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

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Abstract

Antibiotics are used in livestock production (food animals) not only for treatment but also for the control of diseases and as growth promoters. The frequent use of antibiotics may result in residue that can be found at different concentration levels in food products of animal origin, such as milk, meat and egg. Antibiotic residue is a term that refers to small amounts of antibiotic or its active metabolites that remain in animal-derived food after being used by animals for different purposes. Specially antibiotic residues occur due to large-scale application of antibiotics in veterinary practice and create problems not only in the dairy and meat industries but also have immense public health significance because the harmful effects of these residues in animal products may cause the development of antimicrobial drug resistance, hypersensitivity reactions, carcinogenicity, mutagenicity, teratogenicity, bone marrow depression, and disruption of normal intestinal flora. Withdrawal periods and rules pertaining to antibiotic residues should be strictly followed to make animal products safe for human consumption. The present review aimed to show human health hazards after consuming food of animal origin with antibiotic residue. Even though antibiotic residues cause serious public health effects, little is known about them by society, and there is a lack of information about them, so it is important to review antibiotic residue in foods of animal origin to gain insight into their economic and public health significance. 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 about the public health significance of antibiotic residue using different media.

Keywords: Animal, Antibiotic, Drug, Public Health, Residues

1. Introduction

Antibiotics are compounds that can either kill or limit the growth of germs and can be made synthetically in a lab or naturally from living organisms. Antibiotics can be categorized as either bactericidal or bacteriostatic in terms of their effects, as well as having a narrow or broad spectrum of activity. Following its use in humans for the treatment and prevention of disease, antibiotics were soon administered to animals [1]. Antibiotic medications are now utilized to regulate, prevent, treat, and improve the effectiveness of animal development and feed. At the moment, nearly 80% of all animals used for food receive medication for some or all of their lives [2].

The most commonly used antibiotic in food producing animals are the β -lactams, tetracycline, 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, and 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: may cause development of antimicrobial drug resistance, hypersensitivity reaction, carcinogenicity, mutagenicity, teratogenicity, bone marrow depression, and disruption of normal intestinal flora. Withdrawal periods and rules pertaining to antimicrobial residues should be strictly followed to make the animal products safe for human consumption and transfer of antibiotic resistant bacteria to humans,

mutagenicity, allergy (e.g. penicillin) and carcinogenicity (e.g. sulphamethazine) [5].

One of the greatest threats to public health that the human population worldwide faces is the lingering danger of antibiotic residue. In contrast to the situation in Europe, the issue of antibiotic residue in foods of animal origin has rarely been a substantial concern in developing countries. While veterinary drug residues in foods of animal origin are less common than 1% in Europe, they can reach up to 94% in some African nations [6].

In Africa, agricultural sectors employ a significant share (50%) of antibiotics in animal farming to cure illnesses, prevent disease outbreaks, or increase animal health. This is in contrast to the careless use of antibiotics in human medicine.Oxytetracycline was identified in 71.3% of food items of animal origin tested for the presence of tetracycline residue in Ethiopia [7]. The effects of antibiotic residues in foods derived from animals on the nation's economy and public health are still not well understood or readily accessible. Current developments in the market economy are prompting the liberalization of the veterinary profession[8]. The problem is that, in most African countries, there is no control over the distribution of veterinary pharmaceuticals and products Worse still, no appropriate legislation yet exists to guarantee the quality of the phytosanitary various products released onto the market [9]. In addition to the health risk to local populations, the presence of residues from veterinary medicinal products in foods of animal origin could jeopardize international trade [10]. Therefore, based on the above facts the objectives of this seminar paper are:

• To summarize the risk factors for the emergence of antibiotic residues in foods derived from animals
• Reviewing the economic techniques' safety assessments of antibiotic residues
• To assess the effects on the economy and public health as well as the methods taken to prevent and control the presence of antibiotic residues in foods derived from animals.
• To review the current status of antibiotic residues in Ethiopia.

2. Use of Antibiotics in Animal Production

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 sub-therapeutic levels as animal feed additives [11]. Initially, antibiotic usage in the veterinary field was started for control and treatment of disease but nowadays these are widely used as additives for growth promotion. It has been observed that antibiotics are widely used as feed additives and fatteners for broilers to improve their growth and for better protection [12]. Moreover, antibiotics also promote growth by decreasing various mechanisms such as toxin formation, nutrients waste, and the immune system's activity [13]. Antibiotics that are widely used for prophylaxis, growth promotion, and treatment in food animals are sulfamethoxazole, enrofloxacin, benzyl penicillin, tyrosine, amoxicillin, trimethoprim, oxytetracycline, ampicillin, and streptopenicillin, while amikacin, neomycin, enrofloxacin, doxycycline, tetracycline, tilmicosin, and colistin sulfate are used for promotion of growth in the poultry [14].

