Review on Antibiotics Resistance and its Economic Impacts

Gemechu Regea*

Jimma University, Ethiopia

Submission: May 26, 2018; **Published:** June 12, 2018

*Corresponding author: Gemechu Regea, Jimma University, Ethiopia, Email: gemechuregea13@gmail.com

Abstract

Resistant bacteria are increasingly more prevalent, more virulent, and more diverse. Their rise is a direct result of antibiotic use, regardless of its form or necessity. These antibiotic resistant bacteria can infect both humans and animals, sometimes traveling from one to the other, both within and across national borders. Resistance to antibiotics existed even before antibiotics were used throughout the world. However, the misuse and overuse of antimicrobials is accelerating this process. The consequences of antimicrobial resistance include the failure to successfully treat infections, leading to more severe or prolonged illness, death, production losses and negative consequences for livelihoods and food security. The indirect impacts of antimicrobial resistance extend beyond health risks or reduced productivity, and include higher costs for treatment and healthcare, and drain national and global economies. So, measures against antimicrobial resistance including improvement of hygiene, infection control to prevent spread of resistant bacteria, development of new antimicrobials against which bacteria are not resistant, improved conservation efforts to maintain the effectiveness should be taken.

Keywords: Antimicrobial resistance; Bacteria; Misuse; Mutation; Overuse

Abbreviations: AMR: Antimicrobial Resistance; DNA: deoxyribonucleic Acid; HGT: Horizontal Gene Transfer; HGT: Horizontal Transmission; RNA: Ribonucleic Acid

Introduction

Antibiotics and other antimicrobial agents are widely used in veterinary medicine for disease prevention and treatment in animals, to contain disease spread, to prevent contamination of the food chain, and to increase productivity [1]. Antibiotics either are cytotoxic or cytostatic to the micro-organisms, allowing the body's natural defenses, such as the immune system, to eliminate them. They often act by inhibiting the synthesis of a bacterial cell, synthesis of proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), by a membrane disorganizing agent, or other specific actions [2]. Antibiotics may also enter the cell wall of the bacteria by binding to them, using the energy-dependent transport mechanisms in ribosomal sites, which subsequently lead to the inhibition of the protein [2].

To combat against infections or microbes, undoubtedly antibiotics are a blessing to human civilization that has saved millions of people [3]. Multiple varieties of the antibiotics have been used for therapeutic purposes over time [3]. Antibiotics were seen as the 'wonder drug' in the mid-20th century [3]. At the time, there was an optimistic belief that communicable disease was nearly coming to a complete halt [3]. The beginning of modern "antibiotic era" was synonymously associated with two names Alexander Fleming and Paul Ehrlich [4]. Antibiotics were considered a magic bullet that selectively targeted microbes that were responsible for disease causation, but at the same time would not affect the host. Fleming was the first who cautioned about the potential resistance to penicillin if used too little or for a too short period of treatment [4]. The period from the 1950s to 1970s was thus considered as the golden era for the discovery of novel antibiotics classes [5].

Millions of metric tons of newer classes of antibiotics have been produced in last 60 years since its inception. Increased demand for antibiotics across many sectors has allowed for less expensive and off-label uses of drugs. Conversely, due to the enormous and irresponsible use of the antibiotics, has contributed significantly to the advent of the resistant strains [6]. In the previous days, the production of new antibiotics was directly proportional to the development of resistant strains. However, the mainstream approach in fighting against the diseases is now focused on the modification of existing antibiotics to combat emerging and re-emerging resistance of pathogens globally [5].

However, their wide use in humans and animals leads to the emergence of antimicrobial resistance, a general term that encompasses antibiotic resistance [7]. In September 2016,

the United Nations recognized the global rise of antimicrobial resistance as a threat to health and human development (UN, 2016).

Antimicrobial resistance (AMR) occurs when bacteria, parasites, viruses and fungi become resistant to antimicrobial drugs that are used for treating the infections they cause. Every time an antimicrobial medicine is used, it diminishes the effectiveness for all users, because its usage increases the possibility for the bacteria to become resistant [7]. Resistance against antibiotics (medicines used to prevent and treat bacterial infections) is an urgent problem because antibiotics are a cornerstone of modern medicine and most medicinal procedures in human and animal health rely on functioning antibiotics [7]. It will increase infectious disease outbreaks, slowing down livestock productivity and disrupting international trade [8]. And therefore the objectives of this seminar paper are to review antibiotics resistance and its economic impacts.

Literature Review

Resistant bacteria are increasingly more prevalent, more virulent, and more diverse. Their rise is a direct result of antibiotic use, regardless of its form or necessity. These antibiotic resistant bacteria can infect both humans and animals, sometimes traveling from one to the other, both within and across national borders [9]. The chances of antibiotic-resistant bacteria prevailing in the race for survival are in direct proportion to the volume of antibiotics used, a principle which makes it all the more critical to examine current habits and encourage rational and conservative use [9].

The use of antimicrobials in veterinary medicine creates a selective pressure for the emergenceof antimicrobial resistant bacteria, including animal pathogens, human pathogens that have animalreservoirs and commensal bacteria from animals [10]. The bacteria selected by this pressure can spread to humans either by direct contact with animals or food products, or indirectly via environmental pathways and/or non-food producing animals [10].

