

Public Health Importance of Veterinary Drug Residues in Food Animals

¹Yomifan Moti and ²Garoma Desa

¹Jimma University College of Agriculture and Veterinary Medicine,
Jimma, South West Ethiopia, P.O. Box: 307

²National Institute for Control and Eradication of Tsetse Fly and Trypanosomosis,
Kaliti Tsetse Fly Mass Rearing and Irradiation Centre, Addis Ababa, Ethiopia

Abstract: The predicament of fulfilling the dietary supplies of a growing world population is becoming increasingly acute. Drugs that advance the rate of weight gain, improve feed efficiency, or avert and treat diseases in food-producing animals are critically needed to meet the challenge of providing sufficient amounts of food for that population. But, the benefit of improved production from the use of animal drugs in food producing species is not obtained without hazard — the risk associated with drug residues that remain in the tissues of treated animals at the time of slaughter. If animal drugs were not absorbed or were metabolized to safe products, there would be no concern. Unluckily, this is not usually the case. Consumers have expressed concern regarding the health impact of drug residues in their food. Residues in animal tissues beyond the permissible tolerance evidently have an impact on human health. Tolerances represent the maximal level or concentration of antimicrobial residues permitted in animal tissues at the time of slaughter. The tolerances are intended to ensure that residual drugs will have no harmful effects if ingested. The principal focus in this review is on possible public health consequences that may occur as a result of acute exposure to illegal residues. Most residues of veterinary drugs come about in food at such low levels that they rarely cause a chronic or long-term health hazard to consumers. The importance of food safety through the reduction of residues in our food supply cannot be overemphasized. Food safety remains a major challenge confronting contemporary society.

Key words: Drugs • Food • Health • Residues

INTRODUCTION

Residues of antimicrobials in food have received much attention in recent years because of growing food safety and public health concerns [1]. Their presence in food of animal origin constitutes socioeconomic challenges in international trade in animal and animal products. The major public health significances of antimicrobial residues include the development of antimicrobial drug resistance, hypersensitivity reaction, carcinogenicity, mutagenicity, teratogenicity, bone marrow depression and disruption of normal intestinal flora [2]. Antimicrobials have been used for inhibiting the growth or multiplication of a wide range of bacteria in human and veterinary medicine since the discovery of penicillin by Alexander Fleming in 1929. Subsequent development by Ernst Chain and Howard Florey during the World War II led to the antimicrobial revolution,

which has been followed by the development of many other classes of antimicrobials. Today, antimicrobials play a major role in modern livestock production for prevention and treatment of diseases as well as growth promotion. Administration of antibiotics in food animals has been unbridled in many countries due to weak regulations, poor management practices and disease endemicity [3].

Human health is related directly to the environment and in particular the nature and quality of the food. Quality of food from animal products is widely concerning public health agencies around the world since veterinary drugs have played an important role in the field of animal husbandry and agro-industry and increasing occurrence of residues and resistance have become interesting issues [4]. Veterinary drugs or veterinary medicinal products (VMPs) are critically needed to meet the challenges of providing adequate amounts of food for the growing world population as drugs improve the rate of weight

gain, improve feed efficiency, or prevent and treat diseases in food producing animals. However, the benefit of improved productivity from the use of VMPs in food producing animals is not obtained without the risk associated with VMPs residues that remain in the tissues of treated animals at the time of slaughter or residues in animal derived products and poses a health hazard to the customer [5]. Antibacterial drugs and hormonal growth promoters are the main VMPs that potentially contaminate foods of animal origin [3]. Hence, veterinary drug or VMPs residue is one of many global issues concerning food contamination.

Residues, as defined by the European Union (EU) [6] and the Center for Veterinary Medicine, an agency under the Food and Drug Administration (FDA/CVM) [7] in the USA are “pharmacologically active substances (whether active principles, recipients or degradation products) and their metabolites which remain in foodstuffs obtained from animals to which the VMPs in question has been administered”. Under the normal physiological conditions, following administration of a drug to an animal, most drugs are metabolized in order to facilitate elimination and to a large extent detoxification as well. In general, most of the parent product and its metabolites are excreted in urine and to a lesser extent via faeces. However, these substances may also be found in milk and eggs and in the meat [8].

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 is meant that the value of zero became smaller and smaller that depicts the limits corresponding to the sensitivities of parts per million (ppm), parts per billion (ppb) and parts per trillion (ppt). 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 [9].

The Objectives of this Review Were:

- ▶ Awareness creation on the impact of antimicrobial resistance occurring as a result of drug residues and
- ▶ Encouraging all concerned professionals to react on the agenda of drug residues which has become the global challenge.

Antimicrobial Residues: Irrespective of the route or purpose of administration, antimicrobials can accumulate as residues in tissues, before they are completely metabolized or excreted from the body. The occurrence of residues in animal tissues is most likely when animals are harvested for human consumption while still on medication or shortly after medication before the withdrawal period elapses.

