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Review of Antibiotic Resistance in China and its Environment

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Abstract

Antibiotic resistance is a global health crisis linked to increased, and often unrestricted, antibiotic use in humans and animals. As one of the world's largest producers and consumers of antibiotics, China is witness to some of the most acute symptoms of this crisis. Antibiotics and antibiotic resistance genes (ARGs) are widely distributed in surface water, sewage treatment plant effluent, soils and animal wastes. The emergence and increased prevalence of ARGs in the clinic/hospitals, especially carbapenem-resistant gram negative bacteria, has raised the concern of public health officials. It is important to understand the current state of antibiotic use in China and its relationship to ARG prevalence and diversity in the environment. Here we review these relationships and their relevance to antimicrobial resistance (AMR) trends witnessed in the clinical setting. This review highlights the issues of enrichment and dissemination of ARGs in the environment, and also future needs in mitigating the spread of antibiotic resistance in the environment, particularly under the 'planetary health' perspective, i.e., the systems that sustain or threaten human health.

Keywords: Antibiotics; Antibiotic resistance gene; Environment; Clinical setting; Planetary health

1. Introduction

Antibiotics are used for treatment or prevention of bacterial infection. Nearly all classes of antibiotic are based on the structure of antibiotics naturally found in environmental microorganisms; with many of the antibiotics in widespread use being synthetic derivatives of these natural structures (Demain 1999). Ever since penicillin was introduced into medical therapy in 1942, hundreds of other antibiotics have been isolated or synthesized for the treatment of human and animal infections. Antibiotics played a significant role in the increase in life expectancy witnessed in the second-half of the 20th century. Antibiotics transformed modern agriculture and livestock industries, the latter of which used antibiotics for prophylaxis, meta-prophylaxis, treatment for infection, and as a growth promoter to enhance feed efficiency in healthy livestock (Sarmah et al. 2006).

The overuse and misuse of antibiotics stimulated the more rapid emergence of antibiotic-resistant bacteria (ARB) and antibiotic resistant genes (ARGs), reducing their therapeutic potential against human and animal pathogens (Wright 2010). World Health Organization characterises antimicrobial resistance as a global public health crisis that must be managed with the utmost urgency (WHO 2015).

The problem is particularly acute in China because of its antibiotic prescribing practices, strong incentives for overprescribing, and the widespread use and misuse of sub-therapeutic doses of antibiotics in agriculture (Yezli and Li 2012). Multidrug resistance (MDR) bacteria, or 'superbugs', which are resistant to several different antibiotics have been reported in China and antibiotic-resistant bacteria (ARB) previously reported in China are now being seen to cause infections in other countries. For example, Liu et al reported the emergence of the first plasmid-mediated colistin resistance mechanism, *mcr-1*, in *Escherichia coli* from pigs, pork products, and humans in 2015. At the time, it stated the belief that the gene is "currently confined to China." However, since then, scientists have found the MCR-1 gene in countries all over the globe; additional colistin-resistance genes—MCR-2 and MCR-3—and

variants of those genes have also emerged and spread. The global AMR crisis has only recently been met by a substantial increase in the number of studies focusing on antibiotic resistance in the environment, aiming towards bridging the many knowledge gaps (Singer et al. 2016). Here we aim to consolidate this recently-acquired knowledge base on antibiotics and ARGs in the Chinese environment with the intention of informing evidence-based strategies towards mitigating AMR in the environment, a poorly acknowledged goal at the national and international level (Singer 2017).

2. Use and abuse of antibiotics in China

China is one of the world's largest producers and consumers of antibiotics, widely used for disease treatment in humans and livestocks, and as prophylaxis and growth promoters for the latter. A recent study showed that 92,700 tonnes of antibiotic (inclusive of 36 antibiotics), were consumed in China in 2013; 48% of which were consumed by humans, with the remaining by animals (Zhang et al. 2015c). Approximately 46% of the antibiotics were ultimately released into rivers through sewage effluent with the remaining to land through manure and sludge land spreading (Zhang et al. 2015c). These usage estimates exceed usage in the UK and much of northern Europe (normalised by the defined daily dose), by a factor of 6.

Approximately 50% of hospital outpatients in China are reported to use antibiotics. Of these outpatients prescribed antibiotics, 74.0% were prescribed one antibiotic, and 25.3% prescribed two or more antibiotics (Yin et al. 2013). The prescription of antibiotics accounts for around half of all drugs prescribed by hospitals, compared with just 10 percent in hospitals in high-income countries (RFA 2015). Cephalexin, amoxicillin, ofloxacin, tetracycline, and norfloxacin were the top 5 antibiotics used for human in 2013 in China (Zhang et al. 2015c). The excessive use of antibiotics is particularly more problematic in lower-level hospitals and less developed western China (Yin et al. 2013). About 75% of patients with seasonal influenza are estimated to be prescribed antibiotics, and the rate of antibiotic

prescription for inpatients is 80% (Li 2014) which is much higher than the World Health Organization recommended maximum level of 30%. This over prescription may be because the drug sales occupy a significant part of hospital revenues (Currie et al. 2014). Antibiotic prescription in a total of 48 primary health care facilities in China showed that the most frequently prescribed antibiotics were cephalosporins (28%), fluoroquinolones (15.7%), penicillins (13.9%), imidazoles (12.6%) and macrolides (7.3%)(Wang et al. 2014c). The prescribing patterns of antibiotics are not effectively controlled in China until the human medical system reform initiated by the Ministry of Health of China in 2011 (Bao et al. 2015). Xiao et al. reported that the percentage of hospitalised patients who were prescribed antibiotics fell by 10% in just one year, from 68% in 2011 to 58% by the end of 2012. It also dropped10% in outpatients in the same time period, from 25% to 15% (Xiao and Li 2013). Sun et al reported a significant reduction in overall inpatient antibiotic consumption in Chinese public general tertiary hospitals after the interventions (Sun et al. 2015).

Modern animal husbandry often involves large and densely managed herds—optimal conditions for the spread of infectious diseases. Antibiotic are routinely used in an effort to manage this disease risk (Holman and Chenier 2015). Livestock antibiotic use (52% of total antibiotic use) has been estimated at marginally higher than human use (48%), as a percentage of antibiotic use in 2013 (subset of 36 highest use antibiotics) (Zhang et al. 2015c). Consumption of veterinary antibiotics increased from 46% in 2007 to 52% in 2013, totaling approximately 84,240 tonnes. Amoxicillin, florfenicol, lincomycin, penicillin and enrofloxacin are the majority veterinary antibiotics consumed at a rate >4000 tonnes in China (Van Boeckel et al. 2015; Zhang et al. 2015c). It has been estimated that the share of global antibiotic consumption in food animal production for China will increase from 23% in 2010 to 30% in 2030 (Van Boeckel et al. 2015).

For therapeutic usage, animals are typically treated with antibiotics for a period of 3 to 7 days and then treated for another 3 or 4 days at prophylactic dosages (Wei and Zhong 2011). Nontherapeutic use of antibiotics is the major contributor to usage (Collignon and Voss 2015). Sub-therapeutic, in-feed antibiotics have been

investigated for livestock production since the late-1940's, only seven years after the mass production of penicillin (Stokstad and Jukes 1950) and four years after the discovery of chlortetracycline (Moore et al. 1946). Its use as a growth promoter increased year on year, despite the recognition that such a practice selected for resistance in the animals, farmers and veterinarians (Dibner and Richards 2005; Marshall and Levy 2011).

The use of antibiotics in animal feeds has been regulated since 1989 in China (Wang et al. 2008). Antibiotics may be added to feed at concentrations between 2.5 and 125 mg/kg of feed to improve growth for an undefined duration (weeks to months), depending on the type and size of the animal and the type of antibiotic (Marshall and Levy 2011). Therefore, the nontherapeutic use of antibiotics might have played a larger role in the evolution and dissemination of multiple antibiotic resistance than did therapeutic use since it usually involved long-term, continuous exposure in a very large number of animals (McEwen and Fedorka-Cray 2002).

In general, antibiotics are poorly metabolised by humans and animals and as such are excreted as the active parent chemical in the faeces and urine, entering the environment through wastewater and manure. Antibiotic metabolites can also be bioactive, and even if they are not bioactive, they can often be transformed back into the parent compound or another bioactive substance. For example, the composition of excreted sulfonamides (SAs) may contain approximately 9-30% parent compounds, and between 5% and 60% acetylated conjugates. The metabolites, *N*4-acetylsulfapyridine and *N*4-acetylsulfamethazine can be converted back to the parent form (Bonvin et al. 2013; Garcia-Galan et al. 2012). Therefore, it is critical to know about the environmental fate of antibiotics and their metabolites, which invariably contribute to the increased prevalence and diversity of antibiotic resistance in China.

3. Antibiotics residues in the environment

Antibiotics enter into the environment via multiple pathways that include effluents from the disposal of human waste, waste from agricultural food animal

production and aquaculture, direct application to some plants, industrial effluents from pharmaceutical production, and agricultural run-off.

3.1 Antibiotics in sewage treatment plants (STPs)

Many studies have reported the detection of antibiotics in influent and effluent of STPs in China (Chang et al. 2008; Chang et al. 2010; Gao et al. 2012; Gulkowska et al. 2008; Hou et al. 2016; Hu et al. 2012; Jia et al. 2012; Leung et al. 2012; Li and Zhang 2011; Li et al. 2009; Li et al. 2013a; Peng et al. 2006; Shao et al. 2009; Sun et al. 2016; Wang et al. 2014a; Xu et al. 2015; Xu et al. 2007; Yan et al. 2014; Zhang et al. 2013; Zhang et al. 2015b; Zhou et al. 2013b). The frequently reported compounds include sulfadiazine, sulfamerazine, sulfamethazine, sulfamethoxazole, trimethoprim, tetracycline, oxytetracycline, ciprofloxacin, enrofloxacin, norfloxacin, ofloxacin, roxithromycin, and erythromycin-H_2O (Figure S1). The concentrations of these antibiotics in both influents and effluents ranged from a few ng/L to tens of μg/L, reflecting incomplete removal in conventional STPs. Antibiotic removal efficiencies varied among different compounds and STPs. However, the reasons for the difference in removal efficiencies among these STPs remains largely unknown. Different physicochemical properties and daily loading of antibiotics, the types of treatment processes and operational conditions of individual STPs, even the rainwater input, can all affect the removal efficiencies. For example, cephalexin, as one of the most human consumed antibiotics, the removal efficiencies ranged between 9 and 100% (Gulkowska et al. 2008; Li and Zhang 2011; Li et al. 2009) in STPs of Hongkong. β-lactams, like cephalexin and ampicillin, are easy to remove due to the ready hydrolysis of the β-lactam ring and the ubiquity of β-lactamases in wastewater. Despite the labile nature of some antibiotics, they can still be recovered from wastewater, suggestive of their pseudopersistence (i.e., the rate of loss closely matches the rate it enters the wastestream) (Leung et al. 2012). Another three highly human consumed antibiotics, ofloxacin, norfloxacin and tetracycline were also widely detected in STPs of China. The highest concentration of ofloxacin, norfloxacin and tetracycline were found in the STP of Hongkong (7900 ng/L, 5430 ng/L and 1510 ng/L in influent and 7780 ng/L, 3700 ng/L and 1420 ng/L in effluent, respectively)

(Leung et al. 2012). Although their removal efficiencies vary among STPs, the relatively higher removal rates of fluoroquinolones and tetracyclines (>70%) may because these more hydrophobic antibiotics experience substantial removal from wastewater as a result of partitioning to the solid (sludge) phase (Gulkowska et al. 2008; Li and Zhang 2011; Li et al. 2009; Peng et al. 2006; Xu et al. 2007). For many sulfonamides, sorption to sludge was found to be negligible, therefore removal by sorption to sludge is unlikely to be a primary removal mechanism for these compounds. Limited removal of macrolides, like erythromycin-H_2O, were reported in several STPs of China (Gulkowska et al. 2008; Leung et al. 2012; Li and Zhang 2011). It may because macrolides are mainly excreted in bile to faeces and the faecal materials are digested during biological treatment, consequently increasing the dissolved mass loads in effluent (Leung et al. 2012). The highest concentration of ofloxacin (7900 ng/L) and norfloxacin (5430 ng/L) detected in influent of STP in Hongkong was much higher than those reported in the USA (1000 ng/L) (Brown et al. 2006), Finland (960 ng/L) (Vieno et al. 2007) and Italy (980 ng/L) (Verlicchi et al. 2014). While the highest concentration of erythromycin-H_2O (4740 ng/L) was relatively lower than the maximum concentration detected in influent from United Kingdom (10025 ng/L) (Kasprzyk-Hordern et al. 2009). Sulfamethoxazole (SMX) is one of the most frequently detected antibiotic compound in STP. The mean concentration of SMX in STP influent (650 ng/L) in China was higher than that reported in Korea (120 ng/L) (Behera et al. 2011), but comparable to that in Germany (515 ng/L) (Rossmann et al. 2014) (Table S1).

