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Review on Antimicrobial Usage in Food Animals: Challenges in Ethiopia and its Future Perspectives

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Abstract: Antimicrobials are used in livestock production to maintain health and productivity. Antimicrobial agents are used throughout the world, across a diverse array of extensive and intensive livestock production systems, to protect the health and welfare of livestock and to improve their performance. Frequent and unregulated use of antimicrobials in livestock requires public health attention. Antimicrobial drug residues in food animals are one of the major problems for food contamination and have public health significance. 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. In addition there is lack of awareness and preparedness among the controlling authorities and producers in dealing with the risk of indiscriminate use of antimicfobials to the livestock and to the consumers. 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. No formal control mechanisms exist to protect the consumers against the consumption of meat and milk products containing harmful drug residues in the country. Demand for animal protein for human consumption is rising globally at an unprecedented rate. Modern animal production practices are associated with regular use of antimicrobials, potentially increasing selection pressure on bacteria to become resistant. Despite the significant potential usage of antimicrobials in food animals, there has been no quantitative measurement of global antimicrobial consumption by livestock. It is upon this common ground that the human medical and veterinary medical communities call for the proper and prudent use of antimicrobials, and mandate the proper training of human and animal health professionals regarding the judicious, proper and non-wasteful use of Antimicrobials. Prudent use of antimicrobials in the food animals is important the future perspective.
Keywords: Antimicrobial usage, challenges, Ehiopia, Food animals, future perspective.

INTRODUCTION

Antimicrobial is any substance of natural, semisynthetic or synthetic origin that kills or inhibits the growth of microorganisms while hopefully causing minimal damage to the host and includes agents active against bacteria, protozoa, viruses and fungi. Antimicrobials are used in livestock production to maintain health and productivity. Antimicrobial agents are used throughout the world, across a diverse array of extensive and intensive livestock production systems, to protect the health and welfare of livestock and to improve their performance. Frequent and unregulated use of antimicrobials (AM) in livestock requires public health attention. These practices contribute to the spread of drug resistant pathogens in both livestock and humans, posing a significant public health threat [2].

Use of antimicrobials in the livestock production industry for therapeutic, preventative, and growth promotion purposes across the world is widespread. Weak or non-existent regulatory frameworks governing antimicrobial use, sub-optimal enforcement and compliance with existing guidelines, low levels of AMR awareness, and inadequate commitment to responsible antimicrobial stewardship are driving development of AMR [2].

Many bacterial diseases of livestock cause devastating losses of animal life and productivity. As a result, their keepers can lose their livelihoods and see a dramatic reduction in income, so there is often a great sense of urgency to treat affected animals early. However, there are a large number of bacterial pathogens that cause disease and it is frequently difficult to reach a conclusive diagnosis prior to instituting treatment. There are many ways in which existing uses of antimicrobial agents can be improved, amongst the most important are increased utilisation of veterinary professional services, the introduction of enhanced infection control measures, improved point-of-care diagnostic tests, and the application of physiologically based population pharmacokinetic–pharmacodynamic modeling[3].

Demand for animal protein for human consumption is rising globally at an unprecedented rate. Modern animal production practices are associated with regular use of antimicrobials, potentially increasing selection pressure on bacteria to become resistant. Despite the significant potential usage of antimicrobials in food animals , there has been no quantitative measurement of global antimicrobial consumption by livestock [4]. It is upon this common ground that the human medical and veterinary medical communities call for the proper and prudent use of antimicrobials, and mandate the proper training of human and animal health professionals regarding the judicious, proper and non-wasteful use of all antibiotics. Therefore the objectives of this seminar paper were:

General objective

- To Review and give background information on antimicrobial usage in food animals and its challenges

Specific objective

- To offer therapeutic and non-therapeutic antimicrobial usage in food animals
- To raise Challenges of using antimicrobials in food animals
- To recommend appropriate or prudent usage of antimicrobial in food animals

Antimicrobial usages in food animals

The use of antimicrobials in animals closely parallels their discovery and usage in humans. Sulfonamide was the first antimicrobial to be introduced to food animal medicine in the 1940s. The subsequent discoveries and availabilities of newer antibiotics in the early 50's quickly led to their widespread therapeutic usage for a multitude of infectious diseases in virtually all food animal species. The introduction and use of antimicrobials in animals has brought major benefits to both animals and humans. Some of these benefits are: Reduction of animal pain and suffering; protection of livelihood and animal resources; assurance of production of foods of animal origin; prevention or minimizing shedding of zoonotic bacteria into the environment and the food chain; containment of potentially large-scale epidemics that could result in severe loss of animal and human lives [5].

