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Review Article

Public health-associated issues because of chemical drug residues in poultry products

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ABSTRACT

Poultry is among the most efficient sectors providing nutrition in the world. It is now a main source of protein for the increasing population. Poultry eggs and meat provide a wide range of micronutrients and macronutrients including proteins, lipids, vitamins, and minerals. It provides not only nutrition to us, but it also threatens the population because of the vast use of drugs in poultry production. Different types of drugs are used for the treatment or prevention of diseases, but some farmers use them inappropriately, which leads to antimicrobial resistance and issues of drug residues. Antibiotics, including quinolones/fluoroquinolones, lincosamides, macrolide, polymyxins, sulfonamides, and tetracyclines are used for treatment and prevention and are also growth promoters. Penicillin is most important because numerous people show allergic reactions to it. Different anthelmintics, anticoccidials, and antivirals are also used in the poultry industry. Some drugs produce carcinogenic metabolites. Drugs should be used at appropriate times and in an adequate dose. Constant low-dose antibiotics cause modification in microflora and production of resistant pathogens strains. Poultry products containing more than the maximum residual levels permitted upon consumption may cause hypersensitivity, cancer, toxicity, or drug resistance in humans. *E. coli*, *Campylobacter,* and *Salmonella* are now resistant to numerous antibiotics. Drug residues affect human health very seriously. The emergence of drug-resistant pathogens poses a risk to public health. Developing resistance leads to treatment failures and there will be a need for new drugs, which is a challenging task. Drug withdrawal period must be ensured. Regular monitoring must be performed for drugs residing in an edible portion of poultry. Consumer safety should be the priority of production.

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Poultry production

There are more than 23,000 million poultry in the world or per person three birds. In numbers, it has increased five times in the past 50 years (Mottet and Tempio 2017). Different production systems are used worldwide for meat and egg production to fulfill human food and protein needs. Currently, an integrated system is established to increase the efficiency of production and the use of byproducts like manure as crop fertilizer. Globally, poultry eggs and meat are the most common sources of food from poultry production (Windhorst 2006). Different traditions, cultures, and religions play important roles in increasing poultry production. Poultry is the most efficient sector among livestock and agriculture in providing nutrition in the whole world (Nkukwana 2018). Efficient use of natural resources with technology increases the capability of production. Poultry production is classified as rural poultry and commercial poultry (Mack et al. 2005). In rural areas, poor people use them for their food needs, but it has less production potential. Commercial setups are built for urban communities having high meat and egg production to fulfill. In commercial systems, usually, there is a private investment which leads to efficient production. There should be government policies to protect human health, the environment, and animal welfare.

Nutrition

Poultry eggs and meat provide important nutrients for public health, including children, and decrease mortality among newborns and children (Yalçin and Yalçin 2013). It provides a diverse range of micronutrients and macronutrients (vitamins, calcium, iron, zinc, fats, and protein) which cannot be obtained by using only plants or pulses. Poultry provides more affordable protein and nutrients than other animal sources in developing countries (Akinola and Essien 2011). Thirteen essential vitamins, amino acids, and minerals are present in the egg, and it provides about 70 calories (Vaghefi 2002). Eggs can be stored without a refrigerator for adequate time (Brake et al. 1997).

Constraints with Poultry

Poultry also poses a threat to human health because of drug residues and zoonotic diseases (Muaz et al. 2018) like Avian Influenza and *Salmonella,* which are spread by contact with birds (Contreras et al. 2016). The H5N1 outbreak of Avian influenza is a recent example of similar outbreaks (Morens 2013). Avian Influenza caused the death of thirty-five million laying hens in 2015, which resulted in a 50% raised raising the price of eggs and a supply decrease of 11% (Paukett et al. 2018). Antibiotics are used in poultry feed as growth promoters or for disease prevention, which develops AMR (antimicrobial resistance) (Hosain et al. 2021). AMR poses a great risk to human health. In 2023, antimicrobial use may rise to 70%. If any disease comes into the flock, it causes huge economic losses because of less production, treatment costs, and mortality. Poultry welfare is also a new issue for commercial systems because layers are 90% kept in cages and other management practices such as beak trimming (Hughes and Gentle 1995). There should be more production with minimum negative effects on human health (Vaarst et al. 2015).

