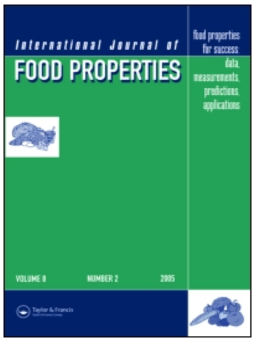

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Antimicrobial drug residues in poultry products and implications on public health: A review

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ABSTRACT
Poultry meat and eggs are important foods for fulfilling the dietary needs of the ever-growing human population. Efficient poultry production, however, necessitates use of pharmaceutical products, such as antibiotics, as prophylactic and curatives to ensure rapid growth and health. Nevertheless, inappropriate and non-judicious use of these drugs results in an accumulation of toxic and harmful residues in meat and eggs of treated birds which affect consumer health by triggering allergic reactions and transmitting antibiotic-resistant microbial infections. Therefore, regulatory authorities must take rigorous steps to curtail inappropriate use of numerous drugs for animal use in order to provide safe animal origin food to humans.

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Introduction

Over the past few decades poultry has gone through tremendous growth; however, with the increase in production, the use of certain drugs and feed additives has become crucial in order to prevent diseases, their treatment, and growth promotion.[1–4] However, one of the drawbacks of excessive use of antimicrobial drugs is that they get accumulated in the tissues and organs of treated animals as residues and eventually become part of the food pyramid,[1–3,6] hence excessive usage has been recognized as illegal and prohibited by the food regulatory and health authorities.[1,3–5] This article elucidates the use of various antimicrobial agents in the poultry industry, their distribution and accumulation in various body parts and tissues and their subsequent effects on human health.

Medicinal drugs and antimicrobial agents used in poultry industry

Modern approaches applied for efficient chicken production have resulted in wide-spread disease havocs across the world. For instance, intensive rearing conditions with high stock densities in poultry houses have provided ideal conditions for manifestation and transmission of parasitic and viral diseases. In addition to that, due to poor condition management, the disease incidences are not only becoming more frequent, pronounced, and unmanageable, but also difficult to control in the long run.[8] The most prevalent diseases are typhoid, mycotoxicosis, *E. coli* infections, coccidiosis, Salmonellosis, enteritis, ascites, Newcastle disease, Marek's disease, hydropericardium syndrome, and Gumboro disease.[8–10] These diseases are not only influencing poultry growth and production, but are also contributing considerably to the economic losses due to a high mortality among the

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flocks.[10,11] Additionally, high disease loads call for heavy uses of veterinary medicines, antiparasitic, or antibiotic drugs in order to prevent and treat microbial infestation.[10,12]

Antibiotics for therapeutic and prophylactic purposes

Antibiotics are naturally occurring, semi-synthetic, or synthetic compounds with antimicrobial activity and are most widely used drugs in the poultry industry. They are administered parenterally or intravenously, topically, and orally.[13,14] Antibiotic drugs are typically used to serve three purposes in poultry, (1) therapeutic use where animals (either individually or in small groups) are administered with high doses of antibiotics for relatively shorter periods, (2) prophylactic use that involves exposure of animals with moderate doses of antimicrobials for longer time durations, and (3) growth promotion where antibiotics in subtherapeutic doses, for example, 10 or 100 times less than therapeutic doses are given for a very long duration or throughout the entire lifespan of the animals.[12,15] The antibiotics are known to inhibit (1) DNA replication, (2) Ribo-nucleic acid (RNA) and protein synthesis, (3) cell division, differentiation and development, (4) target folic acid metabolism, or (5) disrupt cell membrane and cell wall synthesis of microorganisms responsible for dissemination of infections.[16,17]

