Monitoring antimicrobial drug residues in an antibiotic-free poultry supply chain

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Abstract

With poultry consumption projected to rise significantly, understanding the presence and control of antimicrobial residues in poultry products becomes increasingly important for ensuring food safety and public health. Consequently, in the present study, the incidence and concentration of antimicrobial drugs in 919 samples, all from an antibiotic-free poultry supply chain, were investigated using a high-pressure liquid chromatography high-resolution mass spectrometry multiclass antimicrobial residue method, involving a wide range of matrices (water, feed, feathers, livers, muscles, eggs, and retail products, such as chicken nuggets, chicken drumsticks, chicken breast, and chicken thighs) to verify not only the compliance with Regulation 37/2010, but also to investigate the possible administration of antimicrobial drugs or potential bad farm management in the antibiotic-free supply chain. Antimicrobial drug residues were detected in 4% of all the analyzed samples, with concentrations ranging from < detection capability to 57.87 ng g-1, but no residues were detected in muscles, livers, eggs, and retail products (chicken nuggets, chicken drumsticks, chicken breast, and chicken thighs). While the absence of antimicrobic residues in these matrices suggests compliance with maximum residue limits set by Regulation 37/2010 and a framework of substantial safety towards consumers, the presence of antimicrobic residues in drinking water, feathers, and feed, considering the provenience from an antibiotic-free supply chain, highlights the importance of the ongoing monitoring activities to ensure that the results align with antibiotic-free product certification standards.

Introduction

One of the most rapidly and widely expanding meat sources is represented by poultry meat (Singer *et al.*, 2006). In fact, considering social factors such as cultures, traditions, and religions, poultry meat and eggs are among the most widely consumed animal-based foods globally (Mottet *et al.*, 2017). The global human population is estimated to reach 9.6 billion by 2050. Consequently, the growth of animal-derived food demand is expected to be 70% between 2005 and 2050, with the highest rate for poultry meat and eggs (Alexandratos *et al.*, 2012). Nowadays, a recent report from the *Istituto di Servizi per il Mercato Agricolo Alimentare* showed a *per-capita* fresh poultry meat consumption of 21.4 kg *vs.* a consumption of 16.1 and 11.5 kg of fresh bovine and swine meat, respectively (ISMEA, 2024). From this perspective, several advancements, including genetic selection and optimized feeding protocols, have made it possible for modern poultry production units to produce market-ready broiler chickens in less than two months. In this case, a key role is played by comprehensive health management practices that include the use of antibiotics as thera-

peutic agents to address bacterial diseases in intensive farming systems (Singer *et al.*, 2006).

Among the various antimicrobial classes used in poultry farming, it is possible to find cephalosporins, lincosamides, macrolides, quinolones, sulfonamides, and tetracyclines. To guarantee consumer health and to reduce the concentrations of these residues in animal and animal-derived food, these substances must be administered only in approved concentrations, and their respective withdrawal times must be observed (Kozarova *et al.*, 2004).

The balance among several factors, including the disease level, cost of the drug, and withdrawal protocols before slaughter, influences the choice of antimicrobial (Diaz-Sanchez *et al.*, 2015). However, how antimicrobials are used in poultry production has changed considerably during the past decade, mainly because of concerns about potential negative human health consequences caused by these uses (Singer *et al.*, 2006). The main risk is related to antimicrobial resistance (AMR), which is a natural phenomenon that occurs when antibiotics that were initially effective against certain bacterial infections can no longer inhibit the growth and development of causal microorganisms (FAO, 2015). AMR is a growing concern not only in the medical and veterinary fields but also in the food industry, as it compromises the quality and indirectly the safety of the food supply chain. As a result, an ample market of "antibiotic-free", "organic" or "all-natural" labelled products has emerged (Cervantes, 2015).

Since the presence of unauthorized substances, residues of veterinary medicinal products, or chemical contaminants in food may pose a risk factor for public health, Regulation (EU) No 37/2010 and its updates establish maximum residue limits (MRL) for veterinary medicinal products in food of animal origin (European Commission, 2010). Moreover, to use the "antibiotic-free" label on products, adding it as an optional information, the producers must develop and follow a product specification approved by the Italian Ministry of Agricultural, Food and Forestry Policies. These technical specifications can be different for several supply chains (*e.g.*, poultry, bovine, *etc*.). Particularly, for the poultry chain, some of these certifications aim to guarantee, through specific controls, the systematic non-use of antibiotics in any of the production stages subject to certification, ensuring the removal of all declarations of conformity regarding productions that do not comply with the requirements. Thus, the present study aims to evaluate the presence and concentration of antimicrobial residues in 919 samples from the antibiotic-free poultry supply chain, involving a wide range of matrices such as water, feathers, livers, muscles, eggs, and retail products. The retail products involved in this study include fresh and processed products such as chicken nuggets, chicken drumsticks, chicken breast, and chicken thighs, ready to be sold in the markets. It is important to underline that the matrices regulated by Regulation 37/2010 are only muscles, liver, eggs, skin, fat, and kidney (these last three are not considered in this study). The analysis of the matrices considered in this study, some of which are not included in Regulation 37/2010, might contribute to understanding if animals are treated with antimicrobial drugs, even if no residues are found in the regulated matrices (in any case, possible contamination phenomena are to be accounted for). The study also aims to compare the results with the MRLs fixed by Regulation (EU) No 37/2010 and literature data from the antibiotic-free and non-antibiotic-free poultry supply chain.

