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Veterinary Antibiotic Residues in Foods of Animal Origin: Its Public Health Implications and Detection Methods: Review on Literature

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Abstract: The use of veterinary antibiotics in food-producing animals has the potential to generate residues in animal derived products. There are many factors influencing the occurrence of residues in animal products such as distribution, metabolism and excretion of antibiotics, improper withdrawal period and extra label use of antibiotics. Even trace number of residues in food of animal origin may superimpose to a public health impacts to the consumer. Stringent control strategies mainly development of bio control measures, applications of alternative and good hygienic practices over the underhanded use of antibiotics are some of positive approaches to safeguard the public health and to protect the currently available antibiotics for future clinical uses. There is limited information on the magnitude of veterinary antibiotic residues worldwide particularly in developing countries like Ethiopia in spite of its public and animal health impacts. Hence, the objective of this review paper was to bridge information gap regarding antibiotic residues, impacts on public health and its mitigating approaches. Extensive work should be carried out to elucidate the magnitude of the problem and mitigate the occurrence of veterinary antibiotic residues mainly through applying the risk management strategies and enhancing the awareness of animal health professionals with regard to industrial, microbiological and toxicological effects of antibiotic residue.

Key words: Alternative Approach · Antibiotic Residues · Public Health Impacts

INTRODUCTION

Antibiotics are substances either produced naturally by living organisms, synthetically in the laboratory, or through semi synthetic modifications [1]. It can be classified according to their effects as either bactericidal or bacteriostatic and according to their range of efficacy as narrow or broad in spectrum [2].

Antibiotics are the most widely used veterinary drugs for therapeutic and prophylactic purposes and as growth promoter in dairy animals which may appear in milk as residues for a certain time period [3]. Antimicrobial drugs are used to control, prevent and treat infection and to enhance animal growth and feed efficiency [4].

The intensification of animal production in recent decades has been aided using veterinary medicinal products; in particular, anti-infective drugs in modern livestock production [5]. The most commonly used antimicrobials in food producing animals are the beta-lactams, tetracyclines, aminoglycosides and sulfonamides [6].

Residues are pharmacologically active substances and their metabolites which remain in foodstuffs obtained from animals to which the veterinary medicinal products in question have been administered [7]. Moreover, on a broad sense defined as undesirable substances which could be chemical or biological in nature and are present in small amounts in food of animal origin because of medications given to livestock or of processing methods [8].

The presence of antibiotic residues in animal products can be due to a number of different causes such as the misuse of antibiotics in food animals, disease prevention and failure to observe the withdrawal period, the illegal use of antibiotics and the use of antibiotics as growth promoters, among others [9]. Antibacterial drugs

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and hormonal growth promoters are the main veterinary medicinal products that potentially contaminate foods of animal origin [10]. Veterinary drug residues are one of many global issues concerning food contamination [11].

Antibiotic residues in foods of animal origin may be the cause of numerous health concerns in humans. These problems include toxic effects, transfer of resistant bacteriatohumans, carcinogenicity, mutagenicity, nephropathy, hepatotoxicity, allergy and hypersensitivity reactions [12]. The control of antibiotic residues in animal products begins with their correct prescription and administration, careful adherence to withdrawal periods and applying either screening or confirmatory or both of its detection techniques [13].

Despite the fact of the prevailing situation and the presence of a number of public health implications due to antibiotic residues from consumption of different food items of animal origin in most parts of the globe, particularly developing countries, there is limited information on magnitude of antibiotic residues. Therefore, in light of the above facts this review paper was designed to:

- ✓ High light factors contributing to veterinary antibiotic residues.
- ✓ Review its potential public health implications and detection methods
- ✓ Outline possible mitigating approaches towards veterinary antibiotic residues.

Factors for Occurrence of Antibiotic Residues: The presence of antibiotic residues in animal products can be due to a number of different factors such as the misuse of antibiotics in food animals, disease prevention and failure to observe the withdrawal period, the illegal use of antibiotics and the use of antibiotics as growth promoters, among others [9].

Distribution of Antibiotics: 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 [14].