Consumption of such products may result in many health problems in humans [10]. Chiefly among the health concerns is the development and propagation of antimicrobial resistance along the food chain.

Although efforts have been made to harmonize maximum residue limits (MRLs) worldwide under the aegis of World Trade Organization (WTO) and the Codex Alimentarius, MRLs still vary from one geographical location to another. In fact, MRLs in a particular animal product may differ from one country to another depending on the local food safety regulatory agencies and drug usage patterns [11] and most developing countries have yet to develop their own MRLs.

Risk Factors for the Development of Residue in Food-producing Animal: Veterinary drug residues are one of the major problems for food contamination. VMPs and agricultural chemicals used according to label directions should not result in residues at slaughter. However, possible reasons for such residues include: Not following recommended label directions or dosage (extra-label usage); not adhering to recommended withdrawal times; administering too large a volume at a single injection site; use of drug-contaminated equipment, or failure to properly clean equipment used to mix or administer drugs; dosing, measuring, or mixing errors; allowing animals access to spilled chemicals or medicated feeds; animal effects- age, pregnancy, congenital, illness, allergies; chemical interactions between drugs; variations in water temperature; environmental contamination; and improper use of agricultural chemicals such as pesticides [12].

Veterinary drugs or VMPs residues usually accumulate in the liver or kidney rather than other tissues. It has been noted that different residue levels can be found in different tissue positions such as site and route of administration. The most likely reason for drug residues may result from human management, such as improper usage, including extra-label or illegal drug applications. However, the most obvious reason for unacceptable

residues might be due to failure to keep to the withdrawal period including using overdose and long acting drugs [13].

Inadequate good sanitary care during animal or product transportation, including the cross contamination of animal feeding stuffs with inadvertently applied drugs, environmental and animal to animal transfer of drugs may also cause residues. Risk factors responsible for the development of residues are:

Age of Animal: Weaning status and, to a lesser extent, the age of the animal affect drug disposition. For instance, the study conducted on comparisons of the pharmacodynamics of norfloxacin nicotinate between weaning and unweaned calves revealed that the distribution of the drug did not differ between the two groups of calves, but the total body clearance time was increased in weaned calves, possibly due to increased weight from the presence of rumen fluid. Calves fed grain had shorter clearance times (approximately four days) for sulfamethazine than unweaned calves. The elimination half-life of tindazole is shorter in unweaned calves than in adult cows, while the elimination half-life of apramycin is longer in calves than in adult cattle, possibly due to the immaturity of the drug clearance system [14].

Feeding: Diet can affect the bioavailability of drugs [15]. For instances, study conducted to determine the effects of diet content on the bioavailability of orally administered fenbendazole to cattle and Indian buffalo and fed dry hay either with or without fresh green herbage showed that animals receiving feed containing fresh herbage had lowered bioavailability of the drug. Fenbendazole stays in the rumen and is progressively released with digesta and the presence of fresh herbage increases gut activity and the flow rate of digesta, which depletes the available stores of fenbendazole in the rumen. In regard to feeds, actual gut contents can also affect drug uptake and pharmacodynamics.

Disease Status: The disease status of an animal can affect the pharmacokinetics of drugs administered, which can influence the potential for residues [16]. This can occur either when the disease affects the metabolic system (and consequently drug metabolism), or when the presence of infection and/or inflammation causes the drug to accumulate in affected tissues. For example, cattle with acutely inflamed mastitis quarters, apramycin penetrates

these areas of the body and concentrations of the drug have been observed at ten times over the level recorded from cows without mastitis.

Ketoprofen levels in milk increase during clinical mastitis where there is an influx of serum components into the udder. In calves with experimentally induced fasciolosis, the elimination half-life of antipyrine was slightly increased, but was slightly decreased for erythromycin and statistically significant decrease for oxytetracycline. The proposed mechanisms for these changes were the changes in liver function by fasciolosis, which changed the processing of drugs through the liver [17].

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

Absorption: It is described as the process, which a compound passes from its site of administration into the bloodstream. Absorption is influenced by many factors such as the properties of cell membrane, drug properties and route of administration and physiopathological state of the animal. An indication of the rate of drug absorption is obtained from the peak plasma concentration (C_{max}) and time reaching the maximum concentration [18].

Distribution: It is the process whereby a drug is transported to all the tissues and organs. After entering the systemic circulation, in whatever route of administration, drugs are conveyed throughout the body and reach their site of action. There are four major factors responsible for the extent and rate of distribution. These are the physicochemical properties of the drug, the concentration gradient established between the blood and tissue, the ratio of blood flow to tissue mass and the affinity of the drug for tissue constituents and serum protein binding. Only the fraction free form (unbound) of the drug is capable of exiting the circulation to distribute through the body and exert activity at the site of action. The parameter, which defines the process of distribution, is the volume of distribution [19].

