specific efflux pump genes like chloramphenicol, tetracyclines, and macrolides [38,49]. Six drug efflux pumps are classified by structure and energy source: the 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 efflux pumps in gram-positive bacteria are from 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 from the RND superfamily and consist of an outer-membrane protein channel, periplasmic protein, and cytoplasmic membrane pump [50].

Drivers of AMR

Multiple variables, including bacterial characteristics and prescriber and consumer environmental conditions, cause antimicrobial resistance. Environment (population and overcrowding, rapid spread through mass travel, poor sanitation, ineffective infection control program, and widespread agricultural use), drug (fake, substandard, and over-the-counter availability), patient (poor compliance, poverty, lack of education, self-medication, and misconception), and physician-related factors all contribute to AMR. Below are some known AMR drivers.

Antibiotic Misuse and Overuse

Antibiotic resistance is natural, but abuse of antibiotics in people and animals has exacerbated it. Epidemiological studies show that antibiotic usage causes microbial resistance [52]. Despite warnings from health groups, antibiotic misuse and abuse persist at a disproportionate level globally, and the situation seems to be nearing a tipping point. Surveys show that individuals worldwide, particularly uneducated ones, believe medicines treat most viral infections like the common cold or flu. Antibiotics are also often administered for patient care, especially in underdeveloped countries with poor diagnostic facilities [53]. Common antibiotic abuse includes unwarranted usage. Over-the-counter (OTC) medications for humans and animals help drug-resistant bacteria proliferate. In poor nations, absence of antibiotic policy and standard treatment recommendations contributes to antibiotic misuse. In many undeveloped nations, doctors, pharmacists, and veterinarians

overprescribe antibiotics. Substandard antibiotics in the supply chain have worsened AMR in many developing nations. Physicians providing long antibiotic courses or dosage incorrectly may also cause antibacterial resistance. Despite being unethical, many doctors, particularly in underdeveloped countries, give antibiotics without reason to appease patients and earn money from pharma corporations [53,54].

Growth in GDP

Global antibiotic usage has increased due to rising GDP, particularly in underdeveloped nations. GDP growth has improved the quality of life in low- and middle-income countries (LMICs), which positively corresponds with antibiotic usage. Klein et al. estimate 65% worldwide antibiotic usage increased between 2000 and 2015 [55]. Animal protein intake has increased in many developing nations as GDP has increased, thus spreading AMR from animal sources [56].

Unsuitable Prescriptions

AMR is increased by improperly administered antibiotics [57]. Inappropriate antibiotic prescribing includes prescribing unnecessary antibiotics, choosing the incorrect medications, and giving them the wrong dosage and duration [58]. In a research, 50% of hospitalized patients got at least one antibiotic without a good rationale. Bacteria isolation and antimicrobial susceptibility testing should guide antibiotic introduction, but a 2017 CDC report found that one-third of hospital patients were prescribed antibiotics without adequate testing and for longer durations [59]. In nursing homes, 75% of antibiotic prescriptions are inaccurate, with improper dosages and durations [60].

Future antibiotics shortage

Pharma firms must develop new drugs to combat antibiotic resistance [61]. The WHO has repeatedly called for antimicrobial development, but nothing has happened. Surprisingly, only 8 of the 51 newly produced antibiotics are unique treatments to treat antibiotic-resistant bacterium infections; the rest are reformulations. Thus, these novel medications may soon develop resistance. Drug-resistant TB, urinary tract infections, pneumonia, and other gram-negative infections are at risk due to a lack of treatment choices. Due to medicine shortages, elderly people are more susceptible to life-threatening illnesses [62]. Pharmaceutical firms say regulatory limitations and economic responsibility hinder antibiotic manufacturing. Due to that, several corporations have cut research and innovation spending, and 18 major antibiotic producers have stopped making them. Pharma firms increasingly prioritize chronic illnesses above infectious ones for profit.

Agricultural Antibiotic Use

Recently, most emerging nations have expanded livestock farming antibiotic use for numerous reasons, including growing animal protein consumption. Antibiotic residues in animal-derived products (muscles, kidney, liver, fat, milk, and egg) contribute to AMR. Antibiotics are randomly used to treat animal illnesses, prepare feed for growth promotion, increase feed conversion efficiency, and prevent disease [63]. This method is more common in underdeveloped nations to increase food animal farm revenue and owing to a lack of regulated government rules, which has contributed to human AMR [64]. In the US, 70% of medically relevant antibiotics are marketed for animals [65]. The fact that veterinary medicines have similar applications, kinds, and mechanisms of action to human antibiotics is concerning.

