Antibiotic residues in Farm Animal and a Food of Animal Origin with Emphasis on Bacterial Resistance (Review)

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Abstract: World populations increased dramatically yearly and consequently increase the demand for foods of animal origin, from different species (cattle, sheep, caprines, birds, pigs, fish and seafood/shellfish), milk and eggs, to cover their nutritional needs. Antibiotics drugs are used widely in the animal livestock for the purposes of treatment, or as prophylactive and growth promoters. The misuse or sub-therapeutic doses of antibiotics initiate the microorganisms for inducing resistance to the action of antibacterial drugs. Therefore, the animals and animal by-products my exposed to chemical or biological pollutants during their production cycle which could come from drugs and growth promoters, in addition, biologically-derived toxins (mycotoxins, phycotoxins, phytotoxins) and/or environmental contaminants linked to atmospheric pollution, from the soil and/or water are sources of pollution of foods of animal origin, which have harmful effects on animals and consumers and generate high numbers of microorganisms resistant to the traditionally used antibiotics.

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Antibiotics drugs residues

There are many types and generations of antibiotics or antibacterial agents (e.g. aminoglycosides, tetracyclines, macrolides and sulphonamides) which are widely used in domestic animals and human for treatment of certain types of illness or in the improvement of growth rate. Improper administration for disease therapy (higher or sub-therapeutic doses) and as growth promoting agents (low doses for long period) can result in antibiotic residues in milk and dairy products and can contribute to the development of microbial drug resistance and the spread of resistant bacteria, including those with serious health consequences in animals (IFT, 2006; Stolker *et al.*, 2007) and possess a potential risk to the consumer due to the development of allergic reactions and interference with growth of intestinal micro-flora (Dewdney *et al.*, 1991).

1. Aminoglycosides (e.g. Streptomycin, kanamycin, amikacin, neomycin, apramycin).

The differences in substitutions in the basic ring structures between the various aminoglycosides are the reason for the relatively minor variations in antimicrobial scales, duration of action, resistance and toxicity forms. Aminoglycosides given in therapeutic dosages mainly cause ototoxicosis, but may also cause nephrotoxicosis, allergy and neuromuscular disturbances. With respect to the solubility of aminoglycosides, it is high (10-500 g L^{-1}). They are basic strongly polar polycationic compounds (Thiele-Bruhn, 2003). The amino groups of aminoglycosides can be positively charged by protonation under acidic conditions. The positive charge may facilitate adsorption to soil clay minerals that typically possess a negative charge (Huang *et al.*, 2001). Despite their extensive use in livestock farming, no aminoglycosides were found in a broad study on the analysis of animal faeces (Berendsen, *et al*., 2013).

2. Amphenicols (Chloramphenicol, thiamphenicol, florfenicol):

One of the commonly used antibiotics for several years for the treatment or as a prophylactive in the farms of poultry, calves, pigs, sheep and fish is the chloramphenicol. Bone marrow depression is the greatest serious toxic side effect of chloramphenicol. These toxic symptoms was recorded in newborn infants giving large doses of chloramphenicol, these symptoms appeared in the form of vomiting, hypothermia, cyanosis and circulatory collapse followed by death. Moreover, other symptoms may be appearing such as neuritis, encephalopathy with dementia and ototoxicity, while its metabolites could be genotoxic. Therefore, chloramphenicol is restricted in many countries, while it is totally prohibited for use in food-producing animals within the European Union and the USA (Lozano and Arias, 2008).

3. Beta-lactams (Penicillins, cephalosporins).

Penicillin and its derivatives caused allergic reactions in some peoples. The adverse effects associated with cephalosporins are similar to those described for penicillins.

4. Macrolides (Lincomycine-macrolide Erythromycin, spiramycin, kitasamycin, josamycin, desmycosin, mirosamycin, tilmicosin, leucomycin, tylosin).

Macrolides is usually used for the treatment of staphylococcal infections in sheep, goats, calves and pigs; moreover, it is used as a feed additives for increasing the growth rate in growing animals. The long term administration of lincomycine is established to cause gastrointestinal disorders represented in vomiting, nausea and diarrhoea which that may consider fatal. Also, macrolides may cause adverse side effects such as polyarthritis, urticaria, skin rashes, hepatic damage and haematological disorders (WHO, 1989). With respect to the solubility of macrolides, it greatly varies, it ranged between 0.15 and 45 mg L^{-1} (Thiele-Bruhn, 2003). Tylosin is unstable in either acidic or alkaline media and relatively stable under neutral pH media. The degradation of tylosin in the nature is affected by many factors such as organic matter in soil, clay particles, and organic components in manure (Rabølle and Spliid, 2000; Kolz *et al.*, 2005). During a study carried out in USA at 1999 and 2000 on surface waters, it was reported that tylosin is the most frequently detected antibiotic (Kolpin *et al.*, 2002).