Antimicrobial use

Currently, commercially huge numbers of birds are raised in single flocks, which increases the risk of disease transmission. If there are poor management practices and poor house conditions, it leads to production losses because of stress and pathogens (Humphrey 2006). *E. coli*, ND, gumboro disease, typhoid, coccidiosis, enteritis, salmonellosis, HPS, mycotoxicosis, and ascites is more prevalent. These diseases decrease poultry production and growth and cause huge economic losses because of mortality. To deal with infections, antibiotics, antivirals, and anthelminthics are used for therapeutic measures in poultry.

Antibiotics

Chemotherapeutic substances that can kill or inhibit the growth of specific microorganisms are called antibiotics (Etebu and Arikekpar 2016). The route of administration includes oral, parental, or topical (Vermeulen et al. 2002). In poultry, antibiotics are used for the following purposes:

1. Used for treatment of infections in high doses for a specific time (Landoni and Albarellos 2015)
2. Prophylactic use in moderate doses for long periods in case of risk of getting flock infected (Agunos et al. 2020)
3. Given at sub-therapeutic levels as growth promoters for a long period or whole life (Castanon 2007.

Different antibiotics have different modes of action, including inhibition of:

1. RNA/protein synthesis
2. DNA replication
3. Folic acid
4. Cell division
5. Cell wall/cell membrane

(Khokhlov and Blinov1970)

Antibiotics are widely used in developing countries (Istúriz and Carbon 2000). Commonly used antibiotics for gastrointestinal and respiratory problems are gentamicin, tylosin, tetracycline, neomycin, ceftiofur, erythromycin, quinolones, fluoroquinolones, and bacitracin.

For coryza, pullorum disease, fowl typhoid, and coccidiosis; sulphonamides are used as therapeutic and preventive medicine (Prescott 2013).

Quinolones and flouroquinolones

They are broad-spectrum antibiotics that inhibit DNA gyrase including sarafloxacin, ciprofloxacin, enrofloxacin, and danofloxacin (Giguère and Dowling 2013). They are bactericidal and have prolonged half-life in poultry. Both sarafloxacin and enrofloxacin were used in turkeys and chickens. Food and Drug Authority withdraws fluoroquinolones from use in poultry because of increasing infections in humans caused by drug-resistant *Campylobacter*. In 2001 and 2005, sarafloxacin and enrofloxacin were withdrawn by the FDA respectively (Nelson et al. 2007). Danofloxacin has greater protein binding and bioavailability through oral or intramuscular routes than ciprofloxacin (El-Gendi et al. 2001). Ciprofloxacin is produced when enrofloxacin metabolism occurs. Both parent drugs and metabolites can be found in the muscles of chickens for several days (Shim et al. 2003). For monitoring of residues muscles are used according to FDA (Reyes-Herrera and Donoghue 2008). Different muscles contain different concentrations of drugs. Enrofloxacin concentration is higher in breast tissue than in thigh muscles. It is important to know which muscle contains the higher concentration of the drug (Reyes-Herrera et al. 2005). Residues of fluoroquinolones were also present in feathers (Gajda et al. 2019).

