Global irrational antibiotics/antibacterial drugs use: A current and future health and environmental consequences

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Antibacterial/antibiotic drugs have tremendously improved the health of humans and animals since the antibiotic golden age up to date. Currently the emergence of antibiotic/antibacterial resistance due to irrational drug use in medical and veterinary practice, food industries, agriculture and in communities is posing a global health problem. Most of the unused drugs, drug metabolites and residues enter the environment by various means thus affecting the natural ecosystems. They select the antibiotic-resistant mutants and facilitate the acquisition of antibiotic resistance determinants by the gene-transfer elements that are increasingly spreading among the environmental microbiota. They destroy the susceptible microbiota such as the Cyanobacteria that is responsible for production of third of the total free oxygen and carbon dioxide in the environment. They affect the natural metabolic processes of the microbiota by altering the structure and the physiology of all the microorganisms in the environment and thus affecting the maintenance of the global activity of the microbiosphere. Antibiotic/antibacterial resistance increases the cost of treatment, prolonged hospitalization due to resistant bacterial infections in addition to some individuals getting exposed to second and third-line drugs that are highly toxic thus increasing the adverse drug reactions in humans and economic loss in animals.

Keywords antibiotic/antibacterial resistance, irrational antibiotic use, global consequences, humans, animals, environment

1. Introduction

Antimicrobial drugs have been widely used for more than 50 years to improve both human and animal health since the antibiotic golden age up to date [1]. The discovery of the antibiotic and antibacterial agents since 1940’s, revolutionized the treatment of infectious bacterial diseases that used to kill millions of people during the pre-antibiotic golden age worldwide [2, 3]. Antibiotics are chemical substances naturally produced by various species of microorganisms such as bacteria and fungi like actinomycetes and streptomycetes that kill or inhibit the growth of other microorganisms. Among the major sources of antibiotics include Streptomycyes, Penicilliums, Actinomycetes and Bacilli [3, 4]. It is estimated that about 100,000 tons of antibiotics are produced globally [2-4]. About 80% of the antibiotics/antibacterial agents produced are used as feed additives in livestock production as growth enhancers and for prophylactic use due to the suppressed immune system caused by the overcrowding of the animals leading to stress [5, 6]. They are also used in agriculture especially horticulture and tissue cultures [7] and food industries as food preservatives [8] and in commercial ethanol production [9, 10]. In all these, the antibiotics/antibacterial drugs eventually enters the environment and cause deleterious effects to the microbiota.

Box 1 Key definitions

- **Antibiotics** in strict sense are “natural chemical substances produced by microorganisms like bacteria and fungi that destroy or inhibit the growth of other microorganisms like bacteria and fungi” (According to the original definition by the Nobel laureate Selman Waksman) [4]
- **Antibiotics** in broader sense “are selective antimicrobial agents other than disinfectants, antiseptics and substances used solely as antineoplastics that, on application to living tissue or by systemic administration, they kill or prevent the growth of susceptible microorganisms and also include the synthetically or semi-synthetically antibacterial agents like sulfonamides and fluoroquinolones” [1].
- **Antibacterial agents** are chemical substances that are either natural, semi-synthetic or synthetic that kills or inhibits the growth of bacterial microorganisms [1].
- **Antimicrobial drugs** are chemical substances or drugs that kill or inhibit the growth of a variety of microorganisms like bacteria, viruses, fungi, and parasites [1].
- **Sub-therapeutic use or Non-therapeutic use** is “any use of antibiotics/antibacterial drugs as a feed or water additive in the absence of any clinical sign of disease in the animal for growth promotion, feed efficiency, weight gain, routine disease prevention, or other routine purpose” [11].
- **Antimicrobial resistance or Antibiotic-resistant infection** is where new emerging strains of microorganism like bacteria that have been found to survive traditional antibiotic exposure or the bacteria are no longer susceptible to an antimicrobial drug [12].
- **Self-medication** is the “use of drugs or pharmaceutical products by the consumer to treat self recognized disorders or symptoms or the intermittent or continued use of the medication prescribed by the physicians.

