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A short review of human exposure to antibiotics based on urinary biomonitoring

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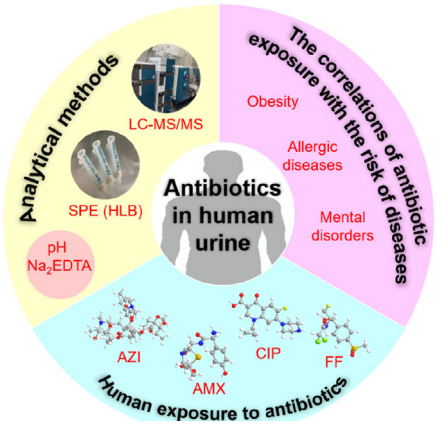
HIGHLIGHTS

- Analysis, occurrence and health risks of antibiotics in human urine are summarized.
- SPE-LC-MS/MS is the common method for simultaneous trace analysis of antibiotics.
- Florfenicol, ciprofloxacin, azithromycin and amoxicillin present higher health risk.
- Antibiotic exposure is related to obesity, allergic diseases and mental disorders.

GRAPHICAL ABSTRACT



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ABSTRACT

Antibiotics play a role in preventing and treating infectious diseases and also contribute to other health risks for humans. With the overuse of antibiotics, they are widely distributed in the environment. Long-term exposure to multiple antibiotics may occur in humans through medication and dietary intake. Therefore, it is critical to estimate daily intake and health risk of antibiotics based on urinary biomonitoring. This review compares the strengths and weaknesses of current analytical methods to determine antibiotics in urine samples, discusses the urinary concentration profiles and hazard quotients of individual antibiotics, and overviews correlations of antibiotic exposure with the risk of diseases. Liquid chromatography-tandem mass spectrometry is most applied to simultaneously determine multiple types of antibiotics at trace levels. Solid-phase extraction with a hydrophilic-lipophilic balance adsorbent is commonly used to extract antibiotics in urine samples. Fifteen major antibiotics with relatively higher detection frequencies and concentrations include sulfaclozine, trimethoprim, erythromycin, azithromycin, penicillin V, amoxicillin, oxytetracycline, chlortetracycline, tetracycline, doxycycline, ofloxacin, enrofloxacin, ciprofloxacin, norfloxacin, and florfenicol. Humans can be easily at microbiological effect-based risk induced by florfenicol, ciprofloxacin, azithromycin, and amoxicillin. Positive associations were observed between specific antibiotic exposure and obesity, allergic diseases, and mental disorders. Overall, the accessible, automated, and environmentally friendly methods are prospected for simultaneous determinations of antibiotics at trace level in urine. To estimate human exposure to antibiotics more accurately, knowledge gaps need to be filled up, including the transformation between parent and metabolic antibiotics, urinary excretion proportions of antibiotics at low-dose exposure and pharmacokinetic data of antibiotics in humans,

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and the repeated sampling over a long period in future research is needed. Longitudinal studies about antibiotic exposure and the risk of diseases in different developmental windows as well as in-depth research on the pathogenic mechanism of long-term, low-dose, and joint antibiotic exposure are warranted.

Contents

1. Introduction

Antibiotics are a group of metabolites derived from microorganisms that have antipathogens or other characteristics and can interfere with the development of other microorganisms (Demain and Sanchez, 2009). Antibiotics can be used as medicines (to prevent and treat infectious diseases for humans and animals) and growth promoters (to gain weight for animals) (Sarmah et al., 2006; Zhou et al., 2013a). The global antibiotic consumption by humans was 34.8 billion defined daily doses in 2015 and is estimated to be of up to 84 billion defined daily doses by 2030 (Klein et al., 2018). The global use of antibiotics in livestock was 63,151 tons in 2010 and is expected to rise by 67% by 2030 (Van Boeckel et al., 2015). Antibiotics have been widely detected in various environmental (Liu et al., 2018; Yang et al., 2018; Zhou et al., 2013a; Zhou et al., 2013b) and food samples (Li et al., 2021; Yang et al., 2020). For example, approximately 65 antibiotics have been reported in major water sources, such as the Yangtze River and Taihu Lake in China, with a maximum level of 1484 ng/L (Buffie and Pamer, 2013; Liu et al., 2018; Wu et al., 2014). Over 70 antibiotics have been detected in animal-originated foods, including pork, chicken, beef, and fish (Chen et al., 2015; He et al., 2012; Yamaguchi et al., 2015).

Human exposure pathways to antibiotics include medication, dietary intake, air inhalation, dust ingestion, dermal contact, and so on (Hamscher et al., 2003; Li et al., 2012; Paul et al., 2019; Sarahroodi and Mikaili, 2012; Tao et al., 2012). Adverse effects of antibiotic exposure include increased bacterial resistance (Luo et al., 2010) and increased risk of obesity (Mikkelsen et al., 2016), allergic diseases (Droste et al., 2000), mental disorders (Cani et al., 2008), and so on. Antibiotic resistance is estimated to cause over 1,000,000 deaths globally in 2050 (Langdon et al., 2016; WHO, 2014). The European Commission, the USA, Australia, and China have taken strategies to limit antibiotics and established the maximum residue limit of antibiotics in animal muscle (e.g., 100 μg/kg for lincomycin by the European Commission) (Wang et al., 2017a).

Because of the widespread environmental occurrence and adverse effects of antibiotics, it is urgent to evaluate the health risk of human exposure to antibiotics. Conventional prescription examination and questionnaire surveys can reflect the antibiotic exposure through medication (Trasande et al., 2013). By contrast, biomonitoring takes advantages of being more full-scale and accurate, and can evaluate the internal antibiotic exposure not only through medication, but also through other pathways (e.g., dietary intake), based on the qualitative and quantitative analysis of antibiotics in biological samples (Wang et al., 2015). Urine is noninvasive and easy to collect compared to other matrices, such as blood, breast milk, and feces (Manzetti and Ghisi, 2014). Large proportions of consumed antibiotics can be excreted through urine in unchanged or glucuronide-conjugated forms (Carvalho and Santos, 2016). The internal antibiotic exposure can be back-calculated on the basis of the antibiotic levels detected in urine and the urinary excretion proportions of antibiotics as mentioned above (Wang et al., 2014; Wang et al., 2017b; Zhang et al., 2015). Therefore, urinary antibiotics may be the potential biomarkers of human exposure to antibiotics (Wang et al., 2014).

Reviews on human exposure to antibiotics and biomonitoring of antibiotics are still very limited. Samanidou et al. (2005) and Sversut et al. (2017) overviewed analytical methods to determine fluoroquinolones and oxytetracycline in biological samples, respectively. These existing reviews are related to a subset of the methods of biomonitoring or target at certain antibiotics. Antibiotic distribution in the human body and corresponding health risks are still not fully recognized. In this review, we discuss analytical methods (including pretreatment methods and detection techniques) to determine antibiotics in human urine, summarize the distribution of urinary antibiotics and compare the hazard quotients of individual antibiotics. Furthermore, the correlations of antibiotic exposure with the risk of diseases are also discussed.

2. Analytical methods to determine antibiotics in human urine

2.1. Detection techniques

Chromatography (e.g., liquid chromatography-tandem mass spectrometry (LC-MS/MS), and LC coupled with spectral detectors), immunoassays (e.g., immunosensors, enzyme-linked immunosorbent assays, fluorescence polarization immunoassays, and lateral flow immunoassays) and electrochemical methods (e.g., electrochemical sensors and capillary electrophoresis along with MS/MS) have been developed to qualify and quantify antibiotics in human urine (Table 1). Each method has its strengths and weaknesses and is applied to different situations.

