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RESEARCH ARTICLE

Occurrence and risk assessment of antibiotics in feces of elderly individuals in Shenzhen

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Abstract

The occurrence of antibiotics in the feces of elderly individuals in Shenzhen, China, was investigated by monitoring 78 compounds to understand the adverse effects and its association with antibiotic residues in animal products collected from local markets. In total, 18 compounds belonging to 5 classes of antibiotics were identified in 74 of 140 fecal samples. Furthermore, 17.9% of the fecal samples contained at least two antibiotics, and 14.3% of the samples showed antibiotic concentrations higher than 100 μg/kg. Cephalothin exhibited the highest detection frequency (22.1%), followed by azithromycin (15.7%) and tilmicosin (12.9%). Oxytetracycline, norfloxacin, and azithromycin showed extremely high concentrations (> 1000 μg/kg). Eight antibiotics were detected in the animal products, with detection frequencies ranging from 4.8 to 40.0%. Five antibiotics exhibited similar detection frequencies and strong correlations between the human fecal and animal product samples. Health risk assessment based on hazard quotients showed that ciprofloxacin in animal products and human feces posed a medium and high risk, respectively. The hazard quotients of oxytetracycline, norfloxacin, and azithromycin in the feces were greater than 1, indicating a high health risk. These findings suggest that the elderly individuals were frequently exposed to antibiotics via the food chain and faced health risks posed by these antibiotics.

Keywords Antibiotics · Elderly people · Feces · Animal food · Health risk assessment

Introduction

Antibiotics have played an important role not only in the treatment of bacterial infections in humans but also as feed additives to prevent diseases and promote growth in livestock. However, owing to widespread and excessive use, an increased number of antibiotics have been detected in water, soil, and animal-derived food products (Done and Halden 2015; Guo et al. 2019; Sun et al. 2017; Yamaguchi et al. 2015). Antibiotic residues in the food and environment finally gain entry into the human body via food chains and exert adverse health effects (Carvalho and Santos 2016; Negreanu et al. 2012; Wang et al. 2020). Recent reports have shown that alterations in the gut microbiota have a potential influence on the development of a variety of human diseases, including human metabolism, immunity, and endocrinology (Jackson et al. 2018; Zhao 2013).

The perturbations of intestinal normal flora by antibiotics require more attention in the elderly than in young individuals. Mariat et al. (2009) reported that the elderly have a different digestive physiology compared with young adults, and

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this difference can be attributed to their different gut bacterial profiles. Generally, elderly individuals take antibiotics more frequently than younger people because of their lower immune function, which increases their susceptibility to bacterial infections. The decreased metabolic activity of intestinal microorganisms in elderly individuals may reduce the excretion of antibiotics (An et al. 2018; Zhu et al. 2020). Moreover, veterinary antibiotic residues in food, even at low concentrations, can disturb the environment of gut microbiota (Wang et al. 2020). With the increase in age, the incidence of adverse drug reactions significantly increases in humans; thus, the adverse effects of antibiotic residues in elderly individuals are considerably greater than those on the young (Zhu et al. 2020).

In recent years, several studies have been performed to monitor antibiotic residues to investigate their potential risk to the elderly. Kong et al. analyzed 45 antibiotics and 2 antibiotic metabolites in urine samples of the elderly, and antibiotics were detected in 92.9% of the subjects. The results also revealed that most of antibiotic residues could produce untoward effect on lipid levels and increase risk of dyslipidemia (Kong et al. 2022). To assess the association between antibiotic exposure and adiposity in elderly, Sang et al. monitored 45 antibiotics and two metabolites in urine samples from a cohort of elderly. The results indicated that exposure to doxycycline and norfloxacin had BMI-based overweight/obesity risk, and ciprofloxacin, norfloxacin, and florfenicol were positively associated with waist circumference-based central preobesity/obesity risk (Sang et al. 2021). Moreover, antibiotic exposure and the potential risk of hypertension (Li et al. 2022) and depression (Liu et al. 2021) were reported in the elderly.

In the literature, most of studies focused on urine samples for antibiotics monitoring and associated health risk assessment (Zhang et al. 2020; Zhu et al. 2020). To the best of our knowledge, few studies have evaluated the antibiotic burden on elderly individuals from animal products via the food chain (Wang et al. 2020). In the present study, we determined 78 antibiotics in fecal samples from 140 elderly individuals as well as in different animal products from local markets in Shenzhen, China. Our results suggest that the occurrence of antibiotics in the feces of elderly individuals is associated with antibiotic residues in animal-derived food products and poses a potential threat to the health of the elderly population.