Types of Antibiotic Resistance

Resistance to antibiotics existed even before antibiotics were used throughout the world. However, the misuse and overuse of antimicrobials is accelerating this process [11]. In many places, antibiotics are overused and misused in animals and people, and often given without professional oversight [11]. Bacteria can be naturally resistant to certain antimicrobial groups or substances (intrinsic resistance), or they can obtain resistance to antimicrobials through a variety of mechanisms, such as mutation (acquired resistance) [12].

Intrinsic Resistance

Intrinsic resistance is mediated by chromosomal genes [13] and is usually linked to physiological or anatomical characteristics of the bacteria [14]. The vast majority of drug-resistant organisms have instead emerged as a result of genetic changes, acquired through mutation or transfer of genetic material during the life of the micro-organisms, and subsequent selection processes. Hence it is usually a trait shared by all organisms within the same genus or species [13]. Resistance to penicillin G expressed by most Gram-negative bacteria is a common example [15], this is due to the complexity of its cell wall with the presence of an outer membrane absent in Gram-positive bacteria [14]. In addition to that all Gram-negative bacteria are naturally resistant to vancomycin due to their cell wall structure, which differs from Gram-positive cell walls [16]. However, this intrinsic form of resistance is not a major source of concern for human and animal health.

Acquired Resistance

Acquired resistance involves a change in the organism's genetic composition via either mutation in the chromosomal DNA or the acquisition of exogenous DNA [17]. Mutations occur randomly at a low frequency, and the mutations can sometimes result in advantageous characteristics that can be selected. For example, mutation accumulation in quinolone targets in DNA gyrase is the main mechanism against quinolone binding [17]. In other word mutational resistance develops as a result of spontaneous mutation in a locus on the microbial chromosome that controls susceptibility to a given antibiotic. The presence of the drug serves as a selecting mechanism to suppress susceptible micro-organisms and promote the growth of resistant mutants (Figure 1). Spontaneous mutations are transmissible vertically or horizontally.

Vertical Transmission

It includes spontaneous gene mutation and Induced gene mutation. Chromosomal mutations are extremely rare (i.e. 10^{-7} to 10^{-9} frequency), but are very relevant to the development of resistance in bacterial clones [13] (Table 1). Mutations can either affect target or regulatory genes [13]. Target mutations occur in structural genes that encode the specific targets of anti-microbial action [13]. Single point mutations are the most commonly observed once an antimicrobial substance is introduced [18], such as that observed with quinolone and macrolide resistance in Campylobacter spp [19].

Regulatory mutations usually affect gene expression mechanisms and are difficult to predict as they can occur spontaneously [13]. Unspecific efflux pumps, encoded at chromosomal level and therefore genus-specific, can confer multidrug resistance to unrelated antimicrobial substances [20].

Horizontal Transmission

It includes bacterial transformation, bacterial transduction, bacterial conjugation. When genes from a cell are transferred into another cell, independently of a reproductive event, this is known as "horizontal gene transfer"(HGT) [20]. HGT occurs through three main mechanisms:

a) Transformation, the uptake of free DNA by a "competent" bacterial cell

b) Transduction, the mobilization of bacterial DNA from one bacterial cell to another by a bacteriophage (i.e. a virus)

c) Conjugation, the mobilization of DNA from a donor bacterium to a recipient bacterium, requiring physical contact and conjugative machinery [20].

Mechanisms of Bacterial Resistance

Not surprisingly, bacteria have evolved sophisticated mechanisms of drug resistance to avoid killing by antimicrobial molecules, a process that has likely occurred over millions of years of evolution [21]. Of note, resistance to one antimicrobial class can usually be achieved through multiple biochemical pathways, and one bacterial cell may be capable of using a cadre of mechanisms of resistance to survive the effect of an antibiotic. According to the biochemical route involved in resistance, as follows:

a) Modifications of the antimicrobial molecule

b) Prevention to reach the antibiotic target (by decreasing penetration or actively extruding the antimicrobial compound)

c) Changes and/or bypass of target sites

d) Resistance due to global cell adaptive processes [21].

Modifications of the Antibiotic Molecule

One of the most successful bacterial strategies to cope with the presence of antibiotics is to produce enzymes that inactivate the drug by adding specific chemical moieties to the compound or that destroy the molecule itself, rendering the antibiotic unable to interact with its target [21].

Chemical Alterations of the Antibiotic

The production of enzymes capable of introducing chemical changes to the antimicrobial molecule is a well-known mechanism of acquired antibiotic resistance in both gram-negative and gram-positive bacteria. Interestingly, most of the antibiotics affected by these enzymatic modifications exert their mechanism of action by inhibiting protein synthesis at the ribosome level [22]. Many types of modifying enzymes have been described, and the most frequent biochemical reactions they catalyze include

a) Acetylation (aminoglycosides, chloramphenicol, streptogramins),

b) Phosphorylation (aminoglycosides, chloramphenicol), and iii) adenylation (aminoglycosides, lincosamides) [22].

Destruction of the Antibiotic Molecule

The main mechanism of β-lactam resistance relies on the destruction of these compounds by the action of β-lactamases. These enzymes destroy the amide bond of the β-lactam ring, rendering the antimicrobial ineffective. β-lactamases were first described in the early 1940s, one year before penicillin was introduced to the market, however, there is evidence of their existence for millions of years [23]. Infections caused by penicillin-resistant S. aureus became clinically relevant after penicillin became widely available and the mechanism of resistance was found to be a plasmid-encoded penicillinase that was readily transmitted between S. aureus strains, resulting in rapid dissemination of the resistance trait. In order to overcome this problem, new β-lactam compounds with wider spectrum of activity and less susceptibility to penicillinases (such as ampicillin) were manufactured.