The main use of antibiotics in animal rearing was for the treatment and prevention of diseases. More recently antibiotics have been used for improved growth, especially in broilers and feed lot animals, antibiotics improve growth rate by thinning of mucous membranes in the gut (which facilitates absorption); alteration of gut motility which enhances assimilation production of favorable conditions for beneficial gut microbes (by destroying harmful bacteria); and partitioning of proteins for muscle growth via cytokine suppression[15]. Antibiotics also favor growth by decreasing the activity of the immune system, reducing the waste of nutrients, and reducing toxin formation[16].

2.1. Concept of Residues

A residue, defined in the simplest terms, results when a drug or pesticide is deliberately applied to a food-producing animal or plant. Residues of veterinary drugs include the parent compounds and/or their metabolites in any edible portion of the animal product and include residues of associated impurities of the veterinary drug concerned [17]. Residual amounts of antimicrobials or their toxic metabolites found in meat, organs or other products such as milk and egg of food producing animals is called veterinary drug residues [18]. Consumption of such food products poses a major health risk due to the failure of treatment following the development of resistant microorganisms[18]. Many livestock producers treat their animals by themselves. Even if they use the same drugs as veterinarians, they have little understanding of the conditions and quantities to administer or the waiting periods[19]. The uncontrolled use of anti-infectious agents can lead to residues in animal products, especially when users fail to respect waiting periods[20].

The concept of drug residues in food was developed over the second half of the 20th Century, resulting in the definition of a 'no observed effect' level, an Acceptable daily intake (ADI) and maximum residue limit [21]. The MRL in various foodstuffs (muscle, liver, kidney, fat, milk and eggs) is determined to minimize the risk of consumer exposure, taking into account dietary intake. Such considerations as food technology, good farming practices and the use of veterinary medicinal products may also be taken into account when setting the MRL [21].

The risks of residues in foodstuffs of animal origin could be reflected into several forms. This reflected advances in our knowledge of toxicological risk assessment and analytical science in the field of pharmacokinetics [22]. For most antimicrobials and anti-infective, the results of microbiological studies are used to determine the maximum dose that has no observed effect. For a few other substances, there is a toxic risk Studies to compare the absorption, distribution, metabolism and elimination in laboratory and target animals are used as the basis for studying the kinetics of total res-

idues, the extractable fraction compared with the bound fraction, the nature of metabolites and their main effects [23]. These data are used to define the marker residue (parent substance, metabolite or combination of substances) whose depletion from the tissue is correlated with that of total residues. Veterinary drugs are generally used in farm animals for therapeutic and prophylactic purposes and they include a large number of different types of compounds which can be administered in the feed or in the drinking water [24]. The great majority of residues found in edible tissues of animals have their source at the farm of origin. In some cases, the residues may proceed from contaminated animal feedstuffs. By far the most common cause of residues is the failure to observe the proper withholding period following treatment [25].

2.2. Veterinary Antibiotics and Their Use in Food Animals

Antibiotics are widely used in animals for many advantages covering carcass quality, promotion of growth, animal health, and cost-effective production [26]. Antibiotics are the commonest drugs and are widely being used in animals as prophylactic and therapeutic agents for the management of infectious diseases. These antibiotics have played an important role in the prevention and cure of certain important infections caused by Escherichia coli, Campylobacter fetus, Enterococcus, Leptospira, Streptococcus suis and Salmonella [27]. Antibiotics enhance growth rate by altering the motility of the gut, by thinning the mucous layers in the gut, by decreasing waste nutrients, immune system activity, and formation of toxins, and by providing favorable conditions for beneficial intestinal microbes to destroy harmful bacteria [28]. The body weight of animals increases up to 4–5% that receive antibiotics compared to those which are grown in the absence of these drugs [29].

As some researchers estimated that annually, 45 mg/kg, 148mg/kg today, more antibiotics are used worldwide in poultry, it is a 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 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, and 605 tons [30]. 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 their growth promoting properties they are routinely used at sub therapeutic levels as animal feed additives [11].