Metabolism (Biotransformation): It is the principal mechanism of elimination for the transformation of drugs or xenobiotics into metabolites of the chemical reaction. Hepatocytes play an extremely important role in the

metabolism of drugs and xenobiotic-compounds that are foreign to the body, some of which are toxic. The kidneys are responsible ultimately to dispose of these substances, but for effective elimination, the drug or its metabolites must be made hydrophilic (polar, water-soluble). This is because reabsorption of a substance by the renal tubules is dependent on its hydrophobicity. The more hydrophobic (non-polar, lipid-soluble) substance is, the more likely it will be reabsorbed [20].

Many drugs and metabolites are hydrophobic and the liver converts them into hydrophilic compounds by using the two classes of enzymatic pathways of biotransformation; phase I (non-synthesis) and phase II (conjugation). Phase I corresponds to functionalization processes including oxidation, reduction, hydrolysis, hydration and isomerization reactions. Phase II reactions involve conjugation of the drug or phase I metabolite with the endogenous substrate such as glucuronic acid, sulfate, acetate and methyl group. Although some drugs are eliminated from the body by uncharged, most drugs undergo metabolism where the liver is the main organ of reaction. In addition, the liver's function may change the drug's form to be inactive and easy to excrete but some drugs may be converted to an activating form Donoghue [21].

Excretion: It is the process by which the parent drug or its metabolites are removed from the body fluids. The kidney is the most important site of drug excretion. There are three renal mechanisms; glomerular filtration, carrier mediated proximal tubular secretion and pH dependent, passive tubular resorption in the distal nephron. Renal insufficiency usually significantly affects drug excretion. The systemic clearance and elimination half-life are important parameters referring to the overall rate of elimination (metabolism and excretion). Although most compounds are excreted primarily by the renal, some drugs are partially or completely excreted through the bile. It has been reported that there is an extensive species variation among animals in their general ability to excrete drugs in the bile; example, chicken are characterized as good biliary excreters, whereas sheep and rabbit are characterized as moderate and poor excreters [22].

Extra-Label Drug Use (ELU): Extra-label Drug Use (ELU) refers to the use of an approved drug in a manner that is not in accordance with the approved label directions. ELU occurs when a drug only approved for human use is used in animals, when a drug approved for one species of

animal is used in another, when a drug is used to treat a condition for which it was not approved, or the use of drugs at levels in excess of recommended dosages. For instances, the use of phenobarbital (a drug only approved for use in humans) to treat epilepsy in dogs and cats; the use of ivermectin in dogs and cats (an antiparasitic only approved for use in cattle); and the use of enrofloxacin solution as a topical ear medication (only approved for use as an injection) are the common ELU in veterinary medicine [23].

There are conditions for ELU in food animals. For example, when considering ELU of an approved human drug in food animals: the veterinarian must have medical rational for the use; the veterinarian may not use an approved human drug if an animal drug approved for use in food-producing animals can be used instead for the particular ELU; and if scientific information on the human food safety aspect of the use of the drug in food-producing animals is not available, the veterinarian must take appropriate measures to assure that the animal and its food products will not enter the human food supply [24].

Improper Withdrawal Time: The withdrawal time (also known as the depletion or clearance period) is the time for the residue of toxicological concern to reach a safe concentration as defined by the tolerance. Depending on the drug product, dosage form and route of administration, the withdrawal time may vary from a few hours to several days or weeks. It is the interval necessary between the last administration to the animals of the drug under normal condition of used and the time when treated animal can be slaughtered for the production of safe foodstuffs [25].

Incidence of Veterinary Drug Residues: The ongoing threat of antibiotic contamination is one of the biggest challenges to public health that is faced by the human population worldwide. Such residues are spreading rapidly, irrespective of geographical, economical, or legal differences between countries. Additionally, the study reported in 2004 by EU also revealed that the majority of residues confirmed in animals were antibacterial agents [26].

Currently, the joint FAO/WHO Expert Committee on Food Additives (JECFA) has also reported various veterinary drugs and other environmental substances residues in a series of working documents. Additionally, the JECFA has been participating in further evaluating the safety of residues of veterinary drugs in food and in

establishing acceptable daily intakes (ADIs) and recommend maximum residue limits (MRLs) for substances when they are administered to food-producing animals in accordance with good veterinary practice in the use of veterinary drug [27].

Potential Effect of Veterinary Drug Residues on Public Health: Drug low-level contamination generally may not generate a violation problem on public health. However, extensive use of drugs may increase the risk of an adverse effect of residues on the customer including the occurrence of antibiotic resistance and hypersensitivity reaction. Therefore, prudent use of drugs in the manner of preventing feed contamination is necessary [28].

Development of Drug Resistance: Human health can be affected either through residues of drugs in food of animal origin, which may cause direct side effects, or indirectly, through selection of antibiotic resistance determinants that may spread human pathogen. 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 an additional load to the reservoir of resistance genes already present in man. 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. 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. It has been documented that human develop drug resistant bacteria such as Salmonella, Campylobacter and Staphylococcus from food of animal origin [29].