Decreased Antibiotic Penetration and Efflux

Decreased Permeability: Many of the antibiotics used in clinical practice have intracellular bacterial targets or, in case of gram-negative bacteria, located in the cytoplasmic membrane (the inner membrane) [24]. Therefore, the compound must penetrate the outer and/or cytoplasmic membrane in order to exert its antimicrobial effect [24]. Bacteria have developed mechanisms to prevent the antibiotic from reaching its intracellular or periplasmic target by decreasing the uptake of the antimicrobial molecule. This mechanism is particularly important in gram-negative bacteria, limiting the influx of substances from the external milieu. In fact, the outer membrane acts as the first-line of defense against the penetration of multiple toxic compounds, including several antimicrobial agents. Hydrophilic molecules such as β-lactams, tetracyclines and some fluoroquinolones are particularly affected by changes in permeability of the outer membrane since they often use water-filled diffusion channels known as porins to cross this barrier [24]. The prime example of the efficiency of this natural barrier is the fact that vancomycin, a glycopeptide antibiotic, is not active against gram-negative organisms due to the lack of penetration through the outer membrane [24].

Efflux pumps

The main resistance mechanisms is efflux pumps [25].Efflux pumps decrease cellular drug accumulation because compounds are pumped out of the inner membrane to the periplasmic space or directly to the external medium [26]. Some efflux pumps are capable of extruding many compounds, including detergents and different antimicrobial classes [27]. In this context, in gram-negative bacteria, the resistance nodulation division (rnd) family forms a protein tripartite complex with the inner membrane, periplasmic space and outer membrane, forming an efficient channel to extrude compounds [26,28]. In contrast, in gram-positive bacteria, the main multidrug efflux pumps belong to the multidrug and toxic compound extrusion (mate) family [28].

Changes in Target Sites

A common strategy for bacteria to develop antimicrobial resistance is to avoid the action of the antibiotic by interfering

with their target site [21].To achieve this, bacteria have evolved different tactics, including protection of the target (avoiding the antibiotic to reach its binding site) and modifications of the target site that result in decreased affinity for the antibiotic molecule [21].

Target Protection

Introducing modifications to the target site is one of the most common mechanisms of antibiotic resistance in bacterial pathogens affecting almost all families of antimicrobial compounds [29]. These target changes may consist of

   i)   Point mutations in the genes encoding the target site,

   ii)   Enzymatic alterations of the binding site (e.g. addition of methyl groups), and/or

   iii)   Replacement or bypass of the original target. As mentioned, regardless of the type of change, the final effect is always the same, a decrease in the affinity of the antibiotic for the target site [29].

Resistance due to Global Cell Adaptations

Through years of evolution, bacteria have developed sophisticated mechanisms to cope with environmental stressors and pressures in order to survive the most hostile environments, including the human body [21]. Bacteria need to compete for nutrients and avoid the attack of molecules produced by other rival organisms in order to gain the "upper hand". Inside a particular host, bacterial organisms are constantly attacked by the host's immune system and in order establish themselves in particular biological niches, it is crucial that they adapt and cope with these stressful situations [21]. Thus, bacterial pathogens have devised very complex mechanisms to avoid the disruption of pivotal cellular process such as cell wall synthesis and membrane homeostasis. Development of resistance to daptomycin (DAP) and vancomycin (low-level in S. aureus) are the most clinically relevant examples of resistance phenotypes that are the result of a global cell adaptive response to the antibacterial attack [21].

Risk Factor For Antibiotics Resistance

Antibiotics are used in food animals therapeutically to treat disease and sub-therapeutically to increase production performance, to increase efficiency in the use of feed for growth or output, and to modify the nutrient composition of an animal product relies on many methods of disease prevention and treatment [30]. The therapeutic treatment of individual sick animals with antibiotic drugs is often essential. It relieves suffering and returns them to economic production. But the non-therapeutic uses enabled the spread of infections on factory farms to be controlled to an extent that had not been possible before, and also unnaturally stimulated growth and productivity [30].

Sub-Therapeutic Doses Antibiotics

The risk of resistance increases if antibiotics are used at too low a dosage (Sub-therapeutic doses) of antibiotics administered over long periods of time to a large group of animals promote natural selection for drug-resistant bacterial strains [31]. This natural selection occurs when an antibiotic used to treat an infection kills off the bacteria most susceptible to that antibiotic, leaving behind the most resistant bacteria to multiply and spread [31]. Antibiotic resistance will eventually occur because of evolutionary natural selection, but the misuse and overuse of antibiotics is dramatically escalating the process. When antibiotics are used incorrectly in human or animal medicine for too short a time, or too small a dose, at inadequate strengths, or for the wrong disease-bacteria are not killed and can pass on survival traits to even more bacteria. This results in stronger infections, increased illness and even death [31].

Excessive Use of Antibiotics

Increasing resistance also comes from the excessive use of antibiotics, including prolonged treatments of insufficient strength to kill all the bacteria, which occurs commonly on industrial animal farms [32]. Antibiotics are used in cattle, poultry, swine and other food animals not only for disease treatment in individuals, but also to stave off disease in entire herds or flocks living in crowded, unsanitary conditions, as well as for growth promotion and improving "feed efficiency" (i.e., the amount of feed it takes to produce a pound of animal). In fact, up to 70 percent of all antibiotics produced in the U.S. are given to food animals, not people [32].