In developing countries, the use of antibiotics is quite common. The most commonly used antibiotics are: tetracycline,[19] gentamicin,[20] neomycin, tylosine, erythromycin,[21] virginiamycin, ceftiofur, and bacitracin which are usually helpful in the reduction and prevention of respiratory diseases and necrotic enteritis infections; flouroquinolones and/or quinolone compounds are used for treating gastroenteritis, skin, or soft tissue infections;[23,24] sulfonamide compounds are administered as preventive and chemotherapeutic agents against coccidiosis, fowl typhoid, coryza, and pullorun disease;[24,26] while, piperazine, oxytetracycline, amoxicillin, amprolium, ciprofloxacillin, and sulfa drugs are used to treat coccidiosis.[27]

Likewise, many anticoccidial drugs (narasin, salinomycin, sulphonamides, clopidol, amprolium, nicarbazin, etc.) and vaccines (derived from non-attenuated or attenuated oocysts of coccidia strains) are widely utilized as antidotes in poultry feed to prevent and treat coccidiosis.[10,39] Coccidiosis, a parasitic disease caused by several *Eimeria* species, is known to inhibit the growth and progression of the poultry industry. The disease manifests itself in intestinal epithelial tissues and inflicts birds with diarrhea (feces with blood), reduction in weight gain, decreased production of eggs, and feed conversion rates, thereby causing higher morbidities and mortalities.[8,11,40] Some of these drugs are employed in combinations for effective poultry production such as, narasin and nicarbazin.[10] However, extensive administration of coccidiostats in hens reared for egg-laying purposes without any knowledge of withdrawal periods, results in deposition of residues within edible tissues and products from animals (such as eggs) in different concentrations and negatively influence human health.[8,41] The majority of antibiotics are administered either through feed or in drinking water.[13] Some of the antimicrobial agents used in poultry along with their derivatives, mode of actions and their withdrawal period is given in Tables 1 and 2.

Antibiotics for growth promotion

The use of antimicrobial agents for growth promotion purposes in farm animals was prescribed in the mid-1950s. Since then tetracycline, chloramphenicol, and procaine penicillin (subtherapeutic doses) supplemented feeds were extensively employed in the poultry industry to promote growth and egg production.[12,42] Virginiamycin, avoparcin, tylosin, and numerous ionophores have also been reported to be used as growth promoters.[12,15,17] In addition to antibiotics, due to role of hormones in better growth and improvement in feed efficiencies, food producing animals are also administered with natural and synthetic hormones in developing countries. For instance, applications of oestradiol (female sex hormone) in castration of young birds, either subcutaneously or as feed additives, in the past has been reported by some authors.[44] As a matter of fact, the mechanisms by which antibiotics promote growth are not yet defined; however, studies have indicated that antibiotics may stimulate growth by their

Table 1. Commonly applied antibiotics in poultry industry.

Antibiotics	Derivatives	Mechanism	References
Beta-Lactams	Amoxicillin (aminopinicillin), penicillin, cephalosporin, ampicillin, monobactam, carbapenem	Bactericidal (prevents bacterial cell synthesis, disrupts cell wall integrity, inhibit transpeptidase)	[22,28]
Tetramisole	Levamisole	Effective against lungworms and gastrointestinal nematodes, mimics thymic hormone thymopoietin which affects many components of immune system	[29,30]
Quinolones/ Fluoroquinolones	Oxolinic acid, nalidixic acid, flumequine, enrofloxacin, norfloxacin, ciprofloxacin	Arrest bacterial cell growth via inhibiting DNA gyrases involved in DNA replication, recombination and repairing	[23,24,31]
Tetracyclines	Chlortetracycline, tigecycline, minocycline, oxytetracycline, chelocardine	Bacteriostatic and bactericidal, inhibit protein synthesis	[19,32]
Sulfonamides	Sulfacetamide, sulfamethoxypyridiazine, sulfamethoxydiazine, sulfamethoxazole, sulfadimidine, suflamethoxine, sulfadiazine, sulfafurazole,	Act as competitive antagonists in microbial cells, block formation of folic acid	[26,32]
Aminocyclitol	Spectinomycin, apramycin	Bacteriostatic and bacteriocidal, irreversible inhibition of protein synthesis	[32,33]
Amphenicols	Chloramphenicol, thiamphenicol, florfenicol	Inhibit protein synthesis	[1,32]
Coccidiostats	Salinomycin, diclazuril, robenidine, naduramicin, lasalocid, toltrazuril, halfoginone, nicarbazin, narasin, monensin, clopidol, ionophores, amprolium	Disrupt ion gradients across parasite cell membrane, inhibit parasite mitochondrial respiration, folic acid pathway, competitive inhibition of thiamine uptake	[10,34]
Macrolide	Erythromycin, tylosin, spiramycin	Act on 50S ribosomal subunit and inhibit protein synthesis	[1,32]
Nitrofurans	Furazolidone, furaltadone, nitrofurantoin, nitrofurazone	Bacteriostatic or bacteriocidal (at high doses)	[1,35]
Aminoglycosides	Neomycin, canamycin, gentamycin, netilmycin	Irreversible inhibition of protein synthesis	[32,36]