Drug Hypersensitivity Reaction: Drug hypersensitivity is defined as an immune mediated response to a drug agent in a sensitized patient and drug allergy is restricted to a reaction mediated by IgE. An allergic or hypersensitive effect following administration of a drug (i.e., drug allergy is quite similar to that typified by allergic response to protein, carbohydrate and lipid macromolecules). Allergic reactions to drugs may include anaphylaxis, serum sickness, cutaneous reaction, a delayed hypersensitivity response to drugs appear to be more commonly associated with the antibiotics, especially of penicillin [30].

Carcinogenic Effect: The term carcinogen refers to an effect produced by a substance having carcinogenic activity. Considerable confusion has existed because a carcinogen applies to substances that are so varied in their qualitative and quantitative characteristics. The potential hazard of carcinogenic residues is related to their interaction or covalently binding to various intracellular components such as proteins, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), glycogen, phospholipids and glutathione [31].

Mutagenic Effect: The term mutagen is used to describe chemical or physical agents that can cause a mutation in a DNA molecule or damage the genetic component of a cell or organisms. Several chemicals, including alkalinizing agents and analogues of DNA bases, have been shown to elicit mutagenic activity. There has been increasing concern that drugs as well as environmental chemicals may pose a potential hazard to the human population by production of gene mutagen or chromosome breakage that may have adversely affects human fertility [32].

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. Consequently, a congenital malformation that affects the structural and functional integrity of the organism is produced. Of the anthelmintics, benzimidazole is embryo toxic and teratogenic when given during early stage of pregnancy because of the anthelmintic activity of the drug. In addition to embryo toxicity including teratogenicity, the benzimidazole drug of oxfendazole, has also exhibited a mutagenic effect [33].

Disruption of Normal Intestinal Flora: The bacteria that usually live in the intestine act as a barrier to prevent incoming pathogen from being established and causing diseases. Antibiotics may reduce the total number of the bacteria or selectively kill some important species. The broad-spectrum antimicrobials may adversely affect a wide range of intestinal flora and consequently cause gastrointestinal disturbance [34].

Safety Evaluation for VMPs Residue

Acceptable Daily Intake (ADI): It is the amount of a substance that can be ingested daily over a lifetime without appreciable health risk. Calculation of ADI is based on an array of toxicological safety evaluation that takes into acute and long-term exposure to the drug and its potential impact [35]. If the drug is not a carcinogen,

the no observed effect level (NOEL) of the most sensitive effect in the most sensitive species divided by a safety factor is used to determine an ADI for drug residues. The FDA will calculate the safe concentration for each edible tissue using the ADI, the weight in kg of an average adult (60 kg) and the amount of the product eaten per day in grams as follows [36].

$$\text{Safe concentration} = [\text{ADI } (\mu\text{g/kg/day}) \times 60 \text{ kg}] / [\text{Grams consumed/day}].$$

Maximum Residue Limit (MRL): It 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. The concentration is expressed in milligrams per kilogram of the commodity (or milligrams per liter the case of a liquid commodity) [37].

Calculating Withdrawal Time: The withdrawal period or the milk discards time is the interval between the time of the last administration of a veterinary drug and the time when the animal can be safely slaughtered for food or the milk can be safely consumed. 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 [38].

Withdrawal times are determined in edible, target tissues by FDA/CVM during the drug approval process. These target tissues are most commonly the liver or kidney. As the primary organs of elimination, they will typically display a residue for the longest time. During withdrawal studies, the target organ is determined and animals are sampled at various times after drug administration is stopped. Statistical procedures are used to determine when almost every animal given the drug would be below the drug tolerance concentration in the target organ. A muscle tolerance has also been established for some drugs. For those drugs for which only a kidney or liver tolerances has been established, if a violative residue is found in the target organ, the whole carcass would need to be discarded. On the other hand, for the drugs for which a muscle tolerance has been established, even if a violative residue is found in the kidney or liver a violative residue is not found in the muscle, the carcass would not need to be discarded.

The disposition of such carcasses cannot be determined by testing of liver, kidney and muscle is completed [39].

Residue Avoidance

Pharmacological Principles: To implement an effective residue avoidance program in a food animal practice, a veterinarian must be aware of pharmacological principles of many drugs. Half-life ($t_{1/2}$) is the time it takes to remove 50% of the drug from the animal and used to estimate withdrawal time. A drug with a large volume of distribution (Vd) generally has relatively good tissue distribution compared with a drug of restricted distribution. The utility of viewing half-life as a function of the Vd and clearance (CL) is that these two independent parameters reflect the underlying physiology of the animal. Finally, another determinant of the elimination half time for slowly absorbed drugs administered extravascular is the rate of absorption. If this process is lower than elimination half-life, functionally becomes the biological half time. With depot and sustained release preparations, this phenomenon takes on increased importance to residue avoidance [40].