Materials and methods

Materials and reagents

All antibiotic standards were purchased from Alta Scientific (Tianjin, China) prepared in mixed solutions for different classes. High-performance liquid chromatography (HPLC)-grade methanol, acetonitrile, and formic acid were purchased from Thermo Fisher Scientific (Waltham, MA, USA). Ammonium acetate and acetic acid were obtained from Beijing Chemical Co. (Beijing, China). Water was produced using a Milli-Q synthesis water purification system (MilliporeSigma, Bedford, MA, USA). Oasis PRiME HLB (200 mg, 6 mL) solid-phase extraction (SPE) cartridges were purchased from Waters Corporation (Milford, MA, USA). Syringe filters (0.2 µm, GHP) were obtained from Pall Corporation (Ann Arbor, MI, USA).

Sample collection

From June 2018 to January 2019, 140 elderly individuals (older than 60 years of age) were recruited from the communities of Shenzhen, China. All participants were healthy when they were enrolled in the study and had not taken antibiotics for at least three months. The fecal samples were fresh, transported to the laboratory on dry ice, and stored at − 80 °C until analysis. All participants provided written informed consent, and the study was approved by the ethics committee of the Shenzhen Center for Disease Control and Prevention (R2018021). Animal product samples, including 12 pork, 10 freshwater fish (grass carp), 19 chicken, and 21 egg samples, were purchased randomly from supermarkets near the communities where the samples were collected, transported to the laboratory at 4 °C, and stored at − 80 °C until analysis.

Sample pretreatment and analysis

The target antibiotics from the fecal and animal product samples were extracted and purified according to our previous method (Li et al. 2017), with some minor modifications. One gram of sample was extracted twice with 20 mL of 0.05 mol/L ammonium acetate by vortex-mixing for 2 min. The sample was centrifuged at 14,000 rpm for 5 min, and the supernatant was collected and adjusted to pH of 5 using acetic acid. The extraction solution was directly loaded on an Oasis PRiME HLB cartridge under gravity. The cartridge was dried under vacuum for 5 min, and the compounds of interest (antibiotics) were eluted using 2 mL of 75% methanol (containing 0.2% formic acid) and 4 mL of acetonitrile (containing 0.2% formic acid). The eluate from the SPE cartridge was evaporated to less than 0.5 mL with nitrogen in a 40 °C water bath and then reconstituted to 1 mL with 5% methanol. The final extract was filtered prior to ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) analysis.

The target antibiotics were analyzed using a Waters Acquity UHPLC system connected to a Xevo TQ-S triple quadrupole mass spectrometer (Waters, Manchester, UK). Chromatographic separations were performed using an Acquity BEH C_{18} column (100 mm × 2.1 mm internal diameter, 1.7 µm particle size) (Waters, Milford, MA, USA) with the column oven temperature maintained at 40 °C. The mobile phase consisted of solvent A (0.1% formic acid in water) and solvent B (methanol:acetonitrile, 20:80, v/v, containing 0.1% formic acid) at a flow rate of 0.4 mL/min. The linear gradient elution program is summarized in Table S1. The MS system was operated using a positive electrospray ionization source in multiple reaction monitoring (MRM) mode. The ionization source parameters were set as follows: source temperature, 150 °C; cone gas (N_2) flow rate, 150 L/h; desolvation temperature, 500 °C; desolvation gas (N_2) flow rate, 800 L/h; capillary voltage, 3.0 kV; and the collision gas flow rate was 0.15 mL/min. Details of the MS/MS transitions for each compound and the corresponding cone voltages and collision energies are presented in Table S2.

Quality assurance and quality control

The matrix-matched calibration curves were prepared for each matrix over a concentration range of 0.5 to 500 µg/L, with regression coefficients (r^2) > 0.99. No target compounds were detected above the limit of quantification (LOQ) in blank samples of each matrix. The recoveries of analytes in fortified blank samples prepared in six replicates at three different concentrations (1 × LOQ, 3 × LOQ, 10 × LOQ), calculated using matrix-matched standards, ranged from 69 to 107% with inter-day relative standard deviations of < 15%. The LOQs of antibiotics in fecal and animal food samples, defined as ten times the signal-to-noise ratio, ranged from 1 to 30 µg/kg. The results of the validation are summarized in Table S3. Quality control samples, including blank, fortified, and matrix-matched standard samples, were prepared for each sample batch.

