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Review on Antibiotic Residues in Food of Animal Origin: Economic and Public Health Impacts

Kibruyesfa Bayou and Naol Haile

Wollega University, College of Medical and Health Science,
School of Veterinary Medicine, P.O. Box: 395, Nekemte, Ethiopia

Abstract: Antibiotics are used in livestock production (Food animals) not only for treatment but also for control of diseases and as growth promoter. The frequent use of antibiotics may result in residue that can be found at different concentration levels in food products from animal origin, such as milk and meat. Antibiotic residue is a term which refers small amounts of antibiotic or its active metabolites remain in animal derived food after using it in animal for different purposes. Specially antibiotic residues occur due to large-scale application of antibiotics in veterinary practice and creates problems not only in dairy and meat industry but also have immense public health significance because harmful effect of these residues residing in foods of animal origins can induce carcinogenic and mutagenic effects and leads to the condition of antibiotic resistance and antibiotic allergy in the individuals who consume those food stuffs. Even though antibiotic residues cause serious public health effects, little is known by the society and there is lack of information about it, so that it is important to review antibiotic residue in food of animal origin to insight it's economic and public health significances. Finally, the safety levels of food must be strictly observed, drug products should be used in accordance with the labeled directions and public awareness should be created on the public health significance of antibiotic residue using different media.

Key words: Antibiotic Residue · Food of Animal Origin · Public Health

INTRODUCTION

Antibiotics are substances either produced naturally from living organisms or synthetically in the laboratory and they are able to kill or inhibit the growth of microorganisms. Antibiotics can be classified according to their effects as either bactericidal or bacteriostatic and also according to their range of efficacy as narrow or broad in spectrum. The use of antibiotics in animals shortly followed their use in humans for the purpose of disease prevention and treatment [1].

Today, antibiotic drugs are used to control, prevent, treat infection and enhance animal growth and feed efficiency [2]. Currently, about 80% of all food-producing animals receive medication for part or most of their lives. The most commonly used antibiotic in food producing animals are the β-lactams, tetracyclines, aminoglycosides, lincosamides, macrolides and sulfonamides [3].

The use of antibiotics in food-producing animals may leave residues in foodstuffs of animal origin like meat, milk, honey and eggs. The occurrence of these residues may be due to any one of the following: a failure to observe the withdrawal periods of each drug, extra-label dosages for animals, contamination of animal feed with the excreta of treated animals, or the use of unlicensed antibiotics [4].

Antibiotic residue in food of animal origin may be the cause of numerous public health concerns in human. These problems may include: transfer of antibiotic resistant bacteria to humans, mutagenicity, allergy (e.g. penicillin) and carcinogenicity (e.g. sulphamethazine) [5]. The ongoing threat of antibiotic residue is one of the biggest challenges to public health that is faced by the human population worldwide. The issue of antibiotic residue in foods of animal origin has rarely been a serious concern in developing countries, in contrast to the situation in Europe. While the prevalence of veterinary drug residues in foods of animal origin is less than 1% in Europe, in some African countries it can be as high as 94%. A study reported in 2004 by European Union revealed that the majority of residues confirmed in animals were antibiotic agents [6].

Corresponding Author: Kibruyesfa Bayou, Wollega University, College of Medical and Health Science, School of Veterinary Medicine, P.O. Box: 395, Nekemte, Ethiopia. Tel: +251-912 05 34 14, E-mail: kibruyesfab@gmail.com.

In Africa, in parallel to the incautious use of antibiotics in human medicine, agricultural sectors consume a large portion (50%) of antibiotics in animal farming to treat, to minimize potential outbreaks of diseases or to promote animal health [7].