5. Nitrofurans (Furazolidone, nitrofurazone, furaltadone, nitrofurantoin).

Different types of nitofurans are used as therapeutic treatment or as prophylactive of bacterial and protozoal infectious diseases in different species of farm animals (cattle, poultry, rabbits, pigs and fish). The routine usage of nitrofurans in food-producing animals has been debatable as residues of such drugs may be carcinogenic and mutagenic. Some studies reported that nitrofurazone is a carcinogenic but not genotoxic agent, while furazolidone has possessed both carcinogenic and genotoxic action (WHO, 1993). In addition nitrofurans metabolites can be found in animal proteins (meat and eggs) for several weeks or months specially in farmyard birds receiving nitrofurans as anticoccidial agents. Due to the serious side effects of nitrofurans and its metabolites, its systemic use is prohibited in food producing animals in many countries as in Europe and USA (EMA, 2008).

6. Quinolones (Ciprofloxacin, danofloxacin, difloxacin, enrofloxacin, flumequine, marbofloxacin, norfloxacin, ofloxacin).

Administration of quinolone antibiotics can cause adverse side effects in the GIT such as gastrointestinal disorders as vomiting, diarrhoea, nausea, headache, visual disturbances and insomnia. In addition, some toxic symptoms may be occur such as pruritus, rashes and epidermal necrolysis (Pérez-Jiménez *et al.*, 2011). With regard to solubility of fluoroquinolones, it possess poor water solubility at pH 6-8 (amphoteric property) and insensitive to hydrolysis, resistant to microbial degradation and increased temperatures, but they can be degraded by UV light (Thiele-Bruhn, 2003) and were found to be very persistent in manure and soil matrixes (Boxall *et al.*, 2004, 2012).

7. Sulphonamides (Sulfadiazine, sulfadimethoxine, sulfamethazine, sulfadoxine, sulfaethoxypyridazine, sulfaguanidine, sulfamerazine, sulfamethoxazole, sulfapyridine, sulfamethoxydiazine, sulfamethoxy-pyridazine, sulfamonomethoxine, sulfathiazole, sulfaquinoxaline)**:**

Sulphonamides residues in animal products may cause hypersensitivity reactions, mainly in the form of skin rashes. With regard to the solubility of sulfonamides, it possess high solubility (0.1 to 8 g L^{-1}), this wide variation in the solubility returned to the type of sulphonamides (Sarmah *et al.*, 2006). Also, sulfonamides are characterized by a low chelating ability and low binding constants (Sukul and Spiteller, 2006). Degradation of sulphonamides can be occurring during exposure to photo (Batchu *et al.*, 2014). Sulfonamides can potentially enter animal wastewaters, ground and surface waters, soils, sediments and in environmental samples (Thiele-Bruhn, 2003; Wei *et al.*, 2011; Zhang *et al.*, 2011).

8. Tetracyclines (Chlortetracycline, oxytetracycline, demeclocycline, doxycycline, methacycline, minocycline).

Oxytetracycline can induces bacterial resistance in coliform microorganisms in GIT of human beings, which result from improper dosage and consequently require higher doses to give efficient antibacterial activity. With respect to the presence of tetracyclines in the environment, tetracyclines are stable in acid media, but not in alkaline conditions, and constitute salts in both conditions (Doi and Stoskopf, 2000; Halling-Sørensen *et al.*, 2002). They are susceptible to photo-degradation (Doi and Stoskopf, 2000). Chelating agents reduces bioavailability and thus reduces the antibacterial activity of tetracyclines. There is minimal degradation of tetracycline in manure (Bansal, 2012). The estimation rate of tetracyclines in manure ranged from 84.9 to 96.8% with a maximum concentration of residual chlortetracycline recovery reaching 764.4 mg kg^{-1} (Pan *et al.*, 2011). Tetracyclines (particularly tetracycline and chlortetracycline) were found to be more persistent in soils than in manure (Bansal, 2012).

Methods for Determination of antibiotic residues

One or more of the different antibiotic drug classes (aminoglycosides, amphenicols, beta-lactams, macrolides, nitrofurans, quinolones, sulphonamides and tetracyclines) could contaminate animal products (meat, milk and egg) or their by products. Therefore, it is of great importance to determine the concentrations of antibiotics or their metabolites in the serum, tissues or by products of animals which considered essential for both farmers or breeders and consumers (Mitchell *et al.,* 2003).