Table 2. Recommended withdrawal periods for some of the antimicrobial substances used in poultry industry.

Antimicrobial substances	Feed withdrawal period (days)	Legislating authority	References
Levamisole	7	Australia	[30]
Nicarbazin Narasin	5	European Commission	[37]
Ciprofloxacin	15–19	European Health Law and National Office of Animal Health, UK	[38]
Lasalocid Salinomycin Narasin Maduramicin Semduramicin	5	Finnish National Feed Control Programme	[2]
Monensin	3	Finnish National Feed Control Programme	[2]
Oxytetracycline Sulphadimidine	5	Saudi Arabia	[21]
Ampicillin	6	Saudi Arabia	[21]

antimicrobial activities against pathogens and harmful bacteria. It has been speculated that antimicrobial agents may protect nutrients against bacterial destruction by reducing growth of intestinal bacteria, facilitate improved nutrient absorption by thinning of intestinal barriers, minimizing toxins production by intestinal bacteria, and lowering subclinical (intestinal) disease incidences.[43]

For years, the use of antibiotics and/or antimicrobials was seen as hallmark and allowed to be used without any restrictions, regulations, and supervision in various commercial poultry enterprises. However, the negative effects of these growth promotants remained undetected until acquisition of resistance against antimicrobials. The concerns about therapeutic and growth promotion deployments of antimicrobials aroused mainly due to emergence of increased number of resistant bacteria.[12,43] The extensive use of antibiotics and growth hormones, however, has been banned in developed countries, but the situation is quiet contrary in developing or underdeveloped countries

Table 3. Permitted MRLs for various anticoccidial drugs in poultry products.

Antimicriobial agents	Derivatives	MRL (μg Kg^{-1})	Poultry item	Legislating authority	References
Anticoccidials	Monensin	2	Eggs	European union	[34,46]
	Narasin	2	Eggs		
	Nicarbazin	100	Eggs		
	Diclazuril	2	Eggs		
	Semduramicin	2	Eggs		
	Maduramicin	2	Eggs		
	Robenidine	25	Eggs		
	Decoquinate	20	Eggs		
	Halofuginone	6	Eggs		
	Toltrazuril	600	Liver		
		400	Kidney		
		100	Muscle		
		200	Skin, fat		
	Lasalocids	150	Eggs		
		100	Liver, skin, fat		
		50	Kidney		
		20	Muscle		

due to inadequate safety standards and regulations or in some cases these standards or regulations do not even exist.[13]

Despite prohibition, many broiler chickens and layers (egg-laying hens) are administered with overdoses or inappropriate doses of antibiotic drugs for therapeutic, prophylactic, as well as non-therapeutic purposes throughout their entire lifespan.[2,42] If these drugs are not absorbed, or if they are metabolized by the animal, it would be harmless to products, not being problematic. Unfortunately, that is not what always happens. Hence, unsafe drug residues tend to accumulate in various concentrations in the edible parts of treated animals.[3] These residues are primarily comprised of parent and derivative compounds (or both) including metabolites, conjugates, and remnants bound with macromolecules.[21,45] Ingestion of tissues and organs (meat, offals, eggs, etc.) containing drug remnants above safe maximum residual levels (MRLs), given in Tables 3 and 4, is associated with numerous health hazards and vulnerabilities (1) directly as initiation of hypersensitive or allergic reactions, cutaneous eruptions, dermatitis, alteration of intestinal microflora etc., (2) indirectly as carcinogens, teratogens, development of antibiotic resistances among microbial strains, and (3) often leads to drug toxicity.[1,3,7,21,50,51]