Health risk assessment

The estimated daily intake (EDI) of antibiotics according to their detected concentrations in the fecal samples was calculated using the following equation:

$$\text{EDI } (\mu\text{g/kg/day}) = \frac{\text{Ca} \times \text{Cc}}{\text{BW} \times \text{P}}$$

where Ca is the antibiotic concentration detected in fecal samples (µg/kg), Cc is the average daily volume of bowel movements of adults (220 g/day) (Jeong et al. 2009), BW is the average human body weight (60 kg), and P is the antibiotic excretion rate in feces (Table S4).

In addition, we calculated the EDI of antibiotics through the food chain from animal products using the following equation (Chen et al. 2022):

$$\text{EDI } (\mu\text{g/kg/day}) = \frac{C \times \text{C0}}{\text{BW}}$$

where C is the residual concentration of antibiotics in animal products (µg/kg), C0 is the average consumption of animal products, and BW is the human body weight (60 kg). According to a report on the dietary structure of local residents, the average daily consumption of animal products is as follows: 65 g/day freshwater fish, 100 g/day pork, 50 g/day eggs, and 75 g/day chicken (National Bureau of Statistics 2019).

Furthermore, the hazard quotient (HQ) was calculated on the basis of EDI and acceptable daily intake (ADI) (Table S4) to evaluate the health risks of antibiotics to elderly individuals. The equation used is as follows:

$$\text{HQ} = \frac{EDI}{ADI}$$

HQ indicates the risk of individual antibiotics to human health. HQ < 0.1 indicates minimal risk, 0.1 ≤ HQ ≤ 1 implies medium risk, and HQ > 1 indicates high risk (Chen et al. 2022).

Statistical analysis

The data of mean values, relative standard deviations, and Pearson correlation coefficient were calculated using Microsoft Excel 2017. Statistical analyses were performed using GraphPad Prism 8.0 (GraphPad Software, Inc., San Diego, CA, USA).

Results and discussion

Occurrence of antibiotics in the feces

The concentrations of the target antibiotics detected in fecal samples of elderly individuals are shown in Table S5. Among the 78 target antibiotics, 18 were identified in 74 of the 140 fecal samples, with concentrations ranging from 0.6 to 5532 µg/kg. The detection frequency of each analyte ranged from 0.7% to 22.1%; the analytes belonged to one of the following five classes of antibiotics: macrolides, β-lactams, tetracyclines, quinolones, and sulfonamides (Fig. 1a). A relatively high percentage of fecal samples (14.3%) exhibited antibiotic concentrations > 100 µg/kg (Fig. 1b). Twenty-five fecal samples (17.9%) were positive for two or more antibiotics. Up to six different antibiotics were simultaneously identified in a single sample. Human antibiotics (HA)/preferred as HA (HA: 17.8%, preferred as HA: 22.8%) and veterinary antibiotics (VA)/preferred as VA (VA: 17.8%, preferred as VA: 21.8%) showed almost the same detection frequency; however, more types of VA/preferred as VA were found than HA/preferred as HA (14 vs. 5) (Table 1). The detection frequencies of three antibiotics, cephalothin (CEP), azithromycin (AZM), and tilmicosin (TMC), were > 10%. Five antibiotics, detected in eight samples, showed high concentrations (> 500 µg/kg), with the