3.2 Antibiotics in receiving aquatic environment

There exist large differences in antibiotic emission from both human and agricultural sources within each of the river basins of China (Zhang et al. 2015c). Pearl River basin, located in south China, has the highest emission densities, followed by the Haihe River basin, located in north China, and Taihu Lake and Qiantang River, located in east China. The megacities of Guangzhou and Shenzhen are located in Pearl River basin, while Beijing is located in the Haihe River basin. The east and west

China basins are separated by the "Hu Huanyong line" (i.e., a line that runs from Tengchong in the south to Aihui in the north), where the basins to the east of the line have 94% of the population of China, but only 43% of the land area. In general, the average emission densities of antibiotics followed the general population trends set by the "Hu Huanyong" line, with six times higher emission in the east and south, than in the west. This spatial trend is consistent with the antibiotic monitoring results for the surface water in China. Most studies reported the occurrence of antibiotics in the fast developing areas of China, such as Pearl River basin, however, little information is available in western China (Zhao et al. 2016).

A wide range of human and animal antibiotics have been detected in surface water and sediments of major Chinese rivers (Chen et al. 2013a; Chen and Zhou 2014; Jia et al. 2012; Li et al. 2014a; Luo et al. 2011; Tong et al. 2014; Xu et al. 2013; Xue et al. 2013; Yan et al. 2013; Yang et al. 2010; Yang et al. 2011; Zhang et al. 2012; Zheng et al. 2011; Zhou et al. 2011; Zhu et al. 2013a). The concentrations of antibiotics in surface water were found to range from below the detection limit (i.e.,<10's ng/L) to the low μg/L (Figure S2). Among them, sulfamethoxazole, oxytetracycline, ciprofloxacin, norfloxacin, ofloxacin, clarithromycin, and erythromycin-H_2O were frequently detected in the aqueous phase of rivers with concentrations up to a few μg/L. A wide range of antibiotics at the upper end of environmental concentrations are typical of rivers routinely receiving urban wastewater discharge and animal waste. The concentrations of antibiotics in sediments ranged from below detection limits (i.e.,<10's ng/g) to the low μg/g (Figure S3). Zhou et al. reported relatively low concentrations for sulfonamides (maximum 22 ng/g) and macrolides (maximum 67 ng/g), but high concentrations for fluoroquinolones (maximum 5770 ng/g) and tetracyclines (maximum 653 ng/g) in the sediments of the Yellow River, Hai River and Liao River in northern China (Zhou et al. 2011). Yang et al. reported similar results in the Pearl River in the southern China (Yang et al. 2010). Antibiotics, like fluoroquinolones and tetracyclines, strongly adsorb to suspended particles and sediment (Kümmerer 2009), indicating sediment could be a reservoir of antibiotics in the environment. Extremely high concentrations

of antibiotics were found in Haihe River, especially for sulfonamides, the highest concentration of sulfachloropyridazine and sulfamethoxazole in tributaries of Haihe River was 37000 ng/L and 3900 ng/L, respectively (Luo et al. 2011). The highest concentrations of tetracyclines (oxytetracycline and tetracycline) and macrolides (erythromycin-H_2O and roxithromycin) were all above 1500 ng/L level in tributaries of Haihe River (Luo et al. 2011). Relatively high concentrations were also found in the Pearl River (Yang et al. 2011), indicating the effects of a high population density. Notwithstanding the high concentrations of antibiotics in the Haihe River, environmental concentrations of antibiotics in surface waters in China are comparable to or slightly higher than those reported in USA (Arikan et al. 2008; Kim and Carlson 2007), France (Tuc Dinh et al. 2011), Germany (Christian et al. 2003), Finland (Vieno et al. 2007), Italy (Verlicchi et al. 2014) and Korea (Kim et al. 2007) (Table S1).

3.3 Antibiotics in livestock farm wastes

The great boom in the number of concentrated animal feeding operations (CAFOs) for swine, poultry, and cattle production has driven demand for antibiotics. Antibiotics use in animal husbandry ends up in the manure, due to the combination of poor absorption and metabolism of the antibiotic in vivo. The total usage of antibiotics for animals was 84240 tonnes in China (Zhang et al. 2015c), with a large fraction of this held within the manure, which exceeds 2000 million tonnes for nearly all animals in 2011 in China (Zhu and Ma 2014). Hence, livestock manure is a major source of antibiotics, which enters through their application as fertilisers and soil enhancers in agricultural fields and as diffuse pollution in stormwater runoff from manure-amended fields.

Multiple classes of antibiotics have been recovered in the manure of swine, chicken and cattle (Hou et al. 2015; Hu et al. 2008b; Hu et al. 2010; Huang et al. 2013b; Ji et al. 2012; Li et al. 2013c; Li et al. 2012; Pan et al. 2011; Qiao et al. 2012; Zhang et al. 2015a; Zhao et al. 2010; Zhou et al. 2013a; Zhou et al. 2012; Zhou et al. 2013c). Fluoroquinolones (FQ), sulfonamides (SA) and tetracyclines (TC) were the most frequently detected antibiotics and exhibited a broad concentration range (Figure

S4). Zhao et al. (2010), recorded the maximum concentration of enrofloxacin in chicken litter ever reported in China, 1421 mg/kg. The authors also reported the highest ever recorded concentration of norfloxacin in chicken manure, 225 mg/kg (Zhao et al. 2010). Notably, the authors reported no appreciable sulfonamide antibiotic concentrations (less than 10 mg/kg) in any animal dung. Zhang (2015), reported oxytetracycline and chlortetracycline were the two most frequently recovered antibiotics in animal manures and the highest concentration was 417 mg/kg in chicken manure (Zhang et al. 2015a) and 764 mg/kg in swine manure (Pan et al. 2011), respectively. In general, tetracyclines and fluoroquinolones were detected with higher occurrence and higher concentrations than SAs; likely a result of the recalcitrance and high partitioning of TC and FQ in manure. The highest concentrations of veterinary antibiotics (enrofloxacin 1421 mg/kg and chlortetracycline 764 mg/kg) exceeded those reported from Turkey (enrofloxacin 0.06 mg/kg and chlortetracycline 0.38mg/kg) (Karci and Balcioglu 2009), Austria (enrofloxacin 8.3 mg/kg and chlortetracycline 46 mg/kg)(Martinez-Carballo et al. 2007), Germany (chlortetracycline 50.8 mg/kg)(Holzel et al. 2010) and Canada (chlortetracycline 0.4 mg/kg)(Aust et al. 2008) (Table S1).

3.4 Antibiotics in soil

Antibiotics can be introduced into soil through irrigation with reclaimed water, sludge and manure land application to crops or landfill, and the use of livestock wastes as soil fertilisers. The concentration of antibiotics varies greatly across soils of different origins, typically in the mid- to high- μg antibiotic per kg soil (Chen et al. 2014; Hou et al. 2015; Hu et al. 2010; Huang et al. 2013b; Ji et al. 2012; Li et al. 2014c; Qiao et al. 2012; Wang et al. 2014b; Wu et al. 2013; Wu et al. 2010; Zhou et al. 2013a; Zhou et al. 2012; Zhou et al. 2013c) (Figure S5). Higher concentrations of antibiotics were detected in soils adjacent to feedlots. For example, the maximum chlortetracycline concentration (12.9 mg/kg) was found in soil near the effluent discharge from a swine farm (Zhou et al. 2013a). Oxytetracycline was found with the highest concentration of 4.24 mg/kg in an agricultural field adjacent to a swine farm

(Ji et al. 2012). Sulfadiazine and sulfamethoxazole from sulfonamide (SA) groups were also found with the highest concentration of 2.45 mg/kg and 2.41mg/kg in soils adjacent to a poultry farm (Ji et al. 2012). Antibiotic residues in organic vegetable production are of particular concern since 'organic' sources of fertiliser (e.g., manure) is often preferred over chemical fertilisers for building soil organic matter (Xie et al. 2016). Higher residues of FQs have been reported in an important vegetable-growing region in Shandong province, China, with the maximum ciprofloxacin and ofloxacin concentration of 0.652 mg/kg (Li et al. 2013b) and 0.288 mg/kg (Li et al. 2014c), respectively. Accumulations of antibiotics were also found in soils irrigated with either reclaimed water (Fang et al. 2015) or wastewater (Li et al. 2014c), but the concentrations were lower as compared to soils sampled around feedlots. The concentration of oxytetracycline in Chinese soils were similar to those in Turkey (20-510 ng/g) (Karci and Balcioglu 2009), but lower than those in UK (322-1691 ng/g) (Kay et al. 2004). Concentrations of sulfonamide in Chinese soils were comparable with many other countries (Aust et al. 2008; Garcia-Galan et al. 2013; Ok et al. 2011; Shelver et al. 2010; Watanabe et al. 2010) (Table S1).

4. Antibiotic resistance in the environment and its potential health impacts

ARGs are a natural component of all environments (e.g., soil, water, microbiomes). However, their increased prevalence as a result of human activities has led to their characterisation as an emerging environmental contaminant (Pruden et al. 2006). The ARG burden in the environment has serious implications for human health owing to the potential transfer of ARGs from environmental bacteria to human pathogens, thereby impairing the efficacy of antibiotic treatment and compromising public health. The frequent detected ARGs and their abundance levels in different environmental media of China are listed in Table S2.

4.1 ARGs in sewage treatment plants (STPs)

STPs contribute to a reduction in the load of antibiotics and pathogenic

microorganisms into the receiving water body, however, this might not translate into a significant reduction in overall risk, as the ratio of ARGs to total bacteria in STP effluent can increase during treatment as could the frequency of recovering multi-drug resistance (Czekalski et al. 2012). STPs are a highly favourable environment for the selection of ARB or the horizontal gene transfer and propagation of ARGs because of high microbial density, high nutrient content and sub-inhibitory concentrations of antibiotics, biocides and metals.

Based on culture-dependent methods, 109 lactose-fermenting *Enterobacteriaceae* (LFE) strains, important human pathogens, were isolated from the activated sludge of the STP in Hong Kong and tetracycline-resistant LFE accounted for 32% of the total 109 LFE strains (Zhang et al. 2009a). Huang et al. investigated the antibiotic tolerance of total heterotrophic bacteria and the concentration distribution of bacterial resistance to six different antibiotics in the secondary effluent of the STP in Beijing. The average percentages of chloramphenicol-, penicillin-, cephalothin-, ampicillin-, rifampicin- tetracycline-resistant heterotrophic bacteria in the effluents were: 69%, 63%, 55%, 47%, 11% and 2.6% respectively. Above six ARB species were widely distributed in four types of enterobacteria (*Aeromonas, Enterobacter, Escherichia or Shigella,* and *Klebsiella*) from the secondary effluent (Huang et al. 2012).