Biotransformation (Metabolism) of Antibiotics: Many sites in the body are involved in drug metabolism including the gut wall, lungs, kidney and plasma. However, the liver is the most metabolically active tissue per unit weight and is thus responsible for the majority of drug metabolism. Other factors responsible for its contribution include its large size; it is perfused by blood containing drugs absorbed from the gut (enterohepatic circulation) and its very high concentration of most of the drug metabolizing enzymes relative to other organs. The largest family of membrane-bound, non-specific, mixed-function enzymes is called the cytochrome P450 system in the liver are involved in the metabolism of endogenous and exogenous compounds [15].

Excretion of Antibiotics (Elimination): The excretion of the drug is directly related to creatinine clearance. In the presence of impaired renal function, the urine levels fall below the therapeutic range while the serum levels increase into the toxic range. Thus, its efficacy is limited in the setting of renal impairment, with an associated greater risk of toxic effects and adverse reactions [16].

Extra Label Use of Antibiotics: The use of extra-label antibiotic treatments like different dosage form than what is approved on label, different routes of administration, different species of animal, longer or shorter duration of treatment and greater or lesser frequency of administration than what is indicated on label is directly related to antibiotic residues as there are no specific withdrawal period for those substances applied beyond legislated label [17].

Improper Withdrawal Period of Antibiotics: Miscalculating withholding times can lead to antibiotic residues which have both financial implications for the dairy producer and public health implications for consumers. Whenever drug preparations are administered to food producing animals, the veterinarian may alert owners to the necessity of withholding animals from market or slaughter during or following the treatment period. Withdrawal period of medication is necessary so that volatile or illegal levels of drug residue above tolerance level are avoided in meat, milk and eggs marketed for human consumption thereby safeguarding humans from unnecessary exposure to antimicrobials [12].

Major Veterinary Antibiotic Residues in Food of Animal Origin

Beta Lactams Residues: The beta-lactams antibiotics, including the penicillins, cephalosporins, carbapenems and others, make up the largest share of antibiotics used in most countries [18]. Beta-lactams antibiotics are broad spectrum antibiotics interfering with cell wall synthesis, used generally to treat Gram positive and Gram negative bacterial infections [19]. Among the beta-lactams antibiotics, penicillins and cephalosporins forms the major category used in veterinary medicine and are frequently used for the treatment of animals all over the globe. The residues of these antibiotics in milk cause problems in dairy industries and human health hazards [20].

Penicillin residues are not inactivated at pasteurization temperature or on drying and may cause allergic reaction manifested by skin rashes in very sensitive individuals at very low concentration in milk as effect of heat on antibiotic residue studied [21]. Cross reactivity is observed between penicillins and cephalosporins for development of allergic reactions. Approximately 4 % of patients with a history of penicillin allergy experience an anaphylaxis reaction to a cephalosporin [22] and patients with a history of a penicillin related allergic event have increased risk of a reaction when given a sulfonamide or a cephalosporin [23].

Aminoglycoside Residues: Aminoglycosides were the first antibiotics discovered by systematic screening of natural product sources for antibacterial activity [24]. Aminoglycosides are usually used synergistically with beta-lactams for the treatment of serious infections due to Gram positive and Gram negative bacteria. They act by binding to the A site of the 30 S small ribosomal subunit, inhibiting translation process in protein synthesis [25].

In humans, the nephrotoxicity of aminoglycosides is associated with small portions of the drug being accumulated in the renal cortex and leading to reversible renal impairment [26]. In addition to nephrotoxicity, aminoglycosides can cause irreversible ototoxicity that occurs both in a dose-dependent and idiosyncratic manner [27]. Some animal study data demonstrated the probable role of reactive oxygen species to induce specific ototoxicity [28].

Tetracycline Residues: The tetracyclines are broad spectrum antibiotics active against Mycoplasma, Chlamydophila and Rickettsia in addition to bacteria. Tetracyclines are bacteriostatic and acquired resistance is now widespread among bacteria [29].

The rate of metabolism of tetracyclines in cows has been estimated to 25-75 % and a significant percentage of the administrated tetracyclines are excreted in bovine milk [30]. If these antibiotics administrate improperly or if the withdrawal period for the treated cows has not been passed, the parent drug and their metabolites may end up in milk and may cause harmful effects to consumers [31].

