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Levels of Tetracycline Residues in Liver, Kidney, Muscle and Gizzard Tissues from selected Poultry Farms in Obio-Akpor Local Government Area, Rivers State, Nigeria

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ABSTRACT: Poultry farmers around the world utilize antibiotics, albeit indiscriminately, for both preventive and curative purposes. This study assessed tetracycline residues in chicken sampled from 4 poultry farms in Obio-Akpor Local Government Area in Rivers State, Nigeria. Liver, kidney, muscle and gizzard tissues were analyzed using High performance Liquid Chromatography (HPLC) for tetracycline, oxytetracycline and doxycycline residues. All samples reported residue levels within the WHO/FAO Maximum Residue Limits (MRLs) except for the liver sample in Farm 1 which was 895.04 µg/kg. Doxycycline recorded the least residue level within the range of 1.67 µg/kg to 9.30 µg/kg, while oxytetracycline and tetracycline recorded residue levels within the ranges of 1.671µg/kg to 98.662µg/kg and 0.886 to 895.037 µg/kg respectively. These results are indicative of the susceptibility of consumers to health hazards arising from antibiotic residues. It is therefore pertinent for Regulatory agencies to ensure compliance with effective and sustainable agricultural practices such as antibiotics withdrawal periods.

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Approximately 75% of the 12 million kg of antibiotics utilized around the world annually are often in the treatment of infectious diseases caused by microorganisms, while others are used for growth promotion and in some cases growth prevention purposes (Van Boeckel *et al*., 2015). This has resulted in antibiotic residues in the livestock food system. Antibiotic residues occur in livestock production systems in a lot of countries at different concentrations and intensities and can be found in animal products (milk, meat, eggs). This is a predominant occurrence despite regulations and surveillance in many countries. The worst-case scenario (exposure to animal products with antibiotic residues and microbial-resistant genes) is expected in many low and middle-income countries where regulations and surveillance is almost non-existent and where there is indiscriminate sale and high usage of veterinary antimicrobials (Ikhimiukor *et al*., 2022). Nigeria consumes a large amount of antibiotics through poultry production because it is of the five countries with the highest projected increase in antimicrobial drugs and growth hormones use (163%) by 2030 (Oyedeji *et al.*, 2019; Van Boeckel *et al.*, 2019). Also, poultry products produced by farmers in the country are hardly screened for antibiotic residues and other harmful toxins by oversight federal, state and local regulatory agencies (Oyedeji et al., 2021). Monitoring antibiotic residues in food products

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is of utmost importance to ensure food safety and to promote regulatory oversight over locally produced food supplies. Recent studies have identified tetracycline, chlortetracycline, oxytetracycline, sulfonamide, sulfadimethoxine, sulfamethazine, sulfamethoxazole, penicillin, ampicillin, arsenicals, roxarsone, enrofloxacin, erythromycin as the most used antibiotics administered orally in animal husbandry in Nigeria (Lateefat *et al*., 2022; Onipede *et al.,* 2021; Sha'arani *et al.*,2024). Antibiotics such as tetracycline, doxycycline, chlortetracycline, and oxytetracycline are often used in poultry production for the prevention and treatment of diseases, control of microorganisms and growth promotion in animals (Guidi *et al.,* 2018, Li *et al.,* 2017). Although these drugs are highly beneficial in livestock production, benefiting both producers and consumers alike, their indiscriminate use may result in the accumulation and deposition in tissues and organs as residues, and in such levels that may be harmful to man. Studies have shown that these residues are responsible for the development of bacterial resistance to these drugs (Reig and Toldra, 2008). Fifty (50) years ago, Rachel Carson for the first time stated that the widespread use of pesticides is hazardous not only to wildlife but also to humans (Lateefat *et al*., 2022). Tetracycline, doxycycline, chlortetracycline, and oxytetracycline have been used extensively in poultry farms in Nigeria as reported by recent studies (Olalekan *et al.,* 2021; Morufu, 2021; Raimi *et al.,* 2020b). There is however an ongoing concern about its negative effect, considering its indiscriminate use among farmers. To safeguard public health and minimize the potential exposure to antibiotic residues from food products, maximum residue limits (MRLs) have been established by the USA Food and Drug Administration.

