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Factors, impacts and possible solutions of antibiotic resistance: Review article

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ABSTRACT

The discovery of antibiotics has helped to save the lives of an uncountable number of people. Unfortunately, their misuse and other related factors have led to the emergence and development of bacteria that are resistant to antibiotics. Antimicrobial resistance is one of the most serious threats to public health globally and threatens the ability to treat infectious diseases. The factors that contribute for the emergence and spread of antimicrobial resistance are complex non-prudent use of antibiotics in veterinary and human medicine is, in large part, responsible for the emergence of antibiotic resistance. Inappropriate prescription practices, inadequate education, poor drug quality, limited rapid diagnostic test facilities, poor hygiene, infection prevention and control practice are also other factors contribute for the emergence and spread of antimicrobial resistance. Due to the emergency of new resistant bacteria and decrease in efficiency of treating common infectious diseases, it results in failure of microbial response to standard treatment, leading to prolonged illness, higher expenditures for health care, and an immense risk of death. Considering these serious impacts of antibiotic resistance several solutions have been proposed including antibiotic stewardship, educational program, hygiene, infection prevention and control strategy, adapting rapid methods for detecting resistance bacteria as well as developing new antibiotics and alternative therapeutic agents.

Keywords**:** Antibiotics, Antibiotic Resistance Bacteria, Factors, Impacts, Solutions

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1. INTRODUCTION

Microbial infections have been the major cause of disease throughout the history of human population. Mortality as a result of infectious diseases represents one-fifth of global deaths [115]. The discovery of antibiotics during the twentieth century coupled with significant advances in antimicrobial drug development improved human health through improved treatment of infections [51]. Antibiotics are chemicals that either kill or inhibit the growth of bacteria by inhibiting the synthesis of protein, nucleic acid, cell wall and folic acid [64]. Antimicrobial agents have been greatly important basis of clinical medicine since the second half of the 20th century and have saved a great number of people from life-threatening bacterial infections. However, prolonged use of antibiotics led to bacterial adaptation, resulting in the development of resistance in bacteria and the consequent failure of antibiotic therapy, has led to hundreds of thousands of deaths annually [77].

Antibiotic resistance is the ability of a microbe to develop a tolerance to specific antibiotics to which they were once susceptible [115]. Resistance in bacterial pathogens is a worldwide challenge associated with longer hospital stays, higher medical costs and high morbidity and mortality [66]. Resistance of important bacterial pathogens to common antimicrobial therapies and emergence of multidrug-resistant bacteria are increasing at an alarming rate. It typically occurs as a result of four main mechanisms namely alteration of the target site for the antibiotic; production of enzymes that inactivate the antibiotic; alterations in the cell membrane resulting in decreased permeability and thus decreased uptake of the antibiotic and removal of the antibiotic using active transportation. Increasing the resistance rates of several important pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant (MDR) *Pseudomonas aeruginosa*, imipenem-resistant *Acinetobacter baumannii*, and third-generation cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumonia*, poses a serious threat to public health [102].

There are many reasons for the spread of antibiotic resistance, and one of the main factors that promotes the spread and development of resistance is the inappropriate use (both abuse and misuse) of antibiotics in humans and animals [70]. Antibiotics are among the most commonly prescribed drugs used in human medicine. However, up to 50% of all the antibiotics prescribed for people are not needed or are not optimally effective as prescribed. Antibiotics are also commonly used in food animals to prevent, control, and treat disease, and to promote the growth of food-producing animals [18]. They are administered to food animals in agriculture worldwide as veterinary medicine and as growth-promoting agents to obtain sufficient amount of food [102]. Until recently, about 70% of the antibiotics administered to food animals were growth promoter rather than for therapeutic purposes [15].

Due to the lack of education in healthcare professionals and the general population (as well as socio-cultural and economic factors) [104], antibiotics are commonly used to treat a variety of conditions including viral infections, the common cold, and acute watery diarrhea. Unskilled personnel are less aware of the adverse effects of inappropriate antibiotic use and in some cases, the antibiotic prescriptions are inappropriate (i.e., wrong drug, wrong doses, or antibiotic not necessary at all) [29].A substandard antibiotic may cause therapeutic failure due to the lower dosage or absence of the active compounds that finally induce antimicrobial resistance, increase morbidity, mortality and significant economic burden on developing countries [8]. Poor hygiene, infection prevention and control measures also can promote the spread of resistant microorganisms; increases antimicrobial misuse and overuse as well as antimicrobial resistance [113].

Antibiotic resistant infections add considerable and avoidable costs to the already over-burdened healthcare systems. In most cases, antibiotic-resistant infections require prolonged and costlier treatments, extended hospital stays, and additional doctor visits and healthcare use resulting in greater disability and death compared with infections that are easily treatable with antibiotics [66].