Materials and Methods

Chemicals and reagents

Merck (Darmstadt, Germany) provided all the analytical grade solvents and all the reagents used to prepare the EDTA-McIlvaine buffer solution (pH 4.0), and trichloroacetic acid 20% (w/v) aqueous as described by Chiesa *et al*. (2017). The extraction cartridges (Oasis HLB 3 mL, 60 mg) were provided by Waters (Milford, MA, USA). Merck (Darmstadt, Germany) provided the standard of all the investigated analytes: a) β-lactams, including amoxicillin, ampicillin, benzylpenicillin, cloxacillin, dicloxacillin, oxacillin, phenoxymethylpenicillin, cefadroxil, cafalexin, cefalonium, cefalothin, cefapirin, cefazolin, cefixime, cefoperazone, cefquinome, ceftiofur, desacetylcefapirin, desfuroylceftiofur, nafcillin; b) quinolones, including ciprofloxacin, danofloxacin, difloxacin, enrofloxacin, flumequine, oxolinic acid, cinoxacin, enoxacin, fleroxacin, gatifloxacin, levofloxacin, lomefloxacin, marbofloxacin, nadifloxacin, nalidixic acid, norfloxacin, orbifloxacin, pefloxacin; c) Amphenicols, including florfenicol, thiamphenicol, and florfenicol amine; d) Tetracyclines, including chlortetracycline, doxycycline, oxytetracycline, tetracycline; e) nitroimidazoles, including dimetridazole, metronidazole, ronidazole, tinidazole; f) macrolides, including erythromycin, tylosin, and tulathromycin; g) benzimidazoles, such as fenbendazole; h) nitrofurans, including furaltadone and furazolidone; i) lincosamides, such as lincomycin; l) sulfonamides, including sulphachlorpiridazine, sulphadiazine, sulphadimethoxine, sulphadimidine, sulphamerazine, sulphamethoxazole, sulphametoxipiridazine, sulphamonomethoxine, sulphapiridine, sulphaquinoxaline,, sulphatiazole, and trimethoprim; m) pleuromutilin, as tiamulin.

Standard solutions

Stock solutions of the studied molecules were prepared at 1 mg mL^{-1} in methanol and stored at -20°C. Working solutions were prepared daily at 10 and 100 ng mL^{-1}.

Sample collection

Samples were collected from different Italian antibiotic-free chain poultry farms. A total of 919 samples were collected, distributed as follows: water (192), feed (128), feathers (255), eggs (33), livers (129), muscles (127), and retail products (55).

Extraction and detection by using high-pressure liquid chromatography high-resolution mass spectrometry

Chiesa, Nobile *et al.* (2018) and Chiesa, Panseri *et al.* (2018) described the extraction protocols for 46 analytes; the same extraction protocols were also applied in the present study for 69 analytes in liver, muscle, eggs, retail products, feather, feed, and water (with some adjustments depending on the matrices). Briefly, 1 g (0.5 g for feathers, 5mL for water) of homogenized samples was spiked with the Internal Standard (IS) at 2 ng g^{-1}. To promote protein precipitation, 5 mL of McIlvaine buffer at a pH of 4.0 (10 mL for feathers and feed) and 100 µL, 20% w/v of Trichloroacetic acid were added. The samples were vortexed, sonicated (10 min), and centrifugated (2500×g, 4°C, 10 min). The supernatant was collected and defatted with 5 mL of n-hexane and then centrifugated (2500×g, 4 °C, 10 min). The purification was obtained by solid phase extraction(SPE) cartridge, following the steps: preconditioning (3 mL of methanol and 3 mL of Milli-Q water), sample loading, washing [2×3 mL methanol:water (5:95 v/v)], and elution (5 mL of methanol). Water samples were directly purified by the SPE cartridge right after the addition of the IS. After the eluate evaporation, the samples were reconstituted in 200 µL of methanol: 0.1%

Table 1. Results obtained for the samples in which antimicrobic residues have been detected. The table also shows i) the detection percentage of the different antimicrobic residues in the specific matrix based on the total number of samples; ii) the mean values and standard deviations of the residue concentrations obtained considering only the values above the detection capability.