Tetracyclines can cross the placenta and enter the fetal circulation and amniotic fluid. Relative to the maternal circulation, tetracycline concentrations in umbilical cord plasma and amniotic fluid are 60 and 20 % respectively. Relatively high concentrations of these drugs also are found in breast milk. Children receiving tetracyclines for long or short duration may develop permanent brown discoloration of the teeth. The larger the amount received relative to body weight, the more intense the enamel discoloration. Exposure of pregnant women with tetracyclines may produce discoloration of the teeth in her children [32].

Sulfonamide Residues: The sulfonamides are one of the oldest groups of antimicrobials and have been used in food animal production for over 60 years. Sulfonamides are still utilized in cattle, swine and poultry; however, their use has somewhat declined in some jurisdictions in spite of this drug class being the third most commonly used antimicrobial used in food animals. A recent study across 25 European countries found that sulfonamides were the third most popular class of antimicrobials used in veterinary medicine (behind tetracyclines and penicillins) and that sulfonamides represented 11% of the total sales of veterinary antimicrobial drugs across Europe in 2011 [33]. Resistance to sulfonamides has been reported for several of these drugs [34]. Adverse drug reactions in humans to sulfonamide drug exposure are common. Approximately half of the reported cases in humans are skin reactions [35].

Public Health Implications of Antibiotic Residues: The residues of antibacterial may present pharmacological, toxicological, microbiological and immune-pathological health risks for humans [36]. These hazards can be categorized in to two types as direct-short term hazards and indirect-long term hazards, according to duration of exposure to residues and the time onset of health effects [37]. The direct health hazards include the health effects caused due to excretion of antibiotics in milk, as an example the beta-lactams group of antibiotics regardless of their low concentration in milk causes allergic hypersensitive reaction in sensitized individual immediately after consumption

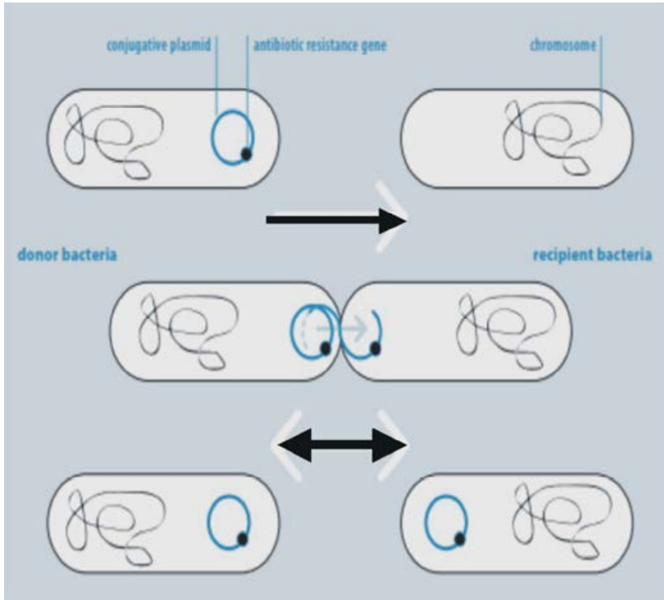

Fig. 1: Horizontal gene transfer: Resistance gene being transferred from one bacterium to another. Source: [42].

[38]. Indirect and long term hazards are the effects caused by long term exposure of an individual to residues and include carcinogenicity and reproductive effects. The long-term exposure to antibiotic residues in milk may result in alteration of the drug resistance of intestinal microflora [39].

Development of Antibiotic Resistance: Emerging antimicrobial resistance, due to use of antimicrobials, is a public health concern in human and animal medicine worldwide. According to the Centre for Disease Control and Prevention (CDC), resistant strains of three micro-organisms causing human illness mainly *Salmonella sp., Campylobacter sp.* and *Escherichia coli* are linked to the use of antibiotics in animals [40]. Resistant microorganism can get access to human, either through direct contact or indirectly with food of animal origin [41].

A microorganism is resistant if it exhibits "significantly reduced susceptibility" when compared with that of the "original isolate" or a group of sensitive strains. Resistance can result from mutations in housekeeping structural or regulatory genes, or alternatively, horizontal acquisition of foreign genetic information [42].

The potential for animal to human transfer of resistance is existed. Clearly, the irrational use of antibiotic in livestock production has been associated with the development of human antibiotic resistance [41].