LC-MS/MS is the most used chromatographic technique to determine antibiotics, with advantages of high sensitivity, reasonable specificity, and simultaneous determination of multiple target analytes and disadvantages of high cost, complexity and high reagent consumption (Pauter et al., 2021). Common applied MS/MS systems are triple quadrupole mass spectrometry (QqQ-MS) and quadrupole time-of-flight mass spectrometry (Q/TOF-MS). QqQ-MS allows multiple reaction monitoring and shows high sensitivity (low noise level) and selectivity (identification of paired precursor and product ions) in quantitative analysis (Huang et al., 2019). Q/TOF-MS is composed of Q-MS (mass filter) and TOF-MS (mass analyzer). It allows no-target or post-target screening in full scan mode and shows higher resolution and excellent ability of qualitative analysis compared to QqQ-MS (Gomez et al., 2010; Gonzalez-Marino et al., 2012; Huang et al., 2019). LC can also be coupled with spectral detectors (e.g., UV, photodiode array, and fluorescence detectors) to determine antibiotic levels based on relevant functional groups' characteristic spectra and spectral intensity (Udalova et al., 2015). Considering the same wavelength emitted or absorbed by some antibiotics, spectral detectors may exhibit poor specificity. For example, cefazolin and ofloxacin could not be analyzed simultaneously by HPLC-UV. The UV spectra between cefazolin and ofloxacin highly matched by 52% and affected their accurate qualification and quantitation (Legrand et al., 2016). For the LC system, chromatographic columns for separation include Zorbax SB-C18, BEH-C18, HSS T3, and so on, of which Zorbax SB-C18 and BEH-C18 are most commonly used. Zorbax SB-C18 takes advantages of high-temperature tolerance (up to 80 °C) and low-pH stability (up to pH 1.0) (Agilent Technologies, 2016) and has been applied for the rapid separation of at least six categories of antibiotics (Chen et al., 2011; Li et al., 2017a; Wang et al., 2019). BEH-C18 is applicable to analyze approximately ten classes of antibiotics (Cazorla-Reyes et al., 2014; Jin et al., 2010; Li et al., 2019; Wang et al., 2020; Yao et al., 2018). It is filled with bridged ethylsiloxane-silica hybrid particles and allows excellent chemical stability (e.g., stable at pH 1–12). However, the matrix of BEH-C18 has weak interactions with analyte functional groups (Jin et al., 2010) and may show bad retention of antibiotics with stronger polarity. Compared with BEH-C18, the HSS T3 column is filled with pure silica particles and offers better retention of polar compounds. The HSS T3 column has been selected to separate six categories of antibiotics (Wang et al., 2014). The mobile phase in LC systems is composed of the organic phase (methanol or acetonitrile) and aqueous phase (pure water), as well as some additives (e.g., formic acid and ammonium hydroxide). Formic acid and ammonium hydroxide can enhance the ionization of antibiotics monitored in positive and negative ion modes, respectively (Javorska et al., 2017; Yao et al., 2018). Ammonium acetate improves the peak intensity and peak shape (Li et al., 2019). Moreover, the proportion of the organic solvent to the injection solution may influence online concentration effects (Wang et al., 2014). Wang et al. (2014) compared the peak intensities and peak shapes of 14 antibiotics with proportions ranging from 5% to 40%, and a ratio of 20% was finally selected. At a higher proportion, most antibiotics presented broadened and asymmetric peaks. At a lower proportion, decreased peak intensities of chloramphenicol, tylosin, azithromycin, and clarithromycin were observed.

Immunoassays can determine the contents of antigens by coloration reactions. Antibiotic concentration is subsequently calculated based on the competitive reactions between antibiotic-antibody and antigen-antibody (Pauter et al., 2020). The competitive reactions are influenced by parameters such as the ionic strength and pH of the buffer solution and detergent content (Galvidis et al., 2015). Immunoassays show advantages of low cost, simplicity and on-site testing (Raysyan et al., 2020). However, the method also shows poor selectivity due to the cross-reactivity between antibodies and structurally similar antibiotics (Munro et al., 1982). Electrochemical sensors operate based on electric signals produced by the oxidation-reduction reactions between target antibiotics and electrodes (Radi et al., 2003). The analytical signal could be enhanced by optimizing pH, pulse amplitude, cleaning potential, and step potential (Moraes et al., 2013). Furthermore, extra electrocatalytic materials could modify the surface of electrodes and enhance the electrochemical response of antibiotics (Chi and Li, 2010). Moraes et al. (2013) determined levofloxacin in urine by electrochemical sensors based on vertically aligned nanotubes. The method presented a 2.5-fold higher signal intensity than bare electrodes without modification. Capillary electrophoresis separates antibiotics according to their different electrophoretic mobilities (Pauter et al., 2021). Electrophoretic mobilities are related to the kind, pH, and ionic strength of the separation buffer solution, the capillary's size and temperature, and the applied voltage (Liu et al., 2008; Pauter et al., 2021). Electrochemical methods have the strengths of low cost, low reagent consumption, and environmental friendliness (Pauter et al., 2021). However, electrochemical sensors have difficulty in simultaneously determining multiple antibiotics due to their cross-affectability.

In general, compared to LC-MS/MS, immunoassay and electrochemical techniques exhibit strengths of low cost, simplicity, and environmental friendliness. However, in addition to poor specificity, the abovementioned two techniques also exhibit low sensitivity, with obviously higher limits of detection (LODs) (0.003–510 ng/mL) than LC-MS/MS (0.002–14.3 ng/mL) (Table 1). These techniques are more suitable for high-amount analysis in clinical practice than trace analysis (Fernandez-Torres et al., 2010).

2.2. Pretreatment methods

Reported pretreatment methods for antibiotics in urine samples include solid-phase extraction (SPE), dispersive liquid-liquid microextraction (DLLME), direct dilution, molecularly imprinted polymer-hollow fiber microextraction (MIP-HFM), and so on. Before extraction, hydrolysis is usually conducted (Li et al., 2019; Li et al., 2017a; Wang et al., 2014; Yao et al., 2018). Specifically, urine was added with the β-glucuronidase solution and incubated in a water bath (37 °C) overnight to hydrolyze antibiotics in glucuronide-conjugated forms. 4-Methylumbelliferone glucuronide can be simultaneously added to urine to monitor the enzymatic hydrolytic rate of β-glucuronidase (Wang et al., 2014).

SPE with reversed-phase hydrophilic-lipophilic balance (HLB) adsorbent is the most common approach to extract antibiotics in urine samples. HLB adsorbents are applicable for antibiotics with a wide range of polarities, pKa values and molecular weights (Chen et al., 2011; Chiesa et al., 2015; Ji et al., 2010; Jin et al., 2010; Li et al., 2019; Wang et al., 2014; Wang et al., 2017b). For amphenicols (chloramphenicol, thiamphenicol, and florfenicol) with low acidic properties (pKa: 7.49–9.76), mixed-mode (reversed-phase and anion-exchange) MAX sorbents are also applicable (Yao et al., 2018). Prime HLB adsorbents can remove more than 95% of impurities (including proteins and salts) in urine and have been used to extract 16 sulfonamides and 8 fluoroquinolones (Li et al., 2019; Wang et al., 2019). During these traditional SPE procedures, factors such as the selection of rinse/elution solvents are associated with extraction efficiency. For example, Yao et al. (2018) indicated that ethyl acetate was a better elution solvent for amphenicols than methanol or acetonitrile, which may be attributed to the hydrophobicity of amphenicols. Furthermore, a time-saving dispersive SPE was developed to analyze 17 antibiotics (five categories) in urine samples. The whole process (vortex and centrifugation) only took 15 min, and acceptable recoveries of 78.3–136% were obtained (Huang et al., 2019). Solid-phase microextraction (SPME) enables combination with LC, with the advantages of simplicity, low cost, and low solvent consumption (Zambonin, 2003). Conditions such as the selection of fiber coating material, extraction time and temperature, pH, ionic strength, and desorption mode are associated with the SPME efficiency (Aresta et al., 2010; Liu et al., 2012). Increased ionic strength is beneficial to the recovery of hydrophilic compounds. A six-fold higher recovery was observed for chloramphenicol after the addition of 200 mg/mL sodium chloride (Aresta et al., 2010). The desorption mode is crucial for analytes to be transferred entirely from the fiber to the LC. Static desorption exhibited improved peak width and peak symmetry of chloramphenicol than dynamic desorption (Aresta et al., 2010).