Lincosamides

Clindamycin and lincomycin are made from *Streptomyces lincolnensis* (Spížek and Řezanka 2004). They have excellent activity against gram-positive bacteria. Their mechanism of action is inhibition of protein synthesis of bacteria by binding to their 50s ribosomal subunit (Dasenaki 2015). In the United States, lincomycin is approved for broilers only for coccidiosis and necrotic enteritis (Lanckriet et al. 2010). The kidney and liver contain a high concentration of their residues (Kowalski et al. 2014). Lincomycin liver metabolites (Patel et al. 2018) include:

1- N-dimethyl lincomycin
2- Lincomycin sulfoxide
3- N-dimethyl lincomycin sulfoxide

Macrolides

Tylosine, erythromycin, spiramycin, tilmicosin, and roxithromycin are produced by *Streptomyces spp.* and are bacteriostatic. They inhibit the protein synthesis of bacteria by binding to their 50s ribosomal subunit and are predominantly suitable in intracellular bacterial infections because they are lipophilic (Lenz et al. 2021). Their metabolism occurs in the liver. Tylosin is approved in the US for poultry (Hofacre et al. 2013). Crop flora hinders the absorption of erythromycin, so the absorption rate is highly variable (Vermeulen et al. 2002). The erythromycin dose rate is 30 mg per kg of body weight and the withdrawal period is 3 days. The Roxithromycin withdrawal period is 7 days after treatment, but it is not approved by the FDA. Tilmicosin also has a longer half-life and its residues in the liver can be found for 9 days after 5-day treatment (Patel et al. 2018).

Polymyxins

Colistin is effective against gram-negative bacteria and is used as a feed additive. In humans, it is nephrotoxic and produces CNS dysfunction, anorexia, and drug fever (Maddison et al. 2008). In ducks, their high concentration is present in the kidneys and muscles upon oral administration (Patel et al. 2018).

Sulfonamides

Sulfamethoxazole, sulfadimethoxine, sulfachlorpyrazine, and sulfaquinoxaline are bacteriostatic and have good activity against gram-positive, and gram-negative organisms, and protozoa (Coccidia). They compete with PABA (para-aminobenzoic acid) and inhibit folic acid synthesis, which stops replication (Henry 1943). They are approved for poultry, but their residues, when consumed by humans cause gastrointestinal disturbances, CNS effects, and hypersensitivity reactions (Baynes et al. 2016). Some of them have high active metabolites and have more protein binding in blood and tissues. Now a main concern is that drug residues are also present in the skin of turkeys and broilers, which is edible and 10% of body weight (Botsoglou and Fletouris 2000).

Tetracyclines

Doxycycline, oxytetracycline, tetracycline, and chlortetracycline are broad-spectrum antibiotics that work by inhibiting protein synthesis through binding to their 30s ribosomal subunit (Chopra and Roberts 2001). They are the most used antibiotics in avian for respiratory diseases. Doxycycline is lipophilic and distributed throughout the body. Oxytetracycline has great bioavailability when administered through the oral route. The oral route is more feasible than injectable. Drug residues of tetracycline can be eliminated by cooking (Heshmati 2015).

Drugs used as growth promoters.

Usually, antibiotics are given orally through water or mixed with feed. During the mid-20th century antibiotics were used as growth promoters in birds. Procaine penicillin, tetracycline, and chloramphenicol are used at sub-therapeutic levels in feed as growth promoters. Commercially feed contains supplements to increase efficient meat and egg production. There is reported use of ionophores, tylosin, avoparcin, and virginiamycin as growth promoters (Castanon 2007).

Hormones increase feed efficiency and growth. It is also reported that in the past hormones were used in developing countries like estradiol either subcutaneously or with feed in young birds for castration purposes (Eaton 1956). Antibiotics mechanism as growth promoters is not clear yet but some studies reveal that antibiotics kill pathogens and bacteria that are harmful to birds, decrease intestinal problems, and minimize production of toxins (Butaye et al. 2003). It kills and reduces the growth of bacteria present in the intestines of birds which ensures nutrient protection against bacterial destruction. The intestinal barrier becomes thin, which increases nutrient absorption. For a long period, antimicrobials or antibiotics have been widely used without any rules, regulations, or restrictions (Meek et al. 2015). Negative effects of antibiotics as growth promoters were not detected until AMR was detected. Bacteria are developing resistance against commonly used antibiotics. Numerous antibiotics are banned in developed countries to ensure human safety, while underdeveloped or developing countries still use banned antibiotics. This is the leading AMR issue across the globe.