The growing threat from resistant organisms calls for concerted action to prevent the emergence of new resistant strains and the spread of existing ones [76]. To address the problem of antibiotic resistance, the factors contribute for this problem, impacts of the problem should be understood and effective solutions should be implemented to minimize the problem. This seminar will discuss antibiotics and mode of action, antibiotic resistance and mechanisms, different factors contribute for this problem, impacts of the problem as well as various solutions to minimize antibiotic resistance.

2. ANTIBIOTICS

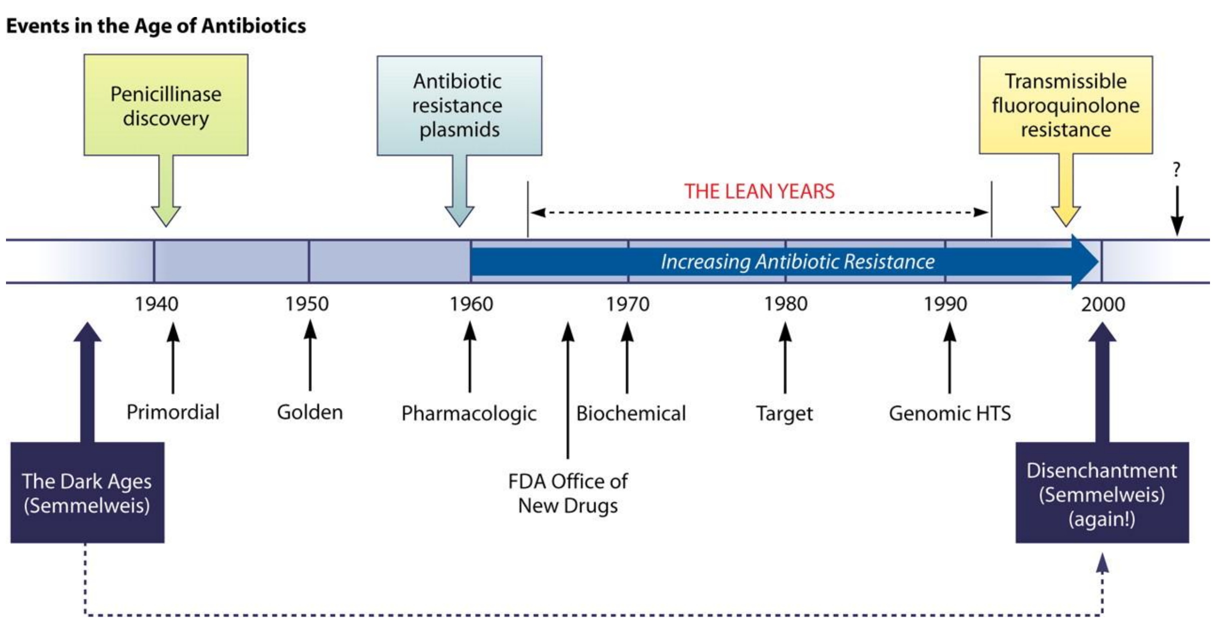

Fig. 1. History of antibiotic discovery and concomitant development of antibiotic resistance. (Adapted from Julian and Dorothy, 2010).

Antibiotics are the first successful class of drugs that can cure disease and have been effective in treating many infections. The first antibiotic was penicillin, discovered by Sir Alexander Fleming in 1929. He put disease causing bacteria in a petridish and found that penicillium mould inhibited their growth [106]. During World War II, penicillin saved literally thousands of people from death from wound infections. Over the next decades, penicillin and subsequent antibiotics significantly improved the life expectancy of millions, more by effectively treating a wide variety of formerly lethal diseases, such as pneumonia and tuberculosis [64]. Most of the antibiotics that are commonly used today were discovered in the ‘‘Golden Age” of antibiotics [30], have lost patent protection, and as with most generic drugs, are low priced.

Antibiotics are among the most potent life-saving interventions in all of medicine. The reductions in death afforded by effective antibiotics for bacterial infections of all types, ranging from simple skin infections to infections of the bloodstream, lung, abdomen, and brain, are enormous [99,100]. Within a few years of their availability, antibiotics had reduced the rate of death from infections by nearly 80 percent, from 280 to 60 deaths per 100,000 populations in the United States [99]. Loss of antibiotic efficacy threatens to return society to a time when one in ten patients with a skin infection died and one in three patients with pneumonia died (greater than 10-fold higher death rates compared to the antibiotic era [99]. Without effective antibiotics, medicine would be paralyzed by an inability to treat infections resulting from intensive specialty care [101].

Effective antibiotic therapy (compared with the pre-antibiotic era) has led to impressive reductions in mortality, from 100% to 25% for bacterial endocarditis, from >80% to <20% for bacterial meningitis, and from 60% to 30% for nosocomial pneumonia [100].