Oriented to being easy, automated and environmentally friendly, other pretreatment approaches except for SPE were also explored. Ehrlich et al.

Table 1
Determination of antibiotics in human urine samples.

Analyte	Sample treatment	Separation technique	Detection characteristics	Recovery (%)	LOD (ng/mL)	Reference
2 TCs		Spectrofluorimetric		96–102		(Chang et al., 1992)
2 BLs	HPLC-integrated sample preparation	HPLC-UV	Nucleosil C18 ACN/50 mM NaH_2PO_4 (pH 5.0)	89.2–95.2	150	(Ehrlich et al., 2001)
CIP, CLO		HPLC-DAD	Nova-Pak C18 MeOH/ACN/100 mM formate buffer (F.A., pH 3.0)	90.0–110	300–510	(Espinosa-Mansilla et al., 2006)
3 SAs		Photochemically induced fluorescence		95.0–108	2.9–8.1	(Lopez Flores et al., 2007)
3 FQs	Dilution by 40% ACN/H_2O	CE with chemiluminescence		89.2–105	16.6–76.2	(Liu et al., 2008)
CAP	Hydrolysis Add Na_2SO_4 SPME	HPLC-UV	Luna C18 ACN/H_2O (10 mM NH_4Ac, pH 4.6)	93.6–98.4	37	(Aresta et al., 2010)
5 SAs, 2 BLs, 2 TCs, 2 APHs	SPE (Bond Elut®Plexa™)	HPLC-DAD-FLD	Gemini C18 ACN/H_2O (0.1% F.A.)	33.2–99.5	10–440	(Fernandez-Torres et al., 2010)
4 MLs	DLLME	SALDI/MS		46.3–55.9	1.47–2.66	(Chen et al., 2012)
4 BLs		Chemiluminescence		103–112	64–169	(Ma et al., 2012)
5 MLs	DLLME-SFO	LC-CAD	BDS C18 column ACN (0.2% F.A.)/H_2O (0.2% F.A.)	94.6–118	10–40	(Jia et al., 2013)
LEV	Dilution 10 times by phosphate buffer (pH 6.0)	Electrochemical sensors		97.4–101	27.2	(Moraes et al., 2013)
CIP, TMP, SMX	SPE (Strata-X)	HPLC-DAD	Kinetex core-shell XB-C18 ACN/10 mM KH_2PO_4 buffer (pH 2.50)	81.6–109	39–189	(Pynnonen and Tuhkanen, 2014)
PCN-G		Immunosensor		101	0.003	(Merola et al., 2015)
4 MLs		ELISA		77.0–116	0.02–0.03	(Galvidis et al., 2015)
LEV	Dilution by 40 times	FPIA			0.50	(Shanin et al., 2015)
OFL		Electrochemical sensors		99.1–100	0.0867	(Elfiky et al., 2019)
3 SAs	Automated LLME	HPLC-UV	Luna C18 column ACN/H_2O (0.1% F.A.)	91–93	60–100	(Shakirova et al., 2021)
2 BLs, CIP, CDM, LZD, MDE and their metabolites	Vortex, ACN Dilution 2 times by H_2O	CE-DAD-MS/MS	Fused-silica capillary ACN/H_2O (0.1% F.A.)	89.5–98.9	20–80	(Pauter et al., 2021)
3 TCs	Add EDTA solution, adjust sample pH to 4.0 SPE (HLB)	UPLC-Q/TOF-MS	BEH C18 ACN (0.1% F.A.)/H_2O (0.1% F.A.)	94.5–108	0.089–0.138	(Jin et al., 2010)
2 SAs, CIP	Adjust sample pH to 3.0 SPE (HLB)	HPLC-MS/MS	Cadenza HS-C18 ACN (0.1% F.A.)/H_2O (0.1% F.A.)	92.7–105.6	0.00207–0.0072	(Ji et al., 2010)
12 BLs, 2 LAs, ATM, VAN	Add phosphate buffer (pH 8.5) SPE (HLB)	UPLC-MS/MS	Zorbax SB-C18 ACN/H_2O (0.1% F.A.)	13.9–96.5	0.05–10	(Chen et al., 2011)
10 BLs, 2 FQs, 2 AGs, 2 GPs, TGC, CTM, DAP	Dilution 3 times by mobile phase.	UPLC-MS/MS	BEH C18 MeOH/H_2O (0.01% F.A.)	70.0–115	0.10–0.30	(Cazorla-Reyes et al., 2014)
2 BLs, 2 FQs, 3 TCs, 3 MLs, 3 SAs, CAP	Add 1.0 M NH_4Ac (pH 5.0) Hydrolysis SPE (HLB)	Two dimensional UPLC-Q/TOF-MS	XBridge C18 HSS T3 MeOH/H_2O (0.1% F.A.) ACN/H_2O	79.6–121	0.04–1.99	(Wang et al., 2014)
3 TCs, 3 SAs, 4 FQs	Add 1.0 M NH_4Ac Hydrolysis SPE	UPLC-MS/MS	Zorbax SB-C18	74.0–95.5	0.01–0.05	(Li et al., 2017a)
VAN	Vortex, ACN	UPLC-QqQ/MS	Meteoric Core C18 Bio ACN (0.1% F.A)/H_2O (0.1% F.A)	92.1		(Javorska et al., 2017)
3 APHs	Add 1.0 M NH_4Ac (pH 6.0) Hydrolysis SPE (MAX)	UPLC-MS/MS	BEH-C18 MeOH (0.1% $NH_3{\cdot}H_2O$)/H_2O (0.1% $NH_3{\cdot}H_2O$)	93.3–118	0.02–0.12	(Yao et al., 2018)
16 SAs	Add phosphate buffer (pH 8.5) Hydrolysis Add EDTA solution, adjust sample pH to 2.0 SPE (Prime HLB)	UPLC-MS/MS	BEH-C18 MeOH (0.01 M NH_4Ac)/H_2O (0.01 M NH_4Ac)	71.6–97.3	0.3–1.7	(Li et al., 2019)
8 FQs	Dilution 9 times by H_2O (0.05% F.A.) SPE (Prime HLB)	HPLC-MS/MS	Zorbax SB-Aq C18 ACN/H_2O (0.1% F.A.)	83.4–117	0.5–1.0	(Wang et al., 2019)
4 FQs	MIP-HFM	UPLC-MS/MS	Kinetex XB-C18 ACN/H_2O (0.1% F.A.)	9.40–24.5	0.1–10	(Barahona et al., 2019)
4 MLs, 3 TCs, 4 FQs, 4 SAs, 2 BLs	D-SPE	UPLC-QqQ/MS	Gemini NX-C18 MeOH (0.1% F.A.)/H_2O (0.1% F.A.)	78.3–136	0.11–14.3	(Huang et al., 2019)
3 APHs	Hydrolysis DLLME	LC-Q/TOF-MS	Zorbax RRHD Eclipse Plus C18 MeOH/H_2O	83–104	0.003–0.029	(Pastor-Belda et al., 2020)

(2001) proposed the HPLC-integrated sample preparation technique to analyze two β-lactams in urine. The method allowed automated pretreatment and exhibited satisfactory recoveries of 89.2–95.2%. Extraction (by acetonitrile) and subsequent dilution (by pure water) procedures were performed to analyze six antibiotics and their metabolites, with recoveries of 89.5–98.9% (Pauter et al., 2021). Chen et al. (2012) used DLLME to extract four macrolides in urine samples and the recoveries of 46.3–55.9% were obtained. Similarly, Jia et al. (2013) also applied DLLME to collect five macrolides from urine, with recoveries of 94.6–118.4% being achieved. The extraction solvent and dispersive solvent are critical parameters in DLLME (Chen et al., 2012). Chen et al. (2012) reported that from six tested solvents, dichloromethane (as extraction solvent) and acetone (as dispersive solvent) showed the best DLLME efficiency for four macrolides in urine samples. However, the abovementioned three methods are only suitable for one group of antibiotics or several antibiotics. Cazorla-Reyes et al. (2014) directly diluted the urine sample three times by mobile phase for injection, with recoveries of 19 antibiotics (seven categories) being 70–116%. Nevertheless, with no clean-up steps, impurities in urine may potentially damage the detection instrument. Recently, Barahona et al. (2019) tried a MIP-HFM method to extract four fluoroquinolones in urine. MIP-HFM combines solid-phase microextraction and molecularly imprinted polymers and takes advantage of selective recognition, low solvent consumption, and on-site testing. However, unsatisfactory recoveries of 9.4–24.5% were achieved, due possibly to poor selectivity of the prepared molecularly imprinted polymer-hollow fiber for multiple target analytes (Barahona et al., 2019).

