



Review

Importance of antibiotic residues in animal food

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ABSTRACT

Veterinary medicines, especially antibiotics, are among the most important components related to animal feed production. Generally, the main use of antibiotics in animals is for the treatment and prevention of diseases and growth promotion. Antibiotic usage in animals may result antibiotic residues in foodstuffs such as milk, egg and meat. These residues may cause various side effects such as transfer of antibiotic resistant bacteria to humans, immunopathological effects, allergy, mutagenicity, nephropathy (gentamicin), hepatotoxicity, reproductive disorders, bone marrow toxicity (chloramphenicol) and even carcinogenicity (sulphamethazine, oxytetracycline, furazolidone). The most important adverse effect of antibiotic residues is the transfer or antibiotic resistant bacteria to the humans due to the mobile properties of resistance. Because of these undesirable effects, it is important to regulate the use of antibiotics in food animals. The individuals and the local procedures should be aware of the problem through education by authorities. In this review, antibiotic use in the foodstuffs and their effects on the human health will be discussed.

1. Introduction

Veterinary medicines, especially antibiotics, are among the most important compounds related to animal feed production. Approximately 80% of the animals used in food production are currently being treated with veterinary drugs in a certain part or all though their lives (Pavlov et al., 2008).

Antibiotics are defined as the substances that are able to kill or inhibit the growth of various microorganisms. They are produced naturally by living organisms or synthetically in laboratory conditions. The growth promoter effect of antibiotics was discovered in the 1940s, when it was observed that animals fed dried mycelia of *Streptomyces aureofaciens* containing chlortetracycline residues improved their growth (Castanon, 2007).

Antibiotics are administered to animals in different ways: oral, parenteral or topical. It is known that residue levels occurring from injectable sources are more than those resulting from feeding (Katz and Brady, 2000). The main use of antibiotics in animals is for the treatment and prevention of diseases including mastitis, arthritis, respiratory diseases, gastrointestinal and other bacterial infections (Darwish et al., 2013). Improvement in growth due to antibiotics was first described in the middle of 1940s and within five years the addition of growth promoting antibiotics has become a common practice. The World Health Organization (WHO), the American Medical Association and the American Public Health Association have urged a ban on growth

promoting antibiotics arguing that their use leads to various health problems in humans (Graham et al., 2007).

Antibiotics may enter to human body in different ways as directly or indirectly by using them as growth stimulants, disease prevention and treatment and contamination in animals (Phillips et al., 2004). Antibiotic usage in animals may leave antibiotic residues in foodstuffs such as milk, egg and meat. These residues may cause various toxic effects such as transfer of antibiotic resistant bacteria to humans, allergy, immunopathological effects, carcinogenicity (sulphamethazine, oxytetracycline, furazolidone), mutagenicity, nephropathy (gentamicin), hepatotoxicity, reproductive disorders, bone marrow toxicity (chloramphenicol) and even anaphylactic shock in humans (Darwish et al., 2013; Nisha, 2008).

In the developing world, multi-resistant bacteria to various antibiotics is becoming very big problem in the treatment of diseases (Willis, 2000).

In this review, antibiotic use in foodstuffs, antibiotic residues in feed and their health effects will be discussed.

2. Data collection

Information about antibiotics was obtained from a literature search of electronic databases such as Sciencedirect, Google Scholar, Pubmed and Scopus for publications on antibiotic residues in feed. “antibiotic”, “antibiotics in animals”, “antibiotic residue”, “antibiotics in food”,

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“antibiotic residues in food”, “antimicrobial drugs in animals”, “antimicrobial drug residues in foods”, “drug residues in food” were used as keywords.

3. Antibiotic usage in foodstuffs

Antibiotics are used in food production, especially in animals for some benefits including the well-being of animals, carcass quality, quality and efficiency of growth, economic production and public health (Van Boeckel et al., 2015).

Antibiotics can be used for the prevention and/or treatment of infectious diseases in the animals. These drugs can improve the animal performance through reducing the physiological costs of limiting growth that are incurred in the process of fighting low level and overt disease (Council, 1999). Antibiotic treatment is effective in controlling the important infections such as *Salmonella*, *Leptospira*, *Campylobacter fetus* *Streptococcus suis*, *Escherichia coli*, *Enterococcus* (Markey et al., 2013).