2. 1. Antibiotic Resistance

Antibiotic resistance is the ability of certain strains of bacteria to develop a tolerance to specific antibiotics to which they were once susceptible [118]. The rise of antibiotic resistant bacteria is a major public health problem as infections from resistant bacteria are becoming increasingly difficult and expensive to treat [34]. Antibiotic resistance is achieved when a bacterium is no longer affected by an antibiotic due to evolution or a change in the bacterial cell's structure rendering the antibiotic useless [81]. Since the resistance to the first commercial antimicrobial agent (penicillin) was identified in 1948, almost every known bacterial pathogen has developed resistance to one or more antibiotics in clinical use [16]. Unfortunately, although antibiotic resistance has increased, the development of novel antimicrobial agents has dramatically declined over the past 30 years [103].

Resistance can be described as intrinsic or acquired resistance. Intrinsic resistance is resistance where by microorganisms naturally do not possess target sites for the drugs and therefore the drug does not affect them or they naturally have low permeability to those agents because of the differences in the chemical nature of the drug and the microbial membrane structures. An example of natural resistance is *Pseudomonas aeruginosa*; whose low membrane permeability is likely to be a main reason for its innate resistance to many antimicrobials. Other examples are the presence of genes affording resistance to self-produced antibiotics, the outer membrane of Gram-negative bacteria, absence of an uptake transport system for the antimicrobial or general absence of the target or reaction hit by the antimicrobial [48].

Acquired or active resistance, the major mechanism of antimicrobial resistance, is the result of a specific evolutionary pressure to develop a counter attack mechanism against an antimicrobial or class of antimicrobials so that bacterial populations previously sensitive to antimicrobials become resistant. This type of resistance results from changes in the bacterial genome. Resistance in bacteria may be acquired by a mutation and passed vertically by selection to daughter cells. More commonly, resistance is acquired by horizontal transfer of resistance genes between strains and species. Exchange of genes is possible by transformation, transduction or conjugation [119].

Finding strategies against the development of antibiotic resistance is a major global challenge for the life sciences community and for public health. The past decades have seen a dramatic worldwide increase in human-pathogenic bacteria that are resistant to one or multiple antibiotics [21].

3. FACTOR THAT CONTRIBUTE FOR THE SPREAD AND DEVELOPMENT OF ANTIBIOTIC RESISTANCE

3. 1. Antibiotic Use Practices

Antibiotic use in the community has been directly linked to resistance [65]. A survey study conducted in San Francisco of urban poor individuals reported that, antibiotic use during the previous 12 months were significantly more likely to be colonized with MRSA [20]. Inappropriate and irrational use of antibiotics occurs by health professionals and users (patients) are a major factor that promotes the spread of resistance [70].

Health professionals play an essential role in the treatment and prevention of diseases, but may risk this if their practices are not evidence-based and led for the development of antibiotic resistance. Unskilled personnel are less aware of the adverse effects of inappropriate antibiotic use and in some cases, the antibiotic prescriptions are inappropriate (i.e., wrong drug, wrong doses, or antibiotic not necessary at all) [29]. A study conducted in Lebanese shown that, in 52% of cases, the prescription dose was inappropriate while 63.7% of physicians prescribed antibiotics with wrong duration of treatment [80]. These incorrectly prescribed antibiotics contribute to the promotion of resistant bacteria [18]. Another study has shown that treatment indication, choice of agent, or duration of antibiotic therapy is incorrect in 30% to 50% of cases [18, 53] and 30% to 60% of the antibiotics prescribed in intensive care units (ICUs) have been found to be unnecessary, inappropriate, or suboptimal [53]

In the absence of an antimicrobial sensitivity test health professionals use more and more broad-spectrum antibiotics to treat infections caused by several bacteria species or those for which establishing the etiology is difficult or takes a long time. This practice contributes to the development of resistance as the drug applies selective pressure, not only upon the etiological agent of the disease episode but also upon a large fraction of the patient's microbiota [88]. A study conducted by [1] stated that, patients' poor adherence to prescribed antibiotics, over use of antibiotics, self-antibiotic prescription and frequent prescription of broad-spectrum antibiotics were the leading causes of AMR.

The second major contributors to the development of AMR under antibiotic use practice are users or patients [107]. In the 2015 WHO survey, two thirds of people reported knowing that antibiotic resistance is an issue but didn't understand how it could affect them or how to address it. 64% of survey respondents believed that antibiotics can be used to treat colds and flu. Similarly, in large segments of the U.S. population self-medication with antibiotics is common, particularly among those who have immigrated from countries where antibiotics are available without prescription [23].

A study was developed in Turkey, with University students from different Faculties with exception of the ones from Faculty of Medicine [13]. The authors showed that the majority of the students (83.1%) took antibiotics for normal cold and 32.1 % to decrease fever. Additionally, near 40% of the student's started antibiotics by themselves when they were ill; and during their last infection, between 12% and 27% used the same antibiotic, as previously prescribed by their doctors. A study by [67] shown that, up to 90% of antibiotic use in certain developing countries is over the counter, without a prescription, and non-prescription sales are common in nearly every such country. According to WHO report, close to one third (32%) of respondents surveyed across the 12 countries believe that they should stop taking the antibiotics when they feel better, and this rises to 62% in Sudan. Younger respondents and those in rural areas across the 12 countries, as well as those in lower income countries, are more likely to think they should stop taking antibiotics when they feel better [116].