During all pretreatment processes, experimental conditions, including the addition of Na_2EDTA and sample pH, need to be considered. Na_2EDTA is helpful to avoid antibiotics (such as tetracyclines and sulfonamides) chelating with possibly present metal cations (Wang et al., 2017a). An improper sample pH may cause ionization and degradation of some antibiotics (Wang et al., 2014). Ampicillin and amoxicillin tend to degrade under acidic conditions (Khuroo et al., 2008). Sulfonamides (alkaline compounds) are prone to ionize in acidic conditions (Wang et al., 2017c). Tetracyclines are unstable at pH < 2.0 (Oka and Patterson, 1995). Azithromycin, clarithromycin, roxithromycin, erythromycin, and dirithromycin (grouped into macrolides) present pKa values of 7.1–9.9 and remain molecular forms under basic conditions (Wang, 2009). In addition, structurally modified aglycone rings of azithromycin, clarithromycin, and roxithromycin allow their acidic stability (Fiese and Steffen, 1990; Hirsch et al., 1999). However, erythromycin tends to hydrolyze to hydro-erythromycin under acidic conditions (Fiese and Steffen, 1990; Hirsch et al., 1999). A rapid decline in the recovery of erythromycin was observed with increased formic acid (Huang et al., 2019). Li et al. (2019) adjusted the pH values of urine samples by hydrochloric acid to 2.0, 4.0, 7.0, 9.0 and 12.0, respectively, and the optimal recoveries of 16 target sulfonamides were obtained at pH 2.0. Wang et al. (2014) reported that target 14 antibiotics exhibited good recoveries of 78.2–93.1% when urine samples were adjusted by 1.0 M ammonium acetate buffer at pH 5.0. However, poor recoveries below 50% were obtained for sulfadimidine, sulfamethoxazole, and azithromycin in buffer solution of pH 4.0, as well as tylosin, clarithromycin, and ampicillin in buffer solution of pH 9.0.

3. Human exposure to antibiotics based on urinary biomonitoring

3.1. Urinary occurrence

A total of 54 antibiotics have been detected in human urine (Table S1). Fifteen major antibiotics with relatively higher detection frequencies and the 95th concentration (P95) in urines include sulfaclozine (range of reported detection frequencies and P95 concentrations: 3.00–35.5%, nd-23.8 ng/mL), trimethoprim (2.01–63.0%, nd-27.0 ng/mL), erythromycin (0–9.70%, nd-78.1 ng/mL), azithromycin (1.30–18.2%, nd-150 ng/mL), penicillin V (1.61–35.5%, nd-2.82 ng/mL), amoxicillin (2.10–15.9%, nd-30.2 ng/mL), oxytetracycline (0–100%, nd-42.6 ng/mL), chlortetracycline (1.2–35.0%, nd-1.26 ng/mL), tetracycline (0–55.0%, nd-105 ng/mL), doxycycline (1.20–30.4%, nd-4.69 ng/mL), ofloxacin (0–55.0%, nd-54.7 ng/mL), enrofloxacin (0.400–100%, nd-1.69 ng/mL), ciprofloxacin (10.6–55.6%, 0.107–30.0 ng/mL), norfloxacin (0–82.5%, nd-5.36 ng/mL) and florfenicol (1.50–30.7%, nd-29.5 ng/mL) (Table S1 and Fig. 1). Amoxicillin, florfenicol, penicillin, norfloxacin, ciprofloxacin, enrofloxacin and ofloxacin were highly used in China, with their usage in 2013 being more than 5000 tons (Zhang et al., 2015). Widespread occurrence of the 14 antibiotics in the environments (such as water and soil) was also reported (Danner et al., 2019; Zhu et al., 2020b). These may explain their high exposure in humans.

Profiles of major antibiotics in human urine were investigated. Children and pregnant women were of most concern. In contrast, children in Shanghai, Eastern China (0–9.90%, nd-9.87 ng/mL), showed relatively lower detection frequencies and P95 concentrations of azithromycin, oxytetracycline, tetracycline, ofloxacin, enrofloxacin, ciprofloxacin, and norfloxacin than those in the Tibetan Plateau, Southwestern China (2.41–18.5%, nd-105 ng/mL) in 2017. This may be related to the fact that over-prescription of antibiotics is more severe in Western China (the proportion of outpatients prescribed with antibiotics: 57.4%) than in Eastern China (47.3%) (Yin et al., 2013). No obvious differences were observed for children in Eastern China from 2013 to 2020. For pregnant women, a decreasing trend for the detection frequencies and P95 concentrations of norfloxacin, enrofloxacin, ciprofloxacin and ofloxacin was observed in urine collected from 2012 to 2013 (39.2–82.5%, 0.55–5.43 ng/mL), 2013–2014 (7.40–38.5%, 0.14–2.43 ng/mL) and 2015 (0.700–16.0%, nd-1.21 ng/mL) (Geng et al., 2020; Wang et al., 2017b; Zeng et al., 2020). Fluoroquinolones (including norfloxacin, enrofloxacin, ciprofloxacin, and ofloxacin) are commonly applied to treat infections during pregnancy (Lee et al., 2008). However, with concerns about the potential risk of fluoroquinolone use during pregnancy (Aboubakr et al., 2014; Yefet et al., 2014) and the publication of administrative measures for the clinical use of antimicrobial agents in 2012 (Ministry of Health of the People's Republic of China, 2012), pregnant women may receive more careful and decreased medication with fluoroquinolones and show decreased exposure to fluoroquinolones. Additionally, the detection frequencies of trimethoprim and erythromycin in the general population from Korea (63.0% and 62.0%) were relatively higher than those from China (19.4% and 9.00%) (Huang et al., 2020; Wang et al., 2018a). This may be attributed to the regional and temporal variations in antibiotic consumption, urine type (spot or first morning urine), and sensitivity of analytical methods. Employees in poultry

Notes to Table 1:

TCs, tetracyclines; SAs, sulfonamides; BLs, β-lactams; APHs, amphenicols; MLs, macrolides; CIP, ciprofloxacin; LEV, levofloxacin; TMP, trimethoprim; SMX, sulfamethoxazole; OFL, ofloxacin; CDM, clindamycin; LZD, linezolid; MDE, metronidazole; LAs, lincosamides; ATM, azithromycin; VAN, vancomycin; FQs, fluoroquinolones; AGs, aminoglycosides; GPs, glycopeptides; TGC, tigecycline; CTM, clarithromycin; DAP, daptomycin; CAP, chloramphenicol; PCN-G, penicillin-G; LCM, lincomycin; ERM, eremomycin; AMP, ampicillin.

DLLME, Dispersive liquid-liquid microextraction; DLLME-SFO, Dispersive liquid-liquid microextraction based on the solidification of floating organic droplets; MIP-HFM, Molecularly imprinted polymer-hollow fiber microextraction; D-SPE, Dispersive solid phase extraction; FPSE, Fabric sorptive phase extraction; HF-LPME, Hollow fiber liquid phase microextraction.

HPLC-DAD-FLD, high performance liquid chromatography-diode array-fluorescence; SALDI/MS, surface-assisted laser desorption/ionization mass spectrometry; LC-CAD, liquid chromatography with charged aerosol detection; ELISA, enzyme-linked immunosorbent assay; FPIA, fluorescence polarization immunoassay; CE-DAD-MS/MS, capillary electrophoresis-diode array detector along with the tandem mass spectrometry; UPLC-QqQ-MS, ultraperformance liquid chromatography-triple quadrupole mass spectrometry; UPLC-Q/TOF-MS, ultraperformance liquid chromatography-quadrupole time-of-flight mass spectrometry; MISPE-PE-MS, molecularly imprinted solid phase extraction-pulsed elution coupled with electrospray mass spectrometry; HPLC-PDA, high performance liquid chromatography and photo-diode array detection; LFIA, lateral flow immunoassay.