2.3. Prohibited Veterinary Antibiotics

Prohibited antibiotics are substances for which it is not possible to determine the Maximum Residue Level (MRL). Chloramphenicol is a broad spectrum antibiotic against Gram positive and Gram negative bacteria. It was not possible to determine its MRL based on the available data [26]. 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 [28]. Dispone, 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 [25].

2.3.1 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 [16]. 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 [13]. Antibiotic residue may also transmit vertically to calves consuming milk from cows receiving antibiotic. 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 [20].

2.3.2 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 consequently drug metabolism) or when the presence of infection and/or inflammation causes the drug to accumulate in affected tissues [26]. 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 [22]. The proposed mechanisms for these changes were the changes in liver function by fasciolosis, which changed the processing of drugs through the liver [29].

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) [25]. 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 [22].

2.3.3 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 [30]. 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 [11].

2.3.4 Improper Withdrawal Time

The withdrawal time can be defined as the interval between the last administration veterinary drug 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 [26]. Withdrawal time are varied for different veterinary drug products depending on different conditions such as: a few hours to several days or weeks and the type of drug, dosage form and route of drug administration [24]. 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 [22]. 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 [14].

2.4 Safety Evaluation and Detection Methods of Antibiotic Residues

2.4.1 Acceptable Daily Intake:

The acceptable daily intake (ADI) for a given compound is the amount of substance that can be ingested daily over a lifetime without appreciable health risk. The ADI calculation is based on an array of toxicological safety evaluations that take into account acute and long-term exposure to the drug and its potential impact. This defines a maximum quantity that may be consumed daily by even the most sensitive group in the population without any outward effects. The ADI is determined by consecutive estimates of a safe ingestion level by the human population at the lowest no-effect level of toxicological safety studies (Kebede, 2021). 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 that can be eaten per day in micrograms per kg of body weight [5].

A high degree of antibiotic residue consumption from animal products to humans might affect immunological reactions and unfavorably influence the digestive microbiota in susceptible people. Nonetheless, farmers utilize VAs for various purposes such as prophylactic, healing, growth promoters, and at times both prophylactic and healing purposes throughout the globe (Lateefat et al., 2022). In the Canadian poultry industry, prophylaxis and growth enhancers are used for various types of antibiotics. Enormous amounts of antibiotics are utilized in Bangladesh each year (Hassan et al., 2021). A large proportion of this is used unreasonably under conditions of lacking or no skilled supervision and, as a rule, without earlier testing on the documentation of the microorganisms and their resilience to the antibiotics recommended (Stawicki et al., 2020).

2.4.2 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 [31]. The MRL is fixed on the basis of relevant toxicological data. 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 [11].

The maximum residue level is defined as the maximum concentration of a residue, resulting from the registered use of an agricultural or veterinary chemical, which is recommended to be legally permitted or recognized as acceptable in or on a food, agricultural commodity, or animal feed[26]. The concentration is expressed in milligrams per kilogram of the commodity or milligrams per liter the case of a liquid commodity. The MRLs are specified for several animal derived food products (different edible tissues and other food commodities)[29]. When veterinary drugs are used according to the period of treatment and the withholding period specified before slaughter or milking, the concentration of drug residues should be at levels that will not cause adverse effect on the health of the consumer[11]. Therefore animals are suitable for food production if the amounts of veterinary antibiotic residues in animal food products are below levels that could cause a health risk for consumers [22].

2.4.3 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 [27]. 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 [32].

2.5 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 [33]. 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 sample. The use of screening tests for the detection of antibiotic residue (AR) in food is therefore very important [31]. 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) [26]. 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 [23]. 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 [11].

Chromatographic and screening methods including the immunological and enzymatic methods are used to detect antibiotic residues. Microbiological methods such as microbial agar diffusion tests or inhibition of acid production by starter organisms were also used for the detection of antibiotic residues in food [34]. Antibiotic residues of sulphanilamide, streptomycin, ciprofloxacin, and tetracycline in meat samples were detected by three techniques i.e. HPLC, ELISA, and TLC. HPLC showed different antibiotic residues concentration i.e. 14.6%, 8.3%, 88.8% and 41.1% for tetracycline, ciprofloxacin, sulphanilamide and streptomycin respectively [24]. ELISA detected that 25.3%, 56%, 18%, and 34% samples were positive for tetracycline, ciprofloxacin, sulphanilamide, and streptomycin, respectively, while TLC showed different concentrations i.e. 14.6% tetracycline, 21.4% ciprofloxacin, 92.5% sulphanilamide, and 29.4% streptomycin [34]. In milk samples, the antibiotic residues were detected in 1960 for the very first time using the chromatographic technique. The analysis showed that sulfonamides tetracyclines, fluoroquinolones, and aminoglycosides have 12.64%, 14.01%, 13.46%, [23].