Easy Travel Routes

There is emerging evidence that human migration helps antibiotic-resistant bacteria originate and spread globally. Easy and contemporary transit routes for people, animals, and products help spread AMR throughout [66]. Travelers sometimes unwittingly bring antimicrobial-resistant germs home. After traveling to highly prevalent AMR locations, antimicrobial-resistant bacteria may remain in the body for up to 12 months, increasing the risk of transmission among vulnerable people [67].

Knowledge Gap

There is strong evidence that both healthcare professionals (HCWs) and the public lack antibiotic usage and resistance information [68]. To quantify the AMR burden and design intervention measures like antimicrobial stewardship, surveillance is needed. Unfortunately, global statistics on antibiotic usage and AMR in healthcare and agriculture are lacking [69]. Surveillance data can identify strategic initiatives to optimize results. The information gap must be closed before international agencies, human and veterinary care sectors, agricultural and animal production companies, and consumers can collaborate to launch viable intervention techniques.

Clinical Implications of AMR

AMR has various clinical consequences, including these top issues [70]:

Antimicrobial resistance hinders effective treatment of bacterial, fungal, and viral infections.

Emergence and spread of new resistant mechanisms threaten effective treatment for common illnesses, including urinary tract infections, upper respiratory tract infections, typhoid, and flu, leading to treatment failure, disability, or death.

Cancer chemotherapy and transplantation surgery success.

Combating AMR

Antimicrobial resistance threatens humans, animals, plants, and the environment. Animals may spread MDR germs by intimate contact or food intake, much as humans. No government agency or independent entity can solve the increasing AMR issue alone. Healthcare businesses including pharmacy, agriculture, banking, commerce, education, and nongovernmental groups must work together to limit and manage AMR at the national and worldwide levels. Multisec-torial cooperation may be horizontal or vertical. Multistakeholder forums are horizontal cooperation across sectors and departments in the country, whereas vertical collaboration incorporates multiple levels within a country, region, and globally [71]. Physicians providing broad-spectrum antibiotics for minor diseases and veterinarians using antimicrobials for animals must be monitored quickly. Rational antibiotic prescribing, restricted prophylactic antimicrobial usage, patient education, compliance with antibiotic treatment, and hospital cleanliness via antimicrobial stewardship are key to combating AMR [72]. Other major developments are speedier diagnostic techniques and reliable antimicrobial profiling for targeted antibiotic treatment.

Five strategic action plans to tackle AMR were endorsed by the World Health Assembly, including these steps: (1) raise awareness and understanding of antimicrobial resistance; (2) improve knowledge through surveillance and research in infection control; (3) implement effective sanitation, hygiene, and infection prevention measures; (4) optimize antimicrobial use in human and animal health; and (5) encourage sustainable investment in new medicines, diagnostic tools, and vaccines [73]. Some key national and worldwide AMR metrics are listed below [69] and shown in Figure 3.

International Measures

The following are international measures that can be taken:

- Improving cooperation among international agencies, governments, NGOs, and professional groupings.
- Globally establishing monitoring networks for antimicrobial usage and AMR.
- Enhancing laboratory capability to identify and report AMR bacteria with global health consequences.
- Enhancing global monitoring systems to detect and address new infections.
- Global surveillance of counterfeit antimicrobials.
- Investing in research, drug discoveries, and vaccinations.

National Strategies

The following are national measures that can be taken:

- Implemented a "Antibiotic policy" for responsible usage in healthcare and agriculture.
- Improving national surveillance, monitoring, and evaluation by integrating public health and veterinary sectors.
- Creating novel point-of-care diagnostics for pathogen detection and resistance monitoring.
- Investing in antibiotic and vaccine research, both fundamental and applied.
- Enhancing worldwide coordination and ability to tackle AMR.
- Adopting antimicrobial stewardship in healthcare with critical drug list.

