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A Review on the Antimicrobial Residues and Their Health Impacts in Ethiopia

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Abstract: 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. Antimicrobial residues are the parent compounds, their metabolites and associated impurities of veterinary drugs in any edible portion of an animal product. It may occur, when administration of drug in extra label fashion and not following of withholding period after treatment. Antimicrobial drug residues in food animals are one of the major problems for food contamination and have public health significance. The application of manure or farm effluents in agricultural land leads to selection of resistant bacteria, development and transmission of antibiotic resistance genes in the microbes. The antibiotic resistance that developed by antibiotic residues in animal originated food in human leads to poor response to treatment during illness. 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. Despite the significant potential usage of antimicrobials in food animals, there has been no quantitative measurement of national 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. In this review, antibiotic residues in the foodstu□s of animal origin and their health impacts will be discussed.

Key words: Antimicrobial · Antimicrobial Residue · Antimicrobial Resistance

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. 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. They are also used in livestock production to maintain health and productivity. Frequent and unregulated use of antimicrobials 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 [1].

Antimicrobial residues are unwanted chemicals which have persistence ability through the food web and potential negative impacts on humans [2, 3]. The antimicrobials/the parent compounds and/or their metabolites are tending to accumulate in tissues to form residues at different concentrations. Although antimicrobial benefit most of its uses, the illegal and frequent use of these drugs has led to the accumulation of hazardous antimicrobial residues in edible animal origin foods destined for human consumption then result in the public health hazard [2, 3].

The antimicrobial residues from milk, meat and egg may persist for longer period after treatment, when administration of antimicrobials in label and extra label fashion and also not following of with holding period after treatment. The minimum with holding period for milk and egg is 7 days and for meat is 28 days after treated with antimicrobials. The extra-label drug use may take the form of increased dose, increased frequency of treatment and use in an unapproved species, by an unapproved route of inoculation or in short, by any means not explicitly described on the drug product label [4].

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The presence of antimicrobial residues in foods of animal origin, combined with failure to comply with the instructions for their use (dosage and waiting period) or poor livestock production practices, can have serious consequences for consumer health [5, 6]. On the other hand Weak or non-existent regulatory frameworks governing antimicrobial use, sub-optimal enforcement and compliance with existing guidelines, low levels of antimicrobial resistance, awareness and inadequate commitment to responsible antimicrobial stewardship are driving development of antimicrobial resistance [1].

Human acquires the risk by ingesting antimicrobial residue in meat, milk, eggs those have residue level higher than maximum residue limits (MRLs) and acceptable daily intake [7, 8]. The immediate effect of antimicrobial residue is allergenicity and toxicity in human through the food chain [3, 7]. In general, the long term harmful effects of drug and chemical residues on health, which may be mutagens, carcinogenic, teratogenic, reduction in reproductive performance, drug allergy and acute toxicity or poisoning in human [9]. The present review forms base on antimicrobial residues in animal products, the detection methods and the risk factors as well their impact on environment and human health.

Use of Antimicrobials in Livestock Production: The use of antimicrobials in animals closely parallels their discovery and usage in humans. 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 [10].

Antimicrobials as Growth Factors: Antimicrobials especially antimicrobials as growth promoting 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 [11]. Growth promoters are antimicrobials which, when administered in low doses in animal feed, have a preventive effect against certain bacterial infections and modify the composition of the intestinal micro-biota and improving feed assimilation. The impact of these protective effects on animal production is to accelerate livestock growth [12].

In the interests of consumer protection, European marketing authorization bodies determined that the animal production benefits of additives in livestock feed failed to justify such use because the risk of the selection of resistant bacteria could have a disastrous impact on public health. Nevertheless, in the United States, a large number of antimicrobials are still authorised for use in low doses as growth factors. In the European Union, only ionophoric antimicrobials (monensin, narasin, salinomycin and lasalocid) are still authorised as coccidiostats and as additives in animal feed [13].

Antimicrobials as Therapeutic Use: Antimicrobials are the main group of veterinary medicinal products used since the 1950s to treat bacterial infectious diseases in both food producing and companion animals. The substances used belong to the same families as those used in human medicine [14]. These medicinal products are administered to prevent and treat infectious diseases that could cause significant morbidity and possible mortality. The most commonly treated disorders are digestive and respiratory diseases [15]. For several types of integrated farm systems where animals (poultry, pigs, calves and fish) are raised in groups indoors, production conditions prompt veterinarians to prescribe these treatments for both preventive and curative purposes.