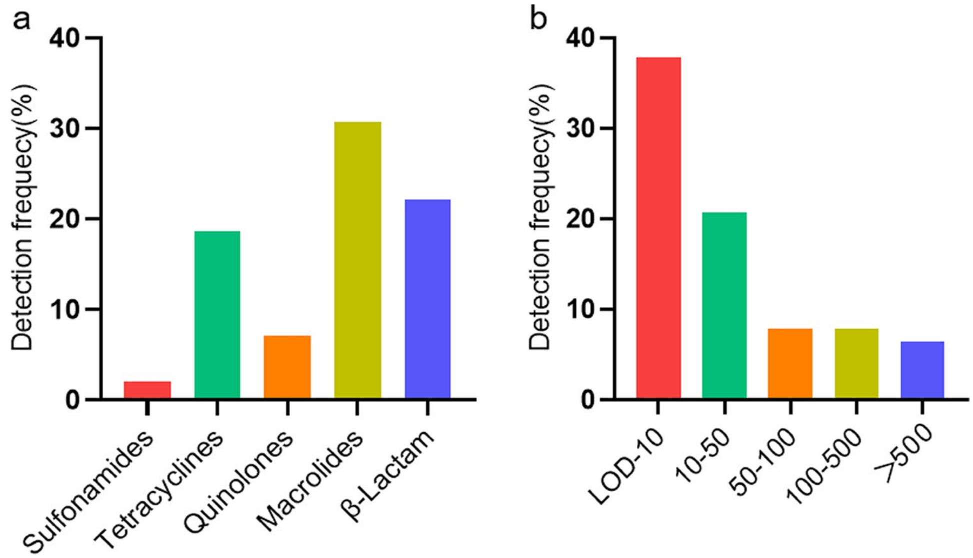

Fig. 1 Occurrence of antibiotics in fecal samples. **a** Detection frequency of five classes of antibiotics in the feces and **b** distribution of detected concentrations of antibiotics

Table 1 Occurrence of antibiotics in human feces

Antibiotics	Abbreviations	Usage	Detection frequency (%)	Maximum concentration (μg/kg)
Sulfonamides			3 (2.1)	
Sulfamethizole	SMT	Preferred as VA	1 (0.7)	206.7
Sulfamethazine	SM_2	VA	2 (1.4)	92.0
Quinolones			26 (18.6)	
Flumequine	FQ	VA	1 (0.7)	9.3
Enrofloxacin	ENR	VA	2 (1.4)	5.2
Ciprofloxacin	CIP	Preferred as VA	5 (3.6)	645.1
Enoxacin	ENX	HA	2 (1.4)	15.3
Ofloxacin	OFLX	Preferred as VA	8 (5.7)	604.7
Norfloxacin	NFX	Preferred as VA	7 (5.0)	5099.8
Sarafloxacin	SFX	VA	1 (0.7)	17.8
Tetracyclines			10 (7.1)	
Tetracycline	TC	Preferred as VA	3 (2.1)	53.7
Doxycycline	DOX	Preferred as VA	4 (2.6)	58.3
Oxytetracycline	OTC	Preferred as VA	3 (2.1)	5532.8
Macrolides			43 (30.7)	
Azithromycin	AZM	HA	22 (15.7)	1676.7
Roxithromycin	ROX	HA	1 (0.7)	1.8
Tilmicosin	TMC	VA	18 (12.9)	376.0
Tylosin	TYL	VA	1 (0.7)	7.6
Spiramycin	SP	Preferred as HA	1 (0.7)	9.8
β-lactams			31 (22.1)	
Cephalothin	CEP	Preferred as HA	31 (22.1)	7.1

HA human antibiotics, *VA* veterinary antibiotics

highest concentration being > 5000 μg/kg (oxytetracycline, OTC), and most of them are preferred as VA.

Our results showed that macrolides were the most frequently detected antibiotics, followed by β-lactams and quinolones, consistent with the findings of a previous study that monitored antibiotics in human feces (Wang et al. 2020). CEP was the only β-lactam detected in the samples, showing the highest detection frequency; however, all detected concentrations were below 10 μg/kg. Two macrolides, AZM and TMC, belonging to HA and VA, respectively, exhibited high detection frequencies with maximum concentrations of > 300 μg/kg. Yamaguchi et al. (2015) reported that the positive percentage of TMC from chicken, pork, and beef in Vietnam was 11.9%, with concentrations of up to 450 μg/kg. In our previous study, we found that AZM was one of the most frequently detected compounds in bottled drinking water in 15 countries (Wang et al. 2021a). In the present study, because all fecal samples were collected from elderly individuals who had not taken antibiotics in three months, our data suggest that the antibiotics detected originated from food or environmental exposure.