In Ethiopia, a study conducted in 2007 revealed that out of the total 384 samples of food stuffs of animal origin analyzed for the presence of tetracycline residue, 71.3% had detectable oxytetracycline [8]. However, there is still lack of clear available information about antibiotic residues in food of animal origin and their economic and public health impacts in the country. Therefore, based on the above facts the objectives of this seminar paper are:

- To review risk factors for the development of antibiotic residues in foods of animal origin.
- To review the safety evaluation and detection methods of antibiotic residues.
- To review the economic and public health impacts along with the control and preventive measures of antibiotic residues in foods of animal origin.
- To review the extent of antibiotic residue in Ethiopia.

Veterinary Antibiotics and Their Use in Food Animals: oday, more antibiotics are used worldwide in poultry, swine and cattle production than in the entire human population. In the United States, approximately 80% of all antibiotics consumed are used in the livestock sector [9]. As some researchers estimated that annually, 45 mg/kg, 148mg/kg and 172 mg/kg are consumed to produce each kilogram of cattle, chicken and pigs, respectively. They reported that the global consumption of antimicrobials will increase by 67% from 2010 levels by 2030, from 63, 151 ± 1, 560 tons to 105, 596 ± 3, 605 tons [10].

Antibiotics are used largely for three purposes in animals, therapeutic use to treat sick animals, prophylactic use to prevent infection in animals and as growth promoters to improve feed utilization and production for their growth promoting properties they are routinely used at subtherapeutic levels as animal feed additives [11].

Authorized Veterinary Antibiotics: The antibiotics authorized for veterinary use are those that have passed the marketing authorization process of the Competent National 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. The statutory marketing authorization mechanism is virtually identical across most African countries. No medicinal product may be marketed unless it has first been authorized by the Competent Authority. However, there are huge shortcomings in the implementation because the technical evaluation of a marketing application is limited to an administrative procedure alone. These countries have no effective scientific control tools to ensure the validity of the data provided by the applicant [12].

Prohibited Veterinary Antibiotics: Prohibited antibiotics are substances for which it is not possible to determine the Maximum Residue Level (MRL). Chloramphenicol is a broadspectrum antibiotic against Gram positive and Gram negative bacteria. It was not possible to determine its MRL based on the available data. The inability to set a threshold value and shortcomings in the marketing authorization, application led to chloramphenicol being classified in1994 as a prohibited substance for use in food-producing animals. Dapsone, which is used to treat leprosy in humans, is not authorized for use in food-producing animals in Europe because of insufficient toxicology data, making it impossible to determine the acceptable daily intake [6].

Risk Factors for Antibiotic Residue Occurrence: It is a common practice among livestock producers to treat entire groups of livestock, such as poultry, fish, or other animals. Such practices unintentionally and unnecessarily expose healthy individuals to antibiotics. Additionally, many livestock producers use sub therapeutic doses of antibiotics to prevent diseases and this of course will lead to antibiotic residue entering the human food chain [10]. Antibiotic residue may also transmit vertically to calves consuming milk from cows receiving antibiotic [13]. Fecal recycling, where the drug excreted in the feces of treated animals contaminates the feed of untreated animals, can be the cause of traces of certain antibiotic substances being passed on Elliott and Crooks [14].

Disease Status: The disease status of an animal can affect the pharmacokinetics of drugs administered, which can influence the potential for residues [15]. 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. The changes in liver function by fasciolosis results of change in the processing of drugs through the liver. In calves with experimentally induced fasciolosis, the elimination half-life 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 [16].

The kidney is the most important site of drug excretion. Renal disease usually significantly affects drug excretion (Retard drug removal from the body). 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 [17].

Extra-Label Drug Use: Extra-label drug use (ELDU) refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. It 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 [18]. For instances, the use of enrofloxacin solution as a topical ear medication (Only approved for use as an injection) are the common ELDU in veterinary medicine [19].

Improper Withdrawal Time: Improper withdrawal time is another risk factor; 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. 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 and fail to wait for withdrawal period results in residue in food of animal origin which is used for human consumption [20].