DNA-based techniques, like PCR and quantitative real-time PCR, are increasingly used to detect and quantify resistance genes in environmental samples in addition to culture-based methods. Tetracycline (*tet*) and sulfonamide (*sul*) ARGs are commonly detected because of the widespread use of the corresponding antibiotics and their persistence in the environment. Mobile elements, such as integrons and transposons, were also included in many studies because of their significant contribution to the horizontal transfer of ARGs among bacterial species. The integrase gene (*intI*1), belonging to class 1 integrons, was proposed to serve as a proxy of pollution for resistant bacteria and other anthropogenic pollutants because of its rapid response to diverse environmental pressures (Gillings et al. 2015). Among the tetracycline resistance genes, three efflux pump genes (*tet*A, *tet*C and *tet*G), four ribosomal protection proteins gene (*tet*M, *tet*O, *tet*Q and *tet*W) and one enzymatic

modification gene (*tet*X) seem to be the most common *tet* genes in the STPs of China (Chen and Zhang 2013a; Du et al. 2014; Wen et al. 2016; Zhang et al. 2009a). Sulfonamide-resistance genes: *su*lI and *sul*II were detected at high frequency across China STPs. The ARG concentrations in STPs varied significantly across a range of STPs; normalized by sample volumes, the concentrations of *tet* genes ranged from 10^2 to 10^{10} copies/mL (Chen and Zhang 2013a; Du et al. 2014; Li et al. 2016c; Pu et al. 2009; Wen et al. 2016; Zhang et al. 2009a). The maximum concentration of *tet* gene in influent was found in a STP in Zhejiang province, in the east of China, $10^{11.17}$ copies/mL (Li et al. 2016c). The concentrations of ARGs in effluent samples (from 10^1 to 10^7 copies/mL) can decrease by 0.3 to 3 orders of magnitude (Chen and Zhang 2013a; Du et al. 2014; Li et al. 2016c; Mao et al. 2015; Pu et al. 2009; Wen et al. 2016; Zhang et al. 2009a). Compared to influent and effluent samples, sludge samples had higher ARG abundance (from 10^7 to 10^{11} copies/g) and diversity (Chen and Zhang 2013a; Du et al. 2014; Li et al. 2016c; Mao et al. 2015; Pu et al. 2009; Wen et al. 2016; Zhang et al. 2009a; Zhang and Zhang 2011). *Tet*A and *tet*C, with a broad host range, were often detected with high concentrations (Huang et al. 2015a; Zhang et al. 2009a). Horizontal co-transfer of *tet*A and class I integrons have been observed among some species like *Aeromonas* in fish farms (Schmidt et al. 2001). A positive correlation between efflux pump gene (*tet*A, *tet*G) and *intI*1 was also observed in some STPs, indicating the role of class I integrons in efflux pump genes (Chen and Zhang 2013b; Huang et al. 2015b). In general, the abundance of *sul* was higher than that of *tet*, likely because *sul*I is often associated with class I integrons. Based on the normalized concentration of ARGs (relative to the total 16S rRNA gene copy number), higher total loads of ARGs was observed in pharmaceutical STPs (10^{-4}-10^0 copies/copy 16SrRNA gene) than in municipal STPs (10^{-9}-10^{-1} copies/copy 16SrRNA gene) (Huang et al. 2015a; Li et al. 2016a; Liu et al. 2012; Xu et al. 2015; Zhai et al. 2016).

In addition to the *tet* and *sul* genes, the occurrence of other ARGs including quinolone (*qnr*), macrolide resistance gene (*erm*) and multidrug-resistant New Delhi metallo-β-lactamase genes (NDM-1) have also been reported in the effluent and

dewatered waste sludge in STPs of northern China (Luo et al. 2014; Mao et al. 2015). In recent years, high-throughput sequencing-based metagenomic analysis has been applied to simultaneously investigate the broad-spectrum profiles and fate of ARGs in STPs, yielding a significantly higher diversity of ARGs than could be demonstrated by qPCR alone. For example, a total of 271 ARGs subtypes belonging to 18 ARGs types were identified in a typical full-scale STP in Hong Kong (Yang et al. 2014). Influent had the highest ARGs abundance, followed by effluent, anaerobic digestion sludge and activated sludge (Yang et al. 2014). Seasonal and geographical distribution of antibiotic resistome from Chinese urban sewage were also characterised based on metagenomic analysis. The demographic "Hu Huanyong line" separated the regional ARG burden into two main regions, suggesting human activities might be the major driver of antibiotic resistance burden distribution (Su et al. 2017).

Extensive studies have illustrated the change in abundance of typical ARGs and intI1 in STPs of China (Chen and Zhang 2013a; Du et al. 2014; Ju et al. 2016; Li et al. 2016c; Mao et al. 2015; Pu et al. 2009; Wen et al. 2016). The removal efficiency varied among different ARGs and different treatment processes. For example, selected *tet* genes were significantly reduced by almost 2 to 3 orders of magnitude (Chen and Zhang 2013b) which exceeds the removal efficiency observed for six ARGs (0.3-2.7) (Wen et al. 2016). However, *tet* genes (1.2-2.7) were found to be more readily lost in STP treatment than *sul* genes (<1) (Wen et al. 2016). Measuring removal of ARGs from the STP influent by sampling the effluent is complicated by the fact that ARGs accumulate in the sludge which has another disposal route into the environment (Zhang and Zhang 2011). It has been reported that the total load of ARGs discharged through dewatered sludge was 7 to 308 fold higher than that in the raw influents and 16 to 638 fold higher than that in the final effluents (Wang et al. 2015). ARGs have also been shown to proliferate through biological treatment stages (Du et al. 2014; Luo et al. 2014; Pu et al. 2009; Zhang et al. 2009a), such as conventional activated sludge, due to microbial growth. Therefore, more advanced technologies such as Advanced Oxidation Processes (AOPs) which have been recommended to improve the removal of ARGs in STP (Chen and Zhang 2013a;

Zhang et al. 2016b).

4.2 ARGs in receiving aquatic environment

Discharges from STPs, antibiotic production plants, livestock farms and aquaculture contribute to the ARBs and ARGs reported in aquatic environment. However, it is largely unknown the extent to which each one contributes to the ARGs/ARBs recovered in any particular location (Singer et al. 2016)

Many studies focused on antibiotic resistance within *Escherichia coli* in the aquatic environment owing to its relevance to environmental standards and human health. For example, *E. coli* resistant to one or more antibiotics among nine antibiotics was screened from Wenyu River Basin in Beijing, China, with mean frequency of 48.7±8.7% of 388 isolates in summer and 47±6% of 236 isolates in winter. The highest proportion of resistance appeared for sulfonamides, tetracycline, and ampicillin (Hu et al. 2008a). *E. coli* isolates from several rivers in Southern China, including Minjiang River, (Chen et al. 2011a) Dongjiang River (Su et al. 2012) and Jiulongjiang River (Ou et al. 2015), were screened for susceptibility to a range of antibiotics, and MDR. MDR was also found in strains of *E. coli* isolated from Taihu Lake based on culture-dependent approaches (Zhang et al. 2015e). Through a combination of culture-dependent approaches and qualitative PCR methods, tetracycline, sulfonamide, fluoroquinolone, ampicillin, extended-spectrum beta-lactamase-producing bacteria, chloramphenicol-resistant bacteria and associated ARGs were detected in fresh and marine water in China (Dang et al. 2008; Li et al. 2010; Sun et al. 2012; Tao et al. 2010; Zou et al. 2012), supporting the hypothesis that human activities contributed to the dispersal and maintenance of antibiotic resistance in the aquatic environment in China.

Among the detected ARGs, *tet* and *sul* are the most common resistance genes quantified by qPCR. For example, two sulfonamide ARGs (*sul*I and *sul*II) and seven tetracycline ARGs (*tet*A, *tet*C, *tet*G, *tet*X, *tet*O, *tet*Q and *tet*M) were quantified in 20 water samples collected in the Beijiang River, South China (Ling et al. 2013) The levels of *sul*I were higher than *sul*II ($p < 0.05$), with the mean values of (1.41 ± 1.12)

$\times 10^{-2}$ and $(1.58 \pm 1.71) \times 10^{-3}$ copies/16S rDNA, respectively. Among *tet* genes, *tet*C had the highest concentration, ranging from 8.30×10^{-2} to 13.20 copies/16S rDNA (Ling et al. 2013). Jiang et al. also quantified two sulfonamide ARGs (*sul*I and *sul*II), eight tetracycline ARGs (*tet*A, *tet*B, *tet*C, *tet*G, *tet*X, *tet*O, *tet*Q and *tet*M) and one β–lactam ARG (TEM) in the Huangpu River, Shanghai, China (Jiang et al. 2013). The average concentrations of ranged from 3.66×10^{1} copies/mL (*tet*B) to 1.62×10^{5} copies/mL (*sul*II). Lake water samples from the northern part of Taihu Lake contained a significant number of *tet*A (10^{4}–10^{5} copies/ml) *tet*C (10^{5} copies/ml) genes and class 1 integron (10^{3} copies/ml) (Zhang et al. 2009b). The absolute abundance of ARGs (*sul*I, *sul*II, *tet*A, *tet*B, *tet*E, *tet*W, *tet*M and *tet*Z) in the urban rivers in Beijing, China, ranged from 7.0×10^{1} to 5.9×10^{6} copies/mL in surface water, and from 4.2×10^{2} to 2.0×10^{8} copies/g in the sediment (Xu et al. 2016). A positive correlation was observed between *int*1 and *sul*I genes in many studies (Chen et al. 2015; Lin et al. 2015; Luo et al. 2010; Na et al. 2014), confirming that the class 1 integron plays an important role in the proliferation of the *sul*I gene.

As compared to water samples, sediment samples can contain higher concentrations of ARGs. For instance, Luo *et al* showed that *sul*I and *sul*II concentrations in sediments were 120 to 2000 times higher than those in water collected from the Haihe River in China (Luo et al. 2010). Similar results were also found in samples from the Northern Yellow Sea where the *sul*I and *sul*II concentrations in sediments were 10^{3} times higher than those in water, indicating sediment was an important reservoir of some ARGs (Na et al. 2014). On a volumetric basis, the Taihu lake sediments contained higher concentrations of intI1, *tet*A and *tet*C genes by four to five orders of magnitude than the overlying water samples. While copy numbers normalized to DNA mass from sediment samples were similar to those from water samples, which highlights the question of the most informative measure of ARG abundance (Zhang et al. 2009b). In this particular case, it might be that differences in the microbial diversity between the sediment and the overlying freshwater or the differential extractability of DNA from the two matrices impacts the comparisons. Tetracycline, sulfonamide, and macrolide resistance genes, as well as

integrons in the sediments were also detected at a catchment scale (Dongjiang River basin of South China), and *sul*II was the most abundant resistance gene, with the concentration of 10^8 copies/g (Su et al. 2014a).

The resistance genotype and mechanisms recovered by metagenomics in the sediments from the highly human-impacted Pearl River Estuary (PRE) and the relatively pristine deep South China Sea (SCS) were more diverse and the ARG abundance was much higher in the polluted PRE sediments than in the relatively pristine SCS sediments (Chen et al. 2013a). In comparison, the three most abundant ARGs in the PRE sediments were related to commonly used antibiotics including sulfonamides, fluoroquinolones, and aminoglycosides, indicating the significant anthropogenic impact on the dissemination of ARGs in this region (Chen et al. 2013a). Culture-based methods and high-throughput qPCR quantified, the abundance of MDR bacteria and ARGs in water samples collected from an urban stream and source of Jiulongjiang River, China. The total abundance of ARGs in urban samples (ranging from 9.72×10^{10} to 1.03×10^{11} copies/L) was over two orders of magnitude higher than that in pristine samples (7.18×10^8 copies/L) (Ouyang et al. 2015). ARGs were also profiled in sediments from 18 estuaries over 4,000 km of coastal China (Zhu et al. 2017). The high abundance and enrichment of diverse ARGs and MGEs further demonstrated the contribution of anthropogenic activities to the emergence and dissemination of ARGs (Ouyang et al. 2015; Zhu et al. 2017).

4.3 ARGs in livestock farm wastes

Livestock manure has routinely been shown to be an important reservoir of resistant bacteria (Bibbal et al. 2007; Enne et al. 2008; Schwaiger et al. 2009), antibiotic resistance genes (Binh et al. 2010; Duriez and Topp 2007; Heuer et al. 2008) and transferable plasmids carrying ARGs (Binh et al. 2008; Heuer et al. 2009). Livestock waste has been shown to be a hotspot of antibiotic residues that can affect the gut microbiota of animals and perpetuate the increased prevalence of antibiotic resistance in bacteria in manure (Langford et al. 2003; Looft et al. 2012; Witte 2000).

In China, the most frequently reported studies on animal manures are on swine, chicken and cattle which are the major food-producing animals. Resistant bacteria

isolated from these animals have largely been reported based on the culture-dependent assays. For example, Yang et al. (Yang et al. 2004) analysed the antimicrobial susceptibility of *E. coli* isolates from pig and chicken farms in Beijing and Heibei Province, China in 2000 and found that most *E. coli* isolates were resistant to multiple classes of antimicrobials. Isolates displayed resistance to tetracycline (98%), sulfamethoxazole (84%), ampicillin (79%), streptomycin (77%), and trimethoprim-sulfamethoxazole (76%). Fluoroquinolones resistance in *E. coli* ranged from 64% for levofloxacin, 79% for ciprofloxacin, and 95% for difloxacin. Meanwhile, class 1 integrons were also identified in 19% (17) of isolates from swine and 47% (42) of isolates from chickens. Similar findings have been reported for *E. coli* isolates from cattle, swine and chicken farms in Shandong Province, Eastern China, where 52% of chicken isolates, 25% of swine isolates and 30% of cattle isolates were resistant to 12, 10 and 1 antimicrobial agents, respectively. The percentage of class 1 gene cassette-positive isolates in dairy cattle, swine and chicken farm was 5%, 20% and 42%, respectively. Resistance rates of chicken farm isolates were highest (Lu et al. 2010b). In addition to the intensively farmed animals, a total of 129 *E. coli* and 84 *Enterococcus* isolates from free-ranging pigs also showed resistance to a variety of antibiotics in Tibet, indicating AMR bacteria in China is widespread (Li et al. 2014b).