Veterinary drug residue monitoring especially antibiotics in foods meant for human consumption is one method of preventing potential harm to consumers, particularly if large doses are ingested. Tetracyclines are an important class of broad-spectrum antibiotics that prevent bacterial growth by inhibiting protein synthesis. The basic structure of tetracycline consists of four linearly condensed benzene rings in a hydronaphtacene nucleus. (Moffa, 2015; Moffa and Brook, (2015). Yellow crystalline compounds, tetracycline possess slight solubility in water, lower solubility in alcohol, and are insoluble in organic solvents (Dai et al., 2020). The distinct properties of tetracyclines are provided by the phenolic hydroxyl group (C-OH), dimethyl amino group ($-N(CH_3)_2$), acylamino group ($-CONH_2$), and the keto-eol conjugated double bond system (Dai *et al.,* 2020). As frequently used antibiotics due to its broad-spectrum activity against bacteria (both gram positive and negative), mycoplasma, fungus (chlamydia), rickettsiae and parasites, tetracyclines are the primary antibiotics used for human therapy, veterinary purpose, and as feed additive in the agricultural sector (Daghrir and Drogui ,2013). It is the second most produced and consumed antibiotic worldwide due to its low cost, less toxicity, broad-spectrum activity, and because it can be orally administered (Jeong *et al.,* 2010). As broad-spectrum antibiotics used routinely in veterinary medicine for the treatment and prevention of some infectious animal diseases, tetracyclines have been used worldwide for the prevention and control of bacterial poultry diseases, to control microbes and promote growth in animals (Guidi *et al.,* 2018; Onipede *et al,* 2021). There is a global increase in the consumption of poultry products; eggs and meat (Subashree, 2022, OECD-FAO, 2015). Poultry products are a major source of animal protein in Nigeria due to its availability and white meat constituent (Mottet and Tempio, 2017). The existence of Tetracyclines (TCs) residue in chicken products is considered a public health hazard as they have an adverse effect on consumer health due to the presence of bacterial resistance, toxicity, and disturbance of natural intestinal micro-flora. The European Commission (EU, 2010) had set the MRLs of TCs as 100µg/kg and 300µg/kg for chicken tissues and liver respectively, however, TC levels above the MRLs have been reported in chicken products in many countries (Salama *et al.,* 2011). This is still a growing concern, and studies have shown that antibiotics injected in poultry were amassed in liver, kidney, muscle and bones surpassing the Maximum Residual Limits (MRL) (Oalekan *et al*. 2020d, Raimi *et al.* 20220b, Hussain *et al.* 2021b, Shaker *et al.* 2016). High level of antibiotic residues consumption from animal products to humans may affect immunological reactions and can possibly influence digestive microbiota in susceptible people (Ramatia *et al*., 2017). In the administration of antibiotics, strict adherence to prescription and withdrawal needs to be followed, failure of which could lead to antibiotics residues in milk, eggs, muscles, and internal organs of these animals. Studies have shown that persistent consumption of animal products containing a high level of antibiotic residues led to allergic reactions in some hypersensitive individuals and generally led to antibiotics resistance in humans (Abou-Raya *et al.,* 2012). Antibiotic residues have been reported in poultry meat in various parts of Nigeria, however, no comprehensive data on the occurrence, distribution patterns and health implications of widely used antibiotics have been reported in the area under study. Given the life-threatening effects associated with antibiotic residues in foodstuffs, the aim of this study is to provide a comprehensive survey and monitoring of antibiotic residues commonly used in poultry production. The veterinary drugs considered were chosen due to their low cost and known use as growth promoters in poultry production. The objective of this paper is to determine levels of tetracycline residues in liver, kidney, muscle and gizzard tissues of chicken from selected poultry farms in Obio-Akpor Local Government Area, Rivers State, Nigeria.

MATERIALS AND METHODS

Study area: Port Harcourt is the state capital of Rivers State in South-South, Nigeria. Lying along the Bonny River and located in the oil rich Niger delta, Port Harcourt's urban population as at 2023 was estimated at 3,480,000. The population of the metropolitan area of Port Harcourt is almost twice its urban area population with a 2015 United Nations estimate of 2,344,000 (World urbanization prospects, 2018). Port Harcourt is the only major city of the state and is highly congested. The city has several Poultry farms and birds were randomly collected from these farms.

Sample collection: Kidney, liver, muscle and gizzard samples were randomly selected from four poultry farms in Port Harcourt. 60 chickens were randomly sampled across Four (4) poultry farms within the city of Port Harcourt. The chicken samples were cut into specific parts to collect the muscles, liver, kidney and gizzard. Each sample was placed into a separate plastic zipper bag, placed in coolers containing ice packs and transferred to the laboratory were they were stored in the freezer at -20^0C until extraction.