Clearly, the advantages generated by the use of antimicrobials for food animals transcends more than just the well-being of the animals, as it has also brought about economic benefits for the food animal producers and a more secured and safer health for the general public. However, there are conflicting opinions regarding the proper role of antimicrobials in the production of poultry and livestock. Many believe that the current scientific evidence sufficiently supports a curtailment of current U.S. antibiotic usage practices because they may pose a serious risk to both animal and human health through ever increasing rates of antimicrobial resistance. Others argue that current U.S. regulatory policies regarding antibiotic usage are appropriate, and that further curtailment in antibiotic usage for food animals would be economically harmful to both consumers and producers, and quite unnecessary given the ill-defined risks of inducing greater rates of antimicrobial resistance. One thing, upon which all can all agree, is that the unnecessary or wasteful use of antimicrobials (especially antibiotic and antihelmintic) should be curtailed when non-antibiotic solutions are readily available or when the use of antibiotics for a particular disease condition are clearly not efficacious [3].

Therapeutic Use in Food Animals

Therapeutic use of antibiotics refers to their use to treat clinically ill animals. Although the importance of good management and preventive medicine should not be underestimated, there are many disease conditions in animals that can only be addressed by antimicrobial therapy. Therapeutic use of antibiotics in animals is probably a little more complicated than it is for human medicine, given the variations between species and the reasons for which animals are owned and are being treated. Ideally, antimicrobial susceptibility testing is done to determine the available options for therapy. It is important to note, however, that bacterial susceptibility is not the only consideration when selecting an antibiotic from a range of options. Aside from the susceptibility and species of the invading pathogen, factors to consider in the appropriate selection of antimicrobial therapies should include the drug's attributes (such as pharmacodynamics, pharmacokinetics, toxicity, tissue distribution), the host characteristics (such as age, species, immune status), the accountability to the public and other issues such as cost effectiveness. Each of these issues is important in making sound decision regarding the advisability of each antimicrobial therapy [6].

Non therapeutic use in food animals

The continuously increasing world demand for animal protein has led to increasingly efficient intensive farming systems where animals are raised to maximize the amount of utilizable product at the least cost. High stocking densities and rapid animal growth, coupled with the reduction of available agricultural space, can sometimes facilitate the transmission of infectious agents and the susceptibility of the animals to infectious diseases. It has long been established that antimicbrobials (antibiotics) may help improve production and prevent disease; for this reason, food animal producers utilize antibiotics for non-therapeutic purposes. These uses are generally referred to as non-therapeutic applications of antimicrobials; of which there are two main categories: use of antimicrobial (antibiotics) in animals for growth promotion and Use of antimicrobial (antibiotics) in animals for prophylaxis and metaphylaxis [7].

Growth promotion

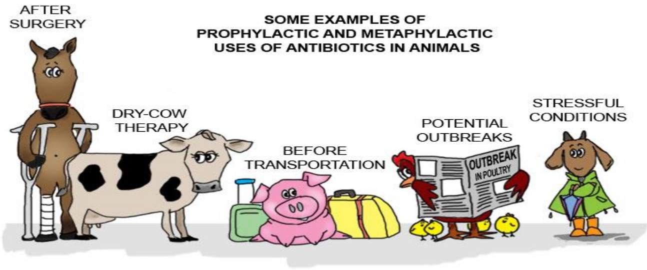
Antimicrobials especially Antibiotics as growth promotant was discovered in the 1940s, when it was observed that chicks improve in growth when fed bacterial shells of Streptomyces aureofaciens from which antibiotics had been extracted. Because the amount of antibiotic that can provide growth enhancement was extremely small, the effect was regarded as largely nutritional by producers and authorities in the food industry [8]. In the years to follow, other countries also allowed the use of antibiotics in animal feeds. Subsequently, however, when the emergence of antibiotic resistance was recognized as an increasing risk, the use of growth promoters became the focus of numerous regulatory interventions, and bans on growth promotants were often enacted on particular classes of antibiotics. To date, different countries have different lists of approved and banned growth promoter antibiotics in their respective livestock industries[9].