High and inadequate doses of antibiotics for different purposes are used in broilers and layers because of a lack of regulations and safety standards. If their proper elimination and metabolism do not occur, they will produce harmful meat and eggs. Banned drugs pose a great threat to human health because of their carcinogenic properties. Drug residues accumulate in the edible tissues of birds in different concentrations (Lozano and Trujillo 2012). Drug residues include the main drug or its derivatives like conjugates, macromolecules bound with remnants, and metabolites. Meat/eggs, which contain residues above permitted MRLs (maximum residual levels) cause health problems. If MRLs are above, then the permitted level of several harmful effects can occur (Hosain et al. 2021):

1. Hypersensitivity reaction
2. Toxicity
3. Cancer

Table 1 describes permitted MRLs for some important drugs and their feed withdrawal period (Bienenmann-Ploum et al. 2012; Mund et al. 2017).

Table 1: Permitted Drug Residue Levels for some important drugs used in the poultry industry.

Drugs	**Poultry product**	**Permitted MRLs** (ug/kg)	**Days to withdraw**
Monensin	Egg	2	3
Narasin	Egg	2	5
Nicarbazin	Egg	100	5
Sulfonamide	Tissue, egg	100	5
Penicillin G	Liver, kidney	50	-
Enrofloxacin	Muscle	100	-
Oxytetracycline	Muscle	100	5
Gentamicin	Egg	100-400	-

Anticoccidials

Coccidiosis is a parasitic disease caused by *Eimeria* that infects birds causing diarrhea, production loss, and mortality. It is treated by oxytetracycline, sulphonamides, amprolium, piperazine, amoxicillin, and ciprofloxacin (Chapman 1999). Many other drugs like narasin, clopidol, nicarbazin, and salinomycin and vaccines derived from oocysts of coccidia strains are used for the prevention and treatment of coccidiosis (Mohamed 2010). Coccidiostats are used in feed for prevention, but their overuse and neglect withdrawal period lead to the deposition of residues in meat and eggs. Ultimately poses a risk to human health (Martins et al. 2022).

Anthelmintics

Anthelmintics include macrocyclic lactones, imidazothiazoles, and benzimidazoles. They either kill or paralyze helminthes. Benzimidazoles including fenbendazole and mebendazole cause depletion of energy sources, inhibit tubulin polymerization, and inhibit waste excretion. Fenbendazole is approved by the FDA for treating *Heterakis gallinarum* and *Ascaridia dissimilis* in the US (Collins et al. 2021).

Mebendazole is slowly absorbed, and its residues are present for 15 days in the kidney and liver while fenbendazole is eliminated rapidly (within 36 hours) after drug administration. Fenbendazole metabolites may be present with sulfone and sulfoxide in meat at 48-96 hours after administration. One study reveals that in chickens the metabolism of fenbendazole is more rapid than in turkeys (Patel et al. 2018).

Antivirals

There is a wide list of viral diseases that can be treated with antivirals but mostly not because of high cost, low availability, and risk of resistance.

Amantadine is used for the treatment of Avian Influenza, but its residues are detectable in poultry products. It is not approved internationally because of AMR, but some countries are still using it (He et al. 2008).

Residues presence and distribution

In developing countries backyard and intensive farming is common and people have access to drugs easily. They use these drugs in higher and improper doses in birds which results in the accumulation of drug residues in edible tissue of the body and eggs (Canton et al. 2021).

Contaminated feed and water with metals, toxic chemicals, and pesticides result in harmful resides in eggs and meat. All residues have direct toxic effects on human health.

Continuous low-dose antibiotics cause alteration in microflora and production of resistant strains (van der Waaij and Nord 2000).