Equipment: Waring laboratory blender (Thomas Scientific, Swedesboro, USA), Vortex mixer-VM18 (Schiltern Scientific, Beds, UK), Centrifuge-ROTOFIX 32A Benchtop centrifuge (Thomas), Agilent 1200 series High Performance Liquid Chromatography (HPLC) machine equipped with a constant flow pump, variable wavelength UV detector, Reverse phase C-18 9 10um, 250 x 4.6mm I D) columns.

Chemicals and reagent: Standard oxytetracycline dehydrate was obtained from Himedia. High Performance Liquid Chromatography (HPLC) grade methanol, acetonitrile and oxalic acid were obtained from Merck. Oxytetracycline, Analytical grade Sodium Hydrogen tetraoxophosphate (V) Ethylenediaminetetracetic acid (Na_2HPO_4 EDTA) and citric acid obtained from Merck, Germany. HPLC grade water filtered through 0.2µm with maximum impurities of 0.0003% and minimum transmission of 100% at 200 and 250nm procured from Qualigens. High purity Milli-Q water generated in the laboratory was used for the study.

Sample extraction: The chromatographic technique is often used over others especially in recent times, due to higher sensitivity and specificity, and higher quantification capability. Samples were blended with a food processor for 3-5mins. It was done in three steps which involves running a blender and a pause for 5-8 seconds followed by running again. This technique was repeated until tissues were blended properly. The blended samples were taken into properly cleaned and sterilized petri dishes with covering. From this, 1g of aliquot sample was transferred into the beaker with the help of electric balance and spatula. Homogenization was done with the addition of 10ml phosphate buffer (pH 6.5). After proper mixing, protein contents of these samples were precipitated with the addition of 2ml trichloroacetic acid (30%). These samples were taken into a clean and sterilized centrifuge tube for centrifugation. Centrifugation was performed at 7000rpm for 15minutes with the help of an automatically time regulated centrifuge machine and filtration of the supernatant was performed with the help of Whatman filter paper and funnel. Filtration fluid was collected into a beaker with sufficient care and the supernatant defated with an equal volume of diethylether. The mixture was kept for 10 minutes to become a separate layer and separated by using a sterilized filter paper. The upper oily layer was discarded and only the bottom layer was collected. This extraction of supernatant was repeated twice with diethyl ether, then the extracts were evaporated to dryness. The dried sample was reconstituted with 2ml of mobile phase, made by mixing methanol and acetone (1:1) and the extracts were collected into screw cap vial with proper care and kept in the refrigerator for further advanced analysis. The procedure was patterned after the reference cited by Poppelka *et al*., (2005).

Preparation of Standard Curve: Standard solution was prepared by weighing 10mg oxytetracycline standard powder accurately and dissolved in methanol to make a stock solution of 1000µg/ml which was mixed thoroughly by vortexing. Stock standard solutions were filtered and stored at 4^0C and several dilutions of the stock solution using concentrations of 10, 20, 30, 40, 50 and 60µg/ml of methanol as the diluents were injected into the HPLC machine to obtain the standard curve by plotting the concentration of oxytetracycline on the x-axis and the corresponding peak areas on the y-axis.

Chromatographic conditions: A mobile phase of methanol and formic acid 0.1% using a gradiant method with a flow rate of 1.5mL/min at 25^0C was carried out. The separation was done on Hypersil gold C18 (10um, 100x4.6mm) columns with mobile phase as described above. Detection was performed with UV detector set at 350nm wavelength UV detection: Run time; 15mins, Flow rate: 1.0mL/min, Column temperature: Room temperature, Injection volume: 20uL, Elution: Isocratic. Quantification of residues in samples was obtained and calculated from areas under curves extrapolated automatically by the software (ChromoQuest 5).

Data Analysis: Descriptive statistics were performed on Microsoft excel 2010. The data was analyzed using mean, concentration range, standard deviation, and charts.