The problem facing veterinarians is that most pharmacokinetic parameters have been determined in healthy animals. Yet diseased animals would be expected to altered physiology. The half-life will increase if CL is reduced due to an increased Vd. This would result in increased elimination a half-life by a factor of six. The disease may also prolong absorption half-life (decreased blood perfusion of muscles, altered gastrointestinal transit time, etc.) to the point that the elimination profile is different from normal animals. Based on this simplified overview of basic pharmacokinetic principles, the relationship of half-life of the withdrawal time can use to reduce the incidence of violative residues. Doubling dose of the drug should only prolong the approved withdrawal time by one half-life; however, doubling the half-life as a result of the disease would double the necessary withdrawal time pathophysiologic states that increased Vd and/or CL would be expected to prolong half-life [41].

Managing Antimicrobial Residues for Food Safety:

Several international organizations have produced recommendations on the responsible and prudent use of antimicrobial agents in aquaculture to reduce the overuse and misuse of antimicrobials in animals in order to protect public health. Identified basic principles for prudent and rational veterinary use of antimicrobials are as follows [42].

Regulation: Regulating the use of antibiotics in food animals is an important part of containing resistance. WHO recommended that national veterinary, agricultural and pharmaceutical authorities and other stakeholders consider eliminating the use of antibiotics as growth promoters, requiring that antibiotics be administered to animals only when prescribed by a veterinarian and requiring that antibiotics identified as critically important in human medicine [43].

Reduced Need for and Prudent Use of Antibiotics: Antibiotics are valuable drugs and should be used only therapeutically and as little as necessary. It is important that national veterinary and agricultural and pharmaceutical authorities promote preventive veterinary medicine and the prudent use of antibiotics in collaboration with the private sector and all relevant stakeholders, particularly veterinary practitioners and farmers [44].

Particularly Important Steps Are:

- The need for antibiotics in food animals should be reduced by improving animal health through bio-security measures (to prevent the introduction of harmful bacteria and the development of infections), disease prevention (including the introduction of effective vaccines, prebiotics and probiotics) and good hygiene and management practices.
- Antibiotics should be administered to food animals only when prescribed by a veterinarian.
- Antibiotics should be used only therapeutically and the use should be based on the results of resistance surveillance (microbial cultures and antibiotic susceptibility testing), as well as clinical experience.
- Use of antibiotics as growth promoters should be eliminated.
- Narrow-spectrum antibiotics should be the first choice when antibiotic therapy is justified.
- The use of antibiotics in food animals should be limited to their approved and intended uses, take into consideration on-farm sampling and testing of isolates from food animals during their production, where appropriate and include adjustments to treatment when problems become evident.
- International guidelines on prudent use of antibiotics, adapted to countries' circumstances, should be followed at the national level. Veterinarians' professional societies should establish guidelines on the appropriate usage of antibiotics for

different classes of food animals, including indications of first-, second- and last-resort choices for treating different bacterial infections.

- Economic incentives that facilitate the inappropriate prescription of antibiotics should be eliminated [45].

Advocacy and Communication: The main objectives of advocacy and communication on antimicrobial residues at the international and national levels should be to raise awareness of the importance of antibiotics in treating bacterial infections and the public health challenges of antimicrobial residues-including within a food safety perspective and to prompt action to use them prudently in all sectors. A participatory approach should be used to develop and implement communication strategies that emphasize the importance and benefits of prudent use principles. These strategies should identify relevant target audiences, such as decision-makers; professionals from the health, veterinary and agricultural sectors; farmers; the media; and the general public. These audiences need trustworthy and evidence-based information to guide their decisions and choices [46].

Training and Capacity Building: Education strategies that emphasize the importance and benefits of the prudent use of antibiotics should be developed and implemented to provide relevant information about antibiotic resistance to farmers, veterinarians and the public. There is an urgent need to develop guidelines on prudent use, with multidisciplinary involvement, to reduce misuse of antibiotics in aquaculture, giving special consideration to antibiotics categorized as critical for human medicine. Veterinarians and farmers should receive training in following these guidelines and, to improve compliance, need to be audited and to receive feedback [47].

Knowledge Gaps and Research Needs: The understanding of antibiotic resistance related to food safety still has many knowledge gaps that research is needed to fill. For example, the available information on the burden of disease from antibiotic-resistant organisms is mainly qualitative; research to quantify the differential burden of disease that results from resistant versus susceptible bacterial strains needs to be promoted. Such information would provide an additional dimension to the magnitude of the issues and support risk assessment and management, including the development of cost-effective strategies to counteract the development and spread of antibiotic resistance [48].

Hazard Analysis of Critical Control Points (HACCP):

The HACCP system, which is science-based and systematic, identifies not only specific hazards but also measures for their control to ensure the safety of food. HACCP is a tool used to assess hazards and establish control systems that focus on prevention rather than relying mainly on end product testing [49]. HACCP can be applied through the food chain from primary production to final consumption and its implementation should be guided by scientific evidence of risks to human health. In addition, the application of HACCP systems can aid control by regulatory authorities and promote international trade by increasing confidence in safety of traded foods.