According to the World Health Organization, "widespread use of antimicrobials for disease control and growth promotion in animals has been paralleled by an increase in resistance in those bacteria (such as Salmonella and Campylobacter) that can spread from animals, often through food, to cause infections in humans (WHO, 2002).Staphylococcus aureusresistance to penicillin and ampicillin was higher on farms that did not sending milk samples for microbiological culture and susceptibility tests [33]. The practice of dry cow treatment was identified as a risk factor for S. aureus resistance to enrofloxacin [33].

Antibiotic Residues

The use of veterinary drugs in food-producing animals has the potential to generate residues in animal derived products (meat, milk, eggs and honey) and poses a health hazard to the consumer [34]. There are many factors influencing the occurrence of residues in animal products such as drug's properties and their pharmacokinetic characteristics, physicochemical or biological processes of animals and their products. The most likely reason for drug residues might be due to improper drug usage and failure to keep the withdrawal period [34]. Concern over antibiotic residues in food of animal origin occurs in two times; one which produces potential threat to direct toxicity in human,

second is whether the low levels of antibiotic exposure would result in alteration of microflora, cause disease and the possible development of resistant strains which cause failure of antibiotic therapy in clinical situations. A withdrawal period is established to safeguard human from exposure of antibiotic added food [35].

The withdrawal time is the time required for the residue of toxicological concern to reach safe concentration as defined by tolerance. It is the interval from the time an animal is removed from medication until permitted time of slaughter [35]. Heavy responsibility is placedon the veterinarian and livestock producer to observe the period for a withdrawal of a drug prior to slaughter to assure that illegal concentration of drug residue in meat, milk and egg do not occur. If use of antibiotics is necessary as in preventionand treatment of animal diseases, a withholding period must be observed until the residues are negligible or no longer detected [35].

Lack of Awareness and Storage Conditions of Antibiotics

In some developing country the knowledge of the farmers concerning antibiotics, withdrawal periods, and dosages was found to be very low [36]. Moreover, the farmers depended more on fellow farmers than veterinarians for antibiotic knowledge, which resulted in the use of the same antibiotics and similar handling practices among farms in close proximity or within the same district [36]. Poor dosing practices, for example, were common when an antibiotic failed to treat an infection. In measuring out the antibiotics, the farmers lacked adequate measuring instruments to mete out correct dosages [36]. Different antibiotics were then tried and also abused till the disease was treated. Because the farmers lacked adequate knowledge in antibiotics, they hardly knew about the similarity of different antibiotic brands with the same active ingredients; thus, different antibiotic brands of the same active ingredient would be used without improvement in the disease condition. Consequently, errors in antibiotic handling and administration were common among the farms [36].

The storage conditions of antibiotics also crucial. The storage environments of the antibiotics were prone to temperature fluctuations which hastens antibiotic decomposition, reducing its concentrations and efficacy [36], thus promoting resistance in exposed intestinal bacteria [37].The dumping sites of antibiotic wastes, used antibiotic containers, and pig faeces inevitably introduce antibiotics, resistance genes, and resistant bacteria into the farm environment, especially, when resistant enteric bacteria have been shown to possess the ability of transferring their resistant genes to soil bacteria [36]. It could also further pollute surface and ground water with antibiotics, resistance genes, and resistant bacteria [38]. Furthermore, the antibiotics could easily be accessed and abused in these storages sites, as drugs intended for use in farm animals may be used in humans voluntarily or involuntarily [36].

Antibiotic Resistance can be Transmitted From Animals to People

There are multiple sources of resistant micro-organisms, both commensal and pathogenic [30]. Animals and their faeces, food of animal origin that may have been contaminated during processing, fruits or vegetables that may come from a contaminated environment, contaminated water and humans are common sources [30].

Handling pigs and poultry and working in a farm environment puts people at risk of picking up resistant bacteria from the animals' bodies or their faeces. Studies in the Netherlands in 2001-2002 showed the same genetic patterns of resistance in E. coli samples from turkeys and broiler chickens and their farmers and slaughterers. Consumption of food contaminated with resistant bacteria (for example, the potentially food-poisoning Salmonella, Campylobacter and E coli) Contamination of meat generally results from faecal material getting onto the carcass during the slaughter and evisceration process (when the animals' guts are removed). Infected meat can also contaminate other foods in domestic or restaurant/catering kitchens.

Controls of Antibiotics Resistance

There are a number of possible measures against antimicrobial resistance including improvement of hygiene, infection control to prevent spread of resistant bacteria, development of new antimicrobials against which bacteria are not resistant, improved conservation efforts to maintain the effectiveness of new antimicrobials and of existing drugs. prudent use of antimicrobials, improve sanitation and prevent the spread of infection, promote new, rapid diagnostics to reduce unnecessary use of antimicrobials and promote development and use of vaccines and alternatives are key important to control antibiotics resistance [39].

Responsible and Prudent use of Antimicrobials

The antibiotic usage in food animals is indeed becoming a global issue associated with food safety and public health. All countries in the world should use the antibiotics in food animals more prudently and rationally. Prudent use of antimicrobials is an integral part of good veterinary practices. It is an attitude to maximise therapeutic efficacy and minimise selection of resistant micro-organisms [39]. Prudent use of antimicrobials, which is also referred to as "judicious use" or "antimicrobial stewardship", is the optimal selection of drug, dose and duration of antimicrobial treatment, along with reduction of the inappropriate and excessive use as a means of slowing the emergence of antimicrobial resistance [40].