RESULTS AND DISCUSSION

All kidney, liver, muscle and gizzard samples obtained from Obio-Akpor Local Government Area recorded detectable levels of tetracycline, oxytetracycline and doxycycline residues. The mean residue levels in liver, kidney, muscle and gizzard were 6.69 µg/kg, 261.31 µg/kg, 4.61 µg/kg and 17.28 µg/kg; 48.31 µg/kg, 50.81 µg/kg, 9.96 µg/kg and 8.88 µg/kg; 4.10 µg/kg, 6.88 µg/kg, 3.76µg/kg and 3.83 µg/kg for tetracycline, oxytetracycline and doxycycline respectively. The result showed presence of all antibiotics residue studied. Farm 1 recorded a residual range of 1.26 µg/kg – 895.04 µg/kg, 33.92 µg/kg – 98.66 µg/kg and 2.13 µg/kg – 3.20 µg/kg for tetracycline, oxytetracycline and doxycycline respectively. Farm 2 recorded a residual range of 2.07 µg/kg – 56.68 µg/kg, 1.76 µg/kg – 22.10 µg/kg and 1.67 µg/kg – 8.37 µg/kg for tetracycline, oxytetracycline and doxycycline respectively. Farm 3 recorded a residual range of 0.89 µg/kg – 2.03 µg/kg, 2.49 µg/kg – 22.10 µg/kg and 3.76 µg/kg – 6.65 µg/kg for tetracycline, oxytetracycline and doxycycline respectively. Farm 4 recorded a residual range of 6.04 µg/kg – 91.51 µg/kg, 1.67 µg/kg – 85.91 µg/kg and 2.02 µg/kg – 9.30 µg/kg for tetracycline, oxytetracycline and doxycycline respectively. The result indicates multi-residues of antibiotics. The residual concentrations of tetracycline, oxytetracycline and doxycycline and the standard deviation across the four farms are reported in tables 1, 2 and 3 respectively with graphical representation in figures 1, 2 and 3. Livestock and agricultural activities are a major source of tetracyclines contamination (Burke *et al.*, 2016; Liu *et al.*, 2018). The utilization of antibiotics in veterinary practices can result in the deposition of tetracyclines residue in meat products (Liu *et al.*, 2018). Several studies reported that the concentration of tetracyclines were above the permissible maximum residual limit in livestock, which implies the widespread misuse of tetracyclines and the poor or outright lack of implementation of the withdrawal period.

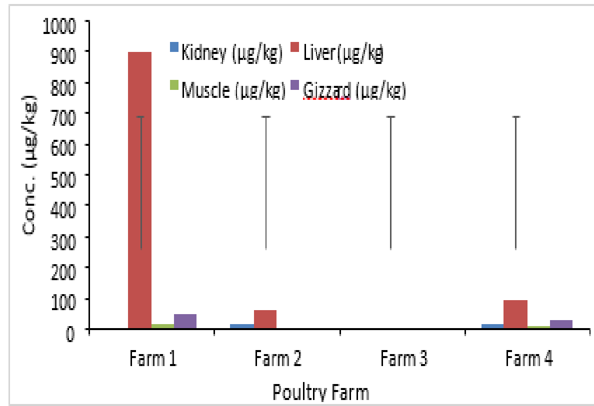

Fig 1: Concentration [mean ± STD; µg/kg] of tetracycline residues from four selected poultry farms from the study area

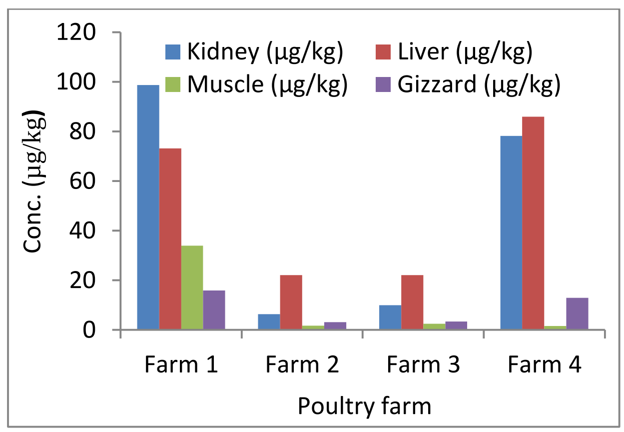

Fig. 2: Concentration [mean ± STD; µg/kg] Oxytetracycline Residues from four selected poultry farms from the study area