Ideally, antimicrobial susceptibility testing is done to determine the available options for therapy. It is important to note, 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 and tissue distribution), the host characteristics (such as age, species and immune status) and 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 [15].

Antimicrobials Usage: The medicinal products containing the antimicrobials authorized for veterinary use are those that have passed the marketing authorization process of the competent national or European authority. After an evaluation of the scientific data proving the efficacy of the product and its safety for humans, animals and the environment, the Competent Authority authorizes its importation, distribution and use [16]. According to EU regulations, antimicrobials and veterinary medicinal products require a veterinary prescription. Drug dispensing procedures vary from one Member State to another [14].

In sub-Saharan Africa, there are massive shortcomings in the organization of the veterinary drug market. These include: a lack of specific legislation geared to the recent liberalization of veterinary pharmaceuticals; failure to enforce current regulations; a lack of veterinary drug inspections, marketing authorization procedures and registration; and the existence of parallel channels alongside the official distribution channel for veterinary drugs [16].

In addition to veterinary drugs imported from the West, products manufactured by laboratories in Africa and Asia, especially those in India and Nigeria, are found on the African market. Nigeria supplies Niger, Cameroon and Benin [16]. This makes them high-risk countries for the distribution of hazardous and prohibited veterinary medicinal products. In terms of effectiveness, treatment with such drugs offers no guarantee of a cure for the disorders and deficiencies in question.

Prohibited antimicrobials are substances for which it is not possible to determine the maximum residue level. These are listed in European Commission Regulation 37/2010 [17]. Chloramphenicol is a broad-spectrum antimicrobial against Gram-positive and Gram-negative bacteria. While it is an effective therapeutic for a wide range of animal diseases, historic epidemiological data have shown that its use in humans may be associated with haematological disorders; in particular, aplastic anaemia. During its assessment, it was not possible to determine a maximum residue level based on the available data. The inability to set a threshold value and shortcomings in the marketing authorisation application led to chloramphenicol being classified in 1994 as a prohibited substance for use in food-producing animals in the European Community. Nitrofurans have been banned from use as a veterinary medicinal product and as additives in the EU since 1998.

Antimicrobial Residues of Medicinal Products: Residues are defined as all active ingredients or metabolites of those ingredients that remain in meat or other foodstuffs from the animal to which the medicinal product in question has been administered [15]. Several antibiotic classes are extensively administered to food-producing animals, including tetracyclines, sulfonamides, fluoroquinolones, macrolides, lincosamides, aminoglycosides, beta-lactams, cephalosporins and others [18].

The concept of drug residues in food was developed over the second half of the 20^{th} Century, resulting in the definition of a no observed effect level, a maximum residue level in food [19]. On the other hand the risk of residue from the milk is higher in developing countries compared to develop one. This might be related with lack of facilities for detection and regulatory bodies that control the drug residues level in foods in the form of maximum residue limits (MRLs). The MRL is defined as the maximum concentration of a residue, resulting from the registered use of an agricultural or veterinary chemical that is recommended to be legally permitted or recognized as acceptable in or on a food, agricultural commodity, or animal feed [20].

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 [21].

Antimicrobial Residue Detection Methods: The methods most often used to detect antimicrobial residues in food obtained from animals are the official methods, which often depend on the matrix. Microbiological and immunological methods are used to detect antimicrobial residues in milk and muscle [22]. The presence of antimicrobials is detected in animal products by screening methods and confirmatory techniques. The screening method is generally performed by microbiological, enzymatic and immunological methods [23, 24]. Premi® (R-Biopharm, Germany) test kit is one of a rapid microbiological screening test. It is a commercially available agar diffusion test based on the principle of growth inhibition of microorganisms [22]. Samples screen testing positive are analysed using various physical and chemical confirmation techniques, such as liquid chromatography, UV detection and fluorimetry, or combined with mass spectrometry. These methods are designed to satisfy a number of performance criteria, which are verified during the required validation studies before being used for statutory control [25, 26].

Microbial Inhibition Test: Microbial inhibition test is one of screening test for antimicrobial residues. It is a qualitative or semi-quantitative test is used to detect antibiotic residues in milk and meat. Muller Hinton or Nutrient agar is commonly used to perform agar diffusion test. These tests comprise spores of specific bacteria (*Bacillus subtilis*, *Bacillus stearothermphillus*, *Micrococcus luteus* etc), sensitive to particular antibiotics on agar gel including nutrients for bacterial growth and a pH indicator [27]. After addition of milk or meat, the plate is incubated at appropriate temperature for growth and germination of bacteria. In the absence of antibiotic residues, the growth of bacteria can be detected visually either by the change of opacity of the agar medium or by the colour change of the pH indicator [28].