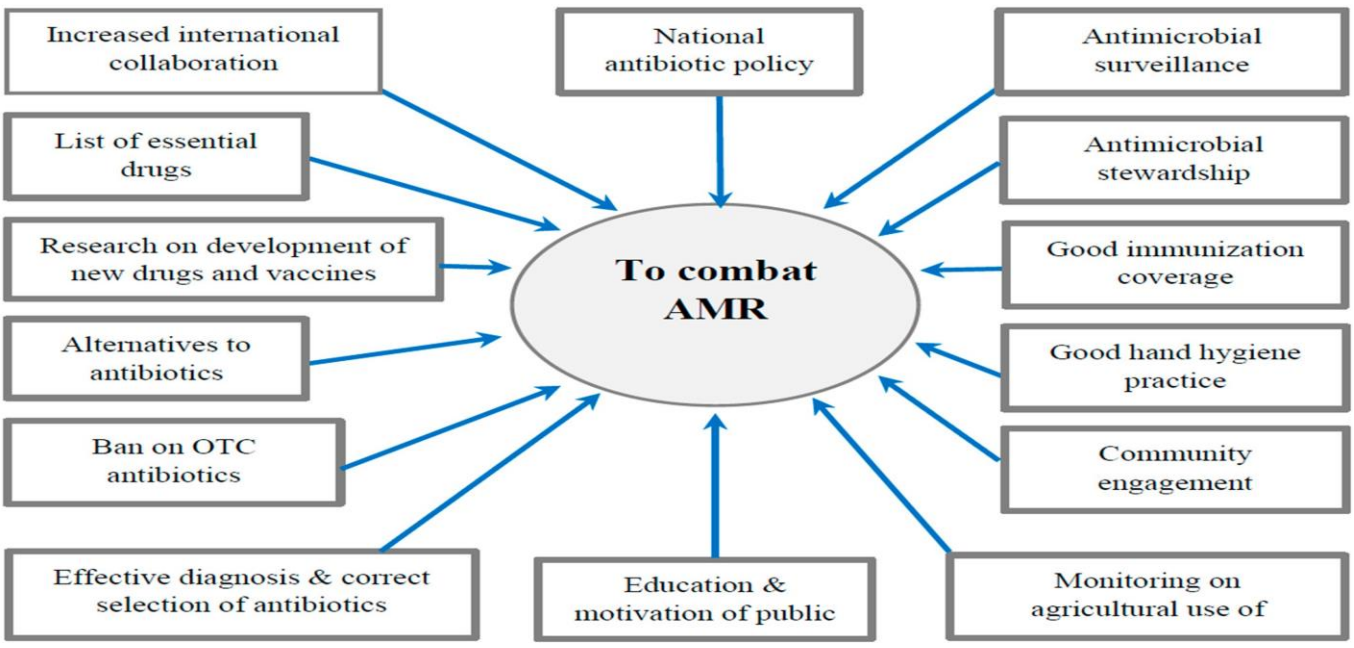

Figure 3. Major interventions to combat AMR.

Reasonable Antibiotic Use

"Rational use of medicine" is described by the WHO as utilizing accurate pharmaceuticals, including antibiotics, in precise dosages, for an acceptable duration, and at the lowest cost [70]. The best treatment of infections requires sensible antibiotic usage to reduce pathogen selection, medication toxicity, and resistance. Healthcare antibiotic stewardship programs (ASPs) focus on sensible antibiotic usage.

Ban on OTC Antibiotics

OTC oral and injectable antibiotic sales and dispensing, which is still popular in many poor nations, should be strictly regulated. A doctor must prescribe antibiotics. Continuous patient and pharmacy drug dispenser awareness campaigns on antibiotics and AMR are advised, coupled with reconsideration of antibiotic policy based on local and regional AMR monitoring data [74].

IPC (Infection Control)

IPC is a crucial and evidence-based practical way to protect patients and healthcare staff against preventable infections, including drug-resistant bacteria. This is essential for healthcare AMR mitigation. Physicians, nurses, pharmacists, and other healthcare personnel are essential to IPC AMR prevention. Direct patient care doctors may help fight AMR by following hospital infection control and antibiotic protocols and reporting resistant cases to the IPC team. Nurses and other healthcare personnel must also learn about AMR and aseptic techniques to prevent infection. Hospital pharmacists are crucial to the IPC team because they educate patients on treatment compliance, especially antibiotic usage, which helps fight AMR [75].

Recommended measures related to IPC in a healthcare facility include:

- Established a "infection prevention and control committee".
- Practices proper hand hygiene.
- Accurate diagnosis and effective infection treatment.
- Properly employ antibacterial agents.
- Ongoing monitoring of antibiotic usage and resistance.
- Creating a high-quality antibacterial supply chain.
- Proper microbiological lab techniques.