Antibiotic residues in the animal products

Based on local dietary habits, four animal products (pork, chicken, freshwater fish, and eggs) were selected for the determination of VA residues. As shown in Fig. 2, two antibiotics (enrofloxacin (ENR) and ciprofloxacin (CIP) were detected in freshwater fish, four (sulfamethazine (SM_2), TMC, tetracycline (TC), and doxycycline (DOX) in pork, three (ENR, CIP, ofloxacin (OFLX) in chicken, and four (ENR, CIP, florfenicol (FFC), SM_2) in egg samples. ENR was the most frequently detected antibiotic in freshwater fish (40.0%), chicken (26.3%), and egg (19.0%) samples and exhibited the highest residual levels in freshwater fish (75.2 μg/kg) and chicken (61.9 μg/kg). In the egg samples, FFC not only had the highest detection frequency (19.0%, the same as ENR) but also the highest detected concentration (113.6 μg/kg). In pork samples, the detection frequency of TMC (33.3%) was the highest, and DOX presented the highest residue level (133.3 μg/kg) among all samples (Table S6). Among the contaminated fish, pork, and chicken samples, only one pork sample was non-compliant, with DOX (133.3 μg/kg) above the maximum residue limit of 100 μg/kg. However, it is prohibited to detect ENR, CIP, FFC, and SM_2 in egg samples. Our results indicated that almost 50% of egg samples was non-compliant (European Commission 2010).

To investigate the association between the occurrence of antibiotics in fecal samples and animal products, we compared the detection frequencies of four classes of antibiotics (sulfonamides, quinolones, tetracyclines, and macrolides), which were detected in both human fecal and animal product samples. The results of the Pearson correlation analysis ($r = 0.44$) showed that the detection frequency of the two sample sets had a moderate correlation (Fig. 3a). We further compared the detection frequency of selected antibiotics, including SM_2, OFLX, TC, DOX, and TMC, in human fecal and animal product samples. As shown in Fig. 3b, the five antibiotics had similar detection frequencies and a strong correlation ($r = 0.80$) between the two sets of samples.

Antibiotics are extensively used worldwide for the treatment of human diseases and growth promotion in animals. Bu et al. (2013) found that the five commonly detected antibiotics in aquatic environment in many countries were macrolides, β-lactams, tetracyclines, quinolones, and

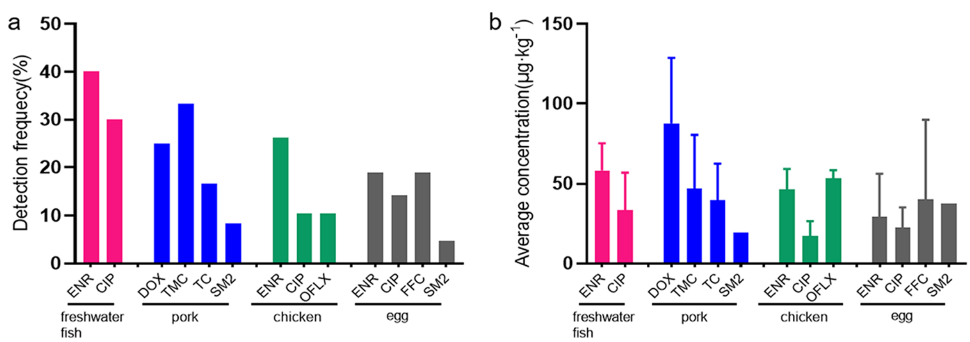

Fig. 2 Occurrence of antibiotics in animal product samples. **a** Detection frequency and **b** average concentrations of antibiotics in different animal samples

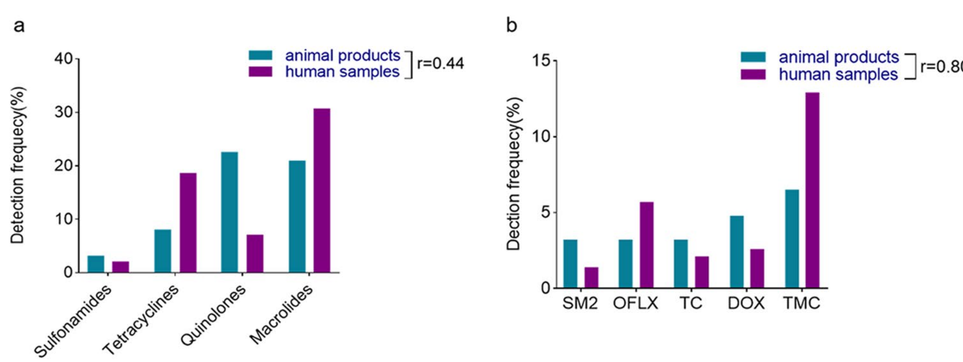

Fig. 3 Correlation analysis of antibiotics between the human fecal and animal product samples. **a** Correlation coefficient for the detection frequency of four classes of antibiotics and **b** correlation analysis results of selected antibiotics