3. 2. Poor Antibiotic Quality

Many antibiotics dispensed in developing countries particularly in Africa are of questionable pharmacological quality [8, 54]. Adverse climatic conditions such as high ambient temperatures and humidity may affect the overall quality of the antimicrobials during storage [105]. Poor storage also increases the risk of degradation of the drug. Degraded medicines contain less than stated dose, implying that patients consume less than optimal dose of the drug. There is also a problem of outright counterfeit, in which the drug may contain little or no active substance of the antimicrobial or the wrong substance [79].

The influx of counterfeit and sub-standard antimicrobials into the pharmaceutical markets in some regions is a major problem as these preparations of reduced potency also result in pathogens being exposed to sub-therapeutic concentrations of the drug [94]. A study from Cameroon revealed that, out of 284 antimalarial obtained from 132 vendors, 32% of chloroquine, 10% quinine, and 13% sulfadoxine/pyrimethamine were likely to be fake [54]. Some pharmacologically active drugs produced in industrialized countries have expired when distributed in developing countries. They were shipped at the end of the drugs shelf lives or their clearance and distribution after transcontinental shipment were delayed. Expired drugs may receive new labels, be dumped without a label change, or be donated rather than sold [94].

Substandard narrow-spectrum antibiotics may make prescriber think that the antibiotics are not effective, thus unnecessarily prescribe a newer broad-spectrum antibiotic as their first-line treatment for many infections [44]. It has been reported that in Laos, ampicillin contained 3-32% and tetracycline contained 8-14% than expected [105], while in Myanmar more than 20 products of antibiotics contain only 13-48% than expected [79].

3. 3. Poor Hygiene, Infection Prevention and Control Practice

Hygiene plays an important role in the prevention of community spread of resistance because many of the infecting organisms are more common among the indigent and homeless and those who are immunocompromised or in institutional settings such as military camps, prisons, sports teams, and day care centres [47, 57, 71].

According to Anderson and Kaye [5], compliance with hand hygiene and other infection prevention and control measures typically in hospitals is poor and approximately 30% to 40% of resistant infections arise from cross-infection via hands of hospital personnel [111]. In low and middle-income countries 1.1 million people infected with diarrhoeal diseases in each and 60% of this disease burden is associated with inadequate access to safe water and sanitation [85]. Poor hygiene, infection prevention and control measures can promote the spread of resistant microorganisms; increases antimicrobial misuse and overuse as well as antimicrobial resistance [116]. A highly resistant infection caused by *Pseudomonas aeruginosa* was recently reported following ear self-piercing [109].

3. 4. Use of Antibiotics in Agriculture and Aquaculture

Antibiotics have also been used in veterinary medicine since the first commercial antibiotic, penicillin, became available for the treatment of human diseases [63]. According to [108], Global consumption of antimicrobials in food animal production was estimated at 63,151 (±1,560) tons in 2010 and is projected to rise by 67%, to 105,596 (±3,605) tons, by 2030. The five countries with the largest shares of global antimicrobial consumption in food animal production were China (23%), the United States (13%), Brazil (9%), India (3%), and Germany (3%). By 2030, this ranking is projected to be China (30%), the United States (10%), Brazil (8%), India (4%), and Mexico (2%). Among the 50 countries with the largest amounts of antimicrobials used in livestock in 2010, the five countries with the greatest projected percentage increases in antimicrobial consumption by 2030 are likely to be Myanmar (205%), Indonesia (202%), Nigeria (163%), Peru (160%), and Vietnam (157%) [108]. Although the use of antibiotics in animals to treat infection is necessary [96], the indiscriminate use of antibiotics among animals and in agriculture is one factor in the spread of antibiotic resistance and has serious public health consequences [6].

Studies have demonstrated that exposure to animals who have been fed antibiotics, either by direct contact or through the food chain, results in human colonization and sometimes serious, life-threatening infection with the same or related drug-resistant strains [46]. Use of antimicrobials in food animals has been a subject of discussion for 30 years [96] but several decades ago the use of antibiotics as growth promoters was banned in a number of other European countries. Even though the use of antibiotics for growth promotion in the feed of food animals was totally banned in the EU and a similar ban is being contemplated in the U.S. [17], medically important antibiotics are still being fed routinely to food animals to promote growth and to ward-off potential bacterial infections in the stressed and crowded livestock and aquaculture environments [15]. Recent reports indicated in that, Extended-spectrum β-lactamase producing and carbapenemase-positive Enterobacteriaceae strains present in food animals, and MRSA in various food animal species and food products [24, 32], as well as plasmid-mediated quinolone resistance in food animals and food products [73].

As global production of aquatic species (fish, shellfish, shrimp, and molluscs) has been growing rapidly in the last decade, the use of antibiotics in aquaculture also increased [15]. Many MDR fish pathogenic bacteria were found in fish farms [93]. In addition, it has been shown that multi-resistance plasmids from some fish pathogens, such as *Aeromonas salmonicida*, can be transferred to human pathogens such as *E. coli* [86].