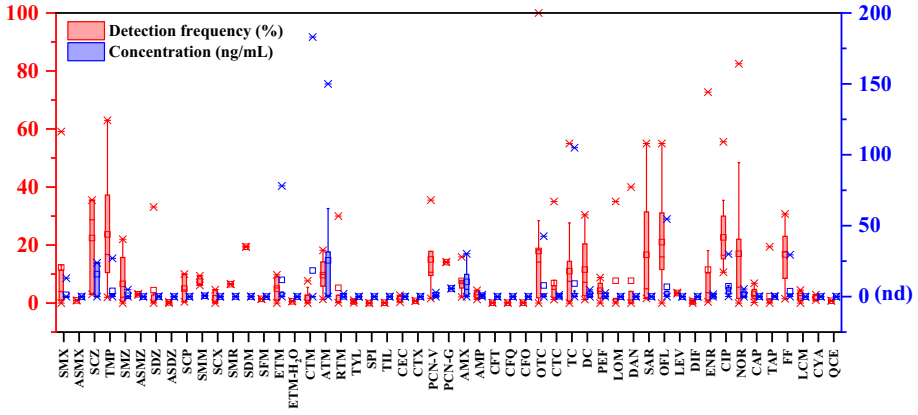

Fig. 1. Reported detection frequencies and the 95th percentile concentrations of antibiotics in human urines (data shown in Table S1). SMX, sulfamethoxazole; ASMX, acetylated sulfamethoxazole; SCZ, sulfaclozine; TMP, trimethoprim; SMZ, sulfamethazine; ASMZ, acetylated sulfamethazine; SDZ, sulfadiazine; ASDZ, acetylated sulfadiazine; SCP, sulfachloropyridazine; SMM, sulfamonomethoxine; SCX, sulfachinoxalin; SMR, sulfamerazine; SDM, sulfadimethoxine; SFM, sulfameter; ETM, erythromycin; ETM-H_2O, dehydrated erythromycin; CTM, clarithromycin; ATM, azithromycin; RTM, roxithromycin; TYL, tylosin; SPI, spiramycin; TIL, tilmicosin; CEC, cefaclor; CTX, cefotaxime; PCN-V, penicillin V; PCN-G, penicillin G; AMX, amoxicillin; AMP, ampicillin; CFT, ceftiofur; CFQ, cefquinome; CFO, cefotaxime; OTC, oxytetracycline; CTC, chlortetracycline; TC, tetracycline; DC, doxycycline; PEF, pefloxacin; LOM, lomefloxacin; DAN, danofloxacin; SAR, sarafloxacin; OFL, ofloxacin; LEV, levofloxacin; DIF, difloxacin; ENR, enrofloxacin; CIP, ciprofloxacin; NOR, norfloxacin; CAP, chloramphenicol; TAP, thiamphenicol; FF, florfenicol; LCM, lincomycin; CYA, cyadox; QCE, quinocetone.

feeding farms in Germany were widely exposed to antibiotics, with detection frequencies of 100% for four target antibiotics (Paul et al., 2019). This may be related to the overuse of veterinary antibiotics in poultry farms (Sarmah et al., 2006). Outpatients in Ghana were exposed to multiple antibiotics except for those medicated. In their urine, the detection frequencies of trimethoprim, amoxicillin, tetracycline, doxycycline, and ciprofloxacin ranged from 1.29% to 30% (Lerbech et al., 2014). Urinary antibiotics were also compared among different populations. Higher detection frequencies and P95 concentrations of trimethoprim, azithromycin, oxytetracycline, chlortetracycline, doxycycline, and florfenicol were found in urine from children (2.10–27.8%, nd-9.87 ng/mL) than in urine from adults (0.200–8.90%, nd-0.460 ng/mL) in Shanghai, Eastern China, in 2017. Children may ingest more antibiotics from food and the environment and through medication due to their high metabolic rates, high mobility, and weak immunity (Landrigan and Carlson, 1995; Orlando et al., 2020; Yoshikawa, 2000). However, opposite trends were found for ofloxacin, enrofloxacin, ciprofloxacin, and norfloxacin, which are all grouped into fluoroquinolones. Fluoroquinolones may contribute to arthropathy in immature animals (Alghasham and Nahata, 2000; Brown, 1996) and thus being more prudently used in children than adults. Children (4.70–22.4%, nd-4.69 ng/mL) also exhibited higher detection frequencies and P95 concentrations of oxytetracycline, chlortetracycline, and doxycycline than pregnant women (2.40–12.7%, nd-1.54 ng/mL) in Jiangsu Province, Eastern China in 2019.

The concurrent exposure to multiple antibiotics was also evaluated by several studies. Simultaneous exposure to at least two antibiotics was found in 13.1–93% of urine samples (Wang et al., 2018a; Wang et al., 2017b; Wang et al., 2018b; Zeng et al., 2020; Zhang et al., 2020; Zhu et al., 2020a). Twelve percent of the general people in Anhui Province, Eastern China, were exposed to at least six antibiotics (Zhang et al., 2020). These results identify the ubiquitous occurrence of multiple antibiotics in human urine.

3.2. Exposure pathways and possible variabilities

Humans can be exposed to antibiotics through medication, dermal and inhalation ingestion, dietary intake (antibiotic-contaminated food and drinking water), and so on (Hamscher et al., 2003; Li et al., 2012; Paul et al., 2019; Sarahroodi and Mikaili, 2012; Tao et al., 2012). Some extraordinary concentrations of human antibiotics were observed in urine samples. For example, Wang et al. (2018b) reported maximum concentrations in human urine of above 3000 ng/mL for tetracycline, norfloxacin, ofloxacin, and azithromycin. This may result from medication with relevant antibiotics shortly before sampling (Wang et al., 2015; Zhang et al., 2020). For humans with occupations involving antibiotics (such as employees in poultry feeding farms), dermal and inhalation ingestion may play essential roles in their daily antibiotic exposure (Hamscher et al., 2003; Paul et al., 2019). Compared to the medication by humans to treat diseases during a short-term period and the dermal and inhalation ingestion by humans with occupations involving antibiotics, dietary intake has received more attention recently, since it may cause long-term, low-dose and concurrent exposure to multiple antibiotics (Ben et al., 2019). Generally, dietary intake contributes to a large proportion of human exposure to various pollutants including antibiotics (Ben et al., 2019; Domingo, 2012; Joseph et al., 2015; Skibniewska, 2003). Notably, dietary intake of animal-originated food rather than drinking water may be the major pathway of daily human exposure to antibiotics, which can be evidenced by following findings. First, the concentrations of antibiotics in drinking water (at the level of ng/L) are much less than those in human biological samples (ng/mL) (Bu et al., 2013; Liu and Wong, 2013; Liu et al., 2017; Wang et al., 2018b; Wang et al., 2020). Wang et al. (2016b) also reported that only two (florfenicol and thiamphenicol) of 19 target antibiotics were detected in drinking water in Shanghai, Eastern China. In addition, no correlation was found between urinary antibiotic levels and water consumption for the general population in Korea (Ji et al., 2010). Second, positive correlations were found between urinary concentrations of enrofloxacin and ciprofloxacin and consumption of beef, pork, and dairy products for the general population in Korea ($p < 0.01$) (Ji et al., 2010). Urinary concentrations of veterinary antibiotics were positively associated with egg (OR [95% CI]: 2.07 [1.01, 4.21], $p = 0.05$) and milk (OR [95% CI]: 1.96 [1.10, 3.49], $p < 0.05$) consumption for pregnant women (Zeng et al., 2020). Higher levels of the sum of all target antibiotics were also observed in children with higher consumption of freshwater fish (OR [95% CI]: 1.60 [0.92, 2.79], $p < 0.05$), marine fish (OR [95% CI]: 1.72 [1.00, 2.97], $p < 0.05$), fresh milk (OR [95% CI]: 1.68 [0.97, 2.91], $p < 0.05$) and pork (OR [95% CI]: 2.01 [1.16, 3.49], $p < 0.05$) (Wang et al., 2018a).