Prudent use of antimicrobials should lead to more rational and targeted use, thereby maximising the therapeutic effect and minimizing the development of AMR [39]. Taking into account cross- and co-resistance, which mean that any exposure to antimicrobials increases the occurrence of AMR, the final

outcome of prudent use should be an overall reduction in the use of antimicrobials, predominantly by limiting their use only to situations where they are necessary [39]. In these situations antimicrobials should be used as targeted treatment and according to best practices, i.e. based on clinical diagnosis and, whenever possible, on the results of microbiological susceptibility tests, and using an antimicrobial agent of as narrow-spectrum as possible [39].

Improve Sanitation and Prevent the Spread of Infection

To reduce our unnecessary use of antibiotics and limit the impact of drug resistant infections, one of the most fundamental steps that can be taken is to break the chain of transmission of infections. By preventing infections from occurring, we reduce the need for treatment and limit the opportunities for drug resistant strains to develop. This principle applies both to human and animal health [41].

Promote New, Rapid Diagnostics to Reduce Unnecessary Use of Antimicrobials

Today, antibiotics are rarely prescribed based on a definitive diagnosis. Diagnostic tests can show whether or not an antibiotic is actually needed, and which one [39]. Having rapid, low-cost, and readily available diagnostics is an essential part of the solution to this urgent problem. 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 [39]. In the future rapid diagnostics should be able to test for resistance allowing doctors to give patients the most appropriate available medicine for them [39]. This will not only improve direct outcomes, but it can also stop transmission rates by shortening the time that people are infectious for, and improving infection control and will allow us to protect our most valuable drugs by only using them when no other drugs will work. 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 drug [39].

Promote Development and Use of Vaccines And Alternatives

Tackling antimicrobial resistance requires a wide range of approaches and developing alternatives to antibiotics, in humans and animals, is critical to the fight. Vaccines have a vital role to play in combating drug resistance, by preventing infections in the first place [39].

Improve Awareness and Understanding of Antimicrobial Resistance

Increase national awareness on AMR through public communication programmes and engaging mass media to reinforce key messages. Ensure engagement with whole of society also very crucial.

Promote and support establishment of multisectoral ("One Health") coalitions to address AMR at local or national level, and participate in such coalitions at regional and global levels. Addressing the rising threat of AMR requires a holistic and multisectoral (One Health) approach because antimicrobials used to treat various infectious diseases in animals may be the same or be similar to those used in humans. Resistant bacteria arising either in animals, humans, or the environment may spread from one to the other, and from one country to another. While access to effective antimicrobials is a prerequisite for productive and sustainable agriculture, in particular in relation to animal husbandry, antibiotics have to be used with more responsibility.

Economic Impacts of Antibiotics Resistance

The consequences of AMR include the failure to successfully treat infections, leading to more severe or prolonged illness, death, production losses and negative consequences for livelihoods and food security. The indirect impacts of AMR extend beyond health risks or reduced productivity, and include higher costs for treatment and healthcare, and drain national and global economies (conference. The health consequences and economic costs of AMR are estimated at 10 million annual human fatalities and a 2 to 3.5 percent decrease in global Gross Domestic Product (GDP), or 100 trillion USD by 2050. Although real consequences of AMR remain unpredictable Because of higher disease incidence, these falls will affect low income countries more severely, with a predicted rise of 6.2 to 18.7 million in the number of extremely poor people by 2030 [7].

Impact On the Owner of the Animal

Antibiotic resistance can also have an economic impact for the owner of the animal. If treatment 'at any cost' is chosen, this impact can be considerable. For example, [7] describe treatment of a dog with MRSP bacteraemia and discospondylitis with linezolid. The dog was treated for 23 weeks, and, using the dose used in the case report and prices of Swedish pharmacies, the cost for the antibiotic amounts to 176,000 Swedish crowns (around US$25,600). Clearly, this cost would be prohibitive for most owners. According to information from Pharmacy checker online, prices in the US are much lower, but the cost for the drug would still amount to US$1,500–4,800 [40-42]. Cost for additional visits, lab work, and other follow-up was presumably also higher than in comparable cases with bacteria that are susceptible to first-choice antibiotics [43]. In surgical site infections in companion animals and horses, there is also a possibility that the original problem does not resolve [43]. If the infection directly leads to the death of the animal, or if euthanasia is chosen, there is a cost for the loss of life of the animal [43]. This aspect is particularly relevant in, for example,

service dogs where a lot of money has been invested in training, in valuable breeding animals, and in some of the animals used for sports. In the case of breeding animals, the broader effects of loss of potentially valuable genetic material must also be considered [43].

Impacts Related to Disease Outbreaks

Hospitals and clinics affected by outbreaks of multi-resistant bacteria can also be impacted economically in several ways. The costs following one outbreak of MRSA at an equine hospital in Sweden, affecting eight horses, was estimated to 1.2 million Swedish crowns (approximately US$170,000) [43]. The financial impact of a more protracted outbreak of a multi-resistant Salmonella Newport at a large animal hospital was estimated to US$4.12 million [44]. Costs included in the estimate were loss of revenue due to closure, decreased case load, decontamination, reconstruction, and coverage of patient bills. In this outbreak, 61 animals were infected (54 horses), and the case fatality rate was 36%. Thus, there was also a substantial loss for the owners of the animals. Following the outbreak, a modified and strengthened infection control programme was implemented [43]. Costs that were not included in the estimates discussed above and that should apply to all premises are investments in continuously improved infection control and prevention and increased laboratory diagnostics. Finally, the potential loss of client confidence for premises experiencing outbreaks is difficult to quantify but probably important [43].