Presence and distribution of drug residues in poultry products

Since traditional backyard and intensive poultry farming is a common practice in many developing countries, and farmers have easy access to veterinary drugs and the use of medicines, the use in indiscriminate and inappropriate higher doses of antimicrobial drugs is common, which eventually accumulates harmful residues in edible tissues of the poultry.[1,42,52,53] The other cases where poultry can have harmful residues in their meat and egg products are (1) unintentional or accidentally cross-contaminated feed in feed mills, (2) recirculation through litter, and (3) administration of feed ingredients or water contaminated with metals, pesticides, or toxic chemicals, etc.[13,42] All these residues produce potential threats of direct toxicity in humans and alteration of micro-flora with possible development of resistant strains due to low and continuous exposure to antibiotics, thus causing failure of antibiotic therapies.[51]

Drug residues in egg matrix

Since eggs are consumed by almost every individual, the deposition of drug residues in various egg components is of considerable concern. Upon administration, antibiotics get absorbed into the

Table 4. Permitted MRLs for various drugs in poultry products.

Antimicriobial agents	Derivatives	MRL (µg Kg^{-1})	Poultry item	Legislating authorities	References
Sulfonamides	—	100	Tissues, eggs	Council Regulation (EEC), Codex Alimentarius, FAO/WHO and Code of Federal Regulations	[25]
	Sulfadiazine	100	Eggs	Codex Alimentarius Commission	[47]
	Chloramphenicol	0	Liver, muscles	European Union (EU)	[48]
Beta-Lactams	Benzylpenicillin (penicillin G)	50	Kidney, liver	FAO/WHO	[49]
Quinolones/ flouroquinolones	Ciprofloxacin + enrofloxacin	200	Liver		[36]
		100	Muscles	European Union	
		300	Kidneys		
	Flumequine	50	Skin, fat		[31]
Aminoglycosides	Neomycin	500	Muscles, liver	European Union, Health Canada Veterinary Drugs Directorate, Australia	[36]
		5000	Kidney	European Union	
		10000		Health Canada Veterinary Drugs Directorate, Australia	
	Gentamicin	100–400	Eggs	USA	[45]
		100		Holland	
		200		Germany	
		100–200		France	
Tetracyclines	Chlortetracycline	100	Muscles/ meat	European Union, Australia	[36,48]
		200		Health Canada Veterinary Drugs Directorate	
		2000		United States Food and Drug Administration (USFDA)	
		300	Liver	European Union	
		600		Health Canada Veterinary Drugs Directorate	
		6000		United States Food and Drug Administration	
		100	Kidney	European Union	
		1200		Health Canada Veterinary Drugs Directorate	
	Oxytetracycline	100	Muscles/ meat	European Union, Australia	
		200		Health Canada Veterinary Drugs Directorate	
		2000		United States Food and Drug Administration	
		100–300	Liver	European Union	
		6000		United States Food and Drug Administration	
		600		Health Canada Veterinary Drugs Directorate	
		1200	Kidney	Health Canada Veterinary Drugs Directorate	
	Doxycycline	300	Liver	European Union	
		100	Muscles		
		600	Kidney		
	Sipromycin	200	Meat	Codex Alimentarius Commission	[74]