Mechanism of action of subtherapeutic levels of antimicrobials to promote growth

Although repeatedly proven in various studies, the mechanism of action for the enhancement of growth of subtherapeutic levels of Antimicrobial (antibiotics) remains unclear [10]. Among the hypotheses tested the mechanism action of growth promoters are the following: Stimulation of intestinal synthesis of vitamins by bacteria, Reduction in total numbers of bacteria in the intestinal tract with a lowering of competition between microorganisms and host animals for nutrients, Inhibition of harmful bacteria which may be mildly pathogenic or toxin-producing, Inhibition of bacterial urease, Improved energy efficiency of the gut, Inhibition of bacterial cholytaurin hydrolase activity, Nutrient sparing, Improved nutrient absorption from morphological changes to small intestinal epithelium, Modification of intestinal enzyme activity, Reduced immune stimulation and Modification of rumen microbial metabolism[11].

Uses of Antimicrobials for Prophylaxis and metaphylaxis

Uses of Antimicrobial in Animals for Prophylactic or Metaphylactic Purposes are indicated in the following figure.



It is not uncommon for veterinarians to give antibiotics to animals that are not currently ill with a particular disease, but are at high risk of acquiring an infection. For example, an animal may be treated with antibiotics after having undergone surgery or injurious trauma (prophylaxis) or herds and flocks may be given antibiotics if they are at risk of suffering an outbreak of infectious disease due to exposure to disease agents or extremely unfavorable host or environmental conditions (metaphylaxis). In companion animal veterinary medicine, antibiotics are commonly used to control secondary bacterial invasions such as during surgical procedures and managing infection-promoting disease conditions such as urolithiasis. In poultry and livestock, mass administration of antibiotics is often practiced when transporting or moving young animals, during dry-cow therapy in dairy cows and in preventing respiratory and intestinal maladies when animals have been subjected to severely stressful conditions. Prophylactic or metaphylactic use of antibiotics can be a substantial aid in the control and prevention of numerous animal diseases in both food and companion animals. However, this use of antibiotics should never be intended to replace the need for good management practices, given that the use of antibiotics will eventually lead to resistance. As was the case with therapeutic uses of antimicrobials, issues to be considered when deciding whether or not to use an antimicrobials include knowledge of the pathogen involved and knowledge of the antimicrobials properties given in the species of animal and its intended use for food or companionship [12].

The challenge of antimicrobial usage in food animals

Worldwide challenges of antimicrobial usage in food animals

Antimicrobials are widely used for disease prevention and growth promotion in food animals. In the United States, antimicrobial use in food animals is estimated to account for ~80% of the nation's annual antimicrobial consumption [13], a significant fraction of which involves antimicrobials that are important in human medicine in the treatment of common infections and also necessary to perform medical procedures such as major surgeries, organ transplantation, and chemotherapy [14].

This widespread use of antimicrobials in livestock contributes to the emergence of antimicrobial-resistant bacteria (ARBs) and has significant public health implications: ARBs of animal origin can be transmitted to humans through the environment and food products and to agricultural workers by direct contact [15]. Although direct causality is difficult to establish because of the ecological nature of antibiotic selection pressure, studies have shown a close association between the prevalence of livestock-associated ARBs in animals and in humans , as well as between the levels of antimicrobial use in animals at a population level, and the prevalence of ARBs in animals and in humans[16]. A recent study from seven European countries (Norway, Sweden, Denmark, Austria, Switzerland, The Netherlands, and Belgium) showed a strong correlation between consumption levels for eight classes of antimicrobials and the prevalence of antimicrobial-resistant commensal *Escherichia coli* in pigs, poultry, and cattle[17]. Several works additionally suggested that repeated exposure to low doses of antimicrobial agents the context in which growth-promoting antimicrobials and prophylactic are administered creates ideal conditions for the emergence and spread of ARBs in animals [18].

In low- and middle-income countries, rising incomes have driven an unprecedented growth in demand for animal protein and, as a result, the global biomass of animals raised for food now exceeds the global biomass of humans. In Asia, daily animal protein intake grew from 7 grams per capita per day to 25 grams per capita per day between 1960 and 2013 while the proportion of the diet coming from rice and wheat progressively decreased, primarily among higher-income adults [19]. To meet this demand, countries such as Brazil, Russia, India, China, and South Africa (BRICS) have shifted toward highly cost-efficient and vertically integrated intensive livestock production systems. Because these production systems necessitate antimicrobials to keep animals healthy and maintain productivity, rising incomes in transitioning countries are effectively driving an increase in antimicrobial consumption and thereby antimicrobial resistance. Meanwhile, multiresistant ARBs have been isolated in food animals in BRICS countries and throughout the developing world where the use of antimicrobials for growth promotion remains largely unregulated [20].

