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Review on antibiotic residues in animal products and its impact on environments and human health

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Abstract
Antibiotics are mainly employed for chemotherapeutic, prophylactic purposes and also used as feed additives to promote growth and improve feed efficiency. However, antibiotic residues in animal products may occur, when administration of drug in extra label fashion and not following of withholding period after treatment. Many of the administered drugs are not completely absorbed from gut and excreted through faeces and urine as either parent compound or its toxic metabolites. The application of manure or farm effluents in agricultural land leads to selection of resistant bacteria, development and transmission of antibiotic resistance genes in the microbes. The antibiotic resistance in animal and human leads to poor response to treatment during illness. The antibiotic residues in animal product causes harmful effect on health and also interfere with the processing of milk and milk products. The present review focuses on antibiotic residues in animal products and its impact on environments and human health.

Keywords: Antibiotic, residue, antibiotic resistance

1. Introduction
Antibiotics are low to medium molecular weight compounds exhibiting a variety of chemical and biological properties. This is mainly employed for chemotherapeutic and prophylactic purposes and also used as feed additives to promote growth and improve feed efficiency [1]. The safe and effective use of antibiotic in animal production has received considerable attention in most of the countries in the world. However, the antibiotic residues from milk, meat and egg may persist for longer period after treatment, when administration of antibiotics in label and extra label fashion and also not following of withholding period after treatment. The minimum withholding period for milk and egg is 7 days and for meat is 28 days after treated with antibiotics [2]. The extra-label drug use may take the form of increased dose, increased frequency of treatment and use in an unapproved species, by an unapproved route of inoculation or in short, by any means not explicitly described on the drug product label [3]. The drug resistance has gained its importance due to the transmission of antibiotic resistance factor to other enteric organisms which have posed a serious public health concern. In general, harmful effects of drug and chemical residues on health, which may be mutagens, carcinogenic, teratogenic, reduction in reproductive performance, drug allergy and acute toxicity or poisoning in human [1]. The present review forms on antibiotic residues in animal products and its impact on environments and human health.

2. Antibiotic residues
Several antibiotic classes are extensively administered to food-producing animals, including tetracyclines, sulfonamides, fluoroquinolones, macrolides, lincosamides, aminoglycosides, beta-lactams, cephalosporins and others [4-5]. Almost 90% of all antibiotics used in farm animals and poultry are reported to be administered at sub-therapeutic concentrations. About 70% of this is for the purpose of disease prevention and 30% are for growth promotion [6]. The risk of residue from the milk is higher in developing countries compared to develop one. This might be related with lack of facilities for detection and regulatory bodies that control the drug residues level in foods in the form of maximum residue limits (MRLs) [6]. The MRL is defined as the maximum concentration of a residue, resulting from the registered use of an agricultural or veterinary chemical that 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 litre in the case of a liquid commodity [6].

Table 1: Recommended MRL for antibiotics in animal products as per Food and Drug Administration (FDA) [7]

Name of the antibiotics	Codex (MRL) µg/kg milk (ppb)	FDA (Safe/Tolerance) µg/kg milk (ppb)
Amoxicillin	-	10/10
Ampicillin	-	10/10
Benzyl penicillin	-	5/10
Cloxacillin	-	10/10
Penicillin	-	5/0
Cetiofur	100	50/1000
Cephapirin	-	20/20
Chlortetracycline	100	30/0
Oxytetracycline	-	30/0
Tetracycline	-	80/0
Erythromycin	-	50/0
Tylosin	-	50/50
Streptomycin	-	125/0
Dihydrostreptomycin	200	125/0
Gentamicin	100	30/0
Neomycin	500	150/150
Chloramphenicol	-	0/0
Sulphadimidine	25	10/0
Sulphadiazine	-	10/0
Sulphamethoxine	-	10/0
Sulphathiazole	-	10/0
Sulphamethazine	-	10/0

The various analytical methods are available for screening and confirmation of antibiotic residues in animal products. They are microbial inhibition test, biosensor, Enzyme Linked Immunosorbent Assay (ELISA), High performance liquid chromatography (HPLC), Liquid chromatography with mass spectrometry (LC-MS), Liquid chromatography-tandem mass spectrometry (LC-MS/MS) and Ultra-performance liquid chromatography-Mass spectrometry (UPLC-MS) widely used for confirmation and quantitative analysis of drug residues in milk, meat and egg [5, 8-13].