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2. Global use and irrational use of antibiotics/antibacterial agents’ in humans, animals, agriculture and food industries

Antibiotics/antibacterial drugs have long been used in treatment and controlling of bacterial diseases in humans, animals and plants [3]. In animals, they are added to feeds to enhance the growth and prevent opportunistic infections caused by stress due to overcrowding of animals [3, 15]. In food industries, they are used as preservatives [8]. However, in all these cases, these drugs are irrationally used contributing to the selection of the pathogenic antibiotic resistant bacterial organisms in the environment that can spread globally thus threatening the lives of both humans and animals [16]. They can also affect the microbiota in the ecosystem leading to the disruption of the various environmental cycling of the organic matter.

2.1. Antibiotics/antibacterial drugs use in humans

In humans, antibiotics/antibacterial drugs are commonly prescribed, sold and used to treat bacterial diseases worldwide in irrational manner [17]. The problem has overwhelmingly increased due to financial and budgetary constraints, market inefficiencies, distortion and behavior of health systems, health workers and pharmaceutical companies [12]. The complementary medicine specialists or traditional herbalist and quacks also use allopathic drugs like antibiotics to treat all types of infections, with lack of expertise and knowledge on their use [12]. It is reported that about 1/3 to 2/3 of primary health care patients receive twice the antibiotics than clinically needed contributing to irrational antibiotic use [18]. Complex socioeconomic and behavioral factors have been associated with antibiotic misuse among health care professionals, unskilled practitioners and public [19]. Poor drug quality and inadequate surveillance by the regulatory authorities especially in poor developing countries greatly contributes to antibiotic misuse [20]. The major key determinants of irrational antibiotic use include[21, 22]: (1) lack of knowledgeable healthcare providers, prescribers that are not qualified, supervised or supported (2) prescribers habit and behaviors where they think that use of guidelines delay process of prescription (3) lack of availability of medicines information such as clinical treatment guidelines, essential drug lists, national formularies and drug bulletins (4) lack of unbiased support for continuing medical education and supervision of the healthcare providers (5) excessive pharmaceutical promotion where some prescribers become biased to particular drugs leading to serious consequences such as side-effects, antimicrobial resistance and high cost of treatment to the patient (6) very short consultation time (one minute) that does not allow sufficient time to explain to patients how to take their medicines (8) peer pressure, where doctors fear to be seen to be prescribing differently from their colleagues especially senior consultants who may set inappropriate prescribing norms (9) patient demand from prescribers to prescribe them certain drugs that are unnecessary (10) lack of diagnostic support services such as laboratory services (11) poor infrastructure like the inability to undertake observation or follow-up of patients (12) economic incentives where prescribers gain income from dispensing or selling the medicines they prescribe (13) inappropriate medicines supply and appropriate ones are not provided [22]. These factors increase irrational antibiotic use and enhance the selection of antibiotic resistant pathogenic bacterial organisms that can cause significant mortality, morbidity and increased health-care costs [22, 23]. Serious antibiotic misuse are reported in cases of (1) viral upper respiratory tract infections and less usage for pneumonia and (2) serious overuse of antibiotics in acute cases of diarrhea and limited use of oral rehydration salt solution [22-25]. Access to affordable health care is limited in many low and middle income countries hence many people rely mainly on self-medication and purchasing of antibiotics directly from pharmacies, street vendors or markets [26]. Self-medication involves the “use of medicinal products by the consumer to treat self recognized disorders or symptoms or the intermittent or continued use of the medication prescribed by the physicians for a chronic or recurring diseases or symptoms” [27, 28]. Self medication with antibiotics or the use of non-prescribed antibiotics including leftover antibiotics is common in both developed and developing countries, in which the point prevalence ranges from 3% to 75% thus increasing irrational antibiotic use globally [13].
2.2. Antibiotic/antibacterial drugs use in treatment of animals