The challenges of the nutritional transition to animal protein-based diets and the rise of antimicrobial resistance are thus closely linked: The use of antimicrobials as growth promoters and therapeutics to support the growing demand for meat is placing ever greater selection pressure for resistant strains of bacteria to evolve. Whereas trends in antibiotic consumption in humans are now being tracked in most high-income and some middle-income countries through databases on antibiotic sales, antimicrobial consumption in livestock has received comparatively little attention. Expert opinion suggests that global consumption of antimicrobials in animals is twice that of humans [21].

Another important Challenges faced by developing countries including Ethiopia regarding surveillance systems in the usage of antimicrobials. A satisfactory and comprehensive survey is needed to understand the epidemiology of antimicrobial usage in both animals and humans. Even though the global action plan by WHO/OIE/FAO to contain antimicrobial resistance requires each nation or country to implement national action plans, developing countries are still to develop a sustainable surveillance system of antimicrobial use and antibiotic resistance [22]. The challenges regarding the surveillance system include: The developing countries have just a few laboratories with the potential to conduct quality-assured microbiology and drug sensitivity testing. strongly affirmed that collection and reporting of data and the strengthening of laboratory capacity are the two related issues in surveillance[23]. Due to the high burden of infectious diseases and low socioeconomic status of these countries, there is a lack of available resources According to Nasir *et al*. the developing countries lack the funds to purchase reagents and consumables essential for testing antibiotic resistance, thus lack necessary plans for the surveillance of antibiotic-resistant bacteria. The cost necessary for the adequate surveillance, together with the small margin profits in the veterinary sector presents a financial drawback to support surveillance in the veterinary and agricultural sector [24].

There is a discrepancy in the selection of isolates. Most of the isolates are from clinical cases that are sick individuals (human or animals). Therefore, the sample of isolates is biased toward a more resistant isolate, owing to the previous antibiotic therapy administered. Also, only a few isolates are involved, since the veterinarian decides on the individual animals to refer to the laboratory. Consequently, the proportion of the isolates is not a representative of the bacteria strains under survey taken from animals [25].

Also, relatively few studies have been conducted on animal-recovered isolates, as well as the criteria for testing isolates differ between countries, likewise, the antibiotics that are tested, Either at the regional, national, and local levels, there exists variation in obtaining data, owing to differences in laboratory protocols, conditions employed for testing, personnel conducting the drug sensitivity assay, antibiotic policies, quality control and assurance of the laboratory, and considerations regarding breakpoints. In reality, there are no well-known breakpoints for the animal, which results in the adoption of breakpoints values from human medicines. Nevertheless, the standard protocols and breakpoints from the Clinical Laboratory Standard Institute (CLSI) have been adopted by most countries, these countries also lack stringent and comprehensive policies and plans to circumvent antibiotic resistance. They lack enforcement of regulations regarding prudent antibiotic use, since many are still faced with the problem of purchasing drugs over the counter or without a prescription, and the presence of counterfeit drugs[26]. Nevertheless, even if some data are collected, they fail to translate the surveillance data into policy, especially in South Africa, At the national level, there is a lack of collaborative measures between the different laboratories regarding surveillance of antibiotic resistance, which might hamper efforts to track emerging resistance and also limit the chances of systematic comparison and evaluation of national activities directed toward the containment of antibiotic resistance[27].

Antimicrobial Drug Residues in Food-animal Products: Its Risk Factors and its challenges on Public Health

Residues, as defined by the European Union (EU) and the Center for Veterinary Medicine, an agency under the Food and Drug Administration (FDA) in the USA are "pharmacologically active substances and their metabolites which remain in foodstuffs obtained from animals to which the VMPs in question has been administered". Under the normal physiological conditions, following administration of a drug to an animal, most drugs are metabolized in order to facilitate elimination, and to a large extent detoxification as well. In general, most of the parent product and its metabolites are excreted in urine and a lesser extent via faeces. However, these substances may also be found in milk and eggs, and in the meat [28].