For breeding farms and racing stables, costs similar to those of an animal hospital may apply if an infection that is difficult to treat is introduced and spreads [43]. In addition, veterinary costs will probably be higher and there will be a cost for loss of foals or horses not racing as planned, for example. Further, bacteria such as MRSA spread between animals and humans, and people who work with animals are at higher risk of being MRSA-positive than people not working with animals [45]. This means that MRSA carriage is an occupational hazard for people working in animal clinics, hospitals, stud farms, or racing stables, and employers are at risk of being sued if personnel have been infected at work [43].

Negative Health Impacts

There are some evidence suggests that agricultural use of antibiotics can have important negative health impacts in poor countries. In developed countries, industrial agriculture is considered to be the most important reservoir for antimicrobial resistant Salmonella and Campylobacter; an increasingly important reservoir for MRSA and an important but not quantified reservoir for E.coli and enterococcal infections [46]. Human illness from pathogens acquired from direct or indirect contact with animals and their waste or through consumption of animal products [47]. In addition human illness from other pathogens that have acquired copies of a resistance gene from antibiotic resistant bacteria acquired from animals or animal products [47]. Resistance has developed to virtually all anti-infectious drugs used in agriculture. But while the impacts of resistance to trypanocidal and anti-parasitic veterinary drugs in developing countries are well documented, there is less information on the impact of antibiotics resistance infections on animal health [47].

Negative Impact on the Trade

Food products with higher than acceptable antibiotic residues may be cause them to be rejected [48]. Currently this mainly applies to food exported from developing countries, especially aquaculture products (as regulations governing residues are rarely enforced in domestic markets) [48]. For example, antibiotic residues accounted for 28% of EU rejections and 20% of US rejections of aquaculture with Vietnam, China, Thailand, Bangladesh, and Indonesia most affected [48]. Since antibiotics resistance is on factor that cause antibiotics resistance, this rejection of animal product is applied.

Status of Antibiotics Resistance in Ethiopia

Infectious diseases of bacterial origin are a major cause of morbidity and mortality in developing countries such as Ethiopia. To minimise such burdens, proper use of antibiotics has played a vital role and saved countless lives. However, use of antimicrobials as therapeutic agents is compromised by the potential development of drug-resistant micro-organisms [49]. Currently, antimicrobial drug resistance has become a public health concern both in developing and developed countries [49]. Antimicrobial drug resistance is dramatically accelerated when antimicrobials are misused. This is critical, especially in developing countries where they are not only misused but are often underused due to financial constraints. Although large-scale studies on antimicrobial resistance in Ethiopia have not yet been conducted, the available reports indicate a trend towards increasing resistance rates among pathogens such as Escherichia coli, Shigella spp, Salmonella spp. and Staphylococcus aureus to commonly prescribed antibiotics, including ampicillin, amoxicillin, penicillin, tetracycline and trimethoprim/sulfamethoxazole [49].

In Ethiopia the control of drugs from the government authorities and information on the actual rational drug use pertaining to veterinary drug use is very limited. In addition, misuses of drugs are common among the various sectors including veterinary and public health [50]. In addition there is lack of awareness and preparedness among the controlling authorities and producers in dealing with the risk of indiscriminate use of antibiotics to the livestock and to the consumers [50]. Food animals slaughtered for domestic and export purposes in the country are not screened for the presence of residues in any of the slaughterhouses in the country [50]. No formal control mechanisms exist to protect the consumers against the consumption of meat and milk products containing harmful drug residues in the country [51].

A cross-sectional study was conducted from October 2006 to May 2007 to estimate the proportion of tetracyclines (oxytetracycline, tetracycline and doxycycline) levels in beef; the study focused on the Addis Ababa, DebreZeit, and Nazareth slaughterhouses. Out of the total 384 samples analyzed for tetracycline residues, 71.3% had detectable oxytetracycline levels. Among the meat samples collected from the Addis Ababa, DebreZeit, and Nazareth slaughterhouses, 93.8%, 37.5%, and 82.1% tested positive for oxytetracycline [50]. The mean levels of oxytetracycline in muscle from the three slaughterhouses were as follows: Addis Ababa, 108.34μg/kg; Nazareth, 64.85μg/kg; and DebreZeit, 15.916μg/kg. Regarding kidney samples, oxytetracycline levels were found to be 99.02μg/ kg in Addis Ababa, 109.35μg/kg in Nazareth, and 112.53μg/kg in DebreZeit. About 48% of the edible tissues had oxytetracycline levels above the recommended maximum limits [50-61].

Conclusion

Generally the development and spread of antibiotics resistance is commonly due to overuse, misuse, and indiscriminate use of antibiotics by doctors, nurses and pharmacists, non-compliance and self-medication by patients and use in animal Husbandry and agriculture. It results in economic lose and health problems. Veterinary Services including veterinarians and veterinary paraprofessionals have a key part to play in the fight against antimicrobial resistance, through their role in regulating and supervising the use of antimicrobials, offering professional advice to farmers and animal owners and collaborating with the human health sector [51-61].

Based on the above conclusion the following recommendations are forwarded:

a) To continue to progress in disease control management and in improving animal welfare is very important rather than use of antibiotics.

b) Veterinarians need to encourage and achieve a sustainable change in behaviour towards a responsible and prudent antimicrobial use.

c) Professionals should recognize the fundamental threat of antimicrobial resistance and has been working with animal healthcare providers to change the nature of antibiotic treatment.

d) Improvement of awareness and understanding of antimicrobial resistance through effective communication, education and training should be performed.