Safety Evaluation and Detection Methods of Antibiotic Residues

Acceptable Daily Intake: Acceptable daily intake (ADI) for a given compound is the amount of substance that can be ingested daily over a life time without appreciable health risk. The ADI calculation is based on the array of toxicological safety evaluation that takes in to account acute and long term exposure to the drug and its potential impact. This defines a maximum quantity which may be consumed daily by even the most sensitive group in the population with any out ward effects. The ADI is determined by consecutive estimate of a safe ingestion level by the human population on the lowest no effect level of toxicological safety studies [21]. For instance, in Tanzania the Food and Drug Administration (FDA) calculates the safe concentration for each edible tissue using the ADI and the amount of the product can be eaten per day in micro-grams per Kg of body weight is given accordingly (Table 1) [22].

Table 1: Acceptable Daily Intake (ADI) for Some Antibiotics

Antibiotics	ADI (µg /kg)
Tylosin	0-30
Erythromycin	0-0.7
Apramycin	0-30
Enrofloxacillin	2
Streptomycin	0-50
Virginiamycin	250
Florfenicol	0-1

Maximum Residue Level: Maximum residue level (MRL) is the maximum concentration of residue resulting from the use of veterinary medicinal product that may be legally permitted or recognized as acceptable on or in food allocated to individual food commodities (Table 2). The MRL is fixed on the basis of relevant toxicological data [23]. Substance for which no MRL can be established is a substance that its presence at whatever limit in the food stuffs of animal origin may constitute a hazard to a health of consumer [24].

Table 2: Maximum Residue Level (MRL) for Some Antibiotics

Antibiotics	MRL (µg /kg)
Benzyl penicillin	4
Oxytetracycline	100
Streptomycin	200
Oxacillin	40
Sulphonamides	100
Tylosine	50
Erythromycin	40

Calculating Withdrawal Period: Use of antibiotics requires observance of the withdrawal period. This is the time between the last doses given to the animal and the time when the level of residues in the tissues (Muscle, liver, in the kidney, skin and fat) and products

(Milk, eggs, honey) is lower than or equal to the MRL. Until the withdrawal period has elapsed, the animal or its products must not be used for human consumption [25]. The withdrawal period is determined when the tolerance limit on the residue concentration is at or below the permissible concentration. A tolerance limit provides an interval within which a given percentile of the population lies, with a given confidence that the interval does contain that percentile of the population [26].

Detection Methods of Antibiotic Residues: Screening tests are aimed at avoiding false negative results while false positive results are tolerable. These tests when used for substances with an established maximum residual limit, the detection should be as low as possible [27]. The advantage of these methods is that they have a wide detection spectrum, they are simple to carry out and they are cheap and can be used for the screening of a large number of samples [28]. The use of screening tests for the detection of antibiotic residue (AR) in food is therefore very important. This includes a large variety of detection methods, ranging from physico-chemical analysis or immunological detection (e.g. ELISA) to microbiological method (e.g. growth inhibition tests) [29].

Microbiological methods are quite suitable for the detection of AR especially as they are less expensive than immunochemical and chromatographic method and are able to screen a large number of samples at minimal cost [30]. However the methods have their drawbacks that limit their use: they do not enable specific antibiotic identification, they have limited detection levels for a serious of antibiotics and they are only qualitative and require a long incubation period [31].

The next step after initial screening consists in the definite identification and confirmation of the AR in foods of animal origin. The full procedure and the methodologies for confirmatory analysis are costly in time, equipments and chemicals. In addition, they require trained personnel with high expertise. Different analytical techniques are available for such purpose. When the target analyte is clearly identified and quantified above the decision limit for a forbidden substance exceeding the MRL in the case of substances having a MRL, the sample is considered as non-compliant (Unfit for human consumption) [25].

Public Health Significance of Antibiotic Residues: The non-restrictive usage of antibiotics in animals may cause problems in humans due to the presence of residues in food materials of animal origin. In humans' health, residues of drugs in foods of animal origin may cause direct side effects, or indirectly through selection of antimicrobial resistance determinant that may spread human pathogen [32].