Control and Preventive Measures: The residue prevention strategy is based on preventing entry of violative 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 [50]:

- ▶ Herd health management; 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;
- ▶ Use of approved drugs; dairy and beef producers should not use or store un- approved drugs, special mixes, or products within adequate labels as unapproved drugs have no data regarding efficacy, safety, or withholding time. The herd veterinarian should be certain that ELU involves only approving products;
- ▶ Establishment of valid veterinarian-client-patient relationship; the use of prescription drug and the ELU necessitate 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. Record the identification of all animals in the permanent health record book;

- ▶ Having proper drug residue testing capabilities really available on and off the farm; 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 drug use and methods to avoid marketing adulterated products principally educational, 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.

CONCLUSIONS

The use of veterinary drugs in food-producing animals has the potential to generate residues in animal derived products and poses a health hazard to the consumer. Veterinarians are facing a dramatic change in attitude and behaviors concerning drug residues because of the therapeutic and prophylactic use of drugs. Until recently, veterinarians did not pay sufficient attention to ensuring that the producers adhered strictly to the withdrawal period for milk, meat and egg from animals treated with a variety of drugs. The most likely reason for drug residues may result from human management, such as improper usage, including extra-label or illegal drug applications. However, the most obvious reason for unacceptable residues might be due to failure to keep to the withdrawal period, including using overdose and long-acting drugs. There is also limited information on the magnitude of veterinary drug residue worldwide. Hence, an extensive work has to be carried out to prevent the occurrence of VMPs residues and to familiarize all animal health professionals with the knowledge of pharmacokinetics, pharmacodynamics and toxicological effects of pharmaceutical preparations that are useful in prevention, control and treatment of animal disease as specified times required for withdrawal of medication from food of animal origin prior to ready for human consumption.

The impact of antimicrobial resistance on animals and humans cannot be overemphasized. For animal health, the main issue is treatment failure due to increases in resistance. For human health, the main concern is adverse health effects associated with the presence of residues in

the food produced or resistance in bacteria associated with human disease. Resistance in bacteria causing human disease may arise either directly via enrichment of these bacteria in the aquaculture environment or indirectly via enrichment of the genes that encode such resistance and which may subsequently be transferred to bacteria associated with human disease. Considering the principle of One Health, policy-makers and health authorities should integrate efforts that embrace human and veterinary disciplines in a holistic pattern.

There could be no doubt that antimicrobial resistance poses a global challenge. No single nation, however effective it is at containing resistance within its boundaries, can protect itself from the importation of resistant pathogens through travel and trade. The global nature of resistance calls for a global response, not only in the geographic sense, i.e., across national boundaries, but also across the whole range of sectors involved. Nobody is exempted from the problem or from playing a role in the solution. Therefore, relevant recommendations must be targeted to policy-makers, health authorities, industry and research.

REFERENCES

1. Dapuelto, G., F. Massa, S. Costa, L. Cimoli, E. Olivari, M. Chiantore, B. Federici and P. Povero, 2015. A spatial multi-criteria evaluation for site selection of offshore marine fish farm in the Ligurian Sea, Italy. *Ocean & Coastal Management*, 116: 64-77.
2. Jeena, S., N. Venkateswaramurthy and R. Sambathkumar, 2020. Antibiotic Residues in Milk Products: Impacts on Human Health. *Research Journal of Pharmacology and Pharmacodynamics*, 12(1): 15-20.
3. Bianchi, M.C.G., F. Chopin, T. Farmer, N. Franz, C. Fuentevilla, L. Garibaldi, N.H.R.
4. Croubels, S. and E. Daeseleire, 2012. Veterinary drug residues in foods. In *Chemical contaminants and residues in food* (pp: 148-182). Woodhead Publishing.
5. Serratos, J., Blass, A., B. Rigau, B. Mongrell, T. Rigau, M. Tortades, E. Tolosa, C. Aguilar, O. Ribó, and J. Balagué, 2006. Residues from veterinary medicinal products, growth promoters and performance enhancers in food-producing animals: a European Union perspective. *Rev. Sci. Tech.*, 25(2): 637-53.
6. Gilbert, J.M., D.G. White and P.F. McDermott, 2007. The US national antimicrobial resistance monitoring system.
7. Eisenbrand, G., B. Pool-Zobel, V. Baker, M. Balls, B.J. Blaauboer, A. Boobis, A. Carere, S. Kevekordes, J.C. Lhuguenot, R. Pieters and J. Kleiner, 2002. *Methods of in vitro toxicology*. Food and Chemical Toxicology, 40(2-3): 193-236.
8. Beyene, T., 2016. Veterinary drug residues in food-animal products: its risk factors and potential effects on public health. *J. Vet. Sci. Technol.*, 7(1): 1-7.
9. Grainger, F. Jara, I. Karunasagar and A.L.G. Laurenti, 2014. *FAO: The State of World Fisheries and Aquaculture*. Rome, Italy: Food and Agriculture Organization of the United Nations.
10. Mo, W.Y., Z. Chen, H.M. Leung and A.O.W. Leung, 2017. Application of veterinary antibiotics in China's aquaculture industry and their potential human health risks. *Environmental Science and Pollution Research*, 24(10): 8978-8989.
11. Van Boeckel, T.P., C. Brower, M. Gilbert, B.T. Grenfell, S.A. Levin, T.P. Robinson, A. Teillant and R. Laxminarayan, 2015. Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences*, 112(18): 5649-5654.
12. Okocha, R.C., I.O. Olatoye and O.B. Adedeji, 2018. Food safety impacts of antimicrobial use and their residues in aquaculture. *Public Health Reviews*, 39(1): 1-22.
13. Beyene, T., 2016. Veterinary drug residues in food-animal products: its risk factors and potential effects on public health. *J. Vet. Sci. Technol.*, 7(1): 1-7.
14. Wilson, J.S., T. Otsuki and B. Majumdar, 2003. Balancing food safety and risk: do drug residue limits affect international trade in beef?. *Journal of International Trade & Economic Development*, 12(4): 377-402.
15. Njoga, E., 2015. Prevalence of and Awareness of the Risks Associated with Antimicrobial Drug Residues in Edible Tissues of cattle And Pigs in Enugu State, Nigeria (Doctoral dissertation), Mention Faculty & University and pages??.
16. Sarmah, A.K., M.T. Meyer and A.B. Boxall, 2006. A global perspective on the use, sales, exposure pathways, occurrence, fate and effects of veterinary antibiotics (VAs) in the environment. *Chemosphere*, 65(5): 725-759.
17. Tollefson, L. and M.A. Miller, 2000. Antibiotic use in food animals: controlling the human health impact. *Journal of AOAC International*, 83(2): 245-254.
18. Lee, M.H., H.J. Lee and P.D. Ryu, 2001. Public health risks: Chemical and antibiotic residues-review. *Asian-Australasian Journal of Animal Sciences*, 14(3): 402-413.