Antibiotics/antibacterial drugs have been widely used globally in animals for more than 50 years, with tremendous benefits in animal production and economic development [1]. Several antibiotic/antibacterial drugs are used in the treatment of many bacterial diseases of animals especially in food-producing animals globally. Many of these agents are at the same time used in bacterial infections in humans (table 1) [3, 6, 8]. However, many of these drugs are abused by veterinarians as healthcare professionals and the general public where many farmers treat their sick animals with antibiotics/antibacterial drugs without seeking professional consultation. The problem is worse in developing poor countries that have privatized veterinary services making the cost of treatments to be very expensive for the farmers. Many farmers access these agents and treat their animals even in cases where use of antibiotic/antibacterial agents would be unnecessary. As a result of this, massive quantities of antibiotics/antibacterial drugs used, are released in the environment thus increasing selection of the antibiotic resistant bacterial organisms that can spread from the animals to humans especially the bacterial zoonoses, increasing the cost of treatments in both animals and humans [29-31]. The problem is likely to increase globally leading to severe future consequences similar to the pre-antibiotic golden age situation.

Table 1 Major classes of antibiotic/antibacterial shared by animals and humans [5, 11]

<table>
<thead>
<tr>
<th>Class of antibiotic/antibacterial drugs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams – penicillins &amp; cephalosporins</td>
<td>Penicillin, amoxicillin; ceftiofur</td>
</tr>
<tr>
<td>Macrolides &amp; lincosamides</td>
<td>Tylosin; tilmicosin; tulathromycin, lincomycin</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Gentamicin; streptomycin, neomycin, spectinomycin</td>
</tr>
<tr>
<td>Fluroquinolones</td>
<td>Enrofloxacin, danofoxacin</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Tetracycline; oxytetracycline, chlortetracycline</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Sulfactine, Sulfisoxazole, Sulfamethizole, Sulfadiazine Sulfafoxazole, Sulfoxpyridine</td>
</tr>
<tr>
<td>Fluroquinolones</td>
<td>Ciprofloxacin, Danoxofacin, Difloxacin, Enrofloxacin, Marbofloxacin, Ortifloxacin</td>
</tr>
<tr>
<td>Streptogramins</td>
<td>Virginiamycin</td>
</tr>
<tr>
<td>Polypeptides</td>
<td>Bacitracin</td>
</tr>
<tr>
<td>Phenicolios</td>
<td>Florfenicol</td>
</tr>
<tr>
<td>Pleuromutilin</td>
<td>Tiamulin</td>
</tr>
<tr>
<td>Bambermycins</td>
<td>Bambermycin (Amprolium®)</td>
</tr>
<tr>
<td>Quinoxalines</td>
<td>Carbadox</td>
</tr>
<tr>
<td>Aminocoumarins</td>
<td>Novobiocin, clorobicin and coumermycin A1</td>
</tr>
</tbody>
</table>

2.3. Antibiotics/antibacterial drugs use in the animal feed industry

Feed industries and farmers have been adding antibiotics to livestock feed since 1946, after it was realized that use of these antibiotics caused animals to grow faster and put on weight in a short time [5, 11]. It is reported that more than 80% of all antibiotics produced globally are used in animals and some are used in aquaculture, prophylactically to control bacterial diseases of the fish and other water animals [12, 29]. The antibiotics/antibacterial drugs cause a change in physiological, nutritional and metabolic processes of the animals. They are used in [15, 32]: (1) stimulation of intestinal synthesis of vitamins by bacteria (2) reduction in total numbers of bacteria (normal flora) in the gastrointestinal tract hence reducing the competition between microorganisms and host animals for nutrients (3) inhibition of harmful bacteria which may be mildly pathogenic or toxin-producing (4) inhibition of bacterial urease (5) improved energy efficiency of the gut (6) inhibition of bacterial chylotaurin hydrolase activity (7) nutrient sparing (8) improvement of nutrient pharmacokinetics especially absorption from the small intestinal epithelium (9) modification of intestinal enzyme activity (10) reduced immune stimulation due to stress caused by overcrowding of the animals (11) modification of rumen microbial metabolism [15, 32].