The benefit to human health is to protect people from serious infections that can be transferred to humans through the contact with the infected animal, consumption of contaminated food or proliferation in the environment (Council, 1999).

An antibiotic must have some properties for use in animals. It should be safe and effective when used on a wide scale. The drug should not be used in human or veterinary medicine although exceptions may be justified to solve serious problems, cause resistant strains to arise or cause cross-resistance to other drugs. It should not antagonize the other drugs, used as a substitute for good sanitation, cause excessive effects on the body flora (Landers et al., 2012). When antibiotic treatment is necessary, it often has to administered to animals in feed or drinking water (Phillips et al., 2004).

Indeed, antibiotics may improve growth rate by thinning of mucous membranes in the gut, alteration of gut motility, production of favorable conditions for beneficial gut microbes by destroying harmful bacteria and partitioning of proteins for muscle growth. They also favor growth by decreasing the activity of immune system and reducing the waste of nutrients and toxin formation (Darwish et al., 2013). Generally, animals are receiving antibiotics in their diet, gain 4–5% more body weight than those that receive no antibiotics (Witte, 1998).

In veterinary medicine, β -lactams (penicillin and cephalosporin), tetracyclines, chloramphenicols, macrolides, spectinomycin, lincosamide, sulphonamides, nitrofurans, nitroimidazoles, trimethoprim, polymyxins, quinolones and macrocyclics (ansamycins, glycopeptides and aminoglycosides) are used for different purposes (Cháfer-Pericás et al., 2010).

In some cases, streptomycin and streptomycin-oxytetracycline combined are in use in the treatment of prophylaxis of plant diseases. They have been reported to be used in the control of halo blight of beans and bacterial diseases of tobacco, tomatoes, peppers, cherries and potatoes. Tetracyclines and aminoglycosides are widely used to prevent fruit trees from bacterial diseases (Vidaver, 2002). Besides, vancocin is used in genetic engineering plants (Teixeira da Silva, 2002).

4. Antibiotic usage in different countries and legislation

Van Boeckel et al. (2015) have demonstrated the antibiotic usage ranking in food animals according to countries. China is the first country in using antibiotics in food animals with a percentage of 23%. The order of the other countries was as follows: United States (13%), Brazil (9%), India (3%) and Germany (3%) (Van Boeckel et al., 2015).

In a number of countries have banned the use of certain antibiotics in agriculture. Legislation regarding the control of antibiotic residues in animals and their products were given in European Union (EU) Council Directive 96/23/EC. Subtherapeutic doses of antibiotic usage in food animals has been banned in the EU countries. The use of antibiotics in animal feed was prohibited in Sweden in 1985. In Denmark, the use of

avoparcin was banned in 1995, followed by a ban on virginiamycin in 1998. The EU banned avoparcin in 1997 and four growth promoters, spiramycin, tylosin phosphate, virginiamycin and zinc bacitracin. The Danish Food Industry stopped the use of all antimicrobials for growth promotion in 1998 (Willis, 2000). In 2005, Food and Drug Administration (FDA) banned the use of enrofloxacin in food animals due to the increased levels of fluoroquinolone-resistant *Campylobacter* spp. (Huyghebaert et al., 2011). Quinolones use in animals prohibited by Australian Pesticides and Veterinary Medicines Authority in 2004 (Cheng et al., 2012). However, in spite of the prohibitions in these countries, most of the antibiotics are still being used in animals for treatment and/or prevention of diseases and growth promotion in many countries (Muaz et al., 2018).

In recent years, antibiotic resistance has become one of the priority areas of legislation authorities. The European Food Safety Authority (EFSA) collects and examines the data on antibiotic resistance from EU Member States and presents them in official reports. WHO has published a list of antibiotics that cannot be used in animals. Cephalosporins, glycopeptides, macrolides, polymyxins and quinolones are in the list of critically important antibiotics (Muaz et al., 2018). The Joint FAO/WHO Expert Committee of Food Additives and Contaminants (JECFA)/Codex Alimentarius Commission (CAC), at its 35th Session of the CAC (July 2012) updated the maximum residue limits (MRLs) for veterinary drugs in food (Moudgil et al., 2018).

5. Antibiotic residues in foods

When high concentrations of antibiotics were used, their residues have been found in the blood and the other tissues of the animals. However, since the antibiotics can be rapidly eliminated, disappearing from both blood and tissue within a few days after the animals are placed on nonmedicated feed (Nisha, 2008).