Possible variables related to human exposure to antibiotics, including age, gender, study site, screen time, and so on, have been evaluated (Wang et al., 2018a; Wang et al., 2015; Wang et al., 2016b; Zhang et al., 2020). Wang et al. (2015) reported that the detection frequencies of macrolides and β-lactams in old children (10–11 years) were lower than those in young children (8–9 years) ($p < 0.05$). The relatively lower immunity of young children may increase their medication with antibiotics to treat infectious diseases (Yoshikawa, 2000). No significant differences in target antibiotic categories (including macrolides, β-lactams, tetracyclines, fluoroquinolones, sulfonamides, amphenicols, lincosamides and quinoxalines) were observed between males and females (both aged 4–91 years) (Zhang et al., 2020). However, human/veterinary antibiotics were more frequently detected in girls than in boys (both aged 8–12 years) (odds ratio (OR) [95%

confidence interval (CI)]: 1.76 [0.99, 3.11], $p < 0.05$) (Wang et al., 2018a). Decreased urinary concentrations of macrolides and fluoroquinolones were observed in districts with higher economic development levels in Shanghai (Wang et al., 2015). Urinary norfloxacin in suburban areas was also higher than that in urban areas ($p < 0.05$) (Zeng et al., 2020). This may be attributed to the poor management of antibiotics and weak public awareness about the rational use of antibiotics in districts with lower economic development levels (Wang et al., 2015). Veterinary antibiotics were more frequently detected in children (8–12 years) with longer screen times (OR [95% CI]: 1.87 [0.88, 3.68], $p < 0.05$) (Wang et al., 2018a). This may be explained by the association of longer screen time with increased intake of animal-originated food and decreased intake of vegetables (Shang et al., 2015).

3.3. Health risk assessment

Estimated daily intakes (EDIs) of antibiotics can be calculated based on urinary antibiotics. The common applied equation is as follows (Ji et al., 2010; Li et al., 2017a; Wang et al., 2018a; Wang et al., 2017b; Wang et al., 2018b; Zeng et al., 2020; Zhang et al., 2020; Zhu et al., 2020b):

$$EDI\ (\mu g/kg\ body\ weight\ (bw)/day) = \frac{C_a\ (\mu g/L) \times M_c\ (g/day)}{C_c\ (g/L) \times M_b\ (kg) \times F}$$

where C_a and C_c are the concentrations of urinary antibiotic and urinary creatinine, M_b is bodyweight, and F is the proportion of the antibiotics excreted through urine in their unchanged plus glucuronide-conjugated forms over the corresponding antibiotics ingested. M_c is the daily output of urinary creatinine and can be derived according to populations of different sexes, ages, and heights (Mage et al., 2008).

The hazard quotient (HQ) and hazard index (HI) were used to evaluate the health risk of exposure to individual and multiple antibiotics, respectively. They can be assessed as follows (Wang et al., 2017b):

$$HI = \sum HQ; HQ = \frac{EDI}{ADI}$$

where ADI is the acceptable daily intake based on microbiological effects of antibiotics. HI or HQ > 1 manifests potential health risks based on microbial effects.

Reported P95 or P90 EDIs were compared among antibiotics (Table S2 and Fig. 2). Azithromycin (nd-66.7 μg/kg bw/day), oxytetracycline (nd-2.13 μg/kg bw/day), sulfaclozine (nd-1.78 μg/kg bw/day), amoxicillin (nd-1.62 μg/kg bw/day) and florfenicol (nd-1.43 μg/kg bw/day) showed relatively higher EDIs than other antibiotics (nd-0.97 μg/kg bw/day).

The proportions of HIs or HQs > 1 in several populations (pregnant women, children, and adults) have been calculated by several studies (Table S3 and Fig. 3). HIs of >1 were observed in 0.93–23.6% of the investigated populations. Three predominant antibiotics with relatively higher proportions include ciprofloxacin (0.530–14.1%), azithromycin (0.200–12.5%), and amoxicillin (1.60–6.70%). Higher daily intake and lower ADIs of these three antibiotics contribute to their high HQs. Ciprofloxacin, azithromycin, and amoxicillin are three necessary human antibiotics, and their high HQs are likely related to the medication shortly before sampling. Florfenicol, merely used as a veterinary antibiotic, exhibited HQs of >1 in 0–1.5% of investigated populations. The human health risk of possibly high-dose and long-term exposure to florfenicol deserves more attention. Furthermore, pregnant women probably have lower health risks than children and adults. Ciprofloxacin presented an HQ of >1 in 0.53–3.8% of pregnant women. The proportion was lower than children (5.6–5.8%) and adults (3.5–14.1%). Analogous tendencies were observed for azithromycin, amoxicillin, and florfenicol. This may be related to pregnant women's more careful daily diet and administration than children and adults (Wang et al., 2017b).

4. The correlations of antibiotic exposure with the risk of diseases

4.1. Obesity

Numerous observational and clinical studies have identified the effects of antibiotic use on the risk of obesity (Baron et al., 2020; Mikkelsen et al., 2016). These studies merely focused on short-term and high-dose antibiotic exposure through medication. Studies based on human urinary biomonitoring have been conducted in recent years to fully estimate the relation of internal antibiotic exposure with the risk of obesity (Table 2). Three indicators of obesity include body mass index (BMI), waist circumference (WC), and body fat percentage (BFP). Generally, positive associations were observed between adiposity and antibiotics. For example, the urinary concentration of norfloxacin was positively correlated with BMI (OR [95% CI]: 1.29 [1.02, 1.40], $p < 0.05$), WC (1.99 [1.24, 2.75], $p < 0.05$) and BFP-based obesity (1.69 [1.21, 2.17], $p < 0.05$) in elderly individuals (Sang et al., 2021). Elevated levels of chlortetracycline and ciprofloxacin were found in adults with higher BMI ($p < 0.05$) (Wang et al., 2018b). Children exposed to more florfenicol (tertile 2 vs. 1, OR [95% CI]: 2.54 [1.27, 5.07], $p < 0.05$; tertile 3 vs. 1, OR [95% CI]: 2.92 [1.45, 5.87], $p < 0.05$) and trimethoprim (tertile 2 vs. 1, OR [95% CI]: 2.54 [1.27, 5.07], $p < 0.05$; tertile 3 vs. 1, OR [95% CI]: 2.92 [1.45, 5.87], $p < 0.05$) showed a higher risk of BMI-based obesity (Wang et al., 2016a). Veterinary antibiotics have been added to livestock feed as growth promoters to increase