Recent examples of highly resistant bacteria to antibiotics are numerous. To mention some of them, Methicillin-resistant S*taphylococcus aureus* (MRSA) are resistant bacteria to several beta-lactams antibiotics (super bugs) and were found on swine in 2005. Moreover, transfer of these resistant bacteria from swine to man was observed [43]. Extended spectrum beta lactamase (ESBL) producing bacteria are also resistant to, among others, pencillins and 3rd and 4th generation cephalosporin antibiotics and its emergence is linked to the excessive antibiotic use in poultry breeding and it was found that a majority of animals carry these resistant bacteria [44]. Enterohaemorragic *Escherichia coli* (EHEC) are other toxin-producing bacteria of which certain strains have developed many antibiotic resistance genes [45].

Antibiotic Allergy and Hypersensitive Reaction: Antibiotic hypersensitivity is defined as an immune-mediated response to antibiotic agent in a sensitized patient and antibiotic allergy is restricted to a reaction mediated by immunoglobulin E (IgE) [46].

Drug induced allergic reactions may occur acute (within 60 min), subacute (1-24 h), or as latent responses (1 day to several weeks). The acute and some sub-acute disorders are often due to Type I IgE-mediated reactions and, more rarely, due to immunoglobulin G (IgG) antibodies (Type II). Immune complex disorders (Type III) are much rarer. Type IV (cell mediated) responses develop more slowly. The principal types of disorder due to antibiotic residues are anaphylactic shock, asthma and hemolytic anemia and serum sickness and allergic vasculitis of type III and allergic dermatitis of type IV [46].

Perturbation of Normal Intestinal Microflora: Disruption of normal human flora in the intestine is another harmful effect of antibiotic residues in human food. The bacteria that usually live in the intestine act as a barrier to prevent incoming pathogenic bacteria from becoming established and causing disease. Antibiotics might reduce total numbers of these benign bacteria or selectively kill some important species [47].

To what extent disturbances in the ecological balance between host and microorganisms occur depends on the spectrum of the antimicrobial agent, the dose, pharmacokinetic and pharmacodynamic properties and *in-vivo* inactivation of the agent [48]. The broad-spectrum antimicrobials may adversely affect a wide range of intestinalflora and consequently cause gastrointestinal disturbance [49]. The consumption of trace levels of antimicrobial residues in foods from animal origin may have consequences on the indigenous human intestinal micro flora [50].

Miscellaneous Effects: Toxic and allergic reactions in humans and animals caused by tetracyclines have been observed at therapeutic doses Berends *et al*. [51] though prolonged ingestion of tetracycline present in the broiler meat has detrimental effects on teeth and bones in growing children [52].

The potential hazard of carcinogenic residues is related to their interaction or covalently binding to various intracellular components such as proteins, deoxyribonucleic acid, ribonucleic acid, glycogen, phospholipids and glutathione [53].

Industrially, the presence of antimicrobials in food may influence starter cultures in food industries [54]. In milk and yoghurt production, presence of antimicrobials in milk may inhibit bacterial fermentation process and cause problems for producers and subsequent losses in the food industry and loss of consumer confidence [55].

Detection of Antibiotic Residues in Food of Animal Origin: Different methods and assays for the detection of residues of antimicrobials, mostly in cow milk, have been developed and validated, whereas few studies have been carried out so far for detection of residues in sheep and goat milk [56]. The analytical methods for antibiotics detection can be divided into two groups, namely confirmatory and screening [57].

Screening Methods: Screening methods are primarily used to obtain semi-quantitative measurements and viable because of the low possibility of false-positive data, easy operation, quick analysis period, cost effectiveness and good selectivity. Screening methods used for the detection of antibiotics in products of animal origin have been reviewed recently [58]. The most commonly applied screening techniques for detection of antibiotics are immunoassays, microbiological inhibition assays and reporter gene assays [59].

Immunoassays: This method is mainly based upon a binding reaction between a compound and an antibody. The most commonly applied immunoassay in antibiotic analysis is the enzyme-linked immunosorbent assay (ELISA) [58]. It is a common serological technique for the detection of antigens and antibodies. ELISA is divided into two forms of assays: direct ELISA and indirect ELISA. Direct ELISA involves the use of monoclonal antibodies for the detection of a specific antigen. Indirect ELISA involves detecting a specific antibody in a sample, such as serum [60].