3. 5. Lack of Rapid Diagnostic Test and New Antibiotics Development

Diagnostic tests for infections are commonly unavailable or unreliable in developing countries [9]. In many countries, diagnostics are still relatively expensive and must be paid for directly by the patient: it is cheaper to use an antibiotic first. Easy to use and inexpensive point-of-care diagnostics could resolve some of these problems, but their development remains a challenge, for technical and economic reasons. Where resources are limited, testing for susceptibility to antimicrobials competes for scarce funding with provision of treatment, and often the costs are met by the patient as an out-of-pocket payment. Even in high-income countries, diagnostic tools are currently not always optimally used. Support for more routine use of diagnostics and development of rapid diagnostic tests adapted for resource-limited settings would improve surveillance as well as the care of individual patients [114].

Improvements have been made regarding diagnostic tools but in low- and middle-income countries (LMIC), there are still few useful and context-appropriate diagnostics. Inexpensive and readily available diagnostic tools are now available for a variety of infectious diseases, the best known being rapid diagnostic tests for malaria [55]. Lack of access to antibiotic susceptibility testing was the most important factor for spread and development of AMR in Ethiopia [1].

According to WHO report, not enough new antibiotics are being developed to combat the threat of deadly drug-resistant infections and the vast majority of the drugs being developed are modifications to existing kinds of antibiotics, which only provide short-term solutions. Traditional drug development methods take time and insufficiently profitable to entice pharmaceutical companies to develop new antibiotics are significant challenges associated with developing new antibiotics to overcome AMR. Among 51 new antibiotics and biological currently in clinical development to treat the most dangerous antibiotic resistant diseases, only eight are classed as innovative treatments that will contribute meaningfully towards the pool of drugs [117]. There is an urgent need for pharmaceutical companies and researchers to focus on new antibiotics as the only line of defence against serious infections that can kill patients in a matter of days.

4. PUBLIC HEALTH AND ECONOMIC IMPACT OF ANTIBIOTIC RESISTANCE

When antibiotics become ineffective, it will lead to increase of morbidity and premature mortality. Patients infected with antibiotic-resistant organisms are likely to have higher health expenditure, longer hospital stays and require a second- or third-line drugs treatment that may be less effective, more toxic and more expensive [50].

According to a recent study in Thailand, in 2010 antimicrobial resistance was responsible for at least 3.2 million extra hospitalization days; 38,481 deaths, and for losses of $84.6–$202.8 million in direct medical costs and more than $1.3 billion in indirect costs [80]. In the United States (US), where approximately 23,000 people die each year as a direct result of AMR, estimates for the total economic cost of antibiotic resistance vary but have ranged as high as $20 billion in excess direct healthcare costs, with additional costs from lost productivity as high as $35 billion a year [88, 18]. The estimated annual human and financial loss caused by a group of resistant bacteria in Europe is 25 000 deaths, 2.5 million extra in-hospital days and $1.6 billion extra costs (due to healthcare expenses and productivity losses [100].

Infection with a resistant micro-organism carries a much higher mortality risk compared with infection with a non-resistant strain. A study from Thailand found mortality as high as 67% for meticillin resistant *Staphylococcus aureus* and 46% for methicillin susceptible *S. aureus*, significantly higher than in high income countries [72]. Cost attributable to infections due to resistant bacteria (compared with infections due to non-resistant bacteria of the same species and site of infection) ranges from US$3758 to US$29 379 per infection, depending on the pathogen and site of infection [49].

From the global perspective, the Independent Review on AMR commissioned by the Government of the United Kingdom (UK) and led by the renowned economist Jim O'Neill commissioned a study in 2014 to estimate the global costs of AMR until 2050 in the absence of any progress in addressing the challenge [107]. The results from this analysis demonstrated that if current trends persist resulting in increasing morbidity and mortality related to AMR, the costs in terms of healthcare, loss of life, productivity, and by extension, global economic development are potentially staggering at orders of magnitude higher than seen at present and render AMR as an urgent public health crisis requiring immediate intervention [88].

From the commissioned analysis, based on various conservative assumptions, on average over a 40-year span, the world GDP loss runs between $53 billion to $3 trillion per year [74]. In some scenarios, up to 10 million lives per year could be lost by 2050 (up from 700,000 estimated deaths presently occurring worldwide) and a cumulative $100 trillion of economic output are at risk due to the rise of drug resistant infections if proactive solutions are not put into place now to slow down the rise of drug resistance.