2.4. Antibiotic/antibacterial drugs use in food industries

Many bacterial organisms from humans, animals and the environment commonly contaminate foods and food products in food industries and other perishable foods especially during processing and transportation to the markets in un-sterile conditions [8]. The bacteria attack and utilize nutrients needed by humans in the foods and also cause spoilage of foods leading to economic and financial loss. The bacterial contamination also increases the cost of de-contamination of industrial facilities [33-36]. As a result, many antibiotic/antibacterial drugs are used irrationally in most cases to control bacterial contaminants in food industries.

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2.4.1. Antibiotic drugs use in ethanol production

During ethanol production especially in commercial brewery plants, yeast is used to convert starch to ethanol [35-37]. However ethanol fermentation tanks occasionally become contaminated with bacteria especially “lactic acid bacteria” [35-37]. Among the lactic acid bacteria species that have been reported to contaminate fuel ethanol fermentations, include both Gram-positive and Gram-negative bacteria such as Lactobacillus, Pediococcus, Enterococcus Acetobacter, Gluconobacter, Leuconostoc, Weissella and Clostridium, with the Lactobacillus species the most predominant contaminant [35-37]. The Lactobacillus species have the capacity to grow rapidly, tolerate ethanol disinfection and the low pH allows these bacterial organisms to effectively compete favorably with the yeast [36, 37]. The increased and prolonged bacterial contamination drains the available sugars that can be converted to ethanol. The bacterial organisms convert the sugars to lactic or acetic acid that lowers the quality and quantity of the ethanol production [36, 37]. Also the bacteria scavenge essential micronutrients required for optimal yeast growth and efficiency in ethanol production. The most commonly used antibiotics/antibacterial agents to selectively kill bacterial contaminants and spare yeast in ethanol production include penicillin, virginiamycin, erythromycin, tylosin and tetracycline [9, 33, 36]. The massive use of the antibiotics/antibacterial agents in commercial ethanol production contributes to destruction of the useful bacteria (normal flora) in the hosts and in the environment as well as increased selection of antibiotic resistant pathogenic bacteria that can spread globally in the environment to human and animals as well as lowering the effectiveness of the antibiotics [10].

2.4.2. Antibiotics as food preservatives

Various antibiotics/ antibacterial drugs have long since 1940’s been used in the preservation of perishable foodstuffs and food products. Among the commonly used antibiotics include chlorotetracycline, oxytetracycline, chloramphenicol, penicillic acid, penicillin and streptomycin. Also these agents are used in preservation of fish [38]. The tetracyclines are commonly used in food industries to prevent growth of harmful bacteria in poultry product, fish, canned foods, cheese, meat, sausages and other non-sterile animal products [39, 40]. Natamycin (pimaricin) is a polyene macrolide antibiotic produced by submerged aerobic fermentation of Streptomyces natalensis and related species [40]. It is used in the food industry as a “natural” preservative for dairy product like cheese and meat, wine, soft drinks like juice, convenient food and baking food [38-40]. In developing and poor countries like Uganda, some local milk coolants commonly use antibiotics to prevent milk spoilage by bacteria especially Lactobacillus organisms thus predisposing consumers to sub-therapeutic levels of these drugs that causes selection of antibiotic resistant bacterial pathogens in humans, animals and environment [41].