Tetracycline and sulfonamide resistance genes and the class 1 integrase gene were widely reported in livestock manures. Ji et al. quantified eight ARGs (*tet*B (P), *tet*M, *tet*O, *tet*W, *su*lI, *sul*II, *sul*III and *sul*A) in manure samples from representative swine, poultry and cattle feedlots in Shanghai, China (Ji et al. 2012). All ARGs tested were detected in the collected samples except *tet*B(P). The relative abundance of sulfonamide and tetracycline resistance genes ranged from approximately 10^{-5} to 10^{-2}, and 10^{-6} to 10^{-3}, respectively. Overall, sulfonamide ARGs were more abundant than tetracycline ARGs and only a weak positive correlation was found between ARGs and their corresponding antibiotics except for *sul*II (Ji et al. 2012). Cheng et al. investigated the abundance and diversity of ten *tet* genes (*tet*A, *tet*B, *tet*C, *tet*G, *tet*L, *tet*M, *tet*O, *tet*Q, *tet*W, and *tet*X), two *sul* genes (*sul*I and *sul*II), and class 1 integron (*intI*1) in eight livestock farms in Hangzhou, eastern China. No significant difference

was found in the abundance of the *tet* and *sul* genes among similar farm types with varying scales (P >0.05). *tet*Q had the highest relative abundance in all manure samples (the average abundance was $7.12 \times 10^{-2} \pm 2.99 \times 10^{-2}$ ARG copies/16S rRNA copies), followed by three ribosomal protection protein (RPP) genes (*tet*M, *tet*W, and *tet*O), with *tet*C having the least relative abundance in their study (Cheng et al. 2013). *tet* and *sul* genes were widely reported in animal manure from many other cities of China (Cheng et al. 2016; Wang et al. 2016a; Zhang et al. 2015d). Quinolone-, macrolide-, aminoglycoside-, and MDR-genes were also analysed in concentrated livestock feedlots of China (Mu et al. 2015; Wang et al. 2016b). With the development of culture-independent methods, including high- capacity q-PCR and metagenomics, hundreds of resistance genes and multiple samples can be detected simultaneously. For example, Zhu et al. used high-capacity qPCR with 313 validated primer sets, which target 244 ARGs from all major classes of ARGs, to assess types and concentrations of ARGs at three stages from manure processing to land disposal at three large-scale swine farms. 149 unique resistance genes were detected and 63 ARGs were enriched from 192-fold (median) up to 28,000-fold (maximum) as compared with their respective antibiotic-free manure or soil control. The potential for horizontal transfer of ARGs was implicated by the enrichment of transposases—the top six alleles being enriched 189-fold (median) up to 90,000-fold in manure (Zhu et al. 2013b). Li et al. used a metagenomic approach to investigate the wide-spectrum profiles of ARGs and their co-occurrence pattern in a range of environmental samples. ARG abundances were consistent with the levels of anthropogenic impacts on these environments (Li et al. 2015).

4.4 ARGs in Soil

The soil is one of the largest and most diverse microbial habitats on earth and a natural habitat for the Actinomycete genus *Streptomyces*, whose species account for the majority of mass-produced antibiotics of natural origin. Soil microbiota represent an ancient evolutionary origin for antibiotic resistance (D'Costa et al. 2011; Forsberg et al. 2012). The transfer of environmentally-derived antibiotic resistance genes into

clinical pathogens has been a long argued aetiology of clinical ARGs (Benveniste and Davies 1973). However, the high antibiotic residues caused by human activities significantly accelerates the selection and expansion of the bacterial resistome in the soil (Graham et al. 2016).

In China, manure and/or manure-based compost application as fertiliser is one of the main pathways for antibiotics release into agricultural soils. Many studies reported a noticeable increase in ARGs diversity and abundance in soils that received long-term applications of livestock manure (Chen et al. 2016; Cheng et al. 2016; Ji et al. 2012; Mu et al. 2015; Wang et al. 2014d; Wu et al. 2010; Zhang et al. 2015d; Zhou et al. 2017). Sulfonamide and tetracycline resistance genes have frequently been detected in manure or composted manure-amended soils (Cheng et al. 2016; Ji et al. 2012; Peng et al. 2015; Wang et al. 2014d; Wu et al. 2010; Zhang et al. 2015d; Zhou et al. 2017). Extended-spectrum beta-lactamase (ESBL)-producing *E. coli* have also been detected from a pig farm in the rural regions of Tai'an, China and the ESBL-producing isolates from compost, treated soil, and manure showed high overlaps in terms of resistance phenotypes, ESBL genes, plasmid replicon type, and genomic backbone characterization, which implies the dissemination of ARB and ARGs of animal origins to soil after treated with animal manure (Gao et al. 2015). The dissipation of plasmid-mediated quinolone resistance (PMQR) genes in arable soil were slowed down by introducing (fluoro) quinolones (FQNs)-containing manure as reported in a soil microcosm experiment (Xiong et al. 2015). Based on the functional metagenomic approach, Su et al. identified multiple ARGs, with the majority of ARGs recovered from manure-amended soil. The results suggest manure amendment increases the diversity of ARGs in soil bacteria (Su et al. 2014b). Fang et al. investigated the diversity and abundance of ARGs, human pathogenic bacteria (HPB), and HPB carrying ARGs in chicken manures and greenhouse soils. The highest relative abundance was tetracycline resistance genes (manures) and multidrug resistance genes (greenhouse soils). A positive correlation was also observed between the levels of antibiotics, ARGs, HPB, and HPB carrying ARGs in manures and greenhouse soils (Fang et al. 2015).

Irrigation water quality is another important factor in stimulating ARGs in soil besides manure application. Chen et al. collected non-irrigated and wastewater-irrigated soils from five wastewater irrigation areas in Beijing and Tianjin, China and analysed the abundances of antibiotic-resistant bacteria and thirteen *tet* and three *sul* resistance genes. No significant difference in antibiotic resistance bacteria was observed between irrigated and non-irrigated soils. However, the concentrations of antibiotics and abundances of ARGs were significantly greater in irrigated soils, indicating the potential role of quality of water on the occurrence of antibiotics and resistance genes in the soils (Chen et al. 2014). Wang et al. used high-capacity qPCR to show enrichment of ARGs in urban park soils as a result of reclaimed water irrigation. A total of 147 ARGs encoding for resistance to a broad-spectrum of antibiotics were detected among all park soil samples. Aminoglycoside and beta-lactam were the two most dominant types of ARGs, and antibiotic deactivation and efflux pump were the two most dominant detoxification mechanisms. Four transposase genes were also detected and were positively correlated with ARGs and transposase abundances, indicating the potential facilitation of ARGs transfer (Wang et al. 2014b).

As antibiotics can migrate to deeper soil layers, an abundance of ARGs with increasing soil depths was observed in some studies (Tang et al. 2015). Selection for ARGs in soils amended with antibiotics free manure was previously reported, a likely result of the co-selective pressure provided by heavy metals that can also be present in manure at high levels (Lin et al. 2016). Therefore, considering the various soil types, climatic regions, and cultivation conditions of China, more field studies should be conducted to identify the relative contribution of each of the factors that influence the fate of ARGs.

Significant positive correlations between ARGs and corresponding antibiotics or a different class of antibiotics were found in multiple environmental media in China (Cheng et al. 2016; Huang et al. 2013a; Luo et al. 2010; Su et al. 2014a; Wang et al. 2016a; Wu et al. 2010; Zhu et al. 2013b). While weak or no correlation was also reported in many studies (Ji et al. 2012; Pei et al. 2006; Wang et al. 2016a; Wang et

al. 2016b). The inconsistencies in the correlations between antibiotics and ARGs can be attributed to several factors. First, ARGs and antibiotics have different environmental fate and transport mechanisms. The environmental degradation of antibiotics and the physicochemical parameters of environmental media, e.g. total organic matter, may affect the correlation analysis results (Wang et al. 2016b). ARGs could have been primarily selected by past activities and microbial populations may retain resistance genes long after their initial exposure, which could contribute to the lack of direct correlation (Hall and Colegrave 2008). Additionally, co-selection and cross-selection effects could also disrupt the correlations (Wardwell et al. 2009). Many ARGs are often found on the same plasmid or mobile genetic elements which results in the correlations found among resistance to different antibiotics. Heavy metals can exert a co-selection pressure for antibiotic resistance also because both the antibiotics and heavy metal resistance genes are commonly found to be encoded on mobile genetic elements together (Berg et al. 2010). Therefore, further studies should be carried out to illustrate the exact reasons of the correlations.

5. Antibiotic resistance in the clinical environment

Antibiotics are among the most commonly prescribed drugs used in human medicine, enabling antibiotic resistance to emerge as the serious public health crisis that it has become (Li et al. 2016b; Zeng et al. 2017). The growth rate of resistance in China is much higher than that of other countries, averaging 22% in 6 years (1994–2000) compared with 6% for the USA (1999–2002) (Zhang et al. 2006). Excessive and often unnecessary use of antibiotics is considered to be the major driving force towards increased antibiotic resistance in clinic settings. Additionally, the frequent use of broad-spectrum antibiotics and the frequent change of antibiotics can contribute to the antibiotic resistance, especially the multi-drug resistance strains (Ding et al. 2008).

In 2004, the Chinese Ministry of Health (MOH) National Antibacterial Resistance Investigation Net (Mohnarin) was established—a nationwide antimicrobial resistant surveillance network. Initially, seventeen tertiary hospitals located in 15

different cities throughout China participated in the network (Xiao et al. 2008). Mohnarin has gradually expanded to more than one thousand member hospitals and in 2014, the network became the China Antimicrobial Resistance Surveillance System (CARSS). To date, CARSS remains the only government-leading surveillance network in China and it includes 1412 member hospitals from 31 provincial-level administrative units, representing the widest coverage in China. In the CARSS 2015 report, it demonstrated the presence of severe bacterial resistance in China. A total of 2,400,786 strains of culturable bacteria in samples (sputum, blood, urine, stool, etc.) from outpatients and inpatients were detected in the surveillance program from October 2014 to September 2015, including 695,066 Gram-positive bacteria (28.9%) and 1,705,720 Gram-negative bacteria (71.1%). The five most frequently detected Gram-positive strains are: *Staphylococcus aureus*, *Staphylococcus epidermidis, Enterococcus. faecalis, Streptococcus pneumoniae* and *Enterococcus faecium*, *E. coli*, *Klebsiella pneumoniae*, *Psuedomonas aeruginosa*, *Acinetobacter baumannii* and *Enterobacter cloacae* are the five most frequently detected Gram-negative bacteria five gram-negative bacteria. The resistance rates of methicillin-resistant *Staphylococci*, erythrocin-insensitive *S. pneumoniae*, cephalosporin-resistant *Enterobacteriaceae*, fluoroquinolone-resistant *E. coli* and carbapenems-resistant *A. baumannii* were all more than 50% in the CARSS 2015 report. Of growing concern is the increase in resistance to imipenem reported in *A. baumannii* and *K. pneumoniae* between 2012 and 2015 (CARSS et al. 2016). Another nation-wide surveillance system, CHINET, was organised in 2005 by Fudan University. It analysed the temporal trend of bacterial resistance in samples (sputum, urine, blood, cerebrospinal fluid, stool, etc) from outpatients and inpatients in 19 hospitals between 2005 and 2014 (two hospitals dropped out in 2012) (Hu et al. 2016a). Most of the hospitals included are the largest in each province or city, representing 14 provinces or cities. During the study period, the number of bacterial isolates ranged between 22,774 and 84,572 annually. The resistance of *E. coli* and *K. pneumoniae* to amikacin, ciprofloxacin, piperacillin/tazobactam and cefoperazone/sulbactam decreased with time, while the resistance increased for cefotaxime. Carbapenem resistance among *K.*

pneumoniae and *A. baumannii* isolates both increased significantly between 2005 and 2014. In the latest CHINET 2015 report, it collected a total of 88,778 clinical isolates from similar samples (sputum, urine, blood, cerebrospinal fluid, stool, etc.) in 18 general hospitals and two children's hospitals. Gram-negative organisms and Gram-positive cocci accounted for 70 % and 30 %, respectively. The prevalence of carbapenem-resistant *K. pneumoniae* and *A. baumannii* continues to increase on 2014 levels, similar to that which was reported in the CARSS report (Hu et al. 2016b). The carbapenem family of antibiotics is the last resort for most Gram-negative bacterial infections. Therefore, infections due to carbapenem-resistant strains become an increasingly serious threat to patients in clinics.