ASP Antimicrobial Stewardship

To prevent microbial resistance and its spread, antimicrobial stewardship educates and persuades prescribers to use the right antimicrobial medicines, dose, and duration for patient outcomes. antibiotic stewardship first ensures that doctors provide the right antibiotic at the right dosage and duration for each patient. Prevention of antibiotic overuse, misuse, and abuse is the second purpose. The third purpose is to minimize resistance. Antimicrobial stewardship has two main goals: optimizing healthcare outcomes and ensuring sustainable access for all. The CDC issued the "Core Elements" of antimicrobial stewardship in 2014 to help hospitals achieve these objectives, with particular recommendations for small and critical-access hospitals [76,77].

Animal Antibiotic Use

The WHO urged for stronger laws on using medically vital antibiotics in animals to reduce antimicrobial resistance. It stresses reducing and restricting antibiotic usage for growth promotion and illness prevention. Antibiotics may be given if other animals in the flock, herd, or fish population have been infected. Alternatives include greater cleanliness, give probiotics or nutritional supplements, better immunization, and animal husbandry modifications [78].

Drug and vaccine development

Due to the fast development of resistance to each new class of antibiotic and the difficulty of developing new effective medications, research into an integrated strategy that incorporates vaccines and newer antibiotics is crucial. To address AMR, academia and industry must collaborate nationally and internationally to spend more in operational research and invention of novel antimicrobials. Vaccines have long been used to prevent infectious infections and reduce antimicrobial medication demand, which helps fight AMR. In addition, they are not responsible for antibiotic resistance. Thus, developing and using vaccines against antimicrobial-resistant bacterial infections, such as carbapenem-resistant enterobacterales and Acinetobacter baumannii, is crucial to fighting AMR [73,75].

Checkpoints Introduced

In poor and low-income nations, where anybody may purchase medications from pharmacies without a prescription, antibiotic sales and self-medication are nevertheless common. Physicians may prescribe antibiotics based on patient preferences, which is irresponsible. To stop these harmful activities that spread AMR, strict controls and checkpoints should be implemented. Proper law and execution might reduce drug trafficking, particularly antibiotics. The effective AMR prevention method of delayed antibiotic prescribing (delaying antibiotic consumption until symptoms occur and the patient is properly educated on when to start an antibiotic) [58,60].

Participation in Community

AMR's formation and spread are usually regarded biological phenomena that affect community activities including house and animal cleanliness, food production, health-seeking, and waste disposal. Additionally, each group may have its own

language and perspective of antimicrobials and medication resistance. Thus, a community involvement strategy to behavioral modification for antibiotic usage may protect current and future therapeutic choices and improve community-level AMR prevention. More study is needed to engage individuals to learn and share their experiences and use these concepts to prevent AMR [79].

Alternatives to Antibiotics

Natural antibiotic alternatives are being sought by researchers. Recent results on polyphenolics, alkaloids, and other plant extracts suggest plants may be untapped sources of antimicrobial drugs [80]. Polyphenolics, alkaloids, and flavonoids have not been tested for antibacterial activity [81–86]. The biggest problem is translating some of these valuable findings from labs to hospitals. Advances in biotechnology, genetic engineering, and synthetic chemistry have expanded options for research on creative alternative medicines, which gives the AMR challenge hope. Microbes including bacteria, viruses, and molds battle for resources and fight each other in chemical warfare to safeguard themselves from their own toxins, according to scientists. New antibiotic alternatives targeting disease-causing microorganisms are being discovered by modulating microbial chemical warfare [87].

Phage Therapy

Phage treatment employs bacterial viruses to fight pathogens. The term “bacteria eaters” refers to viruses that infect bacteria. Bacteriophages have several advantages over antibiotics, including simple availability, variety, autodosing (rise in quantity spontaneously), low intrinsic toxicity, particular host range, absence of antibiotic cross-resistance, and little environmental effect. Phages as antibiotic alternatives have these appealing features. Phage therapy's limitations—proper phage selection, small host range, effective formulation, potential immune response, and clinician understanding—must be solved before its clinical use. Phage treatment has been beneficial in treating topical infections when antibiotics have failed [88].

Drugs that fight viruses

As an alternative to antibiotics, antivirulence medications interfere with bacterial virulence factors instead of killing microorganisms. Antivirulence medications block bacterial proteins that bind to host cells to start infection. Antivirulence medications prevent infection by disarming bacteria, and because they work differently from antibiotics, antibiotic resistance is uncommon. Contrary to traditional antibiotics, antivirulence medications do not allow drug-resistant bacteria to dominate susceptible ones and do not disrupt the healthy microbiome. Recent studies have shown that FDA-approved antivirulence medicines may treat MRSA infections in mice. Antivirulence medications might be used with antibiotics as adjuncts or combinations owing to development and clinical hurdles [89].