The next step after initial screening consists in 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, equipment's and chemicals. In addition, they require trained personnel with high expertise [25]. Different analytical techniques are available for such purpose. When the target analytic is clearly identified and quantified above the decision limit for a forbidden substance exceeding of the MRL in the case substances having a MRL, the sample is considered as non-compliant (Unfit for human consumption) [23].

2.5.1 Allergic Reactions

Allergic reactions to antibiotic the residue in food of animal may include: anaphylaxis, cutaneous reaction and delayed hypersensitivity reactions [29]. 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 urticarial [26].

2.6 Status of Antibiotic Residue in Ethiopia

The mean levels of oxytetracycline in muscle from the three slaughterhouses were described as follows: Addis Ababa, 108.34 g/kg; Nazareth, 64.85 g/kg; and Debre Zeit, 15.916 g/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 [33].

Antimicrobials pass into every tissue and fluids of the body before excreted. High levels of antibiotic residues were detected in milk and meat destined for human consumption [33]. In Ethiopia 70.58 % of farms in Debre Zeit and 83.33% of the farms in Nazareth the oxytetracycline level; similarly, in 20.58% of the farms found in Debre Zeit and 16.16% of the farms found in Nazareth, the penicillin G level were above the maximum residue limit established by FAO [32]. In another on poultry meat 27.4% of chicken contained oxytetracycline. in Ethiopia in which oxytetracycline and penicillin G from milk [33] and tetracycline from beef. 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 [35]. Such residues are spreading rapidly, irrespective of geographical, economical, or legal differences between countries [33].

No	Region	Sample	Prevalence (%)	drug	Author
1	Addis AbabaAdis Ababa	MMM ClemMilk		Oxyto	
		MusMMeat	93.8	“Oxytracycline	(Bayou and Haile, 2017).
2	Debera zeit	Milk milk	70.58 70.8	“Oxytoxytetracycline	[32]
		Meat	37.5	“Oxytracycline	(Bayou and Haile, 2017).
3	Nazaret	Mi milk	8. 83.33	“Oxytoxytetracycline	[32]
		Meat	82.1	‘Oxytracycline	(Bayou and Haile, 2017).

Table 1: Status of antibiotic residue in meat and milk in ethiopia

2.7 Public Health Impacts

Human health risk can result from the presence of residues of veterinary drugs and/or their metabolites in edible organs and tissues of treated animals, in particular residues in concentrations exceeding the MRL established by Council Regulation 2377/90 [36]. Occurrences of veterinary drug residues pose the broad range of health consequences in the consumers. The residues of antibacterial may present pharmacological, toxicological, microbiological and immunopathological health risks for humans [37].

The non-restrictive usage of antimicrobials in animals rearing may lead to problems due to the presence of residues in food and raw materials of animal origin. Human health can either be affected through residues of drugs in foods of animal origin, which may cause direct side effects or indirectly through selection of antimicrobial resistance determinant that may spread human pathogen [38]. Human health problems that may result from intake of sub chronic exposure levels include allergic reactions in sensitive people, toxicity and carcinogenic effect [25]. Penicillin especially, as well as other beta-lactam antibiotics such as cephalosporin could cause allergies if high level of residues persists in milk consumed by penicillin allergic persons. Tetracycline residue also has the potential to stain teeth of young children [11].

2.7.1 Development of Drug Resistance

Resistant microorganism can get access to human, either through direct contact or indirectly via milk, meat, and or egg. As the bacteria of animal origin, they may either colonize human endogenous flora or superimpose and additional load to the reservoir of resistance genes already present in man [39]. 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 [40]. The potential for animal to human transfer of resistance is existed. Clearly, the use of antibiotic in livestock production has been associated with the development of human antibiotic resistance [41]. The animal fed with the low prophylactic level of antibiotic may develop bacteria evolving resistance to this antibiotic during the preparation or consumption of food of animal origin. The animal fed with the low prophylactic level of antibiotic may develop bacteria evolving resistance to this antibiotic during the preparation or consumption of food of animal origin [42]. The resistance of microorganisms, arising from sub therapeutic uses of penicillin, tetracycline and sulfa drugs; in agriculture is suggested by the WHO to be a high priority issue [33].