There are also several provincial surveillance systems, such as in Beijing, Zhejiang, and Guangzhou. And a number of studies have shown the emergence of antibiotic-resistant bacterial strains, including multi-drug resistance of bacteria, in Chinese hospitals during the past decades (Chen et al. 2013b; Dai et al. 2014; Liang et al. 2015; Song et al. 2014; Tang et al. 2016; Xia et al. 2012). However, the current survey system mainly focuses on urban hospitals and does not include the county or rural medical institutions. For example, in the CARSS 2015 report, 76.2% of the member hospitals are tertiary hospitals and 23.8% are secondary hospitals. Taking into account different socioeconomic development, prescription behaviour, etc., it is apparent that antibiotic resistance varies geographically in China. Only a few studies reported resistance prevalence in county medical institutes (Xiao et al. 2015).

In general, the survey systems are based on culture-depended methods to detect the antibiotic resistance in clinics, while isolated studies have characterised antimicrobial resistance using molecular biology approaches (Cui et al. 2015; Yang et al. 2015; Zhang et al. 2016a). The most common resistance mechanism of carbapenem is the production of carbapenemases, including enzymes of Ambler classes A, D and B [metallo-β-lactamases (MBLs)], with the corresponding genes often being associated with mobile genetic elements. New Delhi MBL 1 (NDM-1), a new type of MBL, was first reported in *A. baumannii* isolates in four different provinces in China (Chen et al. 2011b). Later, PCR based detection of carbapenem

resistance associated gene($bla_{\text{NDM-1}}$) unveiled high incidence and sporadic spread of $bla_{\text{NDM-1}}$-positive *Enterobacteriaceae* in many provinces of China (Hu et al. 2013; Liu et al. 2013; Qin et al. 2014; Sun et al. 2014). Jia et al. detected the β-lactam, aminoglycoside, tetracycline, macrolide, glycopeptide resistance genes and the efflux pump genes in 100 multiple-drug resistant enterococcal isolates from a university hospital in China and indicated that the emergence of these antibiotic resistance genes was the main cause of the resistance of enterococci to antimicrobial agents (Jia et al. 2014). High throughput assays such as microarray technology were also applied to determine multiple tetracycline and β-lactam resistance genes from the sputum, urine, blood, bile, liquor puris, and cerebrospinal fluid samples obtained from Chinese hospitals (Lu et al. 2010a). With the emergence and spread of new mechanisms of resistance, infectious diseases are becoming more difficult to treat in China.

6. Prospective and Mitigation strategies

Numerous studies have detected ARB and ARG in a variety of environmental media in China and the increasing prevalence of antibiotic resistance in the environment has attracted greater attention from academia and government. Antibiotic overuse and misuse is likely the most important reason for the observed increased prevalence in environmental and clinical antimicrobial resistance. Therefore, the first and most important measure would be reducing unnecessary use of antibiotics to tackle this problem at the source.

For clinical use of antibiotics, although China has released a series of regulations and strategies to reduce the rate of antibiotic prescriptions during the last decades, inappropriate prescription continues in China, especially in the primary care settings in rural areas. Financial incentives are considered to be the main driver of this over-prescription in China. The Chinese government has recently launched reforms to address these drivers. For example, on April 8, 2017, Beijing started a landmark reform drive that will separate drug sales from medical treatment at public hospitals. This separation is intended to stop over-prescription and help medical practitioners provide more appropriate treatment. Since public hospitals provide over 90% of the

country's inpatient services and more than 50% of outpatient services, it is imperative that greater efforts are needed to pursue health system reform for public hospitals to alter the inappropriate finance incentives.

At least as many antibiotics are used in agriculture than in humans in China, and even some last-line drugs for humans are being used in agriculture. Colistin, for example, has been banned as a growth stimulator in agriculture on Nov1, 2016 and the ban took effect on April 1, 2017. The experiences exemplified by the reduction in antibiotic use in Denmark and The Netherlands in pig farming can provide instructive case studies on the effects of reduced antibiotic use in animal food production (Aarestrup et al. 2001; Dierikx et al. 2016). The World Health Organization has found that the Danish ban reduced human health risk without significantly harming animal health or farmers' incomes (WHO 2003). Antibiotic sales to Dutch livestock farms decreased by 56% without any reduction in production or profits from 2007 to 2012 (McKenna 2014). Therefore, alternative strategies for the control of bacterial infections, such as optimise the living conditions of livestock, are required to reduce antibiotic consumption in food animals in China.

Secondly, a systematic surveillance network should be established that includes regular, continuous measurement of antibiotic utilisation and the patterns of antibiotic resistance from the clinic and agriculture, at a local and national level. Surveillance was recognised as the first step to understanding the current state and progression of resistance over time. Although there are some existing surveillance programs for ARBs in China, they are not inclusive of the primary care settings. Continuous surveillance of antibiotic resistance can contribute to disease diagnosis, treatment and policy making. Reliance on sales data for antibiotic surveillance can tell an incomplete story; hence a nationwide surveillance program is needed to quantify antibiotic prescriptions from all sources i.e., pharmacies, clinics, hospitals. Unlike human use antibiotics, some veterinary antibiotics can be purchased directly by food animal producers. Thus, it's difficult to quantify accurately veterinary antibiotic use. A robust antibiotic surveillance system can facilitate the enforcement of the restriction on the use of antibiotics in animals that are important for human use. It can also

monitor the association between antibiotic use and resistance, as well as inform intervention in much the same way that the surveillance system, DANMAP, has made significant contributions to the control of antibiotic resistance in Denmark (Bager 2000). Antibiotic use in animals should be confined to prescription and dispensed by veterinarians for treatment and not by the whim of the farmer for other purposes. For a surveillance system in China, there needs to be consistency in sampling and testing methods. Strict quality control should also be applied in order to compare trends in antibiotic resistance. The surveillance program should be publicly available, facilitating open science which can bring greater understanding by academia and innovation by industry.

It is critically important to control the environmental spread of antibiotics and ARBs, especially for STPs, which provide favourable conditions for proliferating of ARBs or transferring of ARGs. As conventional sewage treatment facilities were not designed to deal with antibiotics, the removal efficiencies of antibiotics were highly variable among different antibiotics and different STPs. So far, AOPs are not widely used in STPs because of the high cost, and conventional STPs were even absent in rural areas in China. It's urgent to reinforce the operation of STPs in rural areas and the application of more advanced techniques in urban STPs to improve the effluent quality. Current technologies are unable to provide complete removal or destruction of antibiotics which are subsequently transferred to sludge during sewage biological treatment. Further treatment is also needed for these solid matrices. Maximum residue limits for antibiotics in effluent and sludge of STP or animal manure in China should be implemented in the environment. Although beyond the scope of this review, similar residue limits might be appropriate for metals and biocides to address the challenge of co-selection. Some rules should be established to reduce the use of sewage sludge or animal manure on agricultural land, thereby reducing the risk of spreading resistance in the environment to humans, food crops and wildlife. There is also a need to identify the levels of antibiotics at which resistance might occur and develop maximum thresholds for antibiotics or ARGs for environmental compartments.

In August 2016, China presented its National Action Plan to Contain Antimicrobial Resistance (2016-2020). The Action Plan aims to establish comprehensive management strategies and measures at the national level to strengthen the supervision of the search and development, production, circulation, application, and environmental protection for the antimicrobial agents (Xiao and Li 2016). For the first time, 14 departments, including National Health and Family Planning Commission, National Development and Reform Commission, the Ministry of Environmental Protection, the Ministry of Agriculture were involved and collaborated to address AMR. The responsibilities of each department and nine major strategies for the prevention and control of antimicrobial resistance were clearly assigned in the Action Plan, including exploiting the advantages of joint prevention and control; increasing investment in the research and development of antimicrobials; strengthening the management of antibacterial agents supply security; strengthening the construction of antibacterial agent application and antimicrobial resistance control system; optimizing antimicrobial consumption and resistance surveillance system; improving the capacity of professional personnel in antimicrobial resistance prevention and control; strengthening the prevention and management of environmental pollution of antimicrobials; strengthening publicity and education of AMR; conducting extensive international change and cooperation. Actions have already taken place within the country under this plan. For example, the Ministry of Agriculture in China announced the 2017 Antimicrobial Resistance Surveillance Program of Bacteria from Food Animals. China has participated in extensive international collaborative programs to fight antibiotic resistance. At the G20 summit (September, 4-5, 2016) in Hangzhou, China, world leaders reached an important agreement on next steps in the battle with antimicrobial resistance. As the most populous and the largest consumer of antibiotics in the world, China faces the most significant challenge of any country when it comes to tackling antimicrobial resistance. Recent efforts at the national and international level must be seen as only the start of a growing commitment to the implementation of a One Health AMR Action Plan in all of China.

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Supplemental Material

Review of Antibiotic Resistance in China and its Environment

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Figure S1. Concentrations of antibiotics in influent and effluent of Chinese STPs.
(The mean values for each compound are listed on the top x-axes)
Figure S2. Concentrations of antibiotics in surface water of Chinese rivers.
(The mean values for each compound are listed on the top x-axes)
Figure S3. Concentrations of antibiotics in sediments of Chinese rivers.
(The mean values for each compound are listed on the top x-axes)
Figure S4. Concentrations of antibiotics in Chinese animal manures (chicken, duck, cattle and swine manure). (The mean values for each compound are listed on the top x-axes)
Figure S5. Concentrations of antibiotics in Chinese soils.
(The mean values for each compound are listed on the top x-axes)

Table S1 Concentrations of antibiotics in different environment media in China
Table S2 Abundance of antibiotic resistant genes (ARGs) in different environment media in China

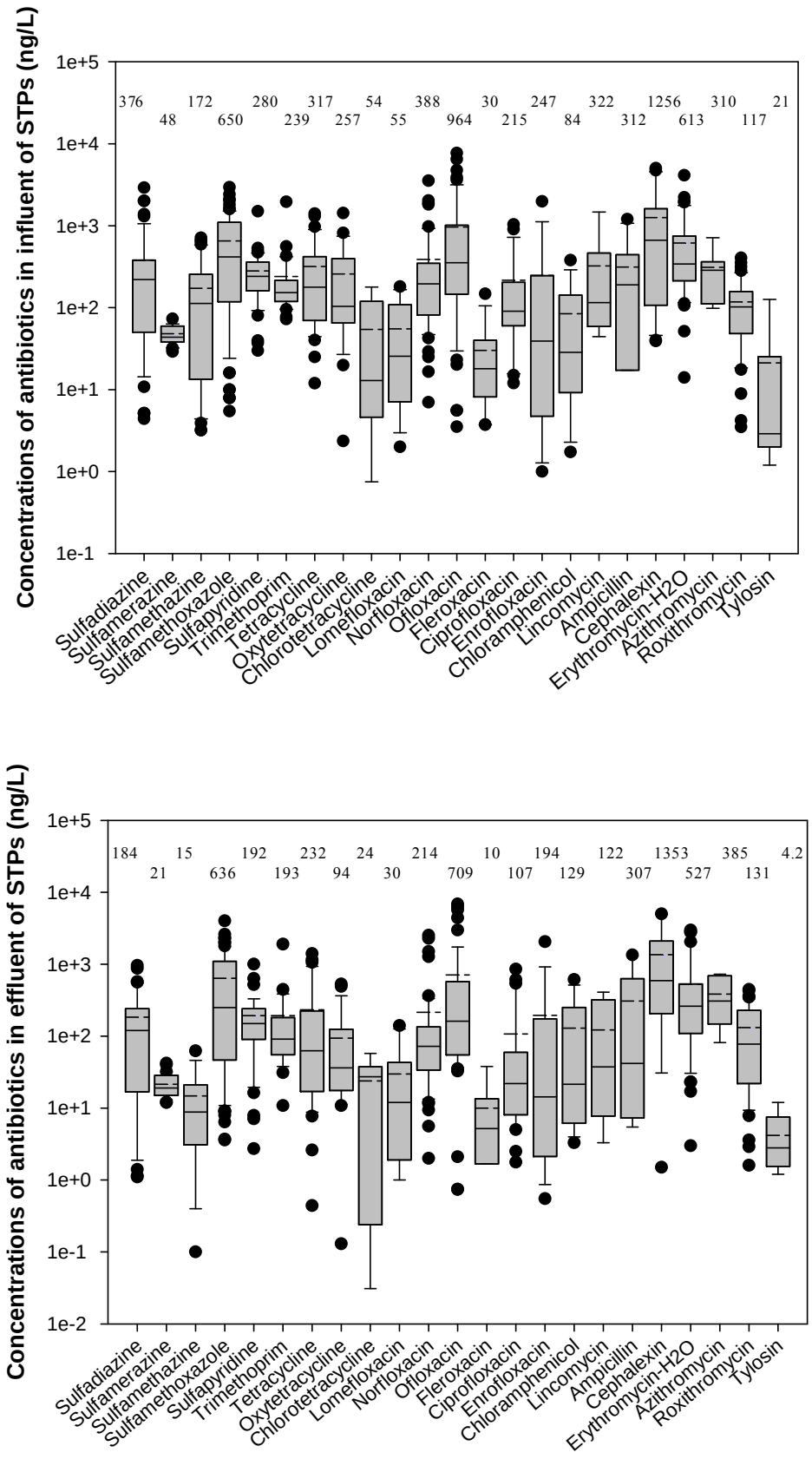

Figure S1. Concentrations of antibiotics in influent and effluent of Chinese STPs. (The mean values for each compound are listed on the top x-axes)