2.5. Antibiotics/antibacterial drugs use in agriculture (horticulture)

Several antibiotics/antibacterial agents are commonly used in horticulture and agronomy to control bacterial diseases. Oxytetracycline and streptomycin have long been used in horticulture since 1950s. They are used in the control of bacterial diseases in high-value fruits, vegetables, trees producing timber and ornamental plants [42]. In 1997, it was reported that more than 30,800 pounds of streptomycin and 26,700 pounds of oxytetracycline were used to control bacterial infections in fruit trees in the USA [43]. Antibiotics are widely used prophylactically in plant tissue culture and biological research to prevent bacterial contaminants that would attack the media rich in sugars [42]. However, the use of these drugs conflicts with the normal principles of prophylactic use, “in that the ‘pathogen’ is unknown and is of uncertain susceptibility and the period of use of these antibiotics is prolonged” [44]. Oxytetracycline, is used in treatment of bacterial spot in peach pecan trees and sometimes its combined with gentamicin . Streptomycin was the first antibiotics used in the treatment of plant diseases since 1955 and some times combined with oxytetracycline and oxolinic acid in the control of fire blight bacterial diseases in rosaceous plants like pears and apples [42]. Chloramphenicol is used to control bacterial leaf blight in rice [42]; polyoxins are used to control rice sheath blight and black spot [42]; the polyene macrolides act as systemic fungicides [42]; celloidin is used to control rice blight spot [42]; griseofulvin used in apple blossom blight and Fusarium wilt of melon [42]; cycloheximide is used in control of downy mildew on onions [42, 43] and blasticidin-S inhibits the growth of many Gram positive and Gram negative bacteria and has antiviral and antifungal activity [42]. However the use of many of these agents in agriculture and horticulture globally has become a public health importance since these drugs are also used in humans and animals to treat bacterial diseases [31]. Their massive use promotes the selection and emergence of resistant bacterial strains in both humans and animals that may be difficult to control.

3. Antibiotics/antibacterial drugs and the bacterial organisms in the environment

Humans and animals health have long benefited from healthy microbial population especially bacteria in the environment. The bacterial organisms are ubiquitous in the environment and are resident in soil, water, air, deep sea hydrothermal vents and soda lime lakes [30, 45]. They are responsible for recycling nutrients in soil and purification of water. Humans and animals have microflora that live on and in the body where they offer first line defense mechanism
and protection against foreign pathogens by competition [46]. Microbes have long been used for centuries to provide humans and animals with food through microbial fermentation of sugars to produce carbon dioxide used in bread baking, beer and wine production using yeast that convert sugars into alcohol, yogurt and cheese produced by bacterial fermentation of lactose, the sugar found in milk [46]. Also microbes like phytoplankton serve as the nutrient source that indirectly feeds all marine animals. Microorganisms are involved in the biodegradation of waste generated by industries and households. They also detoxify acid amines in drainages and other toxins dumped into the soil and water. The biodegradation of these substances releases nutrients that can be used to feed plants or algae that in turn feed all animals and humans globally [46]. The bacterial organisms like *Cyanobacteria* are responsible for more than a third of total free O₂ production and CO₂ fixation in the environment that is utilized by animals, humans and plants in process of respiration and other biochemical reactions in the environment [30]. The microbes are useful in the decomposition of dead animal and human bodies, plants as well as in waste water treatment like sewage septic system or waste water treatment plants where aeration microbes remove organic materials from the filthy waters before it can safely return to the rivers, streams, lakes, seas and oceans [30, 47, 48] (figure 1). The methane produced during sewerage treatment by bacteria can be used to generate heat or electricity. Also some microorganisms are useful in biosynthesis of various food products by bacterial fermentation such as xanthan gum, a food thickener, vitamin B12, riboflavin, and vitamin C and about 70% of antibiotics currently in use, are also the product of microbial fermentation [30, 46, 47]. The increased massive antibiotic pollution in the environmental can interfere with all these processes leading to the destruction of all forms of the ecosystem and the selection of resistant pathogenic bacteria.