There are many advantages of these methods; microbiological tests can be performed by non-professionals, only some tests required sample treatment and can be carried out in a tube or a microplate. However, these methods have some disadvantages such as lack of specificity and the required long incubation time [27].

Biosensor: Biosensor is a latest technique used for screening of antibiotics residues in milk. The sensitivity and selectivity of biosensors are comparable to immunoassay methods [29]. These sensors have shown successful detection of β-lactams (β-Ls), tetracycline, streptogramin and macrolide antibiotics at nanogram per millilitre concentrations in milk and serum [30, 31].

Biosensor contain a biological recognition element (e.g. enzymes, proteins, cells) coupled to a signal transduction element. The biosensors can be classified according to the biological element, the transducer and the biological element immobilization procedure on a solid support [32]. This method is rapid and specific as the bio recognition element used. It has some limitations such as the instability of the biological sensing component and the size of the physico-chemical transducers used in biosensors [27].

Enzyme Linked Immunosorbent Assay: Enzyme Linked Immunosorbent Assay (ELISA) is most useful and specific test for screening of drug residues in meat, milk and egg. The Competitive ELISA is commonly used for quantitative analysis of tetracycline, fluoroquinolones and chloramphenicol in meat [33, 34]. This test has high specificity, high sensitivity and simplicity. Micro plates and magnetic particles are used in this test. The most important advantage of these assays is that both penicillins and cephalosporins can be screened within one assay [35]. At the same time, magnetic particles for target capture/enrichment can minimize matrix interferences and improve method accuracy [27].

Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS): Nowadays, the most frequently used analytical tool for detection of a large number of multiclass veterinary drug residues in food [36, 37]. It is one of the confirmatory tests for drug residue in the food of animal origin. The analysis of antibiotics in milk by LC-MS/MS is more specific and more reliable. However this method is expensive and time consuming and require personnel and adequate laboratory [27].

Antimicrobial Residue Risk Factors: 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 [3]. The factors favouring the presence of antimicrobial residues in foods of animal origin include, failure to comply with the waiting period after the administration of antimicrobials, failure to consult a veterinarian before using antimicrobials, lack of prior training in animal husbandry and the type of livestock production either intensive or extensive practiced by the farm [38].

The waiting period is the period after the administration of a treatment, during which any food produced by the treated animal must not be marketed. It is determined on the basis of experimental studies conducted on target animals that are representative of the conditions of use but are in good health. The defined waiting period takes into account the pharmacokinetic variability between individual animals in the processes of absorption, distribution, metabolism and excretion of residues. These processes depend on the physiological condition of the animal and the genetic traits influencing metabolism or excretion. The majority of the studies are carried out on breeds representative of large scale production in developed countries and do not take into consideration the distinctive characteristics of African animal species, which may not only differ in terms of their genetic heritage (including acetylation rates) but whose physiology may be more suited to local climatic conditions (water consumption, volume of distribution and renal clearance). As these differences influence residue kinetics, an adjustment of the waiting period may be required when medicinal products are administered to local breeds. At this stage of development in veterinary drugs, such variations are not taken into account [39].

There are many other risk 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 [21]. 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 [40].

Antimicrobial Residue Control Methods: In the EU, self-monitoring and the control of residues are based on standardised analytical methods. Much of this analysis is carried out in the laboratory. The regulatory framework in force in the EU is based on Directive 96/23/EC, which structures the network of laboratories approved for official residue control, laying down requirements in terms of quality and performance of analytical methods [25]. In general, the residue control strategy is based on a two-step approach, the detection of residues using sensitive tests with a low rate of false negatives, followed by confirmation, requiring quantification against the maximum residue level and identification with a low rate of false positives [39].

In Europe, the prevalence of contamination by residues from medicinal products in foods of animal origin is less than 1% [41]. In Africa, recent studies on the presence of antimicrobial residues in foods of animal origin are very limited. In Ghana, the prevalence of antimicrobial residues is 30.8% for beef [38] and in Ethiopia 76.4% of beef drug residue in the study of Bahir Dar and Debre Tabor towns [42].

In the EU, processors frequently conduct controls for antimicrobial residues and there are systematic checks of bulk tankers to screen for the presence of inhibitors [17]. The absence of inhibitors is a quality criterion that increases the price that a farmer receives for milk. This is undoubtedly the reason why rates of non-compliant residues in milk are very low in the EU. Very few studies have been devoted to evaluating antimicrobial residues in raw milk in African countries, with the exception of those in North Africa, because milk is not a staple food in these countries [38].