19. Kabir, J., Umoh, J.U. and Umoh, V.J., 1999. Public awareness and health concern with regard to veterinary drug residues in meat in Nigeria. *Health and Hygiene*, 20(1): 20.
20. Verdon, E., D. Hurtaud-Pessel and P. Sanders, 2006. Evaluation of the limit of performance of an analytical method based on a statistical calculation of its critical concentrations according to ISO standard 11843: Application to routine control of banned veterinary drug residues in food according to European Decision 657/2002/EC. *Accreditation and Quality Assurance*, 11(1-2): 58-62.
21. Vranic, M.L., L.Marangunich, H.F. Courel and A.F. Suárez, 2003. Estimation the withdrawal period for veterinary drugs used in food producing animals. *Analytica Chimica Acta*, 483(1-2): 251-257.
22. Burrige, L., J.S. Weis, F. Cabello, J. Pizarro and K. Bostick, 2010. Chemical use in salmon aquaculture: a review of current practices and possible environmental effects. *Aquaculture*, 306(1-4): 7-23.
23. Defoirdt, T., N. Boon, P. Sorgeloos, W. Verstraete and P. Bossier, 2007. Alternatives to antibiotics to control bacterial infections: luminescent vibriosis in aquaculture as an example. *Trends in Biotechnology*, 25(10): 472-479.
24. Donoghue, D.J., 2003. Antibiotic residues in poultry tissues and eggs: human health concerns?. *Poultry Science*, 82(4): 618-621.
25. Raison-Peyron, N., D. Messaad, J. Bousquet and P. Demoly, 2001. Anaphylaxis to beef in penicillin-allergic patient. *Allergy*, 56(8): 796-797.
26. Schwarz, S. and E. Chaslus-Dancla, 2001. Use of antimicrobials in veterinary medicine and mechanisms of resistance. *Veterinary Research*, 32(3-4): 201-225.
27. Jacela, J.Y., J.M. DeRouche, M.D. Tokach, R.D. Goodband, J.L. Nelssen, D.G. Renter and S.S. Dritz, 2009. Feed additives for swine: Fact sheets—acidifiers and antibiotics. *Journal of Swine Health and Production*, 17(5): 270-275.
28. Beltrán, M.C., T. Romero, R.L. Althaus and M.P. Molina, 2013. Evaluation of the Charm maximum residue limit β -lactam and tetracycline test for the detection of antibiotics in ewe and goat milk. *Journal of Dairy Science*, 96(5): 2737-2745.
29. Swapna, K.M., R. Rajesh and P.T. Lakshmanan, 2012. Incidence of antibiotic residues in farmed shrimps from the southern states of India.
30. Hassan, M.N., M. Rahman, M.B. Hossain, M.M. Hossain, R. Mendes and A.A.K.M. Nowsad, 2013. Monitoring the presence of chloramphenicol and nitrofurantol metabolites in cultured prawn, shrimp and feed in the Southwest coastal region of Bangladesh. *The Egyptian Journal of Aquatic Research*, 39(1): 51-58.
31. Olatoye, I.O. and A. Basiru, 2013. Antibiotic usage and oxytetracycline residue in African catfish (*Clarias gariepinus*) in Ibadan, Nigeria. *World Journal of Fish and Marine Sciences*, 5(3): 302-309.
32. Mahmoudi, R., P. Gajarbeygi, R. Norian and K. Farhoodi, 2014. Chloramphenicol, sulfonamide and tetracycline residues in cultured rainbow trout meat (*Oncorhynchus mykiss*). *Bulgarian Journal of Veterinary Medicine*, 17(2): 147-152.
33. Pham, D.K., J. Chu, N.T. Do, F. Brose, G. Degand, P. Delahaut, E. De Pauw, C. Douny, Van K. Nguyen, T.D. Vu and M.L. Scippo, 2015. Monitoring antibiotic use and residue in freshwater aquaculture for domestic use in Vietnam. *Eco Health*, 12(3): 480-489.
34. Darwish, W.S., E.A. Eldaly, M.T. El-Abbasy, Y. Ikenaka, S. Nakayama and M. Ishizuka, 2013. Antibiotic residues in food: the African scenario. *Japanese Journal of Veterinary Research*, 61(Supplement), pp: S13-S22.
35. Joint, F.A.O., World Health Organization and WHO Expert Committee on Food Additives, 2013. Evaluation of certain food additives and contaminants: seventy-seventh report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization.
36. Allen, H.K. and T.B. Stanton, 2014. Altered egos: antibiotic effects on food animal microbiomes. *Annual Review of Microbiology*, 68: 297-315.
37. Kumar, A., A. Patyal and A.K. Panda, 2018. Sub-therapeutic use of antibiotics in animal feed and their potential impact on environmental and human health: a comprehensive review. *Journal of Animal Feed Science and Technology*, 6(15): 25.
38. Cole, D.W., R. Cole, S.J. Gaydos, J. Gray, G. Hyland, M.L. Jacques, N. Powell-Dunford, C. Sawhney and W.W. Au, 2009. Aquaculture: Environmental, toxicological and health issues. *International Journal of Hygiene and Environmental Health*, 212(4): 369-377.