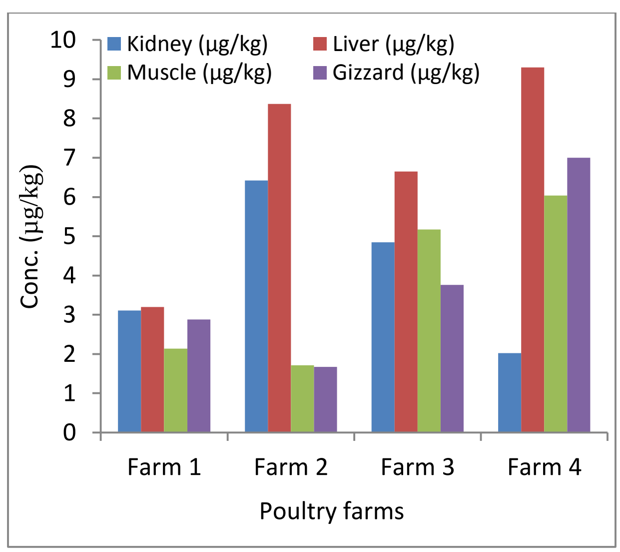

Fig. 3: Concentration of [mean ± STD; µg/kg] Doxycycline Residues from four selected poultry farms from the study area

Vishnuraj *et al.* (2016) found that the tetracyclines residue in poultry follow the range, oxytetracycline = 124-2930 μgkg^{-1}, tetracycline = 25-311μgkg^{-1}, chlortetracycline = 130-8148 μgkg^{-1}, doxycycline = 127-6010 μgkg^{-1}, with liver as the major disposition site. The accumulation of residues in higher concentrations can cause high tetracyclines resistance in livestock, and eventually in humans (Muaz *et al.*, 2018, Nhung *et al.*, 2017). In all the samples analyzed, the highest concentration of antibiotics residue was reported in liver, followed by kidney, then gizzard and muscle having the lowest levels. This is similar to studies conducted by Habeeb *et al.*, (2022) and Onipede *et al.*, (2021) which reported that the highest levels of antibiotic residues were found in liver.

On the other hand, the concentration of oxytetracycline observed in this study was higher than that obtained by *Onipede et al.*, (2021) in which mean concentration of oxytetracycline in Ota 1 and 3 chicken samples were reported to be 0.016µg/kg and 0.031µg/kg respectively. This could be attributed to various factors which affect the variability of residue levels such as dosage, type and age of birds, feeding, disease status, poor management, extra-label drug use, withdrawal time and route of administration. Of all the samples tested, 10% had drug residue levels above the MRL for tetracycline, while none of the samples had drug residue levels above the maximum residue limit for doxycycline and oxytetracycline. The highest concentration of tetracycline obtained was 895.04µg/kg which was above the standard Maximum Residual Limit. According to the FAO/WHO under the Codex Alimentarius Commission, the concentrations of both oxytetracycline and doxycycline were within the maximum residual limit (MRL) range, which indicates that the amount of residues was at the legally permitted or acceptable levels in food. The liver samples reported a mean concentration of 261.31 µg/kg with the highest tetracycline residue reported in Farm 1 with a concentration of 895.04 µg/kg, followed by that of Farm 4 and 2 with concentrations of 91.51 µg/kg and 56.67 µg/kg respectively. Tetracycline concentrations in liver samples showed a high level of variability in concentrations across the different farms as indicated by its standard deviation of 424.08, implying an inconsistent concentration. The kidney samples across the four farms had a mean concentration of 6.70 µg/kg, with highest and lowest concentration of 13.37 µg/kg and 1.26 µg/kg respectively and standard deviation of 6.07 indicating a moderate level of variability in tetracycline concentrations across the farms. Liver reported a mean concentration of 261.31 µg/kg, while gizzard reported 17.28 µg/kg and muscle with the least tetracycline residue reported a mean concentration of 4.61 µg/kg. The standard deviation of 6.07 indicates a moderate level of variability in tetracycline concentrations across kidney samples in the four farms. It can be observed from figure 2 above, comprising liver, kidney, gizzard and muscle analyzed for the presence of tetracycline residue, that the mean residue levels of tetracycline were high.