ELISA tests for analysis of beta-lactams antibiotics have been reviewed recently [61]. The sample that is screened for antibiotic content is incubated with antibodies, under the production of an analyte antibody binding complex. Next, the degree of binding, which is related to the level of antibiotics present in the sample, is determined (e.g. by adding a fluorescent label) [58].

Microbiological Inhibition Assays: They are based on a reaction between bacteria and the antibiotic present in the sample. The tube test consists of a growth medium inoculated with a bacterium, supplemented with a pH indicator. If no specific antibiotics are present, the bacteria start to grow and produce acid, which will cause a detectable color change. If antibiotics are present that inhibit bacterial growth, no color change will occur [62]. An important advantage, compared to immunoassays and confirmatory methods is that microbiological tests can detect any antibiotic compound that shows antibacterial activity Picó and barcelo [63] and they have the potential to cover the entire antibiotic spectrum within one test [64].

Reporter Gene Assays: It consists of a genetically modified bacterium, containing an inducible promoter, responsive to a particular antibiotic, coupled to a reporter gene. Based on the presence or absence of responsive antibiotics, the reporter gene induces a fluorescent signal or the gene affects the transcription to produce or inhibit a signaling process [59].

Confirmatory Methods: Samples testing positive are analyzed using various physical and chemical confirmationtechniques, such as liquid chromatography. Ultraviolet detection and fluorimetry, or combined with mass spectrometry and High performance liquid chromatography. These methods are designed to satisfy a number of performance criteria, which are verified during the required validation studies before being used for statutory control, in accordance with Decision 2002/657/EC [65].

High Performance Liquid Chromatography (HPLC): This technique is used to estimate the quantities of antibiotic residues in food products with good sensitivity and specificity [66]**.** HPLC has been used in the detection of sulphonamides Pecorelli *et al*. [67], tetracyclines Samanidou *et al*. [68] and beta-lactams and macrolides Nagata *et al.* [69] in food of animal origin.

Liquid Chromatography (LC) - Mass Spectrometry (MS): This method emerged as the method of choice for determination of antimicrobials which are rather polar, non-volatile and sometimes heat sensitive. An effective system whereby the mass spectrometry component functions by transforming the ionized (charged) state of molecules using the mass-to-charge ratio [70].

Challenges in Detection of Antibiotic Residues: Most commonly recommended challenge in antibiotic residue analysis is related to the emergence of antibiotic resistance among other. It is recognized only recently that antibiotic usage in veterinary practice and the presence of low levels of antibiotics in food products and the environment contribute to the emergence of antibiotic resistance [71].

A main bottleneck in beta-lactams analysis is that some penicillin antibiotics are unstable (mainly ampicillin, amoxicillin, penicillin G and penicillin V) and that some cephalosporins, including ceftiofur, are known to rapidly metabolize after intra-muscular administration [72].

Situation of Antibiotic Residues in Ethiopia: In many African countries, antibiotics may be used indiscriminately for the treatment of bacterial diseases or they may be used as feed additives for domestic animals and birds. The ongoing threat of antibiotic contamination is one of the biggest challenges to public health that is faced not only by the African people, but alsobythehumanpopulationworldwide [73]. Such residues are spreading rapidly, irrespective of geographical, economical, or legal differences between countries [74].

In Ethiopia, the control of drugs from the government authorities and information on the actual rational drug use pertaining to veterinary drug use is very limited. In addition, food animals slaughtered for domestic and export purposes in the country are not screened for the presence of residues in any of the slaughterhouses in the country. No formal control mechanisms exist to protect the consumers against the consumption of meat and milk products containing harmful drug residues in the country [75].

Myllyniemi *et al*. [47] investigated a total of 384 samples for tetracycline residues and reported that 71.3% had detectable oxytetracycline levels. Moreover, 93.8, 37.5 and 82.1% was found positive for oxytetracycline among the meat samples collected from the Addis Ababa, Debrezeit and Nazareth slaughterhouses, respectively. The mean levels of oxytetracycline in muscle from the three slaughterhouses were as follows: Addis Ababa, 108.34; Nazareth, 64.85 and Debrezeit, 15.916ìg/kg. Regarding kidney samples, oxytetracycline levels were found to be 99.02 in Addis Ababa, 109.35 in Nazareth and 112.53ìg/kg in DebreZeit.