Bacteriocins

Natural antimicrobial peptides generated by certain bacteria kill or inhibit comparable or phylogenetically related microorganisms. Several bacteriocins are being researched as antibacterial agents due to their safety. They are increasingly employed to prevent harmful germs from growing in food, prolonging its shelf life and delaying deterioration. Nisin, a lantibiotic bacteriocin generated by gram-positive bacteria like Lactococcus and Streptococcus species, is frequently used as a food preservative. In addition to food production, nisin has been found to have antibacterial activity against both gram-positive and gram-negative disease-associated pathogens, including drug-resistant strains like MRSA Streptococcus pneumoniae, Enterococci, Clostridioides difficile, and enterobacterales [79].

One Health

In 2008, the WHO, FAO, and OIE established a strategic “One Health” framework to address global health issues and improve public health. According to the One Health Initiative Task Force, it is a collaborative, multisectoral, and transdisciplinary strategy that works locally, regionally, nationally, and globally to improve health for humans, animals, and the environment.

It designs, implements, and monitors AMR monitoring programs, policies, and research to support evidence and improve advanced intersectoral cooperation between humans, animals, plants, and their common environment. AMR, the global health issue that impacts people, animals, and the environment, best exemplifies the One Health concept [90].

The One Health strategy relies on communication, coordination, and cooperation amongst people, animals, and environmental professionals to share their knowledge. Pharmacists, doctors, patients, and other healthcare and epidemiology experts may be engaged in this method. Veterinarians and agricultural workers represent animal health, while ecologists and wildlife professionals represent the environment [91].

AMR prevention would benefit from the global review of the One Health strategy and the FAO–OIE–WHO tripartite commitment via awareness campaigns, antibiotic education, lobbying with political commitment, and antimicrobial stewardship. Advanced computational and sequencing technologies like whole-genome sequencing (WGS) and next-generation sequencing (NGS) may analyze AMR in multiple One Health domains [92].

Conclusions

Bacteria evolve antimicrobial resistance by new chromosomal mutations or HGT. AMR, which has increasingly developed over the last two decades, is currently considered the biggest health threat of the 21st century, restricting therapeutic possibilities. Globally, MDR bacteria are found in respiratory, urinary, sexually transmitted, and TB illnesses. Since the 1980s, antibiotic development and supply have lagged behind AMR development. The lack of novel antimicrobials and the remarkable rise of multidrug-resistant bacteria make the future of antimicrobial treatment dismal. A postantibiotic future for the 21st century is possible unless worldwide concerted steps to eliminate AMR are taken. Multiple factors are spreading antimicrobial resistance worldwide, threatening human and animal health. Antimicrobial-resistant illnesses are harder to treat, resulting in treatment failure, complications, and high financial costs to people and the society. Prudent antibiotic usage with adequate dose and duration is one of the best ways to lessen selection pressure for resistant organisms. Controlling MDR organisms requires strict infection prevention and control in all healthcare institutions [57,58]. All international governmental and nonprofit entities must work together and gain political momentum to combat AMR. This effort requires legislators, researchers, public health practitioners, drug corporations, hospital administrators, agricultural sector executives, and the public to collaborate. The ultimate objective of this collaboration is to slow AMR trends to reduce health and economic consequences. Antimicrobial stewardship and strict antibiotic policy compliance in hospital settings can prevent antibiotic resistance. Good microbiology, surveillance, monitoring, minimizing OTC antibiotics and antibiotics in food animals, increasing access to quality and affordable medicines, vaccines, diagnostics, and legislation are also important for reducing AMR [73,75–78].

Prevention is still the greatest way to stop antimicrobial-resistant diseases worldwide. While rational use of existing antibiotics is crucial, urgent efforts should be made to develop new effective molecules of antibiotics and alternatives, as well as new diagnostic and vaccine technologies. Many efforts have been made to address antibiotic resistance and the treatments needed, but concerted action, notably national and international political will, is lacking. The forcible trend of antimicrobial-resistant infections suggests that within a few years, we may face dire setbacks in the medical, social, and economic sectors, and all our achievements in modern medicine, such as major surgery, organ transplantation, preterm baby treatment, and cancer chemotherapy, will vanish unless strong global coordinated actions are taken [93].

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