intestines of chicken and are transported through the whole body via blood plasma where it reaches the ovaries (follicles and oviducts) responsible for formation and secretion of egg contents, thus upsurges the risks of deposition of drug residues in the yolk and albumen.[28,55] Drugs have been reported to deposit more rapidly in both yolk and albumen.[1,45,56] However, the distribution and deposition pattern of residues varies depending upon the composition, physiochemical properties of antimicrobial agents, physiology of hen, egg formation, and nature of egg compartments.[57,58] Studies have provided evidence of contamination of poultry eggs with various concentrations of drug residues. For example, the deposition of nitrofuran residues (3-amino-2-oxazolidone) employed for treating salmonellosis and other bacterial infections, in eggs has been confirmed by Al-Ghamdi et al.[59] and Amiri et al.[60] The eggs were found to be contaminated with 268.25 ng kg^{-1} of amino-2-oxazolidone metabolite and indicated extensive use of furazolidone drugs.[60] Similarly, contamination of eggs with 103–230 ng g^{-1} of sulfonamide residues (sulfadiazine) exceeding MRLs has also been reported by Mehtabuddin et al.[25] Moreover, deposition of various drug residues including amprolium, furaltadone, furaprol (nitrofuran-amprolium combination), oxytetracycline, soluvite (vitamins and minerals supplement), tylosin, streptomycin, and sulfaquinoxaline within eggs has also been ascertained by Kabir et al.[42] Likewise, deposits of dinitrocarbanilide in egg samples have indicated prevalence of nicarbazin residues.[61]

Additionally, the transmission of administered amoxicillin from egg-laying hens to the eggs and its accumulation in the yolk as well as the egg white has been ascertained by Khattab et al.[28] Even storage at room temperature, refrigeration (4°C) and boiling for 10 mins was not found helpful in minimizing the effect of these residues.[28] Similarly, the administration of gentamycin in different doses either subcutaneously or intramuscularly showed variations in the deposition of residues between egg whites and yolks even after the cessation of drug dosing. These residues accumulated in significantly higher concentrations (90%) within the yolk in contrast to the albumen.[45,56] On the other hand, high levels of chlortetracycline and sulfanilamide residues (above MRLs) in egg whites as compared to yolks have also been predicted.[57] Hence, it is evident that drug residues (exceeding MRL values) get deposited within various egg compartments and the consumption of such contaminated eggs can cause serious consumer health hazards.

Drug residues in meat

Poultry meat offers a better substitution for mutton and beef based on nutritional specifications and affordability. But uncontrolled drug usage and lack of proper biosafety measures for their withdrawal has resulted in a decreased quality of meat.[25] For instance, the deposition of significantly higher concentrations of various antibiotic residues in edible tissues of chickens receiving therapeutic, or prophylactic without observance of recommended withdrawal times have been demonstrated by Kabir et al.[42] and Hind et al.[62] Likewise, the accumulation of oxytetracycline (88.217 ng g^{-1}) enorfloxacin (18.32 ng g^{-1}),[61–64] quinolones (30.81 μg kg^{-1}),[65] chloramphenicol (0.021 and 0.008 μg kg^{-1},[66] and 89.33–223.05 μg kg^{-1}),[48] and oxytetracycline (670–1816 μg kg^{-1})[48] residues also been reported leaving residues in chicken meat. In addition to this, considerably higher concentrations of enrofloxacin (due to lipophilic nature) in the broilers' meat have also been reported by Amjad et al.[31] Sattar et al.[67] also reported the deposition of ciprofloxacin (34%), enorfloxacin (22%), and tetracycline (20%) residues in meat along with amoxicillin (26%) in thigh muscles, ciprofloxacin (30%), tetracycline (24%), amoxicillin (22%), and enorfloxacin (18%) residues in breast muscles of egg-layers and broilers. Furthermore, Karmi[68] also confirmed the presence of aminoglycoside, tetracycline, quinolone, and sulfonamide residues in fresh, local frozen, and imported frozen samples from chickens (breast and thighs) sold for human consumption, while the contamination of poultry meat samples with β-lactam and/or tetracycline (75.81%), macrolide and/or β-lactam (44.35%), sulfonamide (36.29%), and aminoglycoside (13.71%) residues has also been confirmed by Hakem et al.[69] Similarly, widespread misuse of antimicrobial agents due to non-compliance of withdrawal periods also has revealed detectable levels of oxytetracycline residues in chicken fillets.[70]