Direct contamination of animal derived feed may occur from air and water during processing, storage and transportation. Antibiotics in feed given to animals are the examples of indirect contamination (Nisha, 2008). The other problem is the contamination of feed with fecal recycling. The drug excreted in the feces of treated animals. These feces can contaminate the feed of other untreated animals (Darwish et al., 2013). Vegetables may also be contaminated from feces especially in countries in where feces is generally used as a fertilizer (Phillips et al., 2004).

After farming process, resistant microorganisms may be transferred into rivers and other water sources through the waste disposal system or rainwater. In fact, antibiotics is excreted to the urine in humans and animals. Therefore, antibiotics may also enter water courses from farm waste, allowing the possibility for further selection of resistant organisms (Willis, 2000).

In fish farming, antibiotic usage is common and fish as food may be contaminated with resistant microorganisms (Aarestrup et al., 1998).

Only a small proportion of animal-derived foods are consumed raw so the cooking process is very important for the reduction of antibiotic residues in food (Katz and Brady, 2000). Nevertheless, this process is not enough for the removal of antibiotic residues. Herman (1969) studied the effects of cooking procedure on antibiotic residues with cooking rainbow trout fillers in different cooking methods. The fillets were baked at 350 °F for 20 min, boiled for 10 min and fried for 5–10 min to destroy residues at average levels. However, they have found that frying or baking did not destroy all the residues in the fillers (Herman, 1969).

6. Detection of antibiotic residues in foods

There are two different methods for the determination of antibiotic residues: (i) Confirmatory and (ii) screening methods.

Confirmatory methods are based on liquid chromatography (LC) coupled to mass spectrometry (MS) (Blasco et al., 2009; Kokkonen and

Jestoi, 2009). LC with ultraviolet (UV) detection may be also useful in the determination of drug residues in foods (Benito-Peña et al., 2009). In some studies, other methods based on capillary electrophoresis (CE) were shown to be effective in the detection of antibiotic residues (García-Campaña et al., 2009). However, it should be noted that all of these methods are expensive and time consuming and require personnel and adequate laboratory. Among these methods, LC-MS is the most used with a percentage of 38%. LC-UV and enzyme linked immunosorbent assay (ELISA) follow this method with %18 usage percentage. At the same time, usage of the other screening methods (12%) and biosensors (%8) are increasing dramatically (Cháfer-Pericás et al., 2010).

Screening methods are classified as microbiological assays and immunoassays. Qualitative or semi-quantitative microbiological assays based on a specific reaction between a susceptible organism and the antibiotic. These methods have different advantages e.g. reliability, cost effectiveness and simplicity (Cháfer-Pericás et al., 2010; Dey et al., 2005; Kilinc et al., 2007). Unlike LC-MS, these tests can detect any antibiotic or its active metabolite whereas LC-MS are commonly applied to compounds previously selected as targets (Picó and Barceló, 2008). There are many advantages of these methods; microbiological tests can be performed by non-professionals, only some tests required sample treatment and can be carried out in a tube or a microplate. However, these methods have some disadvantages such as lack of specificity and the required long incubation time. Semi-quantitative immunoassays based on a specific reaction between antibody and antigen. These methods can be classified as ELISA, fluoroimmunoassay (FIA) and time-resolved fluoroimmunoassay (TRFIA) (Cháfer-Pericás et al., 2010). These tests have high specificity, high sensitivity, simplicity and cost effectiveness. Microplates and magnetic particles are used in these tests. The most important advantage of these assays is that both penicillins and cephalosporins can be screened within one assay (Wu et al., 2008). At the same time, magnetic particles for target capture/enrichment can minimize matrix interferences and improve method accuracy (Cháfer-Pericás et al., 2010).

Fully automatic biosensors are becoming increasingly important in detecting antibiotics in food. They contain a biological recognition element (e.g. enzymes, proteins, cells) coupled to a signal transduction element. The biosensors can be classified according to the biological element, the transducer and the biological element immobilization procedure on a solid support (Patel, 2002). This method is rapid and specific as the biorecognition element used. It has some limitations such as the instability of the biological sensing component and the size of the physico-chemical transducers used in biosensors (Cháfer-Pericás et al., 2010).