**Fig. 1** Sources and distribution of antibiotics/antibacterial drugs in the environment (Adopted from Kümmerer, 2003 and modified) [49]

### 4. Mechanisms of spread of antibiotic resistance

Several antibiotics are natural compounds that have been in contact with environmental microbiota for millions of years. They are biodegradable and some used as a food resource for several microorganisms [29, 49, 50]. In the environment the bacterial organisms are exposed to sub-therapeutic concentrations of these antibiotics where some are killed and others develop resistant mechanisms to avoid the drugs. The antibiotic resistant bacterial organisms are selected from the several populations of bacteria in the environment mainly by horizontal gene transfer mechanisms and then spread to both humans and animals globally causing severe bacterial diseases that contribute to high morbidity and mortality (figure 2 and figure 3).
Several mechanisms have evolved in bacteria which confer them with antibiotic resistance. These mechanisms can chemically modify the antibiotics/antibacterial drugs and render them inactive. The inactivation of the antibiotics/antibacterial agents by bacterial is achieved by the rapid physical removal of the drug from the cell, or modifying the target site so that it is not recognized by the antibiotic and enzymatic inactivation of the antibiotics by bacteria which is the most common mode of antibiotic resistance [52-54]. Antibiotic resistance in bacteria occur in two ways and it may be an inherent trait of the organism in the cell wall structure that renders it naturally resistant, or it may be acquired by means of mutation in its own DNA or acquisition of resistance from DNA of another source [52-56].

a) Intrinsic or inherent or natural resistance is where microorganisms naturally or inherently become resistant to an antibiotic due to lack of target sites or molecules for the antibiotic, lack of transport system for an antibiotic 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 especially for those that require entry into the microbial cell in order to effect their action [52-56].

b) Acquired resistance is where several mechanisms are developed by bacteria in order to acquire resistance to antibiotics. It occurs by either modifying the existing genetic material or the acquisition of new genetic material from another source [52-56]. There are two major ways in which gene transfer occurs in bacteria and include [52-56]: (1) Vertical gene transfer where there is spontaneous mutation frequency for antibiotic resistance occurring in the order of $10^{-8}$- $10^{-9}$. This is where one in every $10^8$- $10^9$ bacteria in an infection will develop resistance through the process of mutation. And once resistant genes have developed, they are transferred directly to all the bacteria progeny during DNA replication in the process of vertical gene transfer or vertical evolution. In this way, the wild type (non mutants) bacteria are killed and the resistant mutant survives and grows. (2) Horizontal gene transfer is another mechanism beyond spontaneous mutation that is responsible for the acquisition of antibiotic resistance. Lateral or horizontal gene transfer (HGT) is a process in which the genetic material contained in small packets of DNA can be transferred between individual bacteria of the same species or even between different species [52-56]. The spread of antibiotic immunity among bacteria is an evolutionary phenomenon mediated by plasmids, transposons, and integrons that carry DNA that encodes attack enzyme, efflux pumps, and other protective devices [52-56]. Bacterial organisms can acquire resistance through different mechanisms such as [57, 58]: (1) Conjugation where bacteria can fuse and exchange plasmids and sometimes chromosome fragments. The plasmids have a broad host range and are able to cross genus lines during the gene transfer. (2) Transfection or transduction is where viruses can infect bacteria and fungi, passing along genes from one infected organism to the next (phage). These genes sometimes encode resistance factors. The use of antibiotic growth promoters in animal husbandry may increase the amount of free phage in the gastrointestinal tract that may
contribute to the spread of antibiotic resistance. Transformation is where a bacterium lyses in its environment such that some of the actively-growing bacteria in that vicinity can pick up its DNA leading to antibiotic resistance that can be spread in the bacterial population due to plasmids such as R plasmids that are more easily used by the recipient bacterium than chromosomal materials [46, 59].