	Enrofloxacin ng g^{-1}	Fenbendazole ng g^{-1}	Flumequine ng g^{-1}	Oxolinic acid ng g^{-1}	Sulphadiazine ng g^{-1}	Sulphadimethoxine ng g^{-1}	Thiamphenicol ng g^{-1}	Tylosin ng g^{-1}	Trimethoprim ng g^{-1}
Detection %	0.33%	0.98%	0.22%	-	0.11%	-	0.11%	0.22%	0.54%
Water 1	3.23	n.d.	n.d.	n.d.	n.d.	n.d.	< CCβ	n.d.	n.d.
Water 2	0.83	5.48	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<CCβ
Water 3	n.d.	n.d.	n.d.	n.d.	0.15	n.d.	n.d.	n.d.	<CCβ
Water 4	1.25	n.d.	3.43	n.d.	n.d.	n.d.	n.d.	n.d.	0.80
Water 5	n.d.	n.d.	12.29	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Water 6	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0.32
Water 7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<CCβ
Water 8	n.d.	15.25	n.d.	n.d.	n.d.	n.d.	n.d.	57.87	n.d.
Water 9	n.d.	0.1	n.d.	n.d.	n.d.	n.d.	n.d.	7.62	n.d.
Water 10	n.d.	< CCβ	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Water 11	n.d.	0.18	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Water 12	n.d.	10.010	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Water 13	n.d.	0.96	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Water 14	n.d.	1.16	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Water 15	n.d.	1.010	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Mean±STD	1.77±1.046	4.27±5.61	7.86±6.26	-	0.15*	-	-	32.74±35.53	0.56±0.34
Detection %	-	0.11%	-	0.11%	0.11%	-	0.33%	-	0.76%
Feather 1	n.d.	n.d.	n.d.	n.d.	< CCβ	n.d.	n.d.	n.d.	n.d.
Feather 2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<CCβ
Feather 3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<CCβ
Feather 4	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Feather 5	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Feather 6	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<CCβ
Feather 7	n.d.	54.37	n.d.	n.d.	n.d.	n.d.	2.82	n.d.	2.27
Feather 8	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	3.68	n.d.	0.85
Feather 9	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	7.79	n.d.	1.56
Feather 10	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<CCβ
Feather 11	n.d.	n.d.	n.d.	<CCβ	n.d.	n.d.	n.d.	n.d.	n.d.
Mean±STD	-	54.37*	-	-	-	-	4.76±2.66	-	1.56±0.71
Detection %	-	-	-	-	-	0.11%	-	-	0.33%
Feed 1	n.d.	n.d.	n.d.	n.d.	n.d.	2.42	n.d.	n.d.	n.d.
Feed 2	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<CCβ
Feed 3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<CCβ
Feed 4	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	<CCβ
Mean±STD	-	-	-	-	-	2.42*	-	-	-

n.d., not detected; STD, standard deviation; CCβ, detection capability; *STD not calculated because the residue was detected only in one sample.

aqueous formic acid (10:90 v/v). The instrumental analysis was carried out by a Vanquish (Thermo Fisher Scientific, Waltham, MA, USA) coupled to a Thermo Orbitrap™ Exploris 120 (Thermo Fisher Scientific, Waltham, MA, USA). Method performance traits were reported by Bonerba *et al.* (2021) and Chiesa, Nobile *et al.* (2018), relative to validation criteria.

Results and Discussion

Antimicrobial drug residues were detected in 4% of all the analyzed samples. Particularly, they were found in 8% of the analyzed water (15 out of 192), 3% of feed (4 out of 128), and 4% of feathers (11 out of 255). No antimicrobial residues were detected in muscles, livers, eggs, and retail products. Oxolinic acid was found, in trace (< detection capability, CCβ), in only one feather sample. Enrofloxacin, flumequine, and Tylosin were found only in 3, 2, and 2 water samples, with maximum concentrations of 3.23, 12.29, and 57.87 ng g^{-1}, respectively. Fenbendazole was found in nine water samples, with a maximum concentration of 15.25, meanwhile, it was found in only one feather sample, with a concentration of 54.37. Sulphadimethoxine was found only in one feed sample with a concentration of 2.42 ng g^{-1}. Sulphadiazine was found in a low concentration (0.15 ng g^{-1}) in only one water sample, and traces (<CCβ) were found in only one feather sample. Thiamphenicol was found in traces in one water sample, while it was found in three feather samples with a maximum concentration of 7.79 ng g^{-1}. Trimethoprim was found in water, feathers, and feed, with a maximum concentration of 1.56 ng g^{-1} in feathers. Detailed information is reported in Table 1.