Recently different methods for detection of drug residues in animal product and by products samples were developed for rapid estimation of antibacterial drug residues.

One of the assays routinely applied in many countries for detection of beta-lactam antibiotics is the microbial inhibition assays, in which *Bacillus stearothermophilus* was used as the test microorganism due to its sensitivity to some antibiotics particularly β-lactam antibiotics.

Different methods were applied for detection of antibiotics residues at or low the permissible limit such as the tube test and (multi-) plate test systems and many of immunological methods such as ELISA, RIA or biosensor methods (Ferguson *et al.,* 2002; Pikkemaat *et al.,* 2009). All the dependence methods used for detection of antibiotics are validated in accordance with the Council Directive 2002/657/EC (EC, 2002).

With regard to poultry samples, many methods are applied now for detection of drug residues in poultry tissues, comprises microbiological methods, chromatography methods, ELISA and immunochemical methods (Kaya and Filazi, 2010). The microbiological assays are preferred method as they are cheap, easy to perform and able to measure a large number of samples at the same time (Karraouan *et al.,* 2009; Javadi *et al.,* 2011). Four plate test (FPT) which are characterized by high sensitivity and specificity are used for determination of levels of drug residues in poultry tissues and are approved by European Union as a standard assay.

Adverse effects of antibiotics drugs residues

The challenging cause of resistance to antibacterial drugs are the widespread uses of sub-therapeutic doses of antibiotics for long time as growth promoter and lack of perfect control of administration, the risk of drug accumulation and their residuals in animal tissues and their product will increase (Meredith *et al.,* 1965; Lemus *et al.,* 2008). In addition it was recognized to favor the selection, spread, and the establishment of permanent resistant strains in the environment (Andremont, 2003; Kumar, *et al.,* 2005). Owing to the widespread non-therapeutic use of antibacterial drugs and is, therefore, no longer accepted within the EU (EC, 2003).

Many researches focused on the main uses of antibiotics in livestock animals, they found that 87% of antibiotics have been broadly used in farm animals for treatment, control or prevention of infectious diseases and 13% as food supplement to increase growth and productivity (Dipeolu and Alonge, 2002; Donoghue, 2003; Mahgoub *et al.,* 2006).

Antibiotic residues and their metabolites in poultry meat may cause several adverse effects on consumers such as direct toxicity, developing resistant bacteria, and allergies (Kirbis *et al.,* 2007) and leads to adaptation of normal micro flora in the GIT, and exposure to low doses of antibiotics for long term via contaminated foods can gain resistance (Myllyniemi *et al.,* 2004; Javadi *et al.,* 2011). Therefore, due to the high risk of antibiotic residues they established the maximum limits of drug residues (MRLs), which are the maximum concentration of drug residues that could legally allowed to be in the food product without causing adverse effects to the consumers (Myllyniemi *et al.,* 2004; Reyes Herrera *et al.,* 2005).

Antibiotic resistance in food of animal origin

Resistance factors were already recognized to exist in the environment earlier to the introduction of antibiotics for treatment of diseases (D'Costa *et al.,* 2011; Bhullar *et al.,* 2012), though, the variety and distribution of resistant organisms has increased intensely in the past few years (Levy, 2002). Therefore, antibiotic resistance has become a serious and growing risk to modern medicine, and began as one of the leading health distresses of the 21st century (WHO, 2014). The prospects that a continued increase in antimicrobial resistance (AMR) by 2050 will lead to 10 million people dying yearly, and a reduction of 2 to 3.5% in Gross Domestic Product (GDP) (http://amrreview.org/). Also in Europe, more attention was paid for the problem of antimicrobial resistance and gives it a high priority topic in the impending years (EC, 2015).

Antimicrobial resistance developed with the increased number, volume and variety of antimicrobial applications used in humans and animals (Levy, 2002; Kumar *et al.,* 2005). The use of antibiotics in animal production contributes significantly to the development and spread of antibiotic resistance in animals and food of animal origin (EFSA, 2015).