Drug residues in offals

Various researchers have investigated the presence of drug residues in treated animals' edible tissues and/or offals including heart, liver, kidneys, and gizzard through different techniques.[31,60,71–76] Studies have conferred the prevalence of higher concentrations of levamisole residues in liver of broiler chickens as compared to other body tissues, including thigh muscles, due to the lipid-soluble nature of the drug.[30] Moreover, the deposition of oxytetracycline and chloramphenicol residues in substantially higher amounts within the liver and kidney samples of broilers confirmed by Salehzadeh et al.[63] and Shahid et al.[71] indicated non-compliance of established MRLs. Similarly, higher concentrations of ciprofloxacin and enorfloxacin residues in livers and kidneys of broiler chickens along with relatively lower concentrations of flumequine have also been detected.[31] The contamination of liver and kidney samples with enrofloxacin and chloramphenicol residues exceeding MRL values has been reported, respectively, by Salehzadeh et al.[64] and Mehdizadeh et al.[72] Correspondingly, highest concentrations of tetracycline (48%), ciprofloxacin (44%), amoxicillin (42%), and enorfloxacin (40%) residues have been found in boilers and egg-layers livers, whereas kidneys contained 24, 42, 30, and 34% residue of the respective antibiotic substances.[67] Furthermore, the occurrence of high levels of nicarbazin residues (dinitrocarbanilide) in boilers' livers has been reported.[37,61]

Sipramycin isolated from *Streptomyces ambofaciens* is a macrolid antibiotic and is used as a growth promoter in poultry. Amro et al.[75] examined the presence of residual sipramycin in treated chicken tissues. Their results revealed the contamination of liver, thigh, and gizzard samples with sipramycin residues. However, the highest concentration of residues were observed in liver (40%) and with lowest found in gizzard and muscle (10%) samples. Another study reported the contamination of chicken giblets with amoxicillin and sulphaquinoxaline residues. The study reported that out of 90 samples of heart, liver, and gizzard (30 each) examined, were around 3.33, 13.33, and 10% heart, liver, and gizzard samples were containing higher levels of amoxicillin residues, whereas only 10 and 13.33% of gizzard and liver samples were found to be contaminated with higher concentrations of sulphaquinoxaline residues (exceeding MRLs).[76] Similarly, a study conducted by Morshdy et al.[74] showed the incidence of liver and gizzard samples contaminated with tilmicos. Abiola et al.[77] also have reported the contamination of gizzard samples with nitrofuran (41%), tetracycline (14%), sulfamids (8%), and chloramphenicol (5%) residues collected from market and poultry farms. A study conducted by Barbosa et al.[78] concerning the accumulation and distribution of furaltadone, nifursol, and their metabolites (3,5-dinitrosalicylic acid hydrazine [DNSAH] and 3-amino-5-morpholinomethyl-2-oxazolidinone [AMOZ]) in liver and gizzard samples ascertained the prevalence of furaltadone and nifursol residues in animals medicated for 5 weeks without observing withdrawal periods. However, the analysis of treated birds after 3 weeks along with observed withdrawal periods showed no accumulation of furaltadone and nifursol residues, but ascertained a quick conversion of these compounds into respective metabolites (AMOZ and DNSAH) which persisted for longer durations as compared to parent compounds. The AMOZ concentrations in liver and gizzard samples were estimated as 80 and 331 $\mu g\ kg^{-1}$, while for liver and gizzard observed DNSAH concentrations were 6.4 and 10.3 $\mu g\ kg^{-1}$, respectively.[78]