Effects on human health

Consumption of edible tissues leads to the transfer of veterinary drug residues used in poultry birds to humans and has severe effects on human health (Mund et al. 2017). Poultry meat containing drug residues has major hazards to public health, including allergic reactions, the formation of antibiotic-resistant bacteria, and inhibition of useful microflora, and the formation of non-healthy/harmful microflora (Baynes et al. 2016). B-lactams such as cephalosporins and penicillin residues cause cutaneous eruptions, gastrointestinal symptoms, anaphylaxis, and dermatitis in humans because of the consumption of contaminated products. Penicillin is considered the most important because various people are allergic to penicillin residues (Stewart 1967). Severe anaphylactic shock may occur because of penicillin residues. Skin allergy can be caused by consuming eggs containing high concentrations of sulfonamide residues.

Teeth staining of young children, poor fetus development, gastrointestinal disorders, and pro-inflammatory, immuno-pathological, and cytotoxic effects are reported when a diet for human consumption contains tetracycline residues. Tilmicosin residual amount affects hematology including white blood cells and red blood cells and biochemical profile including albumen, triglyceride concentrations, and cholesterol, and total protein (Elsayed et al. 2014).

The persistence of residues of sulfamethazine, furazolidone, and oxytetracycline are recognized to pose immuno-pathological effects like carcinogenicity and autoimmunity (Biswas et al. 2019). Chloramphenicol and gentamicin may be mutagenic, hepatotoxic, and nephropathic or may lead to bone marrow toxicity or abnormalities in the reproductive system (Bacanlı and Başaran 2019). Nitrofuran use has been banned in poultry because their metabolites or residues through poultry products might yield carcinogenic and mutagenic side effects and may spread antibiotic resistance in microflora (Barbosa et al. 2011).

Some drug residues, such as nitroimidazole and 3-nitrofuran produce different cancers in humans. Hinder cytochrome (CYP1A2) mediated metabolism and toxicity in humans is caused by constant quantities of ciprofloxacin residues (Badawy et al. 2021). Renal clearance is also reduced, which results in increased drug concentration in systemic circulation.

Bacteria that are resistant to drugs are formed in human beings because of the intake of chicken, which contains drug residues. It will lead to therapeutic failure when you are ill or infected (DuPont and Steele 1987).

Antimicrobial agents, when used in poultry feed reduce the risk or intensity of infection but if they are used for a long period, it results in the development and stimulation of resistant strains. It is reported that *Salmonella* (Anderson et al. 2003) and *Campylobacter* species develop resistance against third generation cephalosporins and fluoro-quinolones (European et al. 2018). This emerging resistance causes problems in the current treatment of human diseases. Many reports are present which tell of the presence of antimicrobial-resistant bacteria in broiler chickens. Multiple strains of *E. coli* have been reported to be resistant against ciprofloxacin and trimethoprim-sulfamethoxazole (Oteo et al. 2006).

Blanco and co-workers isolated *E. coli* avian strains (468) and showed higher levels of resistance to fluoroquinolones and trimethoprim-sulfamethoxazole (Blanco et al. 1997). 293 strains obtained from slaughterhouses and chicken farms characterized as *S. enterica* serovar Indiana were found to be resistant to enrofloxacin, ciprofloxacin, and norfloxacin (Lu et al. 2015). In these strains, gene mutations were also detected. *E. tenella* isolated from poultry also revealed the development of resistance against salinomycin (Sun et al. 2023).

It is suggested by research that indiscriminate and uninterrupted use of these drugs is increasing the distribution of resistance against several drugs in human pathogens or foodborne bacteria. It leads to a loss of efficiency of antibiotics against human and poultry illnesses.

Main developing foodborne pathogens have been recognized among humans including *Salmonella* species, verotoxigenic *Escherichia coli,* and *C. jejuni* (Meng and Doyle 1998). Poultry meat contamination with antibiotic-resistant *C. jejuni* also occurs (Kurinčič et al. 2005). When meat containing *C. jejuni* is consumed it may cause Campylobacteriosis. *C. jejuni* isolated from poultry were found to be resistant to many antibiotics including sulfamethoxazole-trimethoprim, cephalothin, and ampicillin.