The HPLC analysis indicated that of the three antibiotics analyzed, tetracycline had the highest concentration of residue; 895.04 µg/kg found in liver, this was the highest concentration in all the chicken samples examined in this study and seem to suggest that tetracycline was administered in Farm 1. The tetracycline concentration obtained in Farm 1 was higher than the EU and FAO recommended limit in liver tissue. The tetracycline concentration obtained in Farm 1 in our study was however lower than that obtained in a study carried out in Spain, which had tetracycline concentration in the range 197.80-2564µg/kg in 24 chicken samples examined in the study followed by oxytetracycline with 98.66 µg/kg found in kidney, while doxycycline had the least concentration with 9.03 µg/kg found in liver. The tetracycline levels in the samples ranged from 0.89 to 895.04µg/kg. Farm 1, 2 and 3 chicken samples had oxytetracycline concentration within the range of 1.67 - 98.66 µg/kg, quite high compared to reports obtained in a study carried out by Onipede *et al*, (2021) on chicken samples collected from farms and markets in Ota and Lagos in South-western Nigeria. Standard deviation of 6.07 in kidney indicates a moderate variability in tetracycline concentrations across the four different farms, quite different from liver and gizzard with high standard deviation of 424.08 and 19.78, indicative of a substantial variability. Tetracycline concentrations in muscles reported a standard deviation of 3.91, indicating the lowest variability of tetracycline residue levels across the four different poultry farms. The various factors which affect antibiotic residues such as dosage, type and age of birds, feeding, disease status, poor management, extra-label drug use, withdrawal time and route of administration explain the variability of residue levels across the different farms.

All chicken samples from poultry farms in Obio-Akpor Local Government area had detectable levels of tetracycline, oxytetracycline and doxycycline. However, tetracycline was not detected in muscle and gizzard samples of Farm 3, while farm 1 samples had the highest burden of antibiotics compared to samples from other farms with concentration within the range of 1.26 µg/kg to 895.04µg/kg with liver recording the highest concentration of residues obtained in all the chicken samples examined in this study. This suggests that tetracycline, oxytetracycline and doxycycline were administered in the four poultry farms. All samples screened for oxytetracycline tested positive at various concentrations. The kidney samples of Farm 1 reported the highest oxytetracycline residue with a concentration of 98.66 µg/kg, followed by liver and kidney samples in Farm 4 with concentrations of 85.91 µg/kg and 78.16 µg/kg respectively. Analysis from this study were in contrast to that recorded by Elbayoumi *et al.,* (2018) which showed higher levels of oxytetracycline residues in an increasing order of muscle, liver and kidney. Also, the levels of oxytetracycline residues in this study ranged from 1.67 µg/kg to 98.66 µg/kg, in contrast to studies by Elbayoumi *et al*. (2018) which reported a range of 0.20 µg/kg to 128.10 µg/kg. Across the four different farms, standard deviation of 15.98 in gizzard indicates a moderate variability in oxytetracycline residues, quite different from kidney and liver with a high standard deviation of 47.08 and 33.57, which indicative of a high variability. Oxyetracycline concentrations in muscles across the four farms reported a standard deviation of 6.55, indicating the lowest variability of tetracycline residue levels across the four different poultry farms.

The result of this study shows the presence of residues of tetracycline, oxytetracycline and doxycycline, which are some of the leading antibiotics used in Nigeria. In all the samples analysed, the highest concentrations were found in liver, followed by the kidney, gizzard and then the muscle with the lowest concentration. This is in line with studies carried out by Habeeb *et al.,* (2022). Results from this study were incomparable to that recorded by Elbayoumi *et al.,* (2018) which showed that doxycycline residues were detected in an increasing order of muscle, liver and kidney. Moreover, the levels of doxycycline residues in this study ranged from 1.71 µg/kg to 9.30 µg/kg in contrast to that reported by Elbayoumi *et al*. (2018) which reported doxycycline in a range of 3.40 µg/kg to 15.90 µg/kg, 13.30 µg/kg to 2753.50 µg/kg and 25.10 µg/kg to 3661.60 µg/kg for muscle, liver and kidney respectively. Across the four different farms, standard deviations of 1.93, 2.688, 2.162 and 2.281 in kidney, liver, muscle and gizzard indicates a relatively low variability in doxycycline residues across the four different farms.

Conclusion: This study highlights the need for an intervention to decrease the level of antibiotics residues in chicken samples, highlighting the importance of the safe use of antibiotics in poultry production. The results showed that all samples analyzed were positive with the three tetracycline, oxytetracycline and doxycycline and brings to the forefront the need for a public health intervention to decrease the levels of antibiotics residues in chicken meat. High percentage of antibiotics positive samples highlights the importance of respecting the withdrawal periods of antimicrobials. This is effective as a means of reducing the levels of antibiotic residues in chicken samples, and its related issues such as antimicrobial resistance bacteria in the food chain.

DECLARATIONS

Declaration of Conflict of Interest: The authors declare no conflict of interest.

Data Availability Statement: Data are available upon request from the corresponding author or any of the other authors.

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