39. Karunasagar, I., 2008. Food safety and public health risks associated with products of aquaculture. Understanding and applying risk analysis in aquaculture. FAO fish aqua tech paper. Rome: FAO, pp: 9-25.
40. Rokka, M., S. Eerola, U. Perttilä, L. Rossow, E. Venäläinen, E. Valkonen, J. Valaja and K. Peltonen, 2005. The residue levels of narasin in eggs of laying hens fed with unmedicated and medicated feed. *Molecular Nutrition & Food Research*, 49(1): 38-42.
41. Sallum, U.W. and T.T. Chen, 2008. Inducible resistance of fish bacterial pathogens to the antimicrobial peptide cecropin B. *Antimicrobial Agents and Chemotherapy*, 52(9): 3006-3012.
42. Boscardin, L., 2017. Capitalizing on Nature, Naturalizing Capitalism: An Analysis of the “Livestock Revolution,” *Planetary Boundaries and Green Tendencies in the Animal-Industrial Complex. Animal Oppression and Capitalism [2 volumes]*, pp: 259.
43. Clarke, E.E.K., 2002. Multidisciplinary occupational health services. *Afr Newsletter Occup Health Safety*, 14(1): 3.
44. Hide, J., C. Hide and J. Kimani, 2001. Informal irrigation in the Peri-urban Zone of Nairobi, Kenya: an assessment of surface water quality for irrigation. Report OD/TN. HR Wallingford Ltd, Wallingford, UK, pp: 105.
45. Orand, J.P., 2012. Antimicrobial resistance and the standards of the World Organisation for Animal Health. *Revue Scientifique et Technique-OIE*, 31(1): 335.
46. Mathew, P., C. Jaguga, M. Mpundu and S.J. Chandy, 2019. Building knowledge and evidence base on antimicrobial resistance in Africa, through ‘One Health’ based surveillance. *Clinical Epidemiology and Global Health*.
47. Éloit, M., 2012. The global public good concept: a means of promoting good veterinary governance. *Review of Scientific Technical Oie*, 31: 585-590.
48. FAO, O., 2010. The FAO-OIE-WHO Collaboration: Sharing responsibilities and coordinating global activities to address health risks at the anima-human-ecosystems interfaces: A Tripartite Concept Note.
49. Yahia, K.I.S., 2017. Global action to alleviate the threat of antimicrobial resistance: progress and opportunities for future activities under the “One Health” initiative.
50. Christian, K.A., K. Ijaz, S.F. Dowell, C.C. Chow, R.A. Chitale, J.S. Bresee, E. Mintz, M.A. Pallansch, S. Wassilak, E. McCray and R.R. Arthur, 2013. What we are watching-five top global infectious disease threats, 2012: a perspective from CDC's Global Disease Detection Operations Center. *Emerging Health Threats Journal*, 6(1): 20632.