Another study conducted by Abebaw *et al*. [76] reported about antibiotic residues in food of animal origin and revealed that oxytetracycline and penicillin G were imprudently used in dairy farms of the Nazareth dairy farms. Based on their report, out of 400 samples 48 (12 %) milk samples were positive for antibiotic residues in bulk milk of cows in Nazareth dairy farms. The mean residue level of oxytetracycline was 125.25μg/l and that of penicillin G was 4.52μg/l. Concentrations of oxytetracycline and penicillin G in all samples were between ranges of 45 -192 μg/l and 0-28 μg/l, respectively. The antibiotic residue positive samples which showed residues of oxytetracycline above the established maximum residue limit of 100μg/l were 40 (83.33%). For penicillin G, the number of samples above the maximum residue limit of 4μg/l, were 8(16.66%).

Possible Approaches Toward Mitigating Antibiotic Residues

Prevention of Infectious Disease Through Vaccination: It have been a key component of disease prevention for many years because in food producing animals they have many favorable attributes such as low cost, ease of administration, efficacy, multiple agent efficacy and safety. Adjuvants are sometimes included with vaccines to enhance the immune response. Various delivery systems or routes of administration are used to administer the vaccine into the animal [77]. Veterinarians should ensure that animals are immunized against vaccinable food borne zoonoses. Despite the fact, prevention of food borne zoonoses through animal intervention is more cost effective when compared to prevention in humans [78].

Alternative Practices: These approaches applied on health management programs by veterinary or other professionals attempt to minimize infectious disease outbreaks by using non-antibiotic interventions early in the life of the animals. The rational is to promote healthy animals that do not become ill and are, thus, unlikely to be treated with antibiotic agent. Several current approaches are available. These non-antibiotic approaches have led to a need to establish performance standards for regulatory and commercial purposes [79].

Efficient Diagnosis and Treatment of Animal Disease: Diseased animals on farms should be identified promptly by veterinarians and treated accordingly to reduce risk of passing such diseases to humans via their products. It has been reported in the prevention and control of zoonoses [78].

Responsible Use of Antibiotics: These approaches mainly depend on Guidelines for responsible (proper, appropriate, prudent, or judicious) use of antibiotics in veterinary and human medicine and are similar in the medical and agricultural sectors [13]. One of critical way in minimizing antibiotic residues in food of animal origin. Clinical efficacy requires not only that the pathogen is susceptible to the selected drug, but also that the drug is able to penetrate and be active at the site of infection. Host related factors like low immunity, pregnancy, age and allergies should be considered in order to avoid undesirable effects on the health of the animal. When systemic treatment is necessary in animal production, intramuscular and intravenous injections are preferable to oral administration to avoid disturbance of the normal gut flora [12].

Monitoring and Surveillance of Antimicrobial Residue: Government and stake holders are involved in routine monitoring of farms for observance of withdrawal periods and slaughter houses and food industries for drug residues. Under the monitoring program, a statistically based selection of random samples from normal animal population is collected. The surveillance program focuses on obtaining samples from animals suspected to contain volatile drug residues in their tissues [80]. It is necessary to confirm the presence and concentration of detected antimicrobial residues and identify the specific antimicrobial within a class with quantitative testing methods [81].

CONCLUSIONS AND RECOMMENDATIONS

Extensive use of veterinary antibiotics as growth promoters in animal feed with extra label use results in the threat for development of new resistant strains of bacteria, drug allergy and hypersensitivity reaction, alteration of normal intestinal microflora and other adverse effects. Stringent control strategies mainly development of bio control measures, applications of alternative and good hygienic practices and detection techniques over the underhanded use of these valuable tools are some of positive approaches to safeguard the public health and to protect the currently available antibiotics for future clinical uses. Moreover, these approaches promote animal production systems with reduced occurrence of antibiotic residues in food of animal origin and development of antibiotic resistance in pathogens and other related risks. Because of live food animals and foods of animal origin are exported and imported between most countries, antibiotic residues affecting the food supply of one country becomes a potential problem for other country. Based on informations mentioned in the review and conclusive remarks, the following recommendations are forwarded:

- Rapid screening methods should be developed for detecting and segregating samples containing above maximum residual levels of antibiotics.
- Antibiotic use in food producing animals should be reduced by improving animal health and their welfare.
- Bio-control measures and Ethno-veterinary practices should be developed and followed.
- Further research should be conducted regarding antibiotic residue in food of animal origin.

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