Mutagenic Effects: Mutants are any chemical capable of damage the genetic component of a cell or organism. Several chemicals including alkylating antibiotics (Anticancer antibiotic e.g. Doxorubicin) have been shown to elicit mutagenic activities. There has been an increasing concern that drugs as well as environmental chemicals may pose a potential hazard to the human population by production of genes mutations or chromosome aberrations. Either the general or somatic cell may be affected understandably; injury to either cell group may lead to serious consequences. However, from public health, mutation in the general cells is more immediate importance because of the hazard to further generation [31].

Carcinogenic Effects: Carcinogenic effects refer to an effect produced by a drug having carcinogenic or cancer producing activity. Among the carcinogenic veterinary drugs in current use in many countries are nitrofurans, nitromidazoles and quinoxaline. These drugs are acquired via food of animal origin as antimicrobial residues. The potential hazards of carcinogenic residue are related to their interaction or covalent binding with various intracellular compounds such as proteins, ribonucleic acid, glycogen, phospholipids and glutathione. This leads to change cellular components such as deoxyribonucleic acid (DNA) [33].

Allergic Reactions: Allergic reactions to antibiotic residue in food of animal may include: anaphylaxis, cutaneous reaction and delayed hypersensitivity reactions. These effects are acquired after human beings consume food of animal origin, which contain drug residue that has allergic effects. About 50% of the human population is considered to be hypersensitive for a number of antibiotics including penicillin. Penicillin residue as well as other β-lactams antibiotics such as cephalosporin could cause allergies if high level of residues persists in food products and consumed by penicillin allergic persons. Exposure to penicillin residues in milk has been reported as a cause of chronic urticaria [34].

Disruption of Normal Intestinal Flora: The bacteria that usually live in the intestine acts as a barrier to prevent incoming pathogen from being established and causing diseases. Antibiotic residues may reduce the total number of the bacteria or selectively kill some important species. The broad-spectrum antibiotics may adversely affect a wide range of intestinal flora and consequently cause gastrointestinal disturbance. Antibiotics might reduce total numbers of these benign bacteria or selectively kill some important species when consumed in food which contain their residues [35].

Development of Antibiotic Resistance: Many of the antibiotics used to treat bacterial infections in humans have veterinary applications: prophylactics and growth promoters. In these two cases, the antibiotics are used at a concentration lower than the therapeutics concentrations for a longer period of time, a potentially dangerous practice since it is one of the strongest selective pressures leading to emergence of antibiotic resistance [36].

Development and spread of antimicrobial resistance represents a serious threat with potential public health implications. Antibiotic resistant bacteria such as *Escherichia coli* can colonize the intestine of people. Healthily exposed humans (Farmers who use food containing antibiotics, slaughter house workers, cookers and other food handlers) often have incidence of resistant *Escherichia coli* in their feces than general population [37]. It has been documented that human develop antibiotic resistant bacteria such as *Salmonella, Campylobacter* and *Staphylococcus* from food of animal origin. Examples of antibiotic that have been shown to cause the growth of resistant bacteria in food of animal are fluoroquinolones and avoparcin. The resistance of microorganisms, arising from subtherapeutic uses of penicillin, tetracycline and sulfa drugs; in agriculture is suggested by the WHO to be a high priority issue [38].

Economic Impact of Antibiotic Residues: Major economic losses could arise in veterinary medicine, because antibiotic resistance has been found to cause therapy failure and higher mortality and morbidity rate [39]. A wide spread availability and use antimicrobials have several negative implications on global health care: among these developments of drug resistance is one. The primary economic implications of resistance on the diminishing efficacy of antibiotic treatment includes the need to rely on more expensive drugs that may be practically unaffordable for most primary health care programs [8].

Antibiotic residue remains very significant from the prospective of international trade and consumer confidence, because it results in international trade barrier. As tariff are removed and goods flow freely between countries, importing countries must be in confident that goods available for purchase are safe and in addition to this, from time to time, there is pressure to use antibiotic detection on non-tariffs barrier to importation [20].