References

1. Hao Haihong, Guyue Cheng, ZahidIqbal, Xiaohui, Xiaohui Ai, Hafiz I Hussain Ai, et al. (2014) Benefits and risks of antimicrobial use in food-producing animals. Frontiers in microbiology 5: 288.

2. Levy SB, Marshall B (2004) Antibacterial resistance worldwide: causes, challenges and responses. Nat Med 10(12): 122-129.

3. Sojib Bin Zaman, Muhammed Awlad Hussain, Rachel Nye, Varshil Mehta, Kazi TaibMamun, et al. 2017. A Review on Antibiotic Resistance: Alarm Bells are Ringing. Cureus 9(6): 1403.

4. Aminov RI (2010) A brief history of the antibiotic era: lessons learned and challenges for the future. Front Microbiol 1: 134.

5. Davies J, Davies D, Microbiol (2010) Origins and evolution of antibiotic resistanc. Mol Biol Rev 74(3): 417-433.

6. Chopra R, Alderborn G, Podczeck F, Newton JM, (2002) The influence of pellet shape and surface properties on the drug release from uncoated and coated pellets. Int J Pharm 239(2): 171-178.

7. Poonsuk K, Tribuddharat C, Chuanchuen R (2014) Simultaneous overexpression of multidrug efflux pumps in Pseudomonas aeruginosa non-cystic fibrosis clinical isolates. Canadian journal of microbiology 60(7): 437-443.

8. Goutard, Bordier, Calba, Erlacher-Vindel, Góchez, et al. (2017) Antimicrobial policy interventions in food animal production in South East Asia. bmj 358: 3544.

9. Center for Disease Dynamics, Economics & Policy (2016) Antibiotic Use and Resistance in Food Animals Current Policy and Recommendations. Washington, DC 20005 USA.

10. Argudín, Maria Angeles, Ariane Deplano, AlaeddineMeghraoui, Magali Dodémont, AmelieHeinrichs, et al. (2017) Review Bacteria from Animals as a Pool of Antimicrobial Resistance Genes Antibiotics 6(2): 12.

11. WHO (2018) Health tropics. Antimicrobial resistance. Geneva

12. Prescott JF (2008) Antimicrobial use in food and companion animals. AnimHealth Res Rev 9(2): 127-133.

13. Courvalin P (2008) Predictable and unpredictable evolution of antibiotic resistance. J InternMed 264(1): 4-16.

14. Doyle MP, Busta F, Cords BR, Davidson PM, Hawke J, et al. (2006) Antimicrobial resistance: implications for the food system: an expert report, funded by the IFT foundation. Comprehensive Reviews in Food Science and Food Safety 5(3): 71-137.

15. Boerlin P, White DG (2013) Antimicrobial resistance and its epidemiology. Antimicrobial Therapy in Veterinary Medicine (5th eds), pp.21-40.

16. Madigan MT, Martinko JM, Stahl DA, Clark DP (2012) Cell structure and function in Bacteria and Archaea. Brock biology of microorganisms, p. 49.

17. Jacoby GA (2005) Mechanisms of resistance to quinolones. ClinicalInfectious Diseases 15(41): 120-126.

18. Bergstrom CT, Feldgarden M (2007) The Ecology and Evolution of Antibiotic-Resistant Bacteria. Evolution in Healthand Disease. (2nd edn), p. 126.

19. Wall BA, Mateus A, Marshall L, Pfeiffer DU, Lubroth J, et al. (2016) Drivers, dynamics and epidemiology of antimicrobial resistance in animal production. Food and Agriculture Organization of the United Nations.

20. Demple B, Amabile-Cuevas CF (2003) 'Multiple resistance mediated by individual genetic loci. Multiple drug resistant bacteria. Horizon Scientific Press, Wymondham, UK, pp. 61-80.

21. Munita JM, Arias CA (2016) Mechanisms of antibiotic resistance. Microbiology spectrum, 4(2).

22. Wilson DN (2014) Ribosome-targeting antibiotics and mechanisms of bacterial resistance. Nature Reviews Microbiology 12(1): 35.

23. D'Costa VM, King CE, Kalan L, Morar M, Sung WW, et al. (2011) Antibiotic resistance is ancient. Nature 477(7365): 457-461.

24. Pagès JM, James CE, Winterhalter M (2008) The porin and the permeating antibiotic: a selective diffusion barrier in Gram-negative bacteria. Nature Reviews Microbiology 6(12): 893.

25. Barie PS (2012) Multidrug-resistant organisms and antibiotic management. Surgical Clinics, 92(2): 345-391.

26. Horiyama T, Yamaguchi A, Nishino, K Tol (2010) Dependency of multidrug efflux systems in Salmonella entericaserovarTyphimurium. Journal of Antimicrobial Chemotherapy 65(7): 1372-1376.

27. Da Silva KC, Knöbl T, Moreno AM (2013) Antimicrobial resistance in veterinary medicine. Braz. j. vet.res. anim. sci 50(3): 71-183.

28. Alvarez-Ortega C, Olivares J, Martínez JL (2013) RND multidrug efflux pumps: what are they good for?.Frontiers in microbiology 4: 7.

29. Floss HG, Yu TW (2005) Rifamycin mode of action, resistance, and biosynthesis. Chemical reviews 105(2): 621-632.

30. Marshall BM, Levy SB (2011) Food animals and antimicrobials: impacts on human health. Clinical microbiology reviews 24(4):718-733.