2.7.2 Hypersensitivity Reaction

It is an immune mediated response to a drug agent in a sensitized patient and drug allergy is restricted to reaction mediated by IgE. Drugs are foreign molecules, but their molecular weight is usually too small to be immunogenic, they act as hap-tens, which must combine with drug sensitive person to be immunogenic and elicit antibody formation [43]. Allergic reactions to antimicrobials may include anaphylaxis, serum sickness, 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 of the antimicrobials employed as food additives or in chemotherapy [44]. Penicillin and streptomycin appear from clinical use in humans to be more included to produce hypersensitivity or allergy than others in present milking herd use. About 50% of the human population is considered to be hypersensitive to a number of substances including penicillin [45].

Penicillin residue as well as other β-lactams antibiotics such as cephalosporin could cause allergies if a high level of residues persists in food products and is consumed by penicillin-allergic persons [46]. Such class of humans consuming meat products having penicillin residues is at risk of developing allergy which can manifest as a skin rash or even severe anaphylaxis. Studies have also shown that damages done to hepatic liver cells can be traced to an allergic response to macrolide antibiotics (e.g. erythromycin, clarithromycin) [5].

2.7.3 Carcinogenic Effect

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, and quinoxaline [5]. 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 in cellular components such as DNA [17]. The term carcinogen refers to an effect produced by a substance having carcinogenic activity. According to the International Agency for Research on cancer (IARC) and evidence abounds to suggest that metronidazole is carcinogenic in animal, but insufficient to do so in humans [42]. The following facts prove carcinogenic of metronidazole to humans: it is a mutagen in bacterial systems, it is a genotoxic to human cells and also it is carcinogenic to animals. Carcinogenic veterinary drugs in many countries are quinoxaline, nitrofurans and nitromidazoles [5].

2.7.4. Teratogenic Effect

The term teratogen applies to drug or chemical agent that produces a toxic effect on the embryo or fetus during a critical phase of gestation. According to [42], consequently was produced a congenital malformation, which affects the structural and functional integrity of the organism. For example, when ambicillin had been given during early stage of pregnancy, it is proved that, it has embryo toxic and teratogenic effect. In addition to embryo toxicity; the oxfendazol has also unveiled a mutagenic effect [46]. The term teratogen applies to a drug or chemical agent that produces a toxic

effect on the embryo or fetus during a critical phase of gestation. Consequently, a congenital malformation that affects the structural and functional integrity of the organism is produced [41]. The well-known thalidomide incident involving a number of children in to hazard that may occur when such agent is administered during pregnancy [5]. Tetracycline, the type of antibiotic, can cross the placental membrane and is deposited in the embryo in bones and teeth. Tetracycline exposure can result in yellow staining of the primary or deciduous teeth and diminished growth of the long bones [17].

2.7.5. Disruption of Normal Intestinal Flora

The bacteria that usually live in the intestine act as a barrier to prevent incoming pathogens from being established and causing diseases. For example, the use of drugs like flunixin, streptomycin, and tylosin in animals is known to cause this effect [5].

The broad-spectrum antibiotics may adversely affect a wide range of intestinal flora and consequently cause gastrointestinal disturbances. Antibiotics might reduce the total number of these benign bacteria or selectively kill some important species when consumed in foods that contain their residues (Bajaj et al., 2018). The intake of these residues into the intestinal tract of humans interacts with nearly 800–1000 bacterial species and approximately 7000 different strains [5]. Although 95% of these bacterial species are beneficial for humans, the remaining bacterial species are opportunistic and can be harmful (Roba, 2023). In the human intestinal tract, a micro ecological balance is maintained between the bacteria themselves and the bacteria and the human body, with a predominance of Firmicutes and Bacteroidetes and a lesser number of Proteobacteria, Actinobacteria, Verrucomicrobia, and many other phyla, some of which have not even been identified or isolated (Khan et al., 2020). Various studies have highlighted the fact that exposure to antimicrobial agents is associated with significant changes in the intestinal microbial population and composition. This effect has a broader spectrum on the microbiota community rather than targeting any particular bacterial species [5].

2.7. 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 [46]. 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 [11]. Antibiotic residue remains very significant from the prospective of international trade and consumer confidence, because it results in international trade barrier [42]. 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 [47].