3. Screening method

3.1 Microbial inhibition test

It is a qualitative or semi-quantitative test is used to detect antibiotic residues in milk and meat. Muller Hinton or Nutrient agar is commonly used to perform agar diffusion test. These tests comprise spores of specific bacteria (*Bacillus subtilis, Bacillus stearothermphillus, Micrococcus luteus* etc), sensitive to particular antibiotics on agar gel including nutrients for bacterial growth and a pH indicator [14]. After addition of milk or meat, the plate is incubated at appropriate temperature for growth and germination of bacteria. In the absence of antibiotic residues, the growth of bacteria can be detected visually either by the change of opacity of the agar medium or by the colour change of the pH indicator [8, 15-16]. This method is cheap and simple, showed 100% sensitivity and specificity for screening of residues [16], 85.51% of poultry meat samples were positive for antibiotic residue, most of them contained β-lactams and tetracyclines (75.81%), macrolides (44.35%), sulphonamides (36.29%), aminoglycosides (13.71%) group [7] and macrolides (12.5%) group of antibiotics in commercial eggs of urmia, Iran [17].

3.2 Biosensor

Biosensor is a latest technique used for screening of antibiotics residues in milk. The sensitivity and selectivity of biosensors are comparable to immunoassay methods [9]. These sensors have shown successful detection of β-lactams (β-Ls), tetracycline, streptogramin and macrolide antibiotics at nanogram per millilitre concentrations in milk and serum [18-19]. Microbial biosensor is mostly used for detection of quinolones (Qs) and tetracyclines (TCs). However, these were not sensitive toward detection of macrolides, β-Ls, aminoglycosides and sulphonamides [20].

3.3 Enzyme Linked Immunosorbent Assay (ELISA)

ELISA is most useful and specific test for screening of drug residues in meat, milk and egg. The Competitive ELISA is commonly used for quantitative analysis of tetracycline, fluoroquinolones and chloramphenicol in meat [10, 21]. Competitive indirect chemiluminescent enzyme-linked immunoassay (CL-ELISA) is used to determine the chloramphenicol (CAP) residues in milk and chicken muscle. The sensitivity of CL-ELISA is 2-3 times higher than conventional ELISA [22] and able to detect trace amount of CAP as low as 3.19 ng/kg in chicken muscle. In India (Punjab), Gaurav *et al.* [23] reported that tetracycline residues in milk by competitive ELISA. Out of 133 cattle milk sample, 18 samples were found to be contaminated with tetracycline. The concentration of tetracycline residues in cattle milk samples were found to be in the range 16-134.5 µg/l. Three samples exceeded the maximum recommended tetracycline antibiotic residue levels (MRLs).

Sultan *et al.* [24] reported that enrofloxacin residues in liver sample of poultry, sheep and cattle collected from slaughter house of Mousl city, Iraq. Out 30 samples from each species 17 poultry sample, 8 cattle sample and 5 sheep sample exceeded the maximum residue limits (Permitted MRL by European agency 100-300 µg/kg). The concentration of enrofloxacin in liver sample of poultry, cattle and sheep were 10-10690, 30-3610 and 20-1320 µg/kg respectively. This may be heavy use of enrofloxacin in poultry industry to control diseases.

3.4 High Performance Liquid Chromatography (HPLC)

Currently, HPLC is one of the most powerful tools in analytical chemistry. HPLC usage is increasing day by day in the field of residue analysis because, these having variety of mobile phases, the extensive library of column packings and the variation in modes of operations [5]. The residue analysis of oxytetracycline and penicillin G in milk collected from Nazareth dairy farms, Ethopia [11]. Out of 400 milk samples 48 samples were found oxytetracycline and penicillin G in the range of 45-192 and 0-28 µg/l, respectively. A total of 497 raw milk samples were collected from different region of individual farms at Macedonia and analysed for chloramphenicol, sulfonamides, quinolones and tetracyclines by HPLC-Diode array detection. The concentration of sulphonamides, quinolones and tetracycline in the range of 13.5-147.9, 0.6-22.0 and 17.4-149.1µg/kg, respectively. None of the samples showed chloramphenicol above MRL [25]. In Iran cattle tissue (Triceps muscle, gluteal muscle, diaphargam, kideney and liver) from local market were examined for tetracycline group of antibiotics (tetracycline, oxytetracycline and chlortetracycline) by HPLC method. The tetracycline concentration in Triceps muscle, gluteal muscle, diaphargam, kideney and liver were 176.3, 405.3, 96.8, 672.4 and 651.3 ng/g, respectively. The concentrations of tetracyclines were higher in liver and kidney sample compared to other sample [13] and it was higher in cured meat product [11].