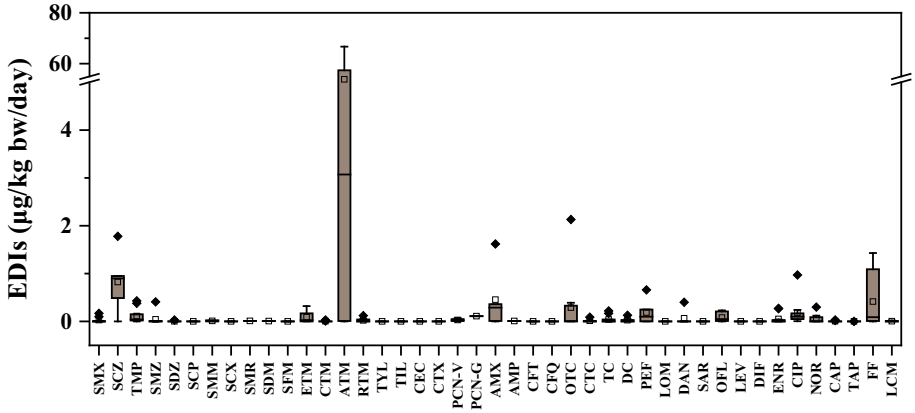

Fig. 2. Reported estimated daily intakes (EDIs) of antibiotics based on their concentrations in urines (data shown in Table S2). SMX, sulfamethoxazole; SCZ, sulfaclozine; TMP, trimethoprim; SMZ, sulfamethazine; SDZ, sulfadiazine; SCP, sulfachloropyridazine; SMM, sulfamonomethoxine; SCX, sulfachinoxalin; SMR, sulfamerazine; SDM, sulfadimethoxine; SFM, sulfameter; ETM, erythromycin; CTM, clarithromycin; ATM, azithromycin; RTM, roxithromycin; TIL, tilmicosin; TYL, tylosin; CFT, ceftiofur; CFQ, cefquinome; CEC, cefaclor; CTX, cefotaxime; PCN-V, penicillin V; PCN-G, penicillin G; AMX, amoxicillin; AMP, ampicillin; OTC, oxytetracycline; CTC, chlortetracycline; TC, tetracycline; DC, doxycycline; PEF, pefloxacin; LOM, lomefloxacin; DAN, danofloxacin; SAR, sarafloxacin; OFL, ofloxacin; LEV, levofloxacin; DIF, difloxacin; ENR, enrofloxacin; CIP, ciprofloxacin; NOR, norfloxacin; CAP, chloramphenicol; TAP, thiamphenicol; FF, florfenicol; LCM, lincomycin; CYA, cyadox; QCE, quinocetone.

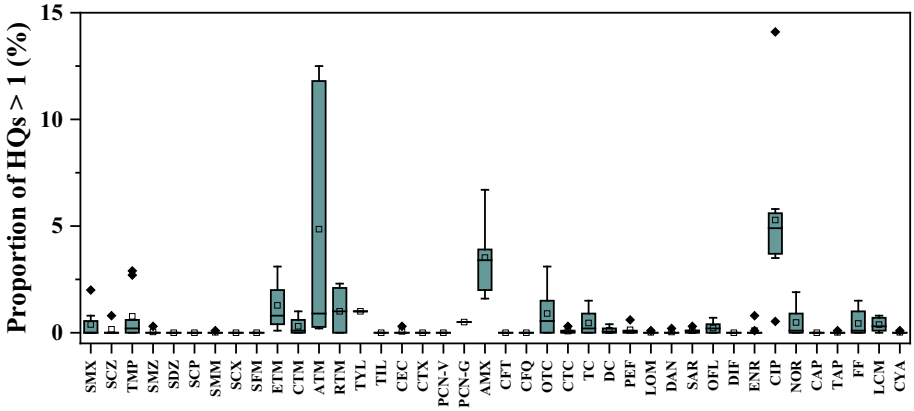

Fig. 3. Reported proportions of hazard quotients (HQs) > 1 for individual antibiotics (data shown in Table S3). SMX, sulfamethoxazole; SCZ, sulfaclozine; TMP, trimethoprim; SMZ, sulfamethazine; SDZ, sulfadiazine; SCP, sulfachloropyridazine; SMM, sulfamonomethoxine; SCX, sulfachinoxalin; SFM, sulfameter; ATM, azithromycin; RTM, roxithromycin; CTM, clarithromycin; ETM, erythromycin; TIL, tilmicosin; TYL, tylosin; CFT, ceftiofur; CFQ, cefquinome; CEC, cefaclor; CTX, cefotaxime; PCN-G, penicillin G; PCN-V, penicillin V; AMX, amoxicillin; AMP, ampicillin; OTC, oxytetracycline; CTC, chlortetracycline; TC, tetracycline; DC, doxycycline; PEF, pefloxacin; LOM, lomefloxacin; DAN, danofloxacin; SAR, sarafloxacin; OFL, ofloxacin; DIF, difloxacin; ENR, enrofloxacin; CIP, ciprofloxacin; NOR, norfloxacin; CAP, chloramphenicol; TAP, thiamphenicol; FF, florfenicol; LCM, lincomycin; CYA, cyadox; QCE, quinocetone.

the weight of animals for over 70 years (Iizumi et al., 2017). According to an experiment on weaned mice, after administration of antibiotics (penicillin, vancomycin, penicillin plus vancomycin, and chlortetracycline) at subtherapeutic levels, mice presented increased adiposity, levels of short-chain fatty acids (SCFAs), and numbers of bacterial genes participating in SCFA metabolism (Cho et al., 2012). After administration of azithromycin or florfenicol at 5 mg/kg/day for four weeks, altered gut microbiota composition, levels of SCFAs, bile acid metabolism, and increased adiposity were also observed in immature mice (Li et al., 2017b). Several probable mechanisms between antibiotic use and weight gain are as follows (Cox and Blaser, 2015; Vangay et al., 2015): (1) improved ability of gut bacteria to digest indigestible polysaccharides; (2) reduced anti-obesity bacteria counts; (3) changes in liver fat formation; (4) changed metabolic signal; and (5) decreased immunity and intestinal defenses. Notably, some opposite results were also reported. Sulfamethoxazole, enrofloxacin, ciprofloxacin, trimethoprim, sulfamethazine, and azithromycin showed negative associations with BMI-based obesity in pregnant women (Geng et al., 2020; Zeng et al., 2020). A negative association was also observed between the birth weight of infants and maternal florfenicol (OR [95% CI]: −39.7 [−69.3, −10.1], $p < 0.05$) and ciprofloxacin (OR [95% CI]: −39.7 [−69.3, −10.1], $p < 0.05$) (Zhang et al., 2021b). This may be attributed to the low detection frequencies and concentrations of certain antibiotics, dichotomous effects (repression and promotion) on growth induced by antibiotics, and differences in the growth-promoting capacity of antibiotics (Cox and Blaser, 2015).

4.2. Allergic diseases

The association between early-life exposure to antibiotics and allergic diseases, such as allergic asthma and atopic dermatitis, has been investigated based on the prescription examination and questionnaire surveys, though some contradictory outcomes were obtained (Kuo et al., 2013; Obiakor et al., 2018). To date, only one biomonitoring-based study has been reported (Geng et al., 2021). The results showed that exposure to certain antibiotics during different trimesters of pregnancy was related to the risk of current asthma and eczema in four-year-old children. Specifically, the risk of current eczema increased by 1.28 (95% CI: 1.10–1.49, $p < 0.05$) and 1.17 (95% CI: 1.07–1.28, $p < 0.05$) times in children with a one-unit increase in urinary concentrations of sulfamethazine in the first trimester and ciprofloxacin in the second trimester, respectively. In the third trimester, a one-unit increase in oxytetracycline concentration was related to a 1.90-fold (95% CI: 1.30–2.78, $p < 0.05$) increased risk of current asthma in children. Possible mechanisms were speculated based on the microbiome-mediated effects of antibiotics (Ferretti et al., 2018; Fujimura et al., 2016). Animal studies have indicated that antibiotic-induced dysbiosis of the microbiota can impact the immune system by increasing

Table 2
Epidemiological studies on the associations of antibiotic exposure with diseases based on urinary biomonitoring.