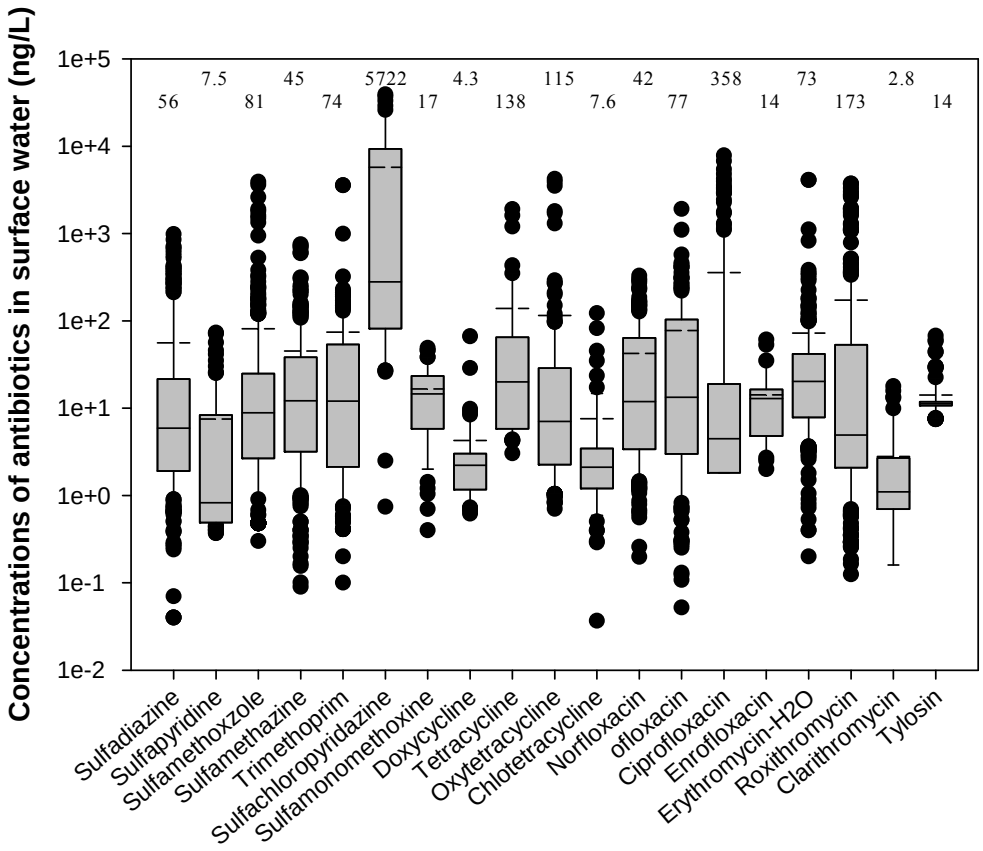

Figure S2. Concentrations of antibiotics in surface water of Chinese rivers. (The mean values for each compound are listed on the top x-axes)

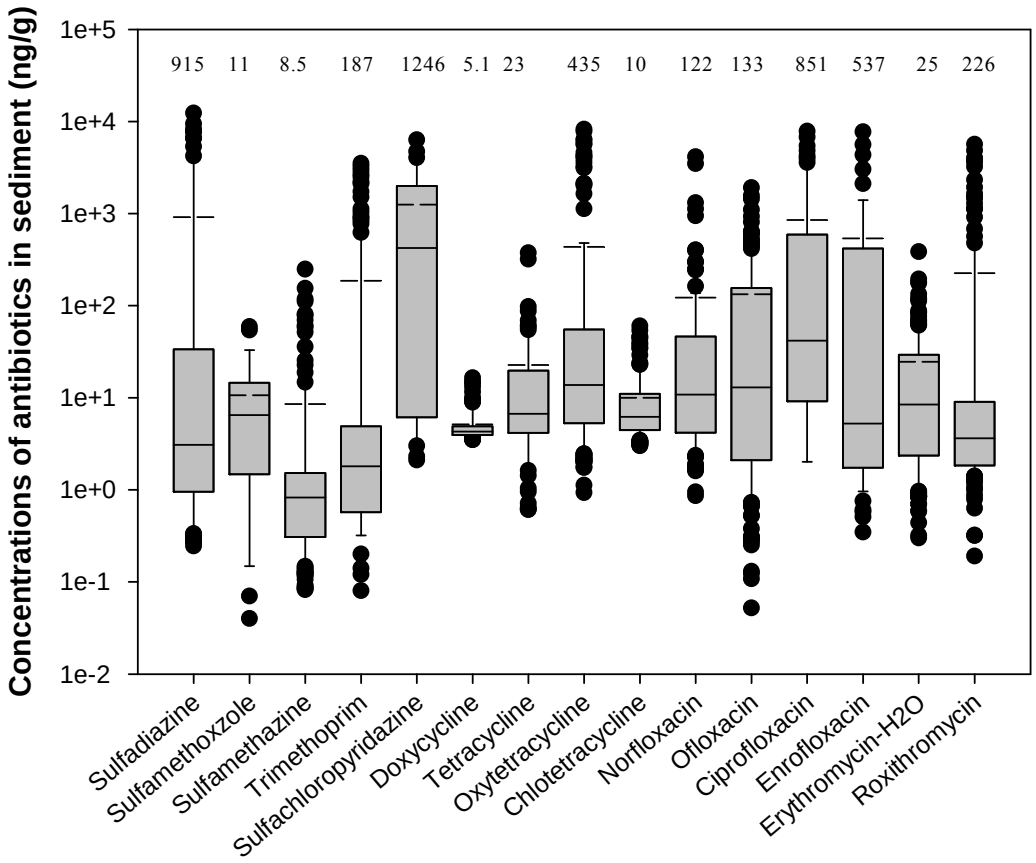

Figure S3. Concentrations of antibiotics in sediments of Chinese rivers.
(The mean values for each compound are listed on the top x-axes)

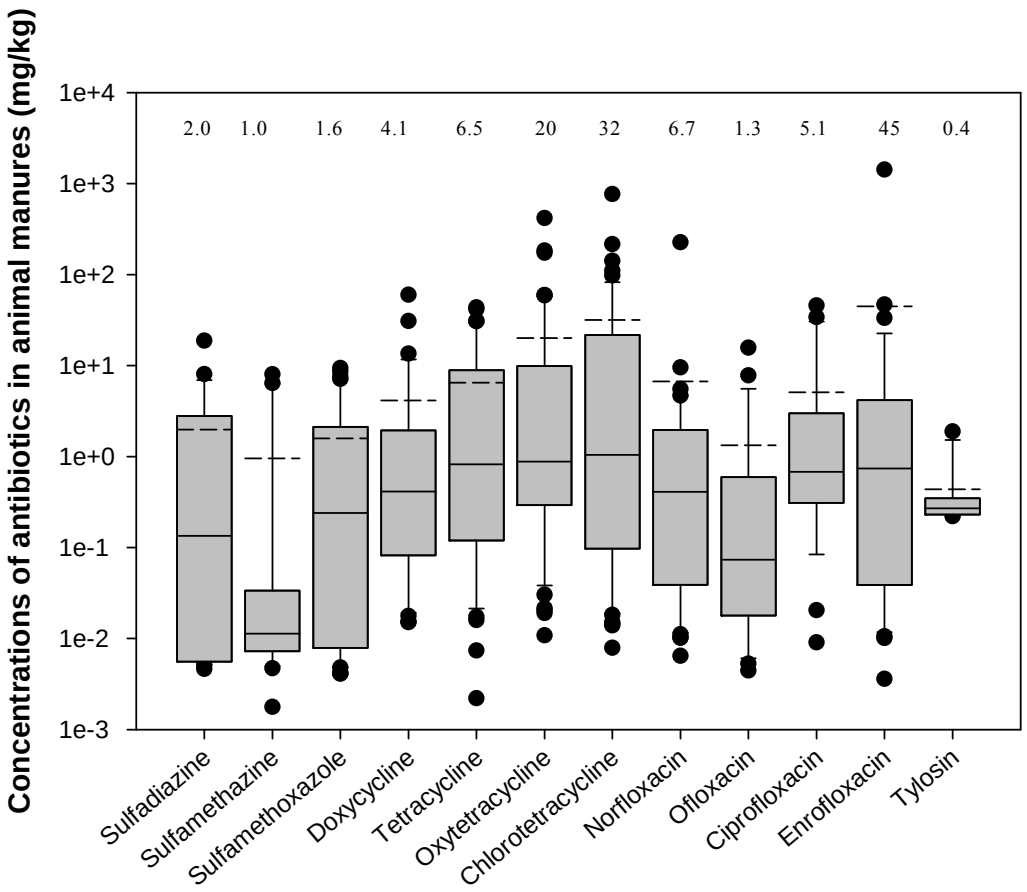

Figure S4. Concentrations of antibiotics in Chinese animal manures (chicken, duck, cattle and swine manure).
(The mean values for each compound are listed on the top x-axes)

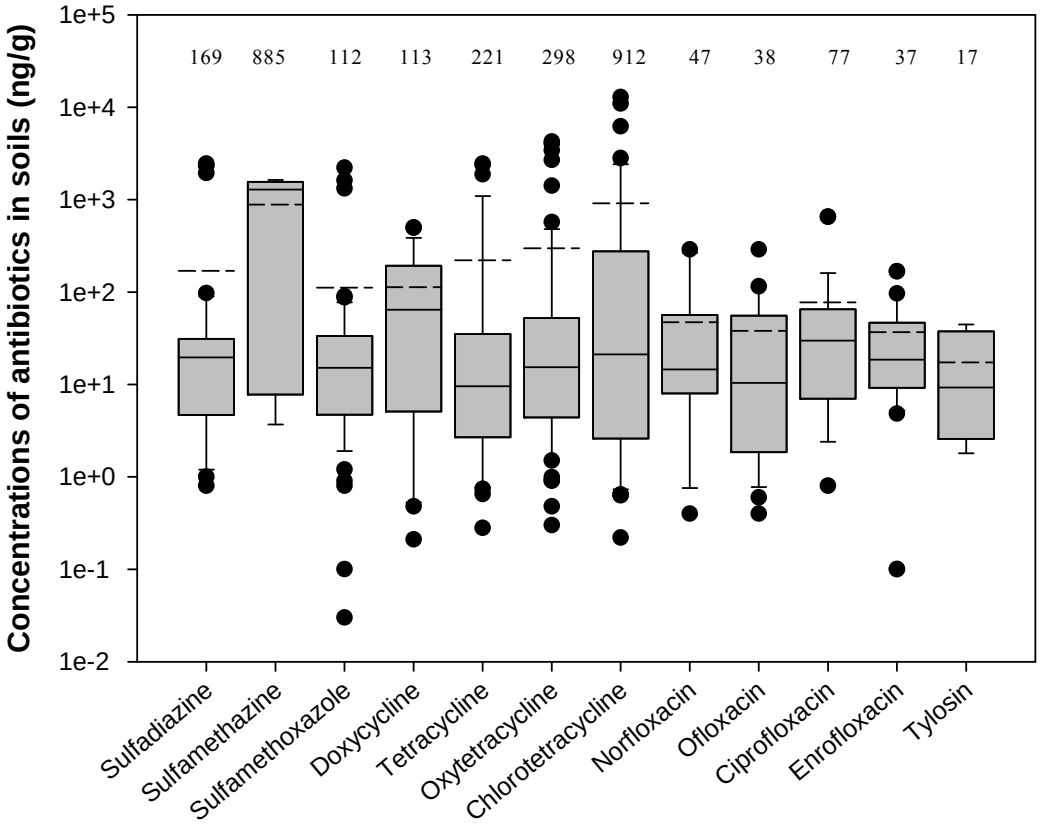

Figure S5. Concentrations of antibiotics in Chinese soils.
(The mean values for each compound are listed on the top x-axes)