7. Toxic effects of antibiotic residues in foods

One of the most important adverse effects of antibiotics in food is allergic reactions. Many of the drugs and antibiotics can elicit allergic reactions. The majority of information is related to hypersensitivity of penicillin, aminoglycosides and tetracyclines (Katz and Brady, 2000). Unfortunately, the long term effects of antibiotics on human health have not been known yet.

β -lactams are known as less toxic antibiotics. However, it is concluded that they were responsible for the most of reported allergic reactions due to antimicrobials in humans (Davies and Davies, 2010).

Idiosyncratic reactions like allergy, skin rashes and phototoxic dermatitis have been reported depending on the use of tetracyclines (Yates, 2003).

Streptomycin has important side effects on vestibular mechanisms in the inner ear. This side effect causes balance lost. Besides this side effect, it exhibits neurotoxicity on newborn animals. Hypersensitivity, skin rashes and induced fever are the other toxic effects of this drug (Katz and Brady, 2000).

Certain macrolides may be responsible for liver injury caused by a

specific allergic response to macrolide metabolite-modified hepatic cells (Dewdney et al., 1991).

The most important adverse effect of antibiotic residues is the transfer of antibiotic resistant bacteria to the humans due to the mobile properties of resistance. More people die from antibiotic resistant bacterial infections. It is estimated that by the year 2050, antibiotic resistant microorganisms will kill more people than cancer. The transfer may occur through the food chain and/or animal handlers (Levy and Marshall, 2004).

8. Antibiotic resistance mechanisms

Antibiotic resistance can be developed by different mechanisms such as changes within the existing genome of a bacterial cell (mutations) and changes within the proteome, formation of bacterial cell interactions and plasmids by horizontal gene transfer (Boerlin and Reid-Smith, 2008; Mah, 2012; Shousha et al., 2015; Woodford and Ellington, 2007). Plasmids are circular DNA molecules which can replicate independently of the chromosome and able to transfer horizontally between bacteria by conjugation (Carattoli, 2013; San Millan, 2018). Antibiotic resistant gene including plasmids have different abilities to replicate depending on the bacterial host (Madec and Haenni, 2018). Horizontal gene transfer, key process in the bacterial adaptation to new environment, is lateral movement of genetic material between organisms in a process of direct DNA exchange alternative to vertical DNA transfer from parent to offspring.

Human gut microbiota is the other important factor in developing antibiotic resistance especially hospitalized patients. (San Millan, 2018). Antibiotic resistant genes present in the gut microbiome can be exchanged between the resident species and can be horizontally transferred from pathogenic species (Francino, 2016). Conjugative plasmids play important role in the dissemination of resistance genes in the gut. Resistant clones can be isolated with relative ease from the gut microbiome (San Millan, 2018). Animal microbiome and environment consist resistance determinants, serving as a genetic bridge into the human microbiome. Antimicrobial agents should be used carefully to maintain or restore the microbiome and/or prevent colonization with multidrug resistant organisms (Tosh and McDonald, 2011). Also, some of the studies have showed that antibiotic resistant genes could be found in the human gut microbiome (Sommer et al., 2009).

The most known antibiotic resistant strains are antibiotic resistant salmonellae, macrolide or fluoroquinolone resistant campylobacters, glycopeptide or streptogramin resistant enterococci and multiply antibiotic resistant *E. coli* (Phillips et al., 2004). *Campylobacter* and *Salmonella* caused infections are the main examples of animal antibiotic use and human health risk. Generally, people infected with these microorganisms after consuming food tainted with these bacteria. *E. coli* is an important indicator of antibiotic resistance which can be frequently found on food surfaces (European Food Safety Authority, 2015). One of the *Salmonella* strain, DT-104 and *Campylobacter jejuni* are resistant bacteria to multiple classes of antibiotics. Thus, the treatment of that infections becomes more difficult and the risk to human health becomes greater (van den Bogaard and Stobberingh, 2000).

In the *Streptococcus*, *Meningococcus* and related microorganisms, antibiotic resistance may be occurring via DNA transformation. Horizontal gene transfer can be seen frequently in *Acinetobacter* spp (Davies and Davies, 2010).