3.5 Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

Nowadays, the most frequently used analytical tool for detection of a large number of multiclass veterinary drug residues in food [26-27]. The analysis of antibiotics in milk by LC-MS/MS is more specific and more reliable. Simultaneous determination of 14 antibiotics from different classes includes five β-lactams, four sulfonamides, three tetracyclines, one macrolide and one cephalosporin by liquid chromatography with electrospray ionization (LC-ESI) and triple quadrupole mass spectrometry (MS/MS) [28], enrofloxacin and tetracycline residues in chicken and pork by LC-MS/MS [21]. Aminoglycoside in animal tissue includes bovine kidney, ovine kidney and poultry liver [29]. Out of seventy two samples, twelve samples showed aminoglycosides includes neomycin (1), streptomycin (5) and dihydrostreptomycin (6) exceeded the MRL. The concentration of neomycin, streptomycin and dihydrostreptomycin were 10000, 300 and 300 µg [29] and doxycycline in poultry muscle was 847.7µg/kg [5].

Table 2: Antibiotic residues in animal products

Name of the antibiotic	Instrumentation	Substrate	Residue level (ppb)	Reference
Quinolone	ELISA	Chicken	30.81	Kim *et al*. 2013 [21]
		Beef	6.64	
	HPLC-DAD	Milk	0.6-22.0	Elizabeta *et al*. 2011[25]
Enrofloxacin	ELISA	Liver-Poultry	10-10690	Sultan *et al*.2014 [24]
		Liver-Cattle	30-3610	
		Liver-Sheep	20-1320	
Tetracycline	ELISA	Milk	16-134.5	Gaurav *et al*. 2014 [23]
	HPLC-DAD	Milk	17.4-149.1	Elizabeta *et al*. 2011[25]
	HPLC-FL	Cattle tissue	176.3	Abbasi *et al*. 2012 [13]
		Triceps muscle	176.3	
		Gluteal muscle	405.3	
		Diaphragm	96.8	
		Kidney	672.40	
		Liver	651.30	
Oxytetracycline	HPLC	Cured meat	42-360	Senyuva *et al*. 2000 [11]
Doxycycline	LC-MS/MS	Poultry muscle	847.7	Jank *et al*. 2017 [5]
Minocycline	LC-MS/MS	Porcine muscle	-	Park *et al*. 2016 [30]
Gentamicin	ELISA	Milk	90	Zeina *et al*. 2013 [31]
Streptomycin			80	
Penicillin	HPLC	Milk	0-28	Abebew *et al*. 2014 [12]
Tilmicosin, Cloxacillin and Ceftiofur	LC-MS/MS	Bovine milk	-	Jank *et al*. 2017 [5]
β-lactams, Sulphonamides, Tetracycline, Macrolides and Cephalosporin	LC-MS/MS	Milk	-	Martin-Junior *et al*. 2007 [28]
Enrofloxacin and Tetracycline	LC-MS	Chicken Pork	-	Kim *et al*. 2013 [21]
Flumequine	UPLC-MS/MS	Milk	2.58	Han *et al*. 2015 [32]
Sulphonamides	HPLC-DAD	Milk	13.5-147.9	Elizabeta *et al*. 2011[25]
Sulfapyridine	UPLC-MS/MS	Milk	1.77	Han *et al*. 2015 [32]
Sulfamethoxazole			4.2	
Lincomycin			11.25	
Chloramphenicol	ELISA	Chicken	12.64-226.62	Yiber *et al*. 2011 [10]

Several studies have been conducted worldwide to determine the antibiotic residues in animal products (Milk, meat, muscle, liver and kidney) summarized in (Table 2). Among the different antibiotic classes, the presence of tetracycline and fluoroquinolone residues in animal products has been commonly reported. The antibiotic residues in milk, chicken and liver in the range of 0.6-149.1, 30.81-226.62 and 10-10690 µg/kg, respectively.

4. Effect of antibiotic residue on environment

The environmental contamination with antibiotics may occur in several ways viz., drug manufacturing process, throwing of unused drugs and containers or application of manure and waste slurries. Animals excrete significant proportion of antibiotics (17-90%) directly into urine and faeces as parent compound or its toxic metabolites, because many of administered antibiotics are not completely absorbed from gut [33-35]. Reports on concentration of antibiotic residue in manure show large variations. It is depend on individual/group treatment (potential dilution), duration of the treatment and the time of sampling after treatment. The highest and most frequently reported concentrations of antibiotic residues in manure belong to the tetracycline group of antibiotics. The reported levels regularly exceed 100 mg/kg [35], with extremes up to 764 mg/kg chlortetracycline in swine manure [36]. The second higher concentration of antibiotic residue in manure is fluoroquinolone, the residue concentration of ciprofloxacin, enrofloxacin and norfloxacin in manure are 45, 1420 and 225 mg/kg, respectively. Penicillins show poor stability in manure and also possibly degradation by soil microbes [37], for aminoglycosides data on the occurrence in manure are lacking.