sulfonamides. These compounds are difficult to completely remove during water treatment and food processing, and therefore, they may enter the human body through drinking water and food (Abriouel et al. 2008; Larrañaga et al. 2018; Wang et al. 2021b; Yu et al. 2018). The results of the correlation analysis, concentration determination, and frequency detection in our samples indicate that antibiotic residues in animal foods are a major source of long-term antibiotic exposure in elderly individuals.

Health risk assessment

The health risks associated with antibiotic exposure in animal tissues and eggs were evaluated based on the calculated HQ values. The HQs of the detected antibiotics are shown in Fig. 4a and Table S6. All the HQs were evidently lower than 1.0, and only the HQs of CIP detected in freshwater fish, chicken, and eggs were in the range of 0.1–0.5, indicating a medium health risk to elderly individuals from animal food products. CIP is a metabolite of ENR generated after it is administered to animals, and the residue marker is the sum of ENR and CIP. These two antibiotics have been frequently detected in environmental and animal tissue samples because of the widespread use of ENR in animal food production. Chen et al. (2018) investigated the bioaccumulation of antibiotics in cultured fish and found that ENR concentrations exceeded the maximum residue limit, but the calculated HQ was below 1.0. Ji et al. (2021) evaluated the risk of dietary exposure to ENR and CIP in duck eggs and found that the health risk was low because the obtained HQs were less than 1.0. Our results are consistent with those of previous reports; however, the health risk of gut microbiota perturbations in elderly individuals resulting from long-term exposure to antibiotics could not be neglected.

We also assessed the HQs of the antibiotics detected in the fecal samples. Among the 18 detected antibiotics, enoxacin was not assessed because of the absence of toxicity information. As shown in Fig. 4b, 28.3% of the HQs were higher than 0.1, originating from nine antibiotics, namely, CIP, AZM, norfloxacin (NFX), OTC, DOX, OFLX, sarafloxacin, SM_2, and TC, which exhibited at least medium health risks to elderly people. Moreover, CIP, AZM, NFX, and OTC in fecal samples presented HQ > 1, representing high risks to human health. We further calculated the HQ of these four antibiotics using the median value of the detected concentrations in the fecal samples; the HQs of CIP (4.56) and OTC (1.14) still indicated high health risks.

A biomonitoring study of the antibiotic burden in the elderly Chinese population found that CIP was the foremost contributor to health risks (Zhu et al. 2020). Moreover,