Table S1 Concentrations of antibiotics in different environment media in China

Location	Media	Antibiotics	Concentration range/Mean	Unit	Reference
Beijing	STP Influent	Sulfamethoxazole	1200	ng/L	(Chang et al. 2008)
		Sulfapyridine	290		
		Sulfamerazine	48		
		Sulfadiazine	350		
		Sulfamethizol	330		
	STP Effluent	Sulfamethoxazole	1400		
		Sulfapyridine	220		
		Sulfamerazine	21		
		Sulfadiazine	220		
		Sulfamethizol	10		
Beijing	STP Influent	Sulfamethoxazole	290-1000	ng/L	(Gao et al. 2012)
		Sulfapyridine	110-530		
		Sulfamethazine	3.2-10		
		Sulfadiazine	380-2000		
		Norfloxacin	51-310		
		Ciprofloxacin	15-140		
		Fleroxacin	16-43		
		Ofloxacin	44-3100		
		Lomefloxacin	5.6-180		
		Spiramycin	nd-160		
		Josamycin	nd-2.7		
		Tylosin	nd-4		
		Erythromycin	130-520		
		Roxithromycin	67-260		
	STP Effluent	Sulfamethoxazole	130-460		
		Sulfapyridine	110-330		
		Sulfamethazine	1.6-11		
		Sulfadiazine	120-560		
		Norfloxacin	9-200		
		Ciprofloxacin	nd-55		
		Fleroxacin	nd-38		
		Ofloxacin	150-1200		
		Lomefloxacin	nd-140		
		Spiramycin	nd-32		
		Josamycin	nd-2		
		Tylosin	nd-3		
		Erythromycin	51-300		
		Roxithromycin	54-360		
Beijing Qinghe	STP Influent	Pipemidic acid	86	ng/L	(Jia et al. 2012)
		Fleroxacin	14		

		Ofloxacin	1287		
		Norfloxacin	775		
		Ciprofloxacin	99		
		Enrofloxacin	8.3		
		Lomefloxacin	162		
		Sarafloxacin	nd		
		Gatifloxacin	66		
		Sparfloxacin	4.4		
		Moxifloxacin	72		
	STP Effluent	Pipemidic acid	33		
		Fleroxacin	5.2		
		Ofloxacin	528		
		Norfloxacin	256		
		Ciprofloxacin	37		
		Enrofloxacin	2.1		
		Lomefloxacin	71		
		Sarafloxacin	nd		
		Gatifloxacin	40		
		Sparfloxacin	1.1		
		Moxifloxacin	40		
Beijing	STP Influent	Sulfathiazole	nd	ng/L	(Li et al. 2013a)
		Sulfamethoxazole	332-646 (496)		
		Sulfisoxazole	nd		
		Sulfapyridine	281-608 (451)		
		Sulfadimethoxine	nd		
		Sulfamethazine	4.63-7.95 (6.32)		
		Sulfadiazine	760-4820 (2009)		
		Sulfamerazine	nd		
		Sulfamonomethoxine	nd		
		Norfloxacin	1368-2746 (1813)		
		Ciprofloxacin	35.0-119 (82.1)		
		Difloxacin	nd-9.55 (2.39)		
		Enrofloxacin	nd-7.92 (3.55)		
		Fleroxacin	nd-375 (147)		
		Ofloxacin	1445-3675 (2794)		
		Lomefloxacin	40.4-97.4 (63.7)		
		Sarafloxacin	nd-23.3 (9.37)		
		Spiramycin	3.08-11.0 (7.46)		
		Josamycin	nd-2.11 (0.86)		
		Tylosin	2.62-17.2 (6.42)		
		Erythromycin	48.6-520 (221)		
		Roxithromycin	25.0-224 (129)		
	STP Effluent	Sulfathiazole	nd		
		Sulfamethoxazole	4.82-20.2 (12.3)		
		Sulfisoxazole	nd		

		Sulfapyridine	0.94-3.98 (2.72)		
		Sulfadimethoxine	nd		
		Sulfamethazine	nd-0.39 (0.1)		
		Sulfadiazine	5.14-19.0 (10.7)		
		Sulfamerazine	nd		
		Sulfamonomethoxine	nd		
		Norfloxacin	nd-124 (40.1)		
		Ciprofloxacin	nd-4.98 (1.77)		
		Difloxacin	nd-0.79 (0.2)		
		Enrofloxacin	nd-1.26 (0.55)		
		Fleroxacin	nd-8.38 (3.75)		
		Ofloxacin	19.4-185 (72.6)		
		Lomefloxacin	nd-11.5 (3.3)		
		Sarafloxacin	nd-1.76 (0.44)		
		Spiramycin	nd		
		Josamycin	nd		
		Tylosin	nd		
		Erythromycin	nd-42.1 (14.7)		
		Roxithromycin	0.43-32.7 (9.99)		
Beijing	STP Influent	Sulfanilamide	nd-1200	ng/L	(Shao et al. 2009)
		Sulfameter	nd-215		
		Sulfachloropyridazine	nd-57		
		Sulfaquinoxaline	nd-103		
		Ofloxacin	38-716		
		Pefloxacin	4-160		
		Norfloxacin	2-120		
		Ciprofloxacin	16-408		
		Enrofloxacin	2-407		
		Lomefloxacin	nd-18		
		Tetracycline	23-980		
		Oxytetracycline	95-2942		
		Tylosin	nd-269		
		Kitasamycin	32-395		
		Erythromycin	12-354		
		Diazepam	nd-16		
		Chloramphenicol	nd-40		
		Clenbuterol	nd-11		
		Metoprolol	nd-32		
	STP Effluent	Sulfanilamide	nd-117		
		Sulfameter	nd-67		
		Sulfachloropyridazine	nd-22		
		Sulfaquinoxaline	nd-35		
		Ofloxacin	18-235		
		Pefloxacin	1-73		
		Norfloxacin	1-72		

		Ciprofloxacin	3-195		
		Enrofloxacin	1-92		
		Lomefloxacin	nd-10		
		Tetracycline	10-210		
		Oxytetracycline	11-916		
		Tylosin	nd-189		
		Kitasamycin	5-40		
		Erythromycin	3-63		
		Diazepam	nd-8		
		Chloramphenicol	nd-8		
		Clenbuterol	nd-6		
		Metoprolol	nd-4		
Beijing	STP Influent	Sulfacetamide	9.5	ng/L	(Xu et al. 2015)
		Sulfamerazine	4.8		
		Sulfadimidine	30.4		
		Sulfamethoxazole	263.3		
		Trimethoprim	1955.2		
		Ofloxacin	3645.2		
		Enrofloxacin	19.1		
		Tetracycline	177.6		
		Oxytetracycline	1425.4		
		Chlortetracycline	12.9		
	STP Effluent	Sulfacetamide	6.9		
		Sulfamerazine	1.2		
		Sulfadimidine	21.7		
		Sulfamethoxazole	192.6		
		Trimethoprim	1777.5		
		Ofloxacin	2068.4		
		Enrofloxacin	20.1		
		Tetracycline	32		
		Oxytetracycline	163.1		
		Chlortetracycline	nd		
Chongqing	STP Influent	Erythromycin	206	ng/L	(Chang et al. 2010)
		Erythromycin-H_2O	703		
		Roxithromycin	nd		
		Tylosin	44		
		Lincomycin	1467		
		Trimethoprim	18		
		Ciproflaxacin	458		
		Lomefloxacin	143		
		Norfloxacin	859		
		Ofloxacin	780		

		Sulfadiazine	1382		
		Sulfadimethoxine	nd		
		Sulfamethazine	18		
		Sulfamethoxazole	2020		
		Iso-Chlortetracycline	105		
		Epi-iso-Chlortetracycline	39		
		Oxytetracycline	41		
		Tetracycline	118		
	STP Effluent	Erythromycin	125		
		Erythromycin-H_2O	537		
		Roxithromycin	nd		
		Tylosin	0		
		Lincomycin	410		
		Trimethoprim	177		
		Ciproflaxacin	101		
		Lomefloxacin	43		
		Norfloxacin	166		
		Ofloxacin	nd		
		Sulfadiazine	875		
		Sulfadimethoxine	nd		
		Sulfamethazine	14		
		Sulfamethoxazole	1050		
		Iso-Chlortetracycline	56		
		Epi-iso-Chlortetracycline	32		
		Oxytetracycline	nd		
		Tetracycline	nd		
Chongqing	STP Influent	Sulfadiazine	202.8-257.8 (229.9)	ng/L	(Yan et al. 2014)
		Sulfamethazine	129-174.4 (150.2)		
		Sulfamethoxazole	2460.4-3180 (2935.4)		
		Trimethoprim	51.9-98.8 (77.37)		
		Ofloxacin	276.7-401.5 (345.9)		
		Norfloxacin	186.3-225.1 (203.0)		
		Moxifloxacin	nd-27.6 (19.9)		
		Erythromycin-H_2O	238.6-275.4 (254.24)		
		Roxithromycin	359.7-434.6 (404.0)		
		Azithromycin	330.27-376.5 (362.5)		
	STP Effluent	Sulfadiazine	117.8-74.8 (155.0)		
		Sulfamethazine	31.7-47.2 (39.9)		
		Sulfamethoxazole	1060.3-1212.2 (1147.9)		
		Trimethoprim	37.9-75.5 (52.6)		
		Ofloxacin	43.0-82.9 (57.9)		
		Norfloxacin	25.5-34.2 (30.4)		
		Moxifloxacin	5.7-7.7 (6.6)		
		Erythromycin-H_2O	135.9-174.0 (153)		

		Roxithromycin	300.6-386.4 (347.5)		
		Azithromycin	58-111.0 (81.5)		
Dalian	STP Influent	Cephalexin	nd-166	ng/L	(Zhang et al. 2013)
		Cefradine	nd-125		
		Norfloxacin	220-542		
		Ofloxacin	276-382		
		Roxithromycin	70-313		
		Azithromycin	98-711		
	STP Effluent	Cephalexin	nd-29		
		Cefradine	nd-34		
		Norfloxacin	80-205		
		Ofloxacin	108-382		
		Roxithromycin	99-444		
		Azithromycin	148-728		
Northern China	STP Influent	Oxytetracycline	2400-334300	ng/L	(Hou et al. 2016)
		Chlortetracycline	800-1800		
		Tetracycline	11900-61000		
	STP Effluent	Oxytetracycline	32000		
		Tetracycline	2600		
Shanghai	STP Influent	Trimethoprim	257	ng/L	(Wang et al. 2014a)
	STP Effluent	Trimethoprim	186		
Xiamen	STP Influent	Sulfamethoxazole	nd-95.2 (25)	ng/L	(Sun et al. 2016)
		Ofloxacin	23.6-786 (200)		
		Sarafloxacin	nd-1.20 (0.1)		
		Oxytetracycline	8.60-230 (91)		
		Tetracycline	nd-189 (48)		
	STP Effluent	Sulfamethoxazole	nd-22.4 (9.1)		
		Ofloxacin	13.3-702 (150)		
		Sarafloxacin	nd-1.3 (0.2)		
		Oxytetracycline	nd-51.4 (20)		
		Tetracycline	nd-37.6 (14)		
Fujian province	STP Influent	Sulfadiazine	2.3-32.1	ng/L	(Zhang et al. 2015a)
		Sulfamethazine	nd-259		
		Sulfamethoxazole	5.41-152		
		n-Acetyl sulfamethazine	4.0-51.5		
		n-Acetyl sulfadiazine	nd-51.4		
		n-Acetyl sulfamethoxazole	72.7-2312		
		Ciprofloxacin	nd-55.8		
		Norfloxacin	nd-130		
		Ofloxacin	6.0-91.5		