Population	Sample size	Model for statistical analysis	Diseases/risk	Association	Targets	Reference
Children	586	Multiple logistic regression	BMI or WC-based obesity	Positive	florfenicol, trimethoprim	(Wang et al., 2016a)
Adults	822	Fisher's exact test or rank sum test	BMI-based obesity	Positive	chlortetracycline, ciprofloxacin	(Wang et al., 2018b)
				Negative	sulfamethazine	
Pregnant women	762	Multiple logistic regression	BMI-based obesity	Negative	sulfamethoxazole, enrofloxacin, ciprofloxacin	(Zeng et al., 2020)
Pregnant women	9136	Linear mixed model with random effects	BMI-based obesity	Negative	trimethoprim, sulfamethazine, azithromycin	(Geng et al., 2020)
The elderly	990	Binomial logistic regression	BMI-based obesity	Positive	norfloxacin, sulfachloropyridazine	(Zhu et al., 2020a)
				Negative	sulfadiazine	
General population	691		BMI-based obesity	Positive	sulfamethazine	(Zhang et al., 2020)
The elderly	990	Multiple linear regression	BMI-based obesity	Positive	doxycycline, norfloxacin	(Sang et al., 2021)
			BFP-based obesity	Positive	ciprofloxacin, norfloxacin, florfenicol	
			WC-based obesity	Positive	norfloxacin	
Children	2453	Generalized estimating equation	Current asthma and eczema	Positive	sulfamethazine, ciprofloxacin, oxytetracycline	(Geng et al., 2021)
Children	326	Multiple logistic regression	Mental disorders	Positive	ciprofloxacin	(Zhang et al., 2021a)
The elderly	990	Binary logistic regression	Depression	Positive	azithromycin, sulfaclozine	(Liu et al., 2021)
Infants	735	Multiple linear regression	Birth weight	Negative	florfenicol, ciprofloxacin	(Zhang et al., 2021b)

BMI, body mass index; BFP, body fat percentage; WC, waist circumference.

the levels of Immunoglobulin E (a key mediator in allergic diseases) (Hong et al., 2019), reducing the counts of regulatory T cells (Russell et al., 2012) and causing T helper type 2 cell responses (Hill et al., 2012). Another study found that mice exhibited food allergies after antibiotic administration, with a reduced abundance of Clostridia. Clostridia plays a role in regulating intestinal epithelial permeability and innate lymphocyte function to inhibit allergen sensitization (Stefka et al., 2014). The first six months of life was suggested as a critical developmental window of the immune system (Prescott et al., 1999; Rautava et al., 2004; Van der Velden et al., 2001). During this period, colonization of maternally disturbed microbiota and transmission of maternally altered cytokines (such as Immunoglobulin E) may occur in the fetus (Msallam et al., 2020). These interactions may have long-term effects on children's immune systems and eventually contribute to their allergic diseases (Fouhy et al., 2019; Fujimura et al., 2016).

4.3. Mental disorders

Positive associations were obtained from biomonitoring-based epidemiological studies on antibiotic exposure with mental disorders (Liu et al., 2021; Zhang et al., 2021a). Mental disorders were evaluated by the Strengths and Difficulties Questionnaire or Mini-Mental State Examination (Liu et al., 2021; Zhang et al., 2021a). Specifically, elderly individuals exposed to more azithromycin (OR [95% CI]: 1.81 [1.09, 3.00], $p < 0.05$) and sulfaclozine (OR [95% CI]: 1.54 [1.05, 2.28], $p < 0.05$) showed increased risks of depression (Liu et al., 2021). Higher concentrations of ciprofloxacin in children were related to an increased risk of mental disorders (tertile 2 vs. 1, OR [95% CI]: 4.06 [1.69, 9.78], $p < 0.05$; tertile 3 vs. 1, OR [95% CI]: 6.04 [2.59, 14.1], $p < 0.05$) (Zhang et al., 2021a). Animal studies have supported the mechanism by which brain functions can be disturbed by antibiotic-induced dysbiosis of the gut microbiota through the gut-brain axis (Cryan et al., 2019), with subsequent mental disorders such as depression, anxiety, and cognitive disorders (Desbonnet et al., 2014; Dinan and Cryan, 2017; Zhang et al., 2017). For example, perinatal exposure to sulfamonomethoxine is related to gut-brain axis dysfunction and depression behavior in male mouse offspring through upregulating the hippocampal mammalian target of rapamycin (Zhang et al., 2017). After short-term exposure to azithromycin, the abundance of gut microbiota and diversity of Shannon in the feces of children were reduced by 23% and 13%, respectively (Wei et al., 2018). Azithromycin-induced adverse effects on brain functions of children and the elderly have been reported clinically (Cone et al., 2003; Schiff et al., 2010). In addition, ciprofloxacin can disturb the production of SCFAs in plasma metabolism (Liu et al., 2018). SCFAs play a role in regulating the gut-brain axis and may affect brain functions by modulating neurotrophin levels, influencing neurotransmission, and strengthening the blood-brain barrier (Liu et al., 2018; Thotsaporn et al., 2016). After exposure to ciprofloxacin for two weeks, considerably increased symptoms of depression were observed in mice (Ilgin et al., 2015).

5. Conclusions and perspectives

LC-MS/MS is most applied to simultaneously determine multiple antibiotics at trace levels. Compared to LC-MS/MS, immunoassay and electrochemical techniques exhibit weaknesses of low sensitivity and poor specificity and strengths of low cost, simplicity, and environmental friendliness. These techniques are suitable for high-amount analysis in clinical practice. For sample pretreatment in urine samples, sample pH needs to be considered to prevent the ionization and degradation of some antibiotics. SPE with an HLB adsorbent is most commonly applied to clean up impurities and enrich target antibiotics. Other time-saving (e.g., HPLC-integrated sample preparation technique) or environmentally friendly methods (e.g., MIP-HFM method) have also been developed, with shortcomings of limited target analytes or unsatisfactory recoveries. Generally, based on trace and simultaneous analysis, further accessible, automated, and environmentally friendly trends are prospected to determine antibiotics in urine samples.

Based on urinary biomonitoring, concurrent exposure to multiple antibiotics is observed in humans. A total of 54 antibiotics have been identified in human urine. Fifteen major antibiotics with relatively higher detection frequencies and concentrations include sulfaclozine, trimethoprim, erythromycin, azithromycin, penicillin V, amoxicillin, oxytetracycline, chlortetracycline, tetracycline, doxycycline, ofloxacin, enrofloxacin, ciprofloxacin, norfloxacin, and florfenicol. In recent years, a decline in urinary fluoroquinolones has been observed in pregnant women. Children also present lower urinary fluoroquinolones than adults. Fluoroquinolones may have adverse effects (e.g., arthropathy) on immature animals and are more prudently administered by pregnant women and children. Other antibiotics in children are relatively higher than in pregnant women and adults. This may be explained by the increased metabolic rates and mobility, as well as and weak children's immunity. Dietary intake of animal-originated food is an essential pathway of daily human exposure to antibiotics. Ciprofloxacin, azithromycin, and amoxicillin are three predominant antibiotics with relatively higher HQs. HQs of >1 are also found in 0–1.5% of investigated populations for florfenicol, which is merely used as a veterinary antibiotic. The human health risk of possibly high-dose and long-term exposure to florfenicol deserves more attention. Pregnant women present lower HQs of ciprofloxacin, azithromycin, amoxicillin, and florfenicol than children and adults. Notably, there are several uncertainties in the health risk assessment of antibiotics. First, parent-metabolite relationships of some antibiotics (e.g., enrofloxacin-ciprofloxacin) are not considered in current studies, and thus, the exposure doses of the metabolites might be overestimated. Second, urinary excretion proportions of antibiotics at high-dose exposure are applied due to the lack of pharmacokinetic data at low-dose exposure. For some antibiotics, such as sulfachlorpyridazine, enrofloxacin, tylosin, and florfenicol, urinary excretion proportions from pigs are also used due to the lack of human pharmacokinetic data. Third, one spot urine samples were collected in most of the current studies. However, the excreted antibiotics may exhibit temporal variations due to their short half-lives, and the repeated sampling over a long period is needed. These factors may lead to uncertainties in the assessments for EDIs of antibiotics. Furthermore, current studies on internal antibiotic exposure mainly focused on Chinese individuals. More information in other countries (with large consumption of antibiotics) needs to be provided in future research.

Urinary antibiotics (even at trace levels of ng/mL) exhibit correlations with the risk of obesity, allergic diseases, and mental disorders. These findings provide possible biomarkers for these diseases, which still need to be verified by in-depth research. A necessity to further study the pathogenic mechanism of long-term, low-dose, and joint antibiotic exposure is also suggested. Meanwhile, longitudinal studies related with different developmental windows are required to observe long-term effects after antibiotic exposure.

CRediT authorship contribution statement

Yu Hu: Investigation and Writing - original draft. **Qingqing Zhu:** Writing - review & editing. **Yawei Wang:** Writing - review & editing. **Chunyang Liao:** Writing - review & editing, Supervision, and Funding acquisition. **Guibin Jiang:** Resources and Supervision. All authors contributed extensively to writing and revising the paper.

Declaration of competing interest

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.154775.

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