5. SOLUTIONS USED TO REDUCE ANTIMICROBIAL RESISTANCE

5. 1. Antibiotic Stewardship

The emergence of antibiotic-resistant bacteria is a major challenge in the treatment of human infections. Inappropriate use of antibiotics contributes to the growing problems of resistance in health care facilities. The medical community has responded to these conditions with the application of antibiotic stewardship or judicious-use programs. Antibiotic (antimicrobial) stewardship programs are coordinated interventions designed to improve and measure the appropriate use of antibiotic agents received by patients and prescription of the right antibiotic, the right route of administration, and the right dose at the right time for the right duration in order to prevent or cure infection while minimizing adverse events and emergence of resistance [33]. Antibiotic stewardship is strategy leads to more rapid resolution of infection with minimal adverse events, in most cases it results in a reduction in treatment costs [26].

Interventions to improve antibiotic use can be implemented in any health care setting from outpatient to hospital to long-term care facility. Antimicrobial stewardship has been shown to be essential in the control of *Clostridium difficile* infections and the emergence of multidrug resistant organisms [22]. Use of antimicrobial stewardship in combination with infection prevention and control efforts limits the emergence and transmission of antimicrobial-resistant pathogens [97]. One study recognized a lower crude mortality among patients who developed nosocomial infection in the stewardship intervention group, implying that these infections may be less drug resistant and hence easier to treat [56]. Stewardship interventions were also associated with reductions in antimicrobial utilization (11%–38% defined daily doses/1000 patient-days), lower total antimicrobial costs (US$ 5–10/ patient-day), shorter average duration of antibiotic therapy, less inappropriate use and fewer antibiotic adverse events [45].

5. 2. Implementing Hygiene, Infection Prevention and Control Practices

Every infection prevented is one that needs no treatment. Prevention of infection can be cost effective and implemented in all settings and sectors, even where resources are limited. Good sanitation, hygiene and other infection prevention measures that can slow the development and restrict the spread of difficult-to-treat antibiotic-resistant infections [113]. Infection control has been identified as one of the key interventions in controlling the threat of antibiotic resistance. Reducing the transmission of multidrug-resistant organisms reduces the need for broad-spectrum antibiotics in particular, while interventions that decrease the risk of infection have an impact on the use of any antibiotic.

Hand hygiene remains the cornerstone of decreasing the transmission of multidrug-resistant organisms. Alcohol-based hand rubs are a cheap, effective and convenient means of performing hand hygiene [112]. Alcohol hand rubs are superior to both ordinary soap and water and medicated soap and water with regard to the efficacy of removal of micro-organisms. A six-year observation study at a tertiary center in the USA compared 3 years of medicated soap use with 3 years of alcoholic hand rub use, and showed reductions in acquisition of both methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant Enterococcus (VRE) (21% and41% reductions, respectively) [35].

5. 3. Adapting Rapid Methods for Detecting Antibiotic Resistance

Emerging antimicrobial-drug resistance affects the ability of the clinical microbiology laboratory to detect and report resistance. Several new resistance mechanisms in gram-positive and gram-negative bacterial organisms are difficult to detect with usual laboratory methods. Rapid diagnostics would be able to reduce use of antibiotics by letting doctors know if a patient has an infection and if this infection is viral or bacterial, meaning that antibiotics will only be given out to patients who need them. In the future rapid diagnostics should be able to test for resistance allowing doctors to give patients the most appropriate available medicine for them. The information garnered from rapid diagnostics, might eventually allow doctors to improve treatment and infection control to such an extent that this places negative selective pressure on resistance pathogens, thus reducing resistance in older drugs [60]. Certainly, rapid diagnostics are being developed to determine the presence of resistant strains of clinically important bacteria [73].

Several studies have shown that patients with documented influenza infection have fewer antibiotics administered, thus reducing indiscriminate antibiotic use in proven viral illness [95, 11].

5. 4. Educational Programs

Education is necessary to ensure that all people understand the severity of antibiotic resistance and wise use of antibiotics in primary care and to communicate the rationale for reduced use in agriculture. Making sure that awareness of the problem of antimicrobial resistance and how to deal with it are part of the educational program or in-service education offerings is a key part of obtaining support to minimize resistance.

As has been the practice in some countries, nurses, clinical pharmacists, and midwives may also be allowed to prescribe some antibiotics in special clinical situations [25, 28]; all healthcare professionals who have to deal with patients must be educated about prudent antibiotic treatment and management of patients demanding an overuse of antibiotic. Medicines interactions may occur as a result of accidental misuse or a lack of knowledge about the active ingredients. Pharmacists' advice on how to use medicines correctly, adverse side effects and potential interactions with other medicines, treatments, food or drinks. For example, calcium in milk decreases the absorption of ciprofloxacin [13]. Pharmacists are ideally placed to counsel people on when and how to take medicines, and the optimal timing in relation to meals [78]. Antibiotic management requires effective teamwork between all healthcare professionals and if patients receive inconsistent messages from healthcare professionals when taking antibiotics, all efforts of prudent antibiotic prescribing may become unsuccessful [31]. Therefore, all healthcare professionals must receive continual education on prudent antibiotic prescribing.