Human health risks associated with drug residues

The veterinary drug residues in poultry products can potentially be transmitted to humans via consumption of contaminated edible tissues and may lead to several pathological implications that are considered as major health issues. Chicken meat contaminated with drug residues may pose serious public health hazards in the form of antibiotic resistant bacterial formation, allergic manifestations, or alteration of useful microflora of digestive tract to no microflora and/or harmful or non-healthy microflora.[79] For instance, residual β-lactams, including cephalosporin and penicillin, have been reported to cause dermatitis, cutaneous eruptions, anaphylaxis, and gastro-intestinal symptoms in humans via ingestion of contaminated poultry products.[80] Penicillin residues are considered as the most problematic because of the vulnerability of a large proportion of people, many are allergic.[81] Moreover, penicillin residues in poultry can lead to severe anaphylactic reactions while eggs containing residues of sulfonamides in higher concentrations cause skin allergies upon consumption.[42,82]

The residual levels of tetracycline in a diet intended for human consumption have been reported to lead to poor development of fetuses, staining of teeth in young children, gastrointestinal disorders, and pro-inflammatory, cytotoxic, and immuno-pathological effects.[13,82,83] Similarly, residual amounts of tilmicosin affect hematological (white blood cell [WBC], red blood cell [RBC]) and biochemical parameters such as total protein, albumen, cholesterol, and triglyceride concentrations.[84] Likewise, the persistence of sulphamethazine, oxytetracycline, and furazolidone residues in humans is known to pose immuno-pathological effects (such as autoimmunity, carcinogenicity), while that of gentamicin and chloramphenicol may be mutagenic, nephropathic, and hepatotoxicor they may lead to reproductive abnormalities or bone marrow toxicity.[51]

Similarly, intake of nitrofuran metabolites as residues via poultry products may produce toxic, mutagenic, or carcinogenic side effects and may transmit antibiotic resistance among human microflora, hence the application of nitrofurans in poultry has been banned.[60] While some drug residues such as nitroimidazole and 3-nitrofuran cause different cancers in humans.[85–88] Continuous doses of ciprofloxacin residues to humans is also known to cause toxicity, impede cytochrome (CYP1A2) mediated metabolism, and can result in increased concentration of drug in systemic circulation due to reduced renal clearance.[38] Moreover, the consumption of drug residues via chicken products may result in the production and proliferation of drug-resistant bacteria in human beings, which could lead to therapeutic failures among such infected individuals.[51,68]

Risks of Dissemination of antimicrobial resistant microbes in humans

Though the applications of antimicrobial agents in poultry feed has lowered disease incidences, but their prolonged and intensive uses in low doses as growth enhancers has resulted in stimulation and emergence of antimicrobial resistant strains. For example, the emergence of resistance in *Salmonella* and *Campylobacter* species against fluoro-quinolones and third-generation cephalosporin's (used to treat human diseases) has been reported by Anderson et al.[88] Similarly, *S. intermedius* strains (221), isolated from the canine family, exhibited different rates of resistance to cephalotin, mupirocin, ciprofloxacin, clindamycin, gentamicin, chloramphenicol, and amoxicillin/clavulanic acid, which could lead to difficulties in effective treatment in human diseases. [89] Moreover, there are several reports on the prevalence of antimicrobial resistant bacteria within on-farm broiler chickens. Around 525 avian *E. coli* strains isolated from broiler have been reported to be resistant to various antimicrobial agents including trimethoprim-sulfamethoxazole and ciprofloxacin. Additionally, the prevalence rate of resistant *E.coli* to ciprofloxacin and erythromycin in broiler with *colibacillosis* was reported to be significantly higher as compared to that of controls.[90]Avian *E. coli* strains (468) isolated by Blanco and co-workers[91] displayed significantly higher resistance levels to trimethoprim-sulfamethoxazole and fluoroquinolones, moreover, these antimicrobials were suggested to lead to cross-resistance in human enteric pathogens. A total of 293 strains isolated from chicken farms and slaughter houses, characterized as *S. enterica Indiana*, were found to be resistant to norfloxacin, enrofloxacin, and ciprofloxacin, moreover, gene mutations were also detected in these strains.[92] Similarly *E. tenella*, isolated from poultry fields, also exhibited a development of resistance against salinomycin.[93] These researches suggest that uninterrupted and indiscriminate employment of these antimicrobial agents is increasing the dissemination of resistance against multiple drugs in foodborne-bacteria and/or human pathogens[94] and is leading to loss of effectiveness of antibiotics against poultry and human ailments.