In equivalent with the increasing prevalence of antibiotic resistant bacteria in domestic farm animals, resistant bacteria are also more and more commonly present on food products of animal origin (Aarestrup *et al.,* 2008; Overdevest *et al.,* 2011; Tham *et al.,* 2012) and even on vegetables (Reuland *et al.,* 2014; Hoek *et al.,* 2015). Some studies which carried out in the Netherlands found that the use of fluoroquinolones caused an amazing increase in the prevalence of ciprofloxacin resistant Salmonella isolates from retail poultry meat; between 2000 and 2007 the prevalence rose from 0 to 60% (MARAN, 2015). Also, another study in the Netherlands concerning presence of ESBL producing micro-organisms in retail poultry with a danger values which reached 100% on conventional and 84% on organic muscle samples (Cohen Stuart *et al.*, 2012). Moreover, ESBL producing bacteria are found in low level in meat of other animal species (MARAN, 2015).

There are relationship between the appearance of fluoroquinolone resistance in poultry and human Campylobacter isolates, the risk of resistant bacteria being transmitted to human being via food is believed to be low (Food Safety authority of Ireland, 2015). Raw food products obviously hold a more substantial risk for transfer of bacteria and thus also antimicrobial resistance. Besides the direct transfer of resistant bacteria, intact DNA coding for resistant might be transmitted through foods, and the potential for uptake by bacteria in the human gut is uncertain (EFSA, 2008).

Antibiotic resistance in livestock

At any time an animal given a dose of antibiotics, there is an opportunity for bacteria to induce resistance to this antibiotic or which similar in structure. Bacteria may exhibit intrinsic (natural) and acquired resistance. Intrinsic one it's a self-defensive mechanism of microorganism in which induced immune action against action of antibiotic drugs. This is a natural (intrinsic) property to all members of a species and is unrelated to the over/misuse of antibiotics. Acquired resistance occurs when the bacteria was previously susceptible to the same drug and become resistant to this drug after second exposure, and have the ability to multiply and spread in the presence of the same antibiotic. Bacteria can acquire resistance in two ways: vertically, through gene transfer i.e. by mutations or horizontally, via gene transfer gained from either new genetic material from resistant bacterium or from the environment. The different types of horizontal gene transfer occurred in the bacteria are included: conjugation, transformation or transduction (Aminov, 2011).

The mechanisms by which the bacteria resist the action of antibiotics through: 1) increased expression of efflux pumps, 2) permeability changes in the bacterial cell membrane which limit the amount of antibiotic penetrating the bacterial cell membrane, 3) physical modification / inactivation of the antimicrobial agent, 4) enzymatic inactivation of the antibiotic, and 5) modification of the molecular binding sites (McDermott *et al.*, 2003; Alekshun and Levy, 2007).

The prevalence of antibiotic resistant bacteria in farm animals is depending on many factors such as the quantities of antibiotics used, type of antibiotics, administration route, and species of animals (Levy, 2001; Catry *et al.*, 2003). There is clear evidence on the relationship between the use of antibiotics and increased resistance development in farm animal production (Dunlop *et al.*, 1998; Aarestrup, 1999; Kruse *et al.,* 1999). A clear example is the rapid development of fluoroquinolone resistant bacteria from poultry in the 1990's, shortly after the introduction of these antibiotics for treatment of poultry (Jacobs-Reitsma *et al.*, 1994). In the Unites States the increasing prevalence of fluoroquinolone resistant Campylobacter in humans provoked the US Food and Drug Administration in 2005 to ban the use of enrofloxacin in poultry. Fluoroquinolones are considered "critically" or "very" important to human medicine (Category I) by the World Health Organization (WHO, 2007). Nevertheless, they are still allowed for veterinary use in Europe. Antibiotic resistance occurs in zoonotic pathogens such as *Salmonella* and *Campylobacter* spp., as well as commensal bacteria. Commensal flora plays an important role in physiological and metabolic processes as well as in the development of the animal's immune system (Ivanov and Honda, 2012). In particular the intestine contains incredible numbers of bacteria that are exposed to resistance provoking antibiotic concentrations during the treatment of an infection or the application of growth promotors. Subsequently, forms an effective and important reservoir for antibiotic resistance (Acar and Moulin, 2006). Not surprisingly, resistance prevalence and profiles of commensal organisms are very similar to their zoonotic counterparts (MARAN, 2015). A particular worrying trend is the increasing occurrence of multidrug resistance. For example, in 2012 more than 60% of the commensal *E. coli* strains from broiler chickens in the Netherlands were found to show resistance to two or more classes of antibiotics (MARAN, 2015). Antimicrobial resistance formed in livestock may be transmitted to humans. Livestock associated MRSA is widely found in farmers and veterinarians (Voss *et al.*, 2005; Wulf *et al.*, 2008). Also the significance of livestock as a reservoir for ESBL (Extended Spectrum Beta-Lactamase) - producing bacteria is increasingly being recognized as a threat to human health care (Dohmen *et al.*, 2015).

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