The use of Antimicrobials in food-producing animals has the potential to generate residues in animal derived products and poses a health hazard to the consumer. 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. The major public health significances of drug residue are development of antimicrobial drug resistance, hypersensitivity reaction, carcinogenicity, mutagenicity, teratogenicity, and disruption of intestinal normal flora. The residual amount ingested is in small amounts and not necessarily toxic. However, there is limited information on the magnitude of veterinary drug residue worldwide. Hence, an extensive work has to be carried out to determine the magnitude of the problem, to prevent the occurrence of veterinary drug residues, and to familiarize all animal health professionals with the knowledge of pharmacokinetics, pharmacodynamics and toxicological effects of veterinary drugs to minimize the potential public health hazards due to drug residues in food of animal origin. Human health is related directly to the environment, and in particular the nature and quality of the food. Quality of food from animal products is widely concerning public health agencies around the world since veterinary drugs have played an important role in the field of animal husbandry and agro-industry, and increasing occurrence of residues, and resistance have become interesting issues [29].

Veterinary drugs or veterinary medicinal products (VMPs) are critically needed to meet the challenges of providing adequate amounts of food for the growing world population as drugs improve the rate of weight gain, improve feed efficiency, or prevent and treat diseases in food producing animals. However, the benefit of improved productivity from the use of VMPs in food producing animals is not obtained without the risk associated with VMPs residues that remain in the tissues of treated animals at the time of slaughter or residues in animal derived products and poses a health hazard to the customer. Antibacterial drugs and hormonal growth promoters are the main VMPs that potentially contaminate foods of animal origin. Hence, veterinary drug or VMPs residue is one of many global issues concerning food contamination [30].

Rationally, there is no product coming from a treated animal should be consumed unless the entire drug administered has been eliminated. This is called zero tolerance, where this concept is in fact equivalent to the idea of total absence of residual amounts. However, because of the improvement of analytical techniques, which meant that the value of zero became smaller and smaller that depicts the limits corresponding to the sensitivities of parts per million, parts per billion and parts per trillion. As a result, by using the high efficacy analytical methods, for instance, using high performance liquid chromatography, it can be concluded that there are nearly always detectable residues, but such residues are at an extremely low concentration and they are not inevitably toxic. There are a number of the risk factors for development of drug residues in food of animal origin which has potential public health significance [31].

Risk Factors for the Development of Residue in Food-producing Animal

Antimicrobial drug residues in veterinary medicine are one of the major problems for food contamination. VMPs and agricultural chemicals used according to label directions should not result in residues at slaughter. However, possible reasons for such residues include: Not following recommended label directions or dosage (extra-label usage); not adhering to recommended withdrawal times; administering too large a volume at a single injection site; use of drug-contaminated equipment, or failure to properly clean equipment used to mix or administer drugs; dosing, measuring, or mixing errors; allowing animals access to spilled chemicals or medicated feeds; animal effects- age, pregnancy, congenital, illness, allergies; chemical interactions between drugs; environmental contamination; and improper use of agricultural chemicals such as pesticides[28].

Antimicrobial drugs residues are sometimes stored in the liver or kidney rather than other tissues. It has been noted that different residue levels can be found in different tissue positions based on site and route of administration. The most likely reason for drug residues may result from human management, such as improper usage, including extra-label or illegal drug applications. However, the most obvious reason for unacceptable residues might be due to failure to keep to the withdrawal period including overdose and long acting drugs. Inadequate good sanitary care during animal or product transportation, including the cross contamination of animal feeding stuffs with inadvertently applied drugs, environmental and animal to animal transfer of drugs may also cause residues. Risk factors responsible for the development of residue are the following [28].

Age of animal: Weaning status and, to a lesser extent, the age of the animal affect drug disposition. For instance, the study conducted on comparisons of the pharmacodynamics of norfloxacin nicotinate between weaning and unweaned calves revealed that the distribution of the drug did not differ between the two groups of calves, but the total body clearance time was increased in weaned calves, possibly due to increased weight from the presence of rumen fluid. Calves fed grain had shorter clearance times (approximately four days) for sulfamethazine than unweaned calves. The elimination half-life of tindazole is shorter in unweaned calves than in adult cows, while the elimination half-life of apramycin is longer in calves than in adult cattle, possibly due to the immaturity of the drug clearance system.

Feeding: Diet can affect the bioavailability of drugs. For instances, study conducted to determine the effects of diet content on the bioavailability of orally administered fenbendazole to cattle and Indian buffalo and fed dry hay either with or without fresh green herbage showed that animals receiving feed containing fresh herbage had lowered bioavailability of the drug. Fenbendazole stays in the rumen and is progressively released with digesta, and the presence of fresh herbage increases gut activity and the flow rate of digesta, which depletes the available stores of fenbendazole in the rumen. In regard to feeds, actual gut contents can also affect drug uptake and pharmacodynamics[32].