Effect of Antimicrobial Residues: The environmental contamination with antimicrobials may occur in several ways through drug manufacturing process, throwing of unused drugs and containers or application of manure and waste slurries. Animals excrete significant proportion of antibiotics (17-90%) directly into urine and faeces as parent compound or its toxic metabolites, because many of administered antibiotics are not completely absorbed from gut [43, 44].

The highest and most frequently reported concentrations of antibiotic residues in manure belong to the tetracycline group of antibiotics. The reported levels regularly exceed 100 mg/kg [44]; with extremes up to 764 mg/kg chlortetracycline in swine manure [45]. The second higher concentration of antibiotic residue in manure is fluoroquinolone, the residue concentration of ciprofloxacin, enrofloxacin and norfloxacin in manure are 45, 1420 and 225 mg/kg, respectively. Penicillins show poor stability in manure and also possibly degradation by soil microbes [46], for aminoglycosides data on the occurrence in manure are lacking.

The presence of antibiotic residues in the environment and its effect on microbial community is depends on the type, amount of residue and species of environmental microbes present [47, 48]. The antibiotic residues in the environment not only changes the structure and abundance of the soil microbial community, but also affects the ability of soil microorganisms to degrade contaminants and their role in ecological functions such as methanogenesis, nitrogen transformation and sulfate reduction in soil and aquatic environments [49]. Persistence of antibiotic residues in the environment depends on physico-chemical properties of drug residue, characteristics of the soil and climatic factors, temperature, rainfall and humidity [50]. Tetracyclines (particularly tetracycline and chlortetracycline) were found to be more persistent in soils than in manure [51]. Poor degradability and strong binding potential of flouroquinolones in the soil result in the long persistence in soils and sediments. Sulphonamides are relatively stable and occur in environment in bioavailable form.

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 [52]. AMR is also a threat to the livestock sector and thus to the livelihoods of millions who raise animals for subsistence [53]. The primary driver for the accumulation of harmful resistance genes in the animal reservoir is the large quantity of antimicrobials used in animal production [52].

The use of antibiotics in food animals selects for bacteria resistant to antibiotics used in humans and these might spread via the food to humans and cause poor response to treatment during illness [54]. Antibiotic resistance can be developed by mechanisms such as changes within the existing genome of a bacterial cell (mutations) and changes within the proteome, formation of bacterial cell interactions and plasmids by horizontal gene transfer [55].

Evidence linking AMR between animals and humans is particularly strong for common foodborne pathogens resistant to quinolones, such as *Campylobacter spp.* and *Salmonella spp* [56]. AMR is also a threat to the livestock sector and thus to the livelihoods of millions who raise animals for subsistence [53]. The primary driver for the accumulation of harmful resistance genes in the animal reservoir is the large quantity of antimicrobials used in animal production [52].

Most of the currently used antibacterials are relatively nontoxic, even at higher concentration but, few antibiotics pose a serious public health issue. Antibiotic residues in milk are of great public health concern since milk is being widely consumed by infants, youngster and adults throughout the globe [57]. One of the most important adverse effects of antibiotics in food is allergic reactions. Many of the drugs and antibiotics can elicit allergic reactions. The majority of information is related to hypersensitivity of penicillin, aminoglycosides and tetracyclines [58]. Β-lactams are known as less toxic antibiotics. However, it is concluded that they were responsible for the most of reported allergic reactions due to antimicrobials in humans [59]. The nitrofurans at higher concentrations cause carcinogenic and mutagenic effects [60].Recently Etminan and coworkers [61] reported the risk of retinal detachment in individuals upon continued exposure to fluoroquinolones. Chloramphenicol is also associated with optic neuropathy [62] and brain abscess [63] with varied intensities and clinical manifestations. Streptomycin has important effects on vestibular mechanisms in the inner ear. This effect causes balance lost. Besides this side effect, it exhibits neurotoxicity on newborn animals. Hypersensitivity, skin rashes and induced fever are the other toxic effects of this drug [58].

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. 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. These are due to of antimicrobial residues. The most likely reason for drug residues may result from human management, such as improper usage, including extra-label or illegal drug applications, failure to keep to the withdrawal period and using overdose. Based on the above conclusion the following recommendations were forwarded: 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, control and surveillance of antimicrobials and their residues in foods of animal origin, developing regulatory mechanisms of residue level and vocational training to meet the objectives of food safety.

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