In dairy industries, the dairy starter cultures currently used for the primary acidification of milk belong mainly to the genera Lacto coccus, Streptococcus and Lactobacillus [47]. 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 [46]. The consequent decrease in pH affects a number of aspects of the cheese manufacturing process and ultimately cheese composition and quality [11]. Antibiotic residue in milk is undesirable from a manufacturing perspective as they can interfere with starter culture activity and hence disrupt the manufacture process [11].

2.8. Prevention and Control of Residue

The residue prevention strategy is by implementing management practice and herd health program that keeps animals healthy and producing efficiently; beef producers ought to carryout correct drug administration of and identification of treated animals [39]. Self-monitoring and the control of residues are based on standardized laboratory analytical methods; the residue control strategy is based on a two-step approach; namely, the detection of residues using sensitive tests followed by confirmation [40]. The responsibility for residue control and prevention cannot lie solely within a governmental agency; rather the responsibility must be shared by the government, producers, veterinarians, teachers and academicians, marketing associations, and other interested parties, who must strive for both healthy and efficiently grown animals as well as a safe food supply [48]. Several approaches can be taken to achieve this goal: The first step in residue prevention is to make individuals and organizations aware of the problem through education [41]. When the animal is slaughtered or its edible products are collected there should be a legal requirement that drug concentrations in these products are not at levels greater than those established as safe by the relevant regulatory authority in the country of origin [48].

Hence, the residue Prevention and control strategy is based on preventing entry of residues in meat or milk intended for human consumption by proper drug use guide developed for use by both veterinarians and food animal (dairy and beef) producers include the following [17]. All food animals should be maintained in a clean and healthy environment whenever possible. Drug residues are best avoided by implementing management practice (good nutritional to meet growth, maintenance and lactation needs) and herd health program that keep animals healthy and producing efficiently, dairy and beef producers should not use or store unapproved drugs, special mixes or products within adequate labels as unapproved drugs have no data regarding efficacy, safety or withholding time [5].

The use of prescription drug and a veterinary-client patient relationship, which is established hence a veterinarian is closely with the owner in health management of the herd; Proper drug administration and identification of treated animals before administering or dispensing drugs one has to: know the drugs approved for all classes of cattle on the farm and be familiar with approved dosage, route of administration, and withholding time; Proper maintenance of treatment records and identification of treated animals; institute a workable health record for each animal to record all health related events, including administration of medication [41]. Antibiotic residues are best avoided by implementing management practice and herd health program that keep animals healthy and producing efficiently; beef producers should carryout Proper drug administration and identification of treated animals [11]. Rapid screening ways ought to be developed for detecting and segregating samples contains above MRL levels of antibiotics. Follow best hygiene practices throughout animal rearing and avoid unwanted use of antibiotics and victimization plant-derived antimicrobial substances and probiotics, could represent a promising option; vaccination against some microorganism diseases could also be of nice worth shortly [17].

2.9. Conclusion and Recommendations

The use of veterinary drugs in food-producing animals has the potential to generate residues in animal derived products and pose a public health hazard to the consumer. Until recently, veterinarians did not pay sufficient attention to ensuring that producers adhered strictly to the withdrawal period for milk, meat, and eggs from animals treated with a variety of drugs. The most likely reason for drug residue 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 adhere to the withdrawal period, including overdose and long-acting drugs, irrational use of drugs, such as misuse, extensive use, and failure to maintain strict adherence to withdrawal and withholding times. Although veterinary drugs have played a great role in the control and prevention of disease in animals and in promoting the growth of food animals, their use is associated with problems such as the development of resistance and residue effects in food animals. In general, when various types of veterinary drugs antimicrobials, ant parasitic and agonists, food additives, industrial and Agricultural products, pesticides, acaricides, herbicides, are used indiscriminately in food.

Producing animals intended for human consumption and in the environment, they pose a great public health risk. Therefore, strict control measures to promote rational veterinary drug use have crucial importance for the global economy and public health. Based on the above conclusions, the following recommendations are forwarded:

• The government should regulate irrational and unauthorized use of drugs and implement residue control strategies such as management practices and herd health programs that keep animals healthy and producing efficiently to avoid drug residues.

• improperly prescribed, dispensed, and sold drugs should be regulated;

• proper maintenance of treatment records and identification of treated animals should be implemented;

• the withdrawal time should be appropriately protected

• creating awareness among farmers, consumers, and health professionals about drug Residues and their public health significance

Availability of Data and Materials

All necessary data supporting our findings can be found in this manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest in publishing this manuscript.

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