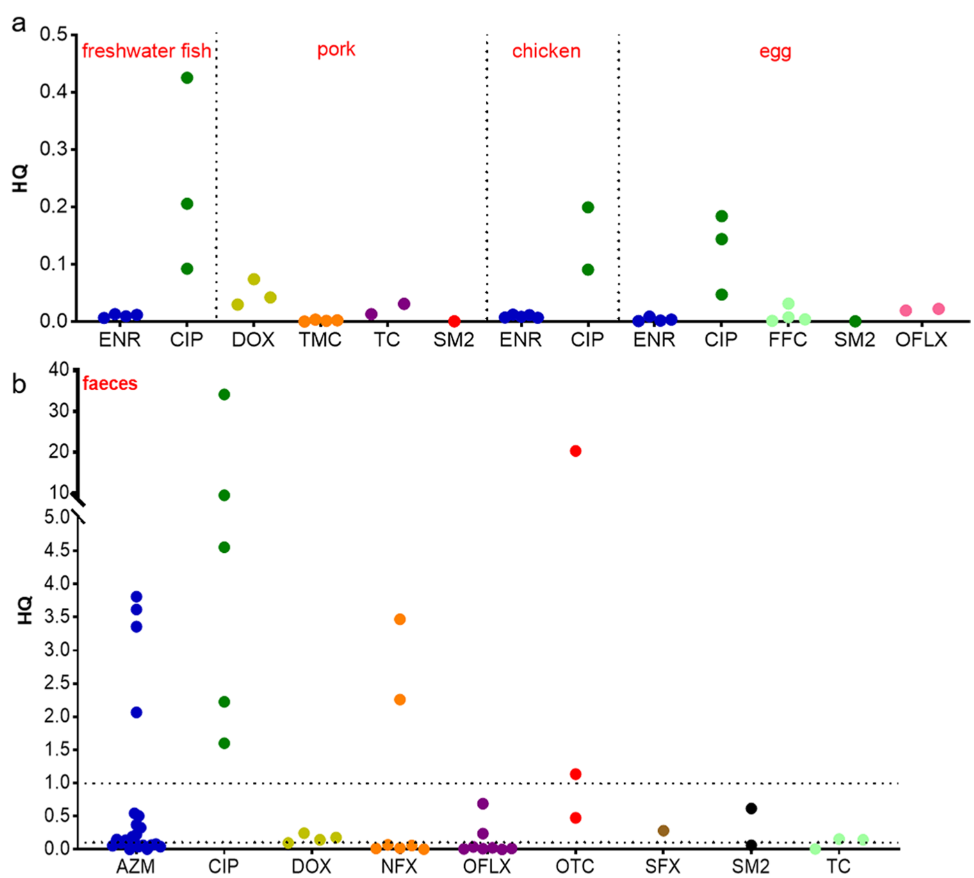

Fig. 4 Hazard quotient values of antibiotics in **a** animal samples and **b** human feces

Zhang et al. (2020) reported that CIP was the largest contributor to the hazard index among three generations of Chinese families. The authors also investigated the association between antibiotic exposure and adiposity in the elderly individuals: exposure to DOX had a body mass index-based overweight/obesity risk, and CIP was related to waist circumference-based central preobesity/obesity risk (Sang et al 2021). A study of urinary antibiotics in pregnant women in eastern China revealed that CIP was the most frequently detected antibiotic (16.0%), and CIP, OFLX, TC, AZM, and trimethoprim showed HQ > 1, calculated using the maximum concentrations (Wang et al. 2017). However, the abovementioned studies were performed based on antibiotic levels in urine samples. Recently, Wang et al. (2020) measured the concentrations of 19 antibiotics in human feces and found that the highest mean concentrations of five classes of antibiotics were observed in the elderly population. In this study, our data showed that CIP in animal products posed a medium risk and in human fecal samples posed a high risk. In addition, AZM, NFX, and OTC exhibited high health risks, based on the results of human fecal samples. The occurrence of antibiotics decreases the richness and diversity of the gut microbiota and alters its taxonomic composition (Doan et al. 2017; Parker et al. 2017). Studies have demonstrated that both AZM and CIP modify the human intestinal microbiota and its functions (Dethlefsen and Relman 2011; Korpela et al. 2016). Moreover, disruption of the interactions between the human microbiota and host can increase the rates of autoimmune disorders, such as asthma and inflammatory bowel disease (Dethlefsen and Relman 2011; Guarner et al. 2006). These adverse effects of antibiotics may be exacerbated in elderly people, causing serious health problems. Further investigations should be performed to monitor and evaluate the impact of long-term exposure to antibiotics on the intestinal flora of the elderly population and the associated health risks.

Conclusions

In this study, the widespread occurrence of antibiotics in fecal samples of elderly individuals and animal products was detected, and a strong correlation of some antibiotics was observed between the two types of samples. Additionally, the health risks to the elderly population exposed to the detected antibiotics were assessed. Generally, the antibiotics in animal products posed low or medium risks to human health; however, extremely high HQs were observed in the fecal samples of the elderly individuals. The potential adverse effects of some antibiotics require further attention. The effects of long-term and multiple antibiotic exposure on the gut microbiota of vulnerable populations, such as the elderly, should be evaluated in future studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-023-25522-7.

Author contribution Xi Xia contributed to the study conception and design. Material preparation was performed by Ziquan Lv, Suli Huang, Yuhua Chen, Yulin Fu, Changfeng Peng, Tingting Cao, and Yuebin Ke. Data collection and analysis were performed by Yuan Zhang, Ziquan Lv, Xiaowei Li, and Kunxia Zhao. The first draft of the manuscript was written by Yuan Zhang, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Anonymized data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This work was approved by the ethics committee of the Shenzhen Center for Disease Control and Prevention (R2018021).

Consent to participate Not applicable.

Consent for publication Agreement to submit the article has been obtained from all the authors. All the authors give consent for this version of the article to be published.

Competing interests The authors declare no competing interests.

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