Analytes from all the main antimicrobial classes were found in the samples: sulphadiazine and sulphadimethoxine (sulfonamides), oxolinic acid, enrofloxacin, flumequine, and ciprofloxacin (quinolones), trimethoprim (diaminopyrimidine), thiamphenicol (amphenicol), fenbendazole (benzimidazole), and tylosin (macrolides). The scientific literature justifies the use of these drugs in poultry. In the poultry supply chain, sulfonamides are generally used to treat several diseases such as Infectious Coryza and Coccidiosis (Giguere *et al.,* 2006). These drugs can be easily absorbed and distributed through the body of the chicken, accumulated in various tissues, and transferred into their products (Weiss *et al.,* 2007). Diaminopyrimidines like trimethoprim are frequently administered to potentiate sulfonamides and increase their effectiveness. These two chemotherapies inhibit different phases in the bacterial folic acid biosynthesis pathway; thus, they have a synergistic antibacterial action in vitro and vivo (Stastny *et al.,* 2023). Eventually, quinolones and fluoroquinolones are used in poultry to treat or prevent gastroenteritis and skin and soft tissue infections (Soni, 2012).

Considering the analyzed matrices, the widest variety of antimicrobials was found in feathers and water samples. In fact, seven analytes (enrofloxacin, flumequine, sulphadiazine, thiamphenicol, tylosin, trimethoprim, and fenbendazole) were found in hen drinking water. This is in line with scientific literature, because studies demonstrated that the majority of therapeutic treatments are given *via* drinking water because sick animals may stop eating but often continue to consume water (Singer *et al.,* 2006). Five analytes (sulphadiazine, trimethoprim, thiamphenicol, fenbendazole, and oxolinic acid) were found in hen feathers. As reported by Chiesa, Nobile *et al.* (2018), feathers could be a matrix suitable for detecting antimicrobial use in poultry production, even when no traces are evident in the edible tissues.

The scientific literature suggests that veterinary drug residues are typically found in higher concentrations in the liver and kidneys, compared to muscle tissue. This higher accumulation in the liver is due to its role in metabolism, as hepatic enzymes deeply contribute to xenobiotic metabolism. In contrast, the muscles generally show the lowest levels of antimicrobial residues (Karimi *et al.,* 2020). The absence of antimicrobial residues in muscle, liver, and eggs underlines not only the compliance of the analyzed matrices with the MRLs set by Regulation 37/2010, but also a framework of substantial safety and the respect of the withdrawal period for the administration of the different drugs (European Commission, 2010). In addition, the feather, water, egg, and feed samples analyzed did not come from laying hen supply chains, for which legislation is even stricter (European Commission, 2010). However, it is important to underline that the analyzed samples were from an antibiotic-free supply chain, which also implies compliance with the technical specifications. The management of the "antibiotic-free" requirement takes place at the farm level, while in the later stages, it is required to implement a traceability system that ensures at all stages of the process that the chain of custody is maintained and thus that the product made from "antibiotic-free" farms is separated from conventional product. The presence of antimicrobial residues in samples from the antibiotic-free supply chain may sometimes result from a lack of awareness among certain farmers, such as unintentional cross-contamination and recirculation through litter, or from deliberate neglect by others (Lawal *et al.,* 2015), or, moreover, from potential cross-contamination during the sampling procedures, particularly for feathers, feed, and eggs. This highlights the critical need for ongoing monitoring to ensure that results align with antibiotic-free product certification standards.

Conclusions

This study provides an insight into the prevalence and concentration of antimicrobial residues within the antibiotic-free poultry supply chain, focusing on several matrices. The analysis of this wide range of matrices—including water, feathers, feed, muscles, livers, eggs, and retail products—revealed that while antimicrobial residues were present in some water and feathers, which may be due to possible accidental contaminations, no residues were detected in edible products like muscle, liver, retail products (such as chicken nuggets, chicken drumsticks, chicken breast, and chicken thighs), or eggs, which is a positive indication of compliance with the MRLs set by EU Regulation 37/2010.

In conclusion, while the results of this study demonstrate a framework of substantial safety for consumers, they also highlight the ongoing need for improvement in both best practice and drug management in farms, and vigilance in monitoring antimicrobic drug use in antibiotic-free farming. Implementing effective traceability systems, educating farmers about best practices, and ensuring proper oversight throughout the supply chain are essential measures to mitigate the possible impact and development of AMR and maintain the integrity of antibiotic-free labels. Also, in the same context of our aims, we can consider the strategies that are being applied as potential antimicrobial alternatives, as probiotics, to mitigate the use of traditional chemical antibiotics in general.

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