Antibiotics can enter the aquatic and terrestrial ecosystem through the discharge of farm effluents [38] with bioactive drug residue. Persistence of antibiotic residues in the environment depends on physico-chemical properties of drug residue, characteristics of the soil and climatic factors, temperature, rainfall and humidity [39]. Tetracyclines (particularly tetracycline and chlortetracycline) were found to be more persistent in soils than in manure [40]. Poor degradability and strong binding potential of flouroquinolones in the soil resulting in long persistence in soils and sediments. Sulphonamides are relatively stable and occur in environment in bioavailable form.

4.1 Effect of antibiotic residue on soil microbes

The presence of antibiotic residues in the environment and its effect on microbial community is depends on the type, amount of residue and species of environmental microbes present [41-42]. The antibiotic residues in the environment not only changes the structure and abundance of the soil microbial community, but also affects the ability of soil microorganisms to degrade contaminants and their role in ecological functions such as methanogenesis, nitrogen transformation and sulfate reduction in soil and aquatic environments [43]. For example sulphadiazine in soil reduce the nitrogen turn over in addition to reducing microbial activity. Oxytetracycline inhibits the nitrification in simple aquatic system. Furthermore, antibiotics significantly reduced numbers of soil bacteria, yielding dose related changes in the fungal to bacterial ratio.

4.2 Antimicrobial resistance

The emergence of drug resistance has been observed following the introduction of each new class of antibiotics [44] and repeated exposure to sublethal dose of antibiotics. However, selection of resistant bacteria in the environment could occur, when antibiotic concentration greater than minimum inhibitory concentration [45]. The use of manure for soil fertilization should be considered a main agricultural contributor to environmental contamination and transmission of antibiotic residues, resistant bacteria and resistance genes. Development of antibiotic resistance genes (ARGs) have been commonly reported due to the overuse of antibiotics worldwide. ARGs for tetracyclines and sulphonamides were detected in rice paddy soils fertilized with swine manure in USA [46]. The use of antibiotics in food animals selects for bacteria resistant to antibiotics used in humans and these might spread via the food to humans and cause poor response to treatment during illness [47] Following introduction of fluoroquinolones use in the poultry industry leads to development of fluoroquinolone-resistant strains of *Campylobacter jejuni* and *Salmonella* sp, which have isolated from poultry meat. Multiresistant *Escherichia coli* have been evolved by the use of broad spectrum antimicrobials in both livestock and humans. The development of antimicrobial resistance in *E. coli* creates problem, because of transmission of antimicrobial resistance genes to next generation [3].

5. Effect on health

Most of the currently used antibacterials are relatively non-toxic, even at higher concentration but, few antibiotics pose a serious public health issue. Antibiotic residues in milk are of great public health concern since milk is being widely consumed by infants, youngster and adults throughout the globe [48]. The long term exposure to antibiotic residues in milk may result in alteration of the drug resistance of intestinal microflora [49]. Several antibiotics are potent antigens or act as a haptens and occupational exposure on a daily basis can lead to allergic reactions. The most of the allergic reactions have been reported against ß-lactam antibiotic residues in milk or meat. It is a one of the hypersensitivity reaction. It may be either IgE-mediated or non IgE-mediated. The IgE-mediated response occurs shortly after exposure to drug. These include urticaria, anaphylaxis, bronchospasm and angioedema. Non IgE-mediated reactions include hemolytic anemia, thrombocytopenia, acute interstitial nephritis, serum sickness, vasculitis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis [50-51].

Antibacterial agents like tetracyclines, nitrofurans and sulfonamides are widely used as feed additives in cattle feed, which may excrete in milk and sometimes associated with toxicological effects in human [51]. The nitrofurans at higher concentrations cause carcinogenic and mutagenic effects [52]. Recently Etminan and coworkers [53] reported the risk of retinal detachment in individuals upon continued exposure to fluoroquinolones. Chloramphenicol is also associated with optic neuropathy [54] and brain abscess [55] with varied intensities and clinical manifestations.

6. Conclusion

Use of antibiotics as feed additives at sub therapeutic dose should be strictly prohibited. For therapeutic purpose, it must be used in proper dose for proper time. There are two major concerns in the presence of antibiotic residues in milk, meat and egg. One is allergic reaction even at smaller dose, another development of antibiotic resistance and disruption of soil microbial community. Monitoring of antibiotic residues in milk and milk products, meat and meat products, egg, faeces and urine is necessary to safeguard the health of the consumers as well as minimise environmental contamination.

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