C. jejuni, Salmonella sp., and Verotoxigenic *Escherichia coli* have been recognized as major emerging foodborne pathogens among human beings.[97] Luber et al.[98] and Chuma et al.[99] have ascertained contamination of poultry meat available in supermarkets with antimicrobial resistant *C. jejuni*, which upon consumption may lead to compylobacteriosis. *C. jejuni* strains isolated from poultry samples were found to be resistant to multiple antibiotics including ampicillin, cephalothin, sulfamethoxizole +trimethoprim.[100] Moreover, exhibition of resistance against ampicillin following ciprofloxacin, tetracycline, erythromycin, and gentamicin by *Campylobacter* strains (*C. coli* and *C. jejuni*) isolated from fresh chicken meat has also been documented by Sison.[101] This reflects emergence of resistance to multiple antibiotics through misuse or overuse of antibiotics. Similarly, *C. jejuni, S. enterica, serotype Enteritidis, L. monocytogenes*, and *E. coli* from chicken carcasses showed higher resistance percentages against multiple drugs including tetracycline, sulfonamides, and quinolones.[102] Idrees et al.[103] and Nsofor et al.[104] ascertained the presence of multi-drug resistant *E. coli* in chickens; being commensal, these can lead to serious public health issues. Ali et al.[105] reported the prevalence of high-level vancomycin, kanamycin, clarithromycin, ampicillin, gentamicin, and erythromycin resistant non-enterococci and enterococci in poultry feed, water, litter/manure, and air. Additionally, the occurrence of streptomycin-, ampicillin-, kanamycin-, neomycin-, tetracycline-, erythromycin-, cefotaxime-, novobiocin-, nalidixic acid-, bacitracin-, and spectinomycin-resistant *Salmonella* serovars in chicken meat has been confirmed by Shah and Korejo[106] and indicated that these multiple drug resistance isolates may cause human infections upon consumption of contaminated meat. Several strains of *E. coli* isolated from poultry carcass have shown resistance to extended-spectrum β-lactamase. These strains are of main concern due to their potential transferability to humans via the consumption of meat.[107] Numerous detailed evidences of linkage between extended animal in-feed antimicrobials applications and escalation in transmission of drug-resistant microbial infections among humans have been cited by Marshell and Levy.[12] Hence, there must be strict legislation for determination of safer drug levels and withdrawal times (to reduce prolonged use of drugs) and implementation for following drug withdrawal periods for safe consumer consumption by health authorities.[84]

Although significant reductions in mortality have occurred due to bacterial infection by the use of antibiotics, some diseases are on the rise because of continuous acquisition of resistance against all available antibiotics.[5,95] Acquisition of multi-drug resistance is now becoming a widespread issue and is of major concern among poultry veterinarians and food microbiologists due to their severe implications on public health. Studies have described that there exists a linkage between applications of antimicrobials in poultry and subsequent transmission of resistant genes in human pathogens. This may be because of the fact that numerous human and animal pathogens treated with identical or related classes of antibiotics are developing diverse resistance mechanisms and ultimately sharing and spreading them within other microbial populations.[15,17] The mechanisms of acquisition of resistance against antibiotics and dissemination of these resistant genes among other microorganisms have been described in detail by Poole and Sheffield.[96]

Conclusion

The deposition and subsequent detection of residual amounts of these antimicrobial substances exceeding MRLs in poultry products is really a matter of concern. Furthermore, emergence and co-occurrence of resistance to various and/or multiple antibiotics in commensal, pathogenic, and mutualistic microbes is also threatening human health. Therefore, strict legislations and control measures at national and local levels should be established for production, sale, and use of veterinary drugs in treatment or as feed supplements. Additionally, the recommended withdrawal periods between administration of drugs and slaughtering must be instigated and enforced by the respective food and drug administration, other regulatory authorities, and professional veterinarians. There should be regular monitoring and assessments for the presence of drug residues in edible tissues of poultry to ensure the consumers safety.

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