31. Lessing A (2010) Killing Us Softly: How Sub-Therapic Dosing of Livestock Causes Drug-Resistant Bacteria inHumans. Boston College Environmental Affairs Law Review 37; 2.

32. Mellon, Margaret, Charles Benbrook, Karen Lutz Benbrook (2001) Hogging It! Estimates of Antimicrobial Abuse inLivestock. Cambridge, MA: Union of Concerned Scientists.

33. Beuron DC, Cortinhas CS, Botaro BG, Macedo SN, Gonçalves JL (2014) Fatores de risco associados com a resistência antimicrobiana de Staphylococcus aureus isolados da mastite bovina. Pesquisa Veterinária Brasileira 34(10): 947-952.

34. Takele Beyene (2016) Veterinary Drug Residues in Food-animal Products: Its Risk Factors and Potential Effects on Public Health. J Veterinar Sci Technol 7: 285.

35. Nisha AR (2008) Antibiotic Residues - A Global Health Hazard. Veterinary World 1(12): 375-377.

36. Osei Sekyere John (2014) Antibiotic types and handling practices in disease management among pig farms in Ashanti Region, Ghana." Journal of veterinary medicine.

37. R Laxminarayan, A Duse, C Wattal, Anita KM Zaidi, Heiman F L Wertheim, et al., (2013) "Antibiotic resistance the need for global solutions," The Lancet Infectious Diseases 13(12): 1057-1098.

38. Sanford, RI Mackie, S Koike, Krapac IG, Lin YF, et al. (2009) "Fate and transport of antibiotic residues and antibiotic resistance genes following land application of manure waste,". Journal of Environmental Quality 38(3) 1086-1108.

39. Official Journal of the European Union, 2015. COMMISSION NOTICE. Guidelines for the prudent use of antimicrobials in veterinary medicine.

40. Weese JS, Dick H, Willey BM, McGeer A, Kreiswirth BN, et al. (2006) Suspected transmission of methicillin-resistant Staphylococcus aureus between domestic pets and humans in veterinary clinics and in the household. Veterinary microbiology 115(3): 148-155.

41. Weinstein RA (2001) Controlling antimicrobial resistance in hospitals: infection control and use of antibiotics. Emerging infectious diseases 7(2): 188.

42. Foster JD, Lauren A Trepanier, Jennifer A Ginn (2014) Use of linezolid to treat MRSP bacteremia and discospondylitis in a dog. Journal of the American Animal Hospital Association 50(1): 53-58.

43. Bengtsson B, Greko, Christina Greko (2014) Antibiotic resistance consequences for animal health, welfare, and food production. Upsala journal of medical sciences 119(2): 96-102.

44. Dallap Schaer BL, Aceto, H, Rankin SC (2010) Outbreak of salmonellosis caused by Salmonella entericaserovar Newport MDR-AmpC in a large animal veterinary teaching hospital. Journal of veterinary internal medicine 24(5): 1138-1146.

45. Catry, Van Duijkeren, Pomba, Greko, Moreno, et al. (2010) Reflection paper on MRSA in food-producing and companion animals: epidemiology and control options for human and animal health. Epidemiology & Infection 138(5): 626-644.

46. WHO (2011) Tackling antibiotic resistance from a food safety perspective in Europe. WHO, Geneva.

47. Molento, Fernanda SF, Deborah Araujo, Fernando de AB, Ana Carolina, et al. (2011) Challenges of nematode control in ruminants: focus on Latin America. Vet Parasitol 180(2): 126-320.

48. UNIDO (2011) Meeting Standards, Winning Markets. Trade Standards Compliance 2010 Vienna: United Nations Industrial Development Organization.

49. Moges F, Endris M, Mulu A, Tessema B, Belyhun, et al. (2014) The growing challenges of antibacterial drug resistance in Ethiopia. Journal of global antimicrobial resistance 2(3): 148-154.

50. Addis M (2015) A Review on Antibiotic Resistant and Implication on Food Chain. Food Science and Quality Management 42: 9-11.

51. Addisalem, H, Bayleyegn M (2012) Tetracycline Residue Levels in Slaughtered Beef Cattle from ThreeSlaughterhouses in Central Ethiopia. Global Veterinaria 8(6): 546- 554.

52. Antibiotics in animal farming public health and animal welfare.

53. Antimicrobial resistance a global epidemic.

54. Antimicrobial Resistance Prevention & Containment.

55. Centres for Disease Control and Prevention (US) (2013) Antibiotic resistance threats in the United States, 2013. Centres for Disease Control and Prevention, US Department of Health and Human Services.

56. Food and Agriculture Organization Regional Office for Asia and the Pacific (2014) Animal Production and Health Commission for Asia and the Pacific. Review of the literature on antimicrobial resistance in zoonotic bacteria from livestock in East, South and Southeast Asia.

57. OIE (2016) Global Conference on One Health. Prudent Use of Antimicrobials in Veterinary Medicine. Paris, France.

58. OIE (2018) World organization for animal health. Risks associated with the use of antimicrobials in animals worldwide. Paris, France

59. United Nations News Centre website. Meeting at the United Nations today, world leaders signalled an unprecedented level of attention to curb the spread of infections that are resistant to antimicrobial medicines.

60. WHO (2002) Impacts of antimicrobial growth promoter termination in Denmark. Department of Communicable Diseases, World Health

Journal of Pharmacology & Clinical Research