The macrolides and related antibiotics act by binding at different sites in peptide exit tunnel of 50S ribosome subunit. Macrolide resistance can occur by the modification of bacterial RNA or protein components of the tunnel. Another important antibiotic fluoroquinolones inactivation based on aminoglycoside *N*-acetyltransferases capacity to modify a secondary amine on the fluoroquinolones. The other mechanism of fluoroquinolone inactivation is known as Qnr, a widespread family of DNA-binding proteins. Sulfonamide and trimethoprim resistance is known as gene amplification (Davies and

Davies, 2010).

Carbapenems are not used in food-producing animals. Plasmids carry carbapenemase genes which are not expected to circulate in the food chain. Limited studies have shown the carbapenem resistance on plasmids in livestock, such as *bla*_{NDM-1} in pigs and *blm*_{NDM-17} in chicken from China, *bla*_{OXA-181} in pigs from Italy (Liu et al., 2017; Pulss et al., 2017). Colistin is generally used in food producing animals for treatment and/or prevention of diseases. In China, plasmid-mediated polymyxin resistance gene, *mcr-1*, was detected in livestock and humans (Liu et al., 2016). After that study, the *mcr-1* gene was found in 30 countries and 5 continents, especially food producing animals (Skov and Monnet, 2016). At the same time, 11 variants of *mcr-1* gene, 10 variants of *mcr-3* gene and *mcr-8* gene were analyzed in pigs, poultry and cattle (AbuOun et al., 2017; Carattoli et al., 2017; Liu et al., 2016; Madec and Haenni, 2018; Wang et al., 2018; Xavier et al., 2016; Yang et al., 2018). *qnrA1* is the first plasmid-mediated quinolone resistant gene which found in food producing animals. *fos* genes are mostly plasmid-borne and related with fosfomycin resistance in chicken (Madec and Haenni, 2018).

9. Recommendations of the reduction of antibiotic residues in food

The individuals and the legal organizations should be aware of the problem of antibiotic residues (Nisha, 2008). The use of alternatives to antibiotics (plant-derived substances and probiotics) may be beneficial. The reduction of unnecessary antibiotic use in animals should be pursued and the reduction of prophylactic antibiotic use should be considered (Darwish et al., 2013).

Every country should adopt laws in antibiotic usage in animals and their residue limits in foods. In 2006, EU banned the use of antibiotics for the purpose of livestock health maintenance (Carlet et al., 2012). In the United States, residues of carcinogenic chemicals and/or their genotoxic metabolites are found in meat and their products. FDA regulations have effectively prevented allergenic, toxic and carcinogenic animal drug residues in the food. Although FDA approves some new animal drugs with some rules: (I) the drug must be used in limited concentrations (ii) the drug must not be carcinogenic (iii) no carcinogenic residues can be detected in the animal tissues or products after a suitable drug withdrawal time (Council, 1999). FDA prohibits the extra label use of chloramphenicol, furazolidone, nitrofurazone, sulphonamides and flouroquinolones in lactating animals. Irrational usage of drugs should also be avoided in veterinary (Nisha, 2008).

Cooking and freezing procedures are important in inactivation of antibiotic residues. The heat treatment of animal foodstuffs may inactivate antibiotics (Darwish et al., 2013). Many of the studies have reported that degradation of β -lactams, quinolones, sulfonamides, macrolides, tetracyclines, and aminoglycosides are temperature-dependent and prolonged heating time helps to induce more degradation (Tian et al., 2017). Activated charcoal, resin and UV irradiation might be beneficial in antibiotic inactivation (Nisha, 2008).

Simple and economic field tests should be developed to identify antibiotic residues in animal products and ethno-veterinary practices may be promoted (Nisha, 2008).

10. Conclusion

Contamination of different foods especially meat and milk with antibiotics is an important problem for human health. Antibiotics usage in foodstuffs is still growing. It should be noted that, antibiotics in foodstuffs may be inherently toxic and may have an accumulative effect. However, there are also some risks associated with not using antibiotics in animal production. The assessment of the risk-benefit ratio for the use of the drug in living organisms should be made before using. Prohibition of antibiotic use in the production of foodstuffs may not be a realistic approach. It is also important to ensure that antimicrobial

agents in animal production are controlled by relevant authorities, and meat and internal organs should be investigated for drug residues before selling and consumption. The elimination half-life of antibiotics must be considered before the introduction of food products to the market.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Transparency document

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