The acquired resistance genes cause the bacterium to express the various resistance mechanisms as a way to avoid the antibiotics exposed to them. The various mechanisms of acquired resistance expressed by bacteria include [54, 58, 60-62]: (1) the presence of an enzyme that inactivates the antimicrobial agent or enzymatic alteration of the antibiotic (2) metabolic bypass of the targeted pathway or the presence of an alternative pathway for the enzyme that is inhibited by the antimicrobial agent (3) a mutation in the antimicrobial agent’s target, which reduces the binding of the antimicrobial agent or drug sequestering by protein binding (4) post-transcriptional or post-translational modification of the antimicrobial agent’s target, which reduces binding of the antimicrobial agent or modification of targets (5) reduced uptake of the antimicrobial agent (6) active efflux of the antimicrobial agent or active pumping of drugs out of the cell (7) overproduction of the target of the antimicrobial agent (figure 4).

Fig. 4 Mechanisms of horizontal gene transfer (HGT) in bacteria and the various antibiotic resistance strategies (Adopted from Todar, 2011, Encyclopædia-Britannica, 2013) [60-62]

5. Current and future consequences of antibiotic/antibacterial drugs pollution in the environment

Antibiotics/antibacterial agents are important ecological factors in the environment that could potentially affect almost all microbial communities. The massive misuse and abuse of antibiotics leads to their accumulation in the environment especially the quinolones that are slowly biodegradable [29, 45, 50]. In the environment, they cause deleterious effects to the bacterial population such as phylogenetic structure alteration, resistance expansion and ecological function disturbance in the micro-ecosystem. The ecological functional disturbances by the antibiotics in the environment include nitrogen transformation, methanogenesis and sulfate reduction [31, 45, 49]. The accumulated antibiotic in the biosphere affects the structure and activity of environmental microbiota leading to alteration of the ecosystem [30]. The increased antibiotic concentrations in natural ecosystems have a significant consequence in human therapy in hospitals and livestock production and in agriculture due to the increased selection of the antibiotic resistant pathogenic bacterial organisms that can spread globally [30]. These changes also contribute to structural alteration of the natural microbial populations and also alteration of the physiology of microorganisms [30]. The selection of the antibiotic-resistant mutants favors the acquisition of antibiotic resistance determinants by gene-transfer of elements that can spread among the environmental microbiota. The antibiotic pollution can enrich the bacterial population with intrinsically resistant microorganisms and reduce the population of susceptible microbiota like Cyanobacteria, which are responsible for more than a third of total free O₂ production and CO₂ in the environment[30]. The increased elimination of the Cyanobacteria population due to antibiotic/antibacterial agents pollution poses a great threat to the natural environment and the survival of all Microbiota, animals and humans and hence the maintenance of the global activity of the microbiosphere and macrobiosphere [30, 50]. Even though a reduction in the prevalence of resistance has been reported after discontinuation of a given antibiotic, the total restoration of bacterial population to its previous antibiotic-susceptible situation is not easily achievable [52, 61]. Many emerging bacterial diseases due to increased resistant pathogenic organisms from the environment are likely to increase in the future that would lead to a significant mortality of both humans and animals if the trend of antibiotics/antibacterial drugs use globally is not changed, the situation may return to the pre-antibiotic golden age.
6. Current and future consequences of irrational antibiotic/antibacterial drugs use on health

Since the period of golden antibiotic age and in the 1950s, there has been a steady occurrence of resistance in many bacteria due to acquisition of the few genetic mechanisms that are transferred through vertical and horizontal antibiotic-resistance genes using the transfer-proficient elements such as plasmids, transposons, and integrons [51, 53, 63]. The selection of the pathogenic resistant antibiotic bacteria has facilitated the global spread of many resistant organisms in humans, animals and the environment and some are zoonotic bacterial infections that does not respect geographical or biological borders [12, 39]. The lack of development of newer and effective antibiotics by the pharmaceutical companies due to the high cost and the emergence of pathogenic resistant bacterial diseases is critical in the management of these bacterial diseases in future especially if nothing is done to preserve the still few effective antibiotics/antibacterial drugs.