Disease status: The disease status of an animal can affect the pharmacokinetics of drugs administered, which can influence the potential for residues. This can occur either when the disease affects the metabolic system (and consequently drug metabolism), or when the presence of infection and/or inflammation causes the drug to accumulate in affected tissues. For example, cattle with acutely inflamed mastitis quarters, apramycin penetrates these areas of the body, and concentrations of the drug have been observed at ten times over the level recorded from cows without mastitis. Ketoprofen levels in milk increase during clinical mastitis where there is an influx of serum components into the udder. In calves with experimentally induced fasciolosis, the elimination half-life of antipyrine was slightly increased, but was slightly decreased for erythromycin and statistically significant decrease for oxytetracycline. The proposed mechanisms for these changes were the changes in liver function by fasciolosis, which changed the processing of drugs through the liver [33].

Pharmacokinetics: The term pharmacokinetics refers to the movement of drug into, through and out of the body: the time course of its absorption, bioavailability, distribution, metabolism, and excretion[28].

Absorption: It is described as the process, which a compound passes from its site of administration into the bloodstream. Absorption is influenced by many factors such as the properties of cell membrane, drug properties and route of administration and physiopathological state of the animal. An indication of the rate of drug absorption is obtained from the peak plasma concentration (Cmax) and time reaching the maximum concentration (Tmax).

Distribution: It is the process whereby a drug is transported to all the tissues and organs. After entering the systemic circulation, in whatever route of administration, drugs are conveyed throughout the body and reach their site of action. There are four major factors responsible for the extent and rate of distribution. These are the physicochemical properties of the drug, the concentration gradient established between the blood and tissue, the ratio of blood flow to tissue mass, and the affinity of the drug for tissue constituents and serum protein binding. Only the fraction free form (unbound) of the drug is capable of exiting the circulation to distribute through the body and exert activity at the site of action. The parameter, which defines the process of distribution, is the volume of distribution [34].

Metabolism (Biotransformation): It is the principal mechanism of elimination for the transformation of drugs or xenobiotics into metabolites of the chemical reaction. Hepatocytes play an extremely important role in the metabolism of drugs and xenobiotic-compounds that are foreign to the body, some of which are toxic. The kidneys are responsible ultimately to dispose of these substances, but for effective elimination, the drug or its metabolites must be made hydrophilic (polar, water-soluble). This is because reabsorption of a substance by the renal tubules is dependent on its hydrophobicity. The more hydrophobic (non-polar, lipid-soluble) substance is, the more likely it will be reabsorbed. Many drugs and metabolites are hydrophobic, and the liver converts them into hydrophilic compounds[35].

Excretion: It is the process by which the parent drug or its metabolites are removed from the body fluids. The kidney is the most important site of drug excretion. There are three renal mechanisms; glomerular filtration, carrier mediated proximal tubular secretion and pH dependent, passive tubular resorption in the distal nephron. Renal insufficiency usually significantly affects drug excretion. The systemic clearance and elimination half-life are important parameters referring to the overall rate of elimination (metabolism and excretion). Although most compounds are excreted primarily by the renal, some drugs are partially or completely excreted through the bile. It has been reported that there is an extensive species variation among animals in their general ability to excrete drugs in the bile; example, chicken are characterized as good biliary excretes, whereas sheep and rabbit are characterized as moderate and poor excretes [35].

Extra-label drug use (ELU)

Extra-label Drug Use (ELU) refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. ELU occurs when a drug only approved for human use is used in animals, when a drug approved for one species of animal is used in another, when a drug is used to treat a condition for which it was not approved, or the use of drugs at levels in excess of recommended dosages. For instances, the use of phenobarbital (a drug only approved for use in humans) to treat epilepsy in dogs and cats; the use of ivermectin in dogs and cats (an antiparasitic only approved for use in cattle); and the use of enrofloxacin solution as a topical ear medication (only approved for use as an injection) are the common ELU in veterinary medicine. There are conditions for ELU in food animals. For example, when considering ELU of an approved human drug in food animals: the veterinarian must have medical rational for the use; the veterinarian may not use an approved human drug if an animal drug approved for use in food-producing animals can be used instead for the particular ELU; and if scientific information on the human food safety aspect of the use of the drug in food-producing animals is not available, the veterinarian must take appropriate measures to assure that the animal and its food products will not enter the human food supply[28].

Improper withdrawal time

The withdrawal time (also known as the depletion or clearance period) is the time for the residue of toxicological concern to reach a safe concentration as defined by the tolerance. Depending on the drug product, dosage form, and route of administration, the withdrawal time may vary from a few hours to several days or weeks. It is the interval necessary between the last administration to the animals of the drug under normal condition of used and the time when treated animal can be slaughtered for the production of safe foodstuffs[28].