In dairy industries, the dairy starter cultures currently used for the primary acidification of milk belong mainly to the genera *Lactococcus, Streptococcus* and *Lactobacillus*. These starter cultures are mainly lactic acid bacteria used in the production of a range of fermented milk products, including cheese, yoghurt and cultured butter. The primary role of starter culture in cheese manufacture is the production of lactic acid from lactose at a consistent and controlled rate. The consequent decrease in pH affects a number of aspects of the cheese manufacturing process and ultimately cheese composition and quality [40]. Antibiotic residue in milk is undesirable from a manufacturing perspective as they can interfere with starter culture activity and hence disrupt the manufacture process [41].

Control and Preventive Measures: Hence, the residue prevention strategy is based on preventing entry of antibiotic residues in animal product intended for human consumption by proper drug use guide developed for use by both veterinarians and food animal (Dairy and beef) and herd health program that keep animals healthy and producing efficiently. Proper maintenance of treatment records and identification of treated animals; health record for each animal to record all health related events, including administration of medication. Record the identification of all animals in the permanent health record book; Having proper antibiotic residue testing capabilities; this control point address the conditions under which residue testing should be considered; the proper selection and interpretation of tests; the inherent limitation and potential misuse of residue testing; and creating awareness of proper antibiotic use and methods to avoid marketing adulterated products. Principally, total residue avoidance program is based upon the objective of improving the livestock producer's management and quality control of marketing animals with emphasis on avoidance of drug residues [42].

The Extent of Antibiotic Residue in Ethiopia: In many African countries, antibiotics may be used indiscriminately for the treatment of bacterial diseases or they may be used as feed additives for domestic animals and birds. The ongoing threat of antibiotic contamination is one of the biggest challenges to public health that is faced not only by the African people, but also by the human population worldwide [43]. Such residues are spreading rapidly, irrespective of geographical, economical, or legal differences between countries [44].

In Ethiopia, a study conducted in 2007 indicated the proportion of tetracycline levels in beef; the study focused on the Addis Ababa, Debre Zeit and Nazareth slaughterhouses. Out of the total 384 samples analyzed for tetracycline residue 71.3% had detectable oxytetracycline levels. Among the meat samples collected from the Addis Ababa, Debre Zeit and Nazareth slaughterhouses, 93.8%, 37.5% and 82.1% tested positive for oxytetracycline respectively. The mean levels of oxytetracycline in muscle from the three slaughterhouses were described as follows: Addis Ababa, 108.34ìg/kg; Nazareth, 64.85ìg/kg; and Debre Zeit, 15.916ìg/kg. Regarding kidney samples, oxytetracycline levels were found to be 99.02ìg/kg in Addis Ababa, 109.35ìg/kg in Nazareth and 112.53ìg/kg in Debre Zeit. About 48% of the edible tissues had oxytetracycline levels above the recommended maximum limits [35, 37].

CONCLUSION

The use of antibiotics in food-producing animals has the potential to generate residues in animal derived products and poses a health hazard to the consumer. Once antibiotics are administered to animal body, antibiotic residues are present in high or low concentrations in their food products, eventhogh; this depends on the duration of the administration of antibiotics and rational use of the drugs. So that, failure to adhering withdrawal period and improper use of antibiotics result in exposure to antibiotic residue; this can lead to allergy, cancer, antibiotic resistance and other public health impacts. Therefore, based on the above conclusion, the following recommendations are forwarded:

- Strict observation of withdrawal times of antibiotics should be practiced.
- Indiscriminate use of antibiotics at subtherapeutic doses for prophylaxis in animals should be ceased.
- There should be strict adherence to scientific guidelines and precaution to minimize antibiotic residue in food of animal origin.
- Public awareness should be created on the public health significance of the problem.
- Animal diseases and infections should primarily be prevented by ensuring biosecurity, following good production and good management practices; this reduces antibiotic use in animal production.

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