In Thailand, a multifaceted response as part of an Antibiotic Smart Use programme used patient education measures, along with treatment guidelines, to reduce antibiotic use by 18%–46% [114]. A 3-year trial was conducted in Massachusetts by [39], to determine the impact of a community-wide educational intervention on parental misconceptions which could influence antibiotic overprescribing. Although no significant intervention impact was observed in the population overall, there was a subgroup of parents where there was a significant intervention impact. Another group of authors [92] compared the success of two approaches of providing information to parents, an animated video and a pamphlet. The animated video proved to be highly effective in educating parents on correct antibiotic use and resulted in long-term retention.

In an interventional point of view, [7] evaluated the impact of education and an antibiotic control program on antibiotic prescribing practices in a tertiary care teaching hospital in Thailand. After the intervention, there was a 24% reduction in the rate of antibiotic prescription and the incidence of inappropriate antibiotic use was significantly reduced. Consequently, rates of use of third-generation cephalosporins and glyco- peptides, the incidence of infections due to methicillin-resistant *Staphylococcus aureus*, extended-spectrum beta lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* and third generation cephalosporin-resistant *Acinetobacter baumannii* were all significantly reduced.

A survey study conducted by WHO on the levels of awareness of respondents on antibiotic resistance states that, 89% of respondents in Mexico are aware of the term antibiotic resistance, only 21% of those in Egypt [116], indicted that, it is not uniform across the countries surveyed. Abera *et al*. [1] also states that, among participants 72.2% had expected level of knowledge on AMR but 13.5% of senior physicians, 29.7% general practitioners, 49.3% of nurses replied that they had no up-to-date information about AMR and only 9.3% of respondents have had training on antimicrobial stewardship education.

5. 5. Developing New Antimicrobial Drugs and Alternative Therapeutic Agents

There are challenges in the combat of bacterial infections and accompanied diseases and the current shortage of effective drugs, lack of successful prevention measures and only a few new antibiotics in the clinical pipeline will require the development of novel treatment options and alternative antimicrobial therapies [89].

5. 5. 1. Photochemical

Phytochemicals are pharmacologically active compounds. These include alkaloids have an antispasmodic, antimalarial, analgesic, diuretic activities; Terpenoids are known for their antiviral, anthelmintic, antibacterial, anticancer, antimalarial, anti-inflammatory properties; Glycosides are reported for antifungal and antibacterial properties; Phenols and flavonoids have an antioxidant, anti-allergic, antibacterial properties etc. and Saponins are reported to have anti-inflammatory, antiviral, plant defence activities [59].

In the early 1900's, 80% of all medicines were obtained from roots, barks and leaves and approximate estimation is that, 25% of all drugs prescribed today still originate from plants [61,90]. The plant kingdom, with 300,000 to 400,000 higher species is always a key source of new chemical entities (NCEs) for active pharmaceutical ingredients and lead compounds [10]. It is estimated that only 5% to 15% of these terrestrial plants have been chemically and pharmacologically investigated in a systemic fashion [61].

Researchers identified several chemical compounds used in modern medicine, which were derived from plant sources include quinine, digoxin, Aspirin, ephedrine, atropine, and colchicine [68, 82].

5. 5. 2. Probiotics

Probiotics are live microorganisms, basically bacteria that when ingested in adequate amounts would confer health benefit beyond the basic nutrition [2]. Most of the probiotic products currently available contain lactic acid bacteria (LAB) which belong to the genera Lactobacillus and Bifidobacterium. The direct benefit of probiotic consumption is to help the host with the maintenance of intestinal microbial balance, the decrease of potentially pathogenic gastrointestinal microorganisms, the improvement of bowel regularity, and the restoration of intestinal microbiota homeostasis in antibiotic-associated diarrhea [87].They are extensively studied for their health promoting effects because they repopulate the beneficial bacteria which can help to kill pathogenic bacteria and fight against infection [91].

Several studies have documented the effects of probiotic on a variety of gastrointestinal and extraintestinal disorders, including prevention and alleviation symptoms of traveller's diarrhea and antibiotic associated diarrhea, irritable bowel disease [69], lactose intolerance [38], protection against intestinal infections [84], and irritable bowel syndrome. Some probiotics have also been investigated in relation to reducing prevalence of atopic eczema later in life [36], vaginal infections, and immune enhancement [43], contributing to the inactivation of pathogens in the gut, rheumatoid arthritis, improving the immune response of in healthy elderly people [40], and liver cirrhosis.

Probiotics can beneficially improve the intestinal microbial balance in host animal. Several numbers of scientific studies have quantified the efficacy of probiotics for growth promotion and disease prevention in swine, cattle and chickens [110, 41]. Dersjant *et al*., [27] also reported that, probiotics improved productivity and intestinal health in newly hatched birds and reduced mortality by over 20 percent compared with control flocks; the reduction in mortality was similar to that achieved with antibiotics.