The Antimicrobial Usage in Food Animals and its ch allenges in Ethiopia

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. 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. 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. No formal control mechanisms exist to protect the consumers against the consumption of meat and milk products containing harmful drug residues in the country[36].

Infectious diseases of microbial origin are a major cause of morbidity and mortality in Ethiopia. To minimize such burdens, proper use of antimicrobials 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. Currently, antimicrobial drug resistance has become a public health concern both in developing and developed countries. 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. The spread of antimicrobial resistance in developing countries including Ethiopia is associated with complex and interconnected factors, such as excessive and unnecessary prescribing of antimicrobials, increased self-prescribing by the people and poor quality of available antimicrobials. Moreover, the failure to implement infection control practices and the dearth of routine susceptibility testing and surveillance magnify the problems. This may spread the inappropriateness of prescribing, ending up with the spread of antimicrobial resistance[37].

Rational use of drugs is based on the use of right drug, right dosage and right cost which is well reflected in the world health organization. Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, at the lowest cost to them and their community". Now, in the clinical practice of human and veterinary medicine throughout the world large amount of antibiotics are used. Equally, many scientists intensively work on discovery and synthesis of new drugs with broader antimicrobial spectrum, stronger action and more satisfactory safety profile. Most failures during antimicrobial therapy may occur when the pathogenic microorganism is unknown and combination of two or more drugs administered empirically. To avoid these mistakes, clinically confirmed, effective antimicrobial combinations should be used. Globally, more than half of all medicines are prescribed, dispensed or sold improperly, and 50 % of human patients fail to take them correctly. This is more wasteful, expensive and dangerous, both to the health of the individual patient and to the population as a whole that magnifies the problem of misuse of antimicrobial agents. Irrational use of drugs in veterinary medicine as well as the need for control of their use becomes even bigger problem when used on food producing animals. In this case, there is the possibility that minimal quantities of drugs and their metabolites (residues) which remain in edible tissues or in animal products induce certain harmful effects in humans as potential consumers of such food. When drugs are used to improve the productivity of food animals that are intended for human consumption, then there is possibility for producing adverse effects on humans. To prevent this risk, it is necessary to use drugs rationally, i.e., to use them only when they are really indicated, in the right way, at the right time, in the right dose, right route and respecting withdrawal period [29].

Over use of antimicrobials in veterinary practice, for both food producing and companion animals, favors the development of both intrinsic or acquired antimicrobial and anthelmintic resistance. Acquired resistance develops due to widespread and irrational use of drugs while intrinsic resistance is a result of inherent structural or functional characteristics, which allows tolerance of a particular drug or antimicrobial class. Antimicrobial/anthelmintic drug resistance is a growing problem; and indeed developing new drugs may not be the solution for this problem. Some of the common causes that contribute to the development of antimicrobial resistance are unnecessary use of antimicrobial drugs, inappropriate dose, inadequate duration of therapy, use of irrational antimicrobial fixed dose drug combinations [29].

ANIMICROBIALS USAGE IN FOOD ANIMALS I N THE FUTURE PERSPECTIVE

Prudent use of antimicrobials in the future perspective is important. 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 . Although this may be more straightforward for human medicine, the nature by which antimicrobials are utilized in animals and the influences of various stakeholders in the standards by which these are raised, make such practice more complicated for veterinary medicine. The prudent use of antimicrobials in veterinary medicine are principled guidelines created to prevent abusive use of antimicrobials in animals, primarily to curb or mitigate the imminent risk of breeding resistant microorganisms unresponsive to currently available chemotherapy in both animals and humans. Veterinarians are on the forefront of upholding such manner of use having dual roles of protecting animals from pain and suffering, while safeguarding the interest of the public health. Some Points to Consider in Making Antibiotic-Related Decisions to treat or not to treat are: does condition necessitate treatment, Are there other options besides treatment?, Will the potential consequences outweigh the benefit of treatment?, What is the host species involved?, Is it worth treating?, Ill treatment work for the pathogen involved? And any risks to public health when this is done? [38].

Researchers and policymakers have a responsibility to improve prescribing practice and rational drug use in veterinary medicine. The government, private animal health care institutions, individual animal health care providers and animal owners all have a responsibility to promote rational use of medicines. Hence, integrated national databases to support a rational, visible, science-driven decision-making process and policy development for regulatory approval and use of antimicrobials in food animals, which would ensure the effectiveness of these drugs and the safety of foods of animal origin, should be established [29].