It was documented by Sison that *Campylobacter coli* and *C. jejuni* isolated from fresh meat also showed resistance against ampicillin succeeding erythromycin, ciprofloxacin, and tetracycline.

Resistance is developing against several antibiotics through overuse or misuse of antibiotics.

Likewise, *E. coli*, *S. enterica*, *C. jejuni*, *L. monocytogenes,* and serotype *Enteritidis* from carcasses of chicken have resistance against numerous antibiotics including tetracycline, sulfonamides, and quinolones (Grudlewska-Buda et al. 2023).

Nsofor discovered multiple *E. coli* which are resistant to drugs in chickens. It may lead to many public health issues (Nsofor et al. 2013).

In poultry water, litter & feed enterococci and non-enterococci are found which develop high levels of resistance against erythromycin, kanamycin, gentamicin, clarithromycin, vancomycin, and ampicillin.

Salmonella is resistant to multiple antibiotics. Its serovars are resistant to ampicillin, neomycin, streptomycin, kanamycin, erythromycin, novobiocin, bacitracin, cefotaxime, tetracycline, and nalidixic acid. *Salmonella,* when present in meat and consumed produces infection (Mund et al. 2017).

B lactams are broad-spectrum antibiotics, but multiple *E. coli* strains have developed resistance to them.

There is a risk of getting infection for humans upon the consumption of meat contaminated with resistant bacteria strains.

There is much evidence present that describes the connection between the use of antimicrobials in poultry feed and the acceleration in the spread of drug-resistant infectious agents among people. For human safety, there should be strict rules and regulations. Proper regulations must be ensured for proper safety levels of drugs and their withdrawal periods. Health authorities ensure the safety of consumers through strict implementation of drug withdrawal periods.

Antibiotic use reduces the rate of mortality in poultry production, but their repeated use results in antimicrobial resistance issues against commonly used antibiotics.

Resistance to multiple drugs is becoming a major throughout the world. It is also a major concern currently for veterinarians who are working in poultry and food microbiology because of the risk to public health. Studies show that there is a relationship between drug use in poultry and resistant gene transfer in human pathogens. This is because of common or identical drugs used to treat pathogens.

Conclusion

Antimicrobials play an important role in poultry production by preventing and treating infectious diseases. In poultry, antibiotics use is now threatening human health seriously because of AMR development. When infection occurs because of resistant bacteria or pathogens, they cannot be treated with commonly used drugs. Thus, effective measures are required to deal with this problem by:

1- Checking antibiotics in poultry manure and feed
2- Enhancing the efficacy of antibiotics
3- Minimize transfer of resistant gene

Drug residues and antibiotic-resistant genes (AGRs) in manure can be destroyed by composting. There is a need for further research on the elimination of AGRs to deal more effectively in the future.

Poultry products which contain more MRLs than permitted MRLs are also very risky for human health.

Moreover, for human health resistance development of various drugs in pathogenic, mutualistic, and commensal microorganisms is also alarming. There should be strict control measures and regulations at the national level for poultry production, feed supplements, and drugs. Drug withdrawal time between drug administrations and slaughtering must be ensured. Regular tests and monitoring must be performed for drugs residing in edible portions of poultry. Lastly, the safety of consumers should be the priority of production.

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This study was conducted according to the bioethical committee of the Islamia University of Bahawalpur.

Availability of data and material

The data can be obtained from the corresponding author upon reasonable request.

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Consent to participate

All the authors gave their consent to participation.

Consent for publication

All the authors agreed to publish.

Competing Interest

The authors declare that they have no relevant financial or non-financial interests to disclose.

Author Contribution

MSA, ZR, and MAS wrote the manuscript MAQ MS and MAFK managed reference MKK, AS and IA provided APC.

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