5. 5. 3. Vaccines

The use of vaccines is another possible way of reducing antibiotic resistance. Vaccination is an important part of any infection control strategy. It helps reduce the misuse of antimicrobials. In the case of viral vaccines, protection from a virus will reduce the number of viral infections (and, consequently, bacterial super infections), which in some cases are mistakenly diagnosed as a bacterial infection and so treated with antimicrobials. For example, there is a common misuse of antibiotics against influenza [42].

Vaccination is the best mechanism to reduce antibiotic resistance by preventing disease requiring antibiotic treatment for vaccine-preventable bacterial infections [37]. The study conducted by [62] in Maryland shown that, invasive streptococcal infections resistant to erythromycin decreased by >50% and the percentage of penicillin-resistant pneumococci associated with acute otitis media decreased from 73% to 53% among children following introduction of the pneumococcal conjugate vaccine. Vaccines also have been widely used in veterinary medicine to prevent diseases caused by viruses or certain bacteria, and they are promising substitutes for some antibiotic uses [4]. Notably, reducing viral infections may lead to decreased antibiotic use because of the risk of misdiagnosis and because antibiotics may be used to prevent or treat secondary bacterial infections [75].

5. 5. 3. Phage Therapy

Phage therapy has been extensively researched and utilized as a therapeutic agent for over 60 years, especially in Russia, as an alternative that might help solve the problem of resistance. It was also widely used in US until the discovery of antibiotics in the early 1940s [19]. Phage therapy is the therapeutic use of lytic bacteriophages to treat pathogenic bacterial infections. It can be of immense help in control of antibiotic resistance. Bacteriophages invade bacterial cells and, in the case of lytic phages, disrupt bacterial metabolism and cause the bacterium to lyse. From different studies, phage therapy has proved to be an important alternative to antibiotics for treating multi-drug resistant pathogens [58].

Bacteriophage therapy is widely used to treat severe infections caused by multi-drug resistance pathogenic bacteria in human, animals and plants and it is now also employ to enhance the shelf life of meats, vegetables, fruits and stored plant parts [3, 83]. The US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, now list phages as a research priority to address the increasing drug resistance bacteria [12]. The relatively narrow host range exhibited by most phages limits the number of bacterial types with which selection for specific phage-resistance mechanisms can occur. Thus, there is low pressure of resistance associated with phage therapy because phages infect and kill using mechanisms that differ from those of antibiotics, specific antibiotic resistance mechanisms do not translate into mechanisms of phage resistance [52].

6. CONCLUSIONS

Antibiotics have saved millions of lives and transformed modern medicine, but they are becoming less effective due to development of resistance in bacteria and the consequent failure of antibiotic therapy, has led to hundreds of thousands of deaths annually. The issue of antibiotic resistance is of global concern because of the spreading and developing resistance of most common bacteria to most inexpensive common antibiotics. Inappropriate prescription and consumption of antibiotics, together with self-medication in human as well as the massive use of antibiotics to prevent and treat infections in farm animals; lack of rapid diagnostic test and new antibiotics; poor quality of antibiotics; lack of awareness on the risks of antibiotic resistance have significant contribution for the spread and development of antibiotic resistance.

Without effective antibiotics, diverse medical procedures will be severely hampered with a corresponding increase in morbidity and mortality from resistant microbial infections. The benefits of winning the battle are not only medical but also economical: antibiotic-resistant causes an estimated loss of 23,000 people life, $20 billion in excess direct healthcare costs, with additional costs from lost productivity as high as $35 billion a year in USA and 25 000 deaths, 2.5 million extra in-hospital days and $1.6 billion extra costs in Europe.

Antibiotic resistance is certainly a complex and multifactorial problem in the world. Proper understanding of the problem is necessary for effective control solution because non prudent use of antibiotics in human and animal reflect a lack of awareness on the risks of antibiotic resistance. To combating this problem the establishment of educational programs with antibiotic stewardship on the rational use of antibiotics addressed to different community sectors. Development of better detection methods, novel antibiotics and alternative therapeutic agents, based on innovative strategies that combine pharmaceutical and public health interests have a vital role in combating antibiotic resistance. Avoiding catching and spreading bacterial infections, by taking measures such as washing hands also play a vital role in combating antibiotic resistance.

The challenge of global antimicrobial resistance is comparable to climate change and global warming. Tackling the problem of antibiotic resistance will require global and collaborative effort from the general population, the scientific community and policymakers. Efforts to improve antibiotic use will succeed only if everyone plays a role and make a serious commitment to change the dynamics of non-prudent use of antibiotics. Success will depend upon coordinated efforts to promote and adopt principles of responsible antibiotic prescribing and use across the globe, from government agencies, foundations, professional organizations, companies, hospitals, clinics, nursing homes, patients, and healthcare providers. When everyone plays their part to improve antibiotic use, patient safety is preserved and lifesaving antibiotics will be available for generations to come. Therefore, as the world gives serious attention and work in collaboration to protect the climate for the future generation, it has a responsibility to work in collaboration to combat antibiotic resistance that not to pass over microbial population that is resistant to antibiotics to the next generation.

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