Reducing Antimicrobial Use in Food Animals

Due to the increased demand of animal protein in developing countries, intensive farming is instigated, which results in antibiotic residues in animal-derived products, and eventually, antibiotic resistance. The large and expanding use of antimicrobials in livestock, a consequence of growing global demand for animal protein, is of considerable concern in light of the threat of antimicrobial resistance (AMR). Use of antimicrobials in animals has been linked to drug-resistant infections in animals and humans[39]. In September 2016, the United Nations (UN) General Assembly recognized the inappropriate use of antimicrobials in animals as a leading cause of rising AMR. In September 2018, the interagency group established by the UN Secretary General will report on progress in the global response to AMR, including antimicrobial consumption in animals. They provide a baseline to monitor efforts to reduce antimicrobial use and assess how three global policies might curb antimicrobial consumption in food animal production: (i) enforcing global regulations to cap antimicrobial use, (ii) adherence to nutritional guidelines leading to reduced meat consumption, and (iii) imposing a global user fee on veterinary antimicrobial use. Evidence linking AMR between animals and humans is particularly strong for common foodborne pathogens resistant to quinolones, such as Campylobacter spp. and Salmonella spp [40]. AMR is also a threat to the livestock sector and thus to the livelihoods of millions who raise animals for subsistence[41]. The primary driver for the accumulation of harmful resistance genes in the animal reservoir is the large quantity of antimicrobials used in animal production [42]. Antimicrobial use in livestock, which in many countries outweighs human consumption, is primarily associated with the routine use of antimicrobials as growth promoters or their inappropriate use as low-cost substitutes for hygiene measures that could otherwise prevent infections in livestock. In Europe, regulations have been the principal instrument to limit antimicrobial use in animal production. In the United States, consumer preferences have driven companies to reduce antimicrobial use in animals, although the impact on livestock rearing practices is still nascent [43]. Some European countries maintain highly productive livestock sectors while using less than half the current global average amount of antimicrobial per kilogram of animal (50 mg/kg). Therefore, this threshold has been proposed as a potential target for global regulations on veterinary antimicrobial use. However, the impact that such policies would have on the global consumption of antimicrobials has yet to be quantified. A second solution to reduce antimicrobial consumption in animal production may be to promote low-animal-protein diets: China has recently revised downward its nutritional guidelines for meat intake to 40 to 70 g/day [44], which is approximately half the current consumption level in the country. If followed, this measure could have an indirect but substantial impact on the global consumption of veterinary antimicrobials. A third solution to cut antimicrobial use would be to charge a user fee, paid by veterinary drug users, on sales of antimicrobials for nonhuman use[45]. This approach has recently received support from the World Bank on the basis that the associated revenues could be injected into a global fund to stimulate discovery of new antimicrobials and support efforts to preserve existing drugs[46]. Without further analysis, however, it is unclear whether a user fee policy could achieve a meaningful reduction in the global consumption of veterinary antimicrobials, let alone generate sufficient revenues to support improved livestock rearing practices or the development of new drugs, vaccines, and diagnostics [47].

CONCLUSION

Antimicrobial agents are agents used throughout the world, across a diverse array of extensive and intensive livestock production systems, to protect the health and welfare of livestock and to improve their performance. Antimicrobial especially Antibiotic use plays a major role in the emerging public health crisis of antibiotic resistance. Although the majority of antimicrobials use occurs in agricultural settings, relatively little attention has been paid to how antibiotic use in farm animals contributes to the overall problem of antibiotic resistance and public health challenges. The use of Antimicrobial drugs in food producing animals has also the potential to generate residues in animal derived products and poses a health hazard to the public. The most likely reason for drug residues may result from human management, such as improper usage, including extra-label or illegal drug applications. However, the most obvious reason for unacceptable residues might be due to failure to keep to the withdrawal period, including using overdose and long-acting drugs. It is a major public health responsibility of veterinarians to advocate the prudent and judicious use of antimicrobials to preserve their future usefulness in treating both animals and people. Based on the above conclusion the following recommendations were forwarded:

- Rational use of drugs and establishment of valid veterinarian-client-patient relationship
- Proper drug administration and identification of treated animals
- Creating awareness of proper drug use, and usage of animal products in relation to their withdrawal period and
- Prudent use of Antimicrobials in the future perspective.

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Competing interests

The author declares that they have no competing interests

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