6.1. Implication of antibiotic resistant bacterial infections and diseases to human health

The increased emergence of pathogenic antibiotic resistant bacterial diseases causes detrimental effects to human and the burden is likely to worsen in the future [22, 64]. Among the serious consequences due to these resistant bacterial diseases include [14, 22, 64]: (1) reduction in the quality of antibiotics/antibacterial drug therapy available in the management of these resistant diseases and the situation may return to the pre-golden antibiotic age. (2) Wastage of resources especially where finances are diverted to purchase expensive drugs to manage resistant diseases may lead to lack of vital drugs used to treat other common diseases [65]. (3) There is increased risk of unwanted side effects such as adverse drug reactions since many of the patients with resistant bacterial diseases in most cases are put on either the second- or third-line drugs that are expensive and toxic like in the case of multi-resistant tuberculosis. (4) There are increased cases of treatment failures due to the resistant bacterial diseases causing prolonged hospitalization, increased cost of treatment to the society and death. (5) High mortality caused by resistant bacterial diseases could be a serious burden globally and it is reported that more than 25 000 people in the European Union die of antibiotic resistant bacterial diseases annually [12] and this may have a serious consequences on healthcare systems especially in poor nations. (6) The resistant bacterial diseases may cause a psychosocial impact, where patients believe that there is "a pill for every illness" leading to increased demand for drugs. (7) The increased use of antibiotics especially the broad spectrum antibiotics like tetracycline by communities may lead to the destruction of microflora making such individuals more susceptible to fungal infections especially Candida infection [16, 66]. (8) There is a possibility of global spread of the pathogenic resistant bacterial in both humans and animals leading to socio-economic impact and stress among the global population.

6.2. Implication of antibiotic resistant bacterial diseases to animal health

Like in humans, bacterial diseases of animals are a burden globally and many of them are zoonotic thus making animals as reservoirs of bacterial infections to humans. It is reported that about 75% of the total global antibiotics/antibacterial drugs produced are used in animals as growth promoters, for chemoprophylaxis and treatment of sick animals. The overuse and misuse of these agents leads to increased selection of resistant pathogenic bacteria that can spread among different species of animals and to humans. The consequences of these bacterial diseases are similar to humans in addition to the [20]: (1) poor animal production and increased death of the animals leading to increased cost of production. (2) Increased emergence and spread of resistant zoonotic bacterial diseases that can affect the human population worldwide. (3) The countries that rely on agriculture as their source of income will be greatly affected due to reduced animal production, quarantine and embargo on export and imports of animal products as well as the high cost of production. (4) Many food and animal industries will be affected due to lack of raw materials. (5) Malnutrition can be a major problem since many people especially children from poor developing countries will lack animal products as nutrients [25].

7. Conclusion

The global use of antibiotics/antibacterial drugs have improved the health of humans and animals since the antibiotic golden age and the economy of many countries worldwide. These agents are used in the treatment of both human and animal bacterial diseases. They are used by livestock farmers as feed additives to enhance growth of livestock animals. They are used in food industries as preservatives and in commercial ethanol production to prevent bacterial contaminants of the fermentation plants. They are used in horticulture to treat plant diseases as well as in tissue cultures. However massive use of the antibiotics/antibacterial drugs in irrational manner has affected the environmental microbiota of the ecosystem, destruction of useful bacteria in the environment including the normal flora as well as increasing the selection of the pathogenic antibiotic resistant bacterial organisms that have led to their spread globally.
This has led to economic loss in animal industry and in humans; it has also caused prolonged hospitalization, adverse drug reactions, treatment failures, increased cost of treatment, and reduced socioeconomic status of many individuals globally. These problems are likely to increase in future unless there is an urgent instituting of control measures involving all stakeholders on the rational use of antibiotics/antibacterial drugs globally.

References