		Enrofloxacin	nd-16.8		
		Roxithromycin	6.5-63.7		
		Erythromycin	1.12-1.67		
		Cephalexin	33.4-822		
		Cephradine	92.5-11850		
		Tetracycline	nd-175		
		Oxytetracycline	nd-167		
		Chlortetracycline	nd-261		
		Doxycycline	nd-51		
		4-epitetracycline	nd-87.7		
		4-epioxytetracycline	nd-287		
		Isochlortetracycline	nd-233		
	STP Effluent	Sulfadiazine	1.46-28.4		
		Sulfamethazine	nd-233		
		Sulfamethoxazole	2.96-145		
		n-Acetyl sulfamethazine	2.50-52.9		
		n-Acetyl sulfadiazine	nd-51.4		
		n-Acetyl Sulfamethoxazole	38.7-208		
		Ciprofloxacin	nd-49.8		
		Norfloxacin	nd-172		
		Ofloxacin	5.70-53.4		
		Enrofloxacin	nd-18.5		
		Roxithromycin	12.7-104		
		Erythromycin	1.20-4.40		
		Cephalexin	25.0-187		
		Cephradine	21.4-369		
		Tetracycline	nd-101		
		Oxytetracycline	nd-178		
		Chlortetracycline	nd-154		
		Doxycycline	nd-87.3		
		4-Epitetracycline	nd-82.1		
		4-Epioxytetracycline	nd-296		
		Isochlortetracycline	nd-651		
Guangzhou	STP Influent	Sulfadiazine	5100-5150	ng/L	(Peng et al. 2006)
		Sulfamethoxazole	5450-7910		
		Ofloxacin	3520-5560		
		Chloramphenicol	1730-2430		
	STP Effluent	Sulfadiazine	nd		
		Sulfamethoxazole	nd		
		Ofloxacin	nd-740		
		Chloramphenicol	nd		
Pearl River Delta	STP Influent	Ofloxacin	80-368	ng/L	(Xu et al. 2007)
		Norfloxacin	54-263		

		Roxithromycin	75-164		
		Erythromycin-H_2O	253-1978		
		Sulfadiazine	nd-72		
		Sulfadimidine	nd-696		
		Sulfamethoxazole	10-118		
		Chloramphenicol	nd-31		
	STP Effluent	Ofloxacin	41-165		
		Norfloxacin	27-85		
		Roxithromycin	35-64		
		Erythromycin-H_2O	216-2054		
		Sulfadiazine	nd-36		
		Sulfadimidine	nd-346		
		Sulfamethoxazole	9-78		
		Chloramphenicol	nd-17		
Guangdong province	STP Influent	Trimethoprim	72.3-162	ng/L	(Zhou et al. 2013b)
		Lincomycin	44.2-129		
		Chloramphenicol	22.1		
	STP Effluent	Trimethoprim	31.1-64		
		Lincomycin	nd-53.9		
		Chloramphenicol	5.8		
Hong Kong	STP Influent	Erythromycin-H_2O	470-810	ng/L	(Gulkowska et al. 2008)
		Trimethoprim	120-320		
		Tetracycline	96-1300		
		Norfloxacin	110-460		
		Cefalexin	670-2900		
		Cefotaxim	nd-1100		
	STP Effluent	Erythromycin-H_2O	510-850		
		Trimethoprim	120-230		
		Tetracycline	180-620		
		Norfloxacin	85-320		
		Cefalexin	240-1800		
		Cefotaxim	nd-34		
Shenzhen Nan Shan	STP Influent	Erythromycin-H_2O	590		
		Trimethoprim	200		
		Tetracycline	150		
		Norfloxacin	370		
		Penicillin G	29		
		Cefotaxim	1100		
Hong Kong	STP Influent	Cefalexin	1020-5640	ng/L	(Leung et al. 2012)
		Ofloxacin	142-7900		
		Erythromycin-H_2O	243-4740		

		Norfloxacin	28-5430		
		Roxithromycin	nd-500		
		Sulfamethoxazole	38-444		
		Tetracycline	16-1510		
		Oxytetracycline	nd-230		
		Trimethoprim	72-700		
		Chloramphenicol	26-452		
	STP Effluent	Cefalexin	170-5070		
		Ofloxacin	96-7870		
		Erythromycin-H_2O	246-4330		
		Norfloxacin	nd-3700		
		Roxithromycin	nd-547		
		Sulfamethoxazole	5-278		
		Tetracycline	nd-1420		
		Oxytetracycline	nd-842		
		Trimethoprim	59-465		
		Chloramphenicol	nd-1050		
Hong Kong	STP Influent	Ampicillin	nd-383	ng/L	(Li and Zhang 2011)
		Cefotaxime	nd-93.0		
		Cefalexin	65.7-1718		
		Sulfamethoxazole	52.0-291		
		Sulfadiazine	4.4-530		
		Sulfamethazine	nd-54.7		
		Norfloxacin	7.0-264		
		Ciprofloxacin	98.6-1033		
		Ofloxacin	188-1042		
		Tetracycline	59.8-353		
		Oxytetracycline	nd-107		
		Chlortetracycline	nd-178		
		Roxithromycin	4.2-141		
		Erythromycin-H_2O	169-409		
		Trimethoprim	100-172		
		Vancomycin	nd-60.6		
	STP Effluent	Ampicillin	nd-17.4		
		Cefotaxime	nd-56.7		
		Cefalexin	nd-1176		
		Sulfamethoxazole	3.6-67.4		
		Sulfadiazine	nd-2.8		
		Sulfamethazine	nd		
		Norfloxacin	5.6-165		
		Ciprofloxacin	30.2-851		
		Ofloxacin	32.6-610		
		Tetracycline	18.5-236		
		Oxytetracycline	nd-49.0		
		Chlortetracycline	nd-30.9		

		Roxithromycin	1.6-76.7		
		Erythromycin-H_2O	104-410		
		Trimethoprim	38-120		
		Vancomycin	nd-28.9		
Hong Kong	STP Influent	Ampicillin	nd-389.5	ng/L	(Li et al. 2009)
		Cefalexin	175.4-539.4		
		Sulfamethoxazole	146.5-355.5		
		Sulfadiazine	nd-73.0		
		Norfloxacin	nd-59.5		
		Ciprofloxacin	99.2-720.0		
		Ofloxacin	104.4-335.9		
		Tetracycline	134.5-270.8		
		Roxithromycin	3.5-25.3		
		Erythromycin-H_2O	51.3-216.7		
		Trimethoprim	128.7-161.2		
	STP Effluent	Ampicillin	nd-126.4		
		Cefalexin	nd-375.6		
		Sulfamethoxazole	15.3-46.6		
		Sulfadiazine	nd-16.2		
		Norfloxacin	nd-13.9		
		Ciprofloxacin	7.6-73.3		
		Ofloxacin	2.1-556.4		
		Tetracycline	nd-89.4		
		Roxithromycin	2.9-14.2		
		Erythromycin-H_2O	37.9-96.3		
		Trimethoprim	10.8-66.2		
Other countries					
Korea	STP Influent	Sulfamethazine	nd-343 (132)	ng/L	(Behera et al. 2011)
		Sulfamethoxazole	79-216 (120)		
		Trimethoprim	101-277 (205)		
		Lincomycin	3095-19401 (8176)		
	STP Effluent	Sulfamethazine	nd-408 (114)		
		Sulfamethoxazole	20-162 (57)		
		Trimethoprim	13-154 (63)		
		Lincomycin	1437-21278 (9089)		
US	STP Influent	Sulfamethoxazole	390-1000	ng/L	(Brown et al. 2006)
		Trimethoprim	590-1400		
		Ofloxacin	400-1000		
		Ciprofloxacin	200-1000		
	STP Effluent	Sulfamethoxazole	310		
		Trimethoprim	180		
		Ofloxacin	110		
UK	STP Influent	Trimethoprim	1514-4673 (2925)		(Kasprzyk-Hordern et al.
		Sulfamethoxazole	20-274 (115)		

		Chloramphenicol	150-452 (248)		2009)
		Erythromycin-H_2O	144-10025 (2530)		
	STP Influent	Trimethoprim	385-1218 (876)		
		Sulfamethoxazole	4-44 (19)		
		Chloramphenicol	<6-69 (21)		
		Erythromycin-H_2O	23-2772 (696)		
Germany	STP Influent	Azithromycin	50-946 (285)	ng/L	(Rossmann et al. 2014)
		Ciprofloxacin	78-1570 (422)		
		Doxycycline	nd-2393 (259)		
		Roxithromycin	nd-771 (92)		
		Sulfamethoxazole	12-2204 (515)		
		Trimethoprim	22-372 (186)		
	STP Effluent	Azithromycin	nd-956 (277)		
		Ciprofloxacin	19-920 (146)		
		Doxycycline	nd-1110		
		Roxithromycin	nd-281 (84)		
		Sulfamethoxazole	18-8263 (191)		
		Trimethoprim	25-554 (208)		
Italy	STP Influent	Azithromycin	120	ng/L	(Verlicchi et al. 2014)
		Ciprofloxacin	2200		
		Erythromycin	46		
		Norfloxacin	210		
		Ofloxacin	980		
		Roxithromycin	65		
		Trimethoprim	59		
	STP Effluent	Azithromycin	130		
		Ciprofloxacin	630		
		Erythromycin	15		
		Norfloxacin	150		
		Ofloxacin	400		
		Roxithromycin	290		
		Trimethoprim	40		
Finland	STP Influent	Ciprofloxacin	nd-4230 (600)	ng/L	(Vieno et al. 2007)
		Norfloxacin	nd-960 (120)		
		Ofloxacin	nd-350 (100)		
	STP Effluent	Ciprofloxacin	nd-130 (60)		
		Norfloxacin	nd-110 (nd)		
		Ofloxacin	nd-30 (14)		
Tianjin (Panjiakou Reservoir)	Surface water	Oxytetracycline	0.2-19.93	ng/L	(Li et al. 2014a)
		Chlortetracyclin	nd-22.33		
		Tetracycline	0.14-14.05		

		Doxycycline	0.19-13.69		
		Nalidixic Acid	nd-11.20		
		Oxolinic Acid	0.31-2.70		
		Flumequine	0.79-3.70		
		Chloramphenicol	0.29-7.15		
		Thiamphenicol	nd-45		
		Florfenicol	nd-73.66		
		Penicillin G	nd-5.59		
		Erythromycin	nd-3.15		
		Roxithromycin	nd-3.90		
		Josamycin	nd-3.70		
		Kitasamycin	0.25-6.27		
		Spiramycin	nd-58.81		
		Sulfaguanidine	nd-8.67		
		Sulfacetamide	1.32-43.10		
		Sulfamethazine	0.21-3.70		
		Sulfapyridine	nd-3.40		
		Sulfadiazine	0.35-1086		
		Sulfadimethoxine	0.95-3.56		
		Sulfachlorpyridazine	nd-4.78		
		Sulfamethizole	0.39-3.47		
		Sulfamonomethoxine	nd-3.20		
		Sulfamethoxypyridazine	0.16-3.10		
		Sulfameter	0.28-3.30		
		Sulfamethoxazole	nd-7.23		
		Sulfamerazine	0.19-3.80		
Haihe River	Surface water	Trimethoprim	nd-230	ng/L	(Luo et al. 2011)
		Sulfadiazine	nd-550		
		Sulfamethoxazole	nd-3900		
		Sulfachloropyridazine	nd-39000		
		Ciprofloxacin	nd-1700		
		Ofloxacin	nd-460		
		Tetracycline	nd-1900		
		Oxytetracycline	nd-4200		
		Erythromycin	nd-4200		
		Roxithromycin	nd-3700		
Laizhou Bay	Surface water	Enoxacin	nd-209 (62)	ng/L	(Zhang et al. 2012)
		Norfloxacin	7.5-103 (40)		
		Ciprofloxacin	nd-66 (31)		
		Enrofloxacin	nd-7.6 (1.8)		
		Ofloxacin	nd-6.5 (0.24)		
		Trimethoprim	1.3-330 (53)		
		Sulfamethoxazole	1.5-82 (19)		
		Sulfamethazine	nd-1.5 (0.13)		

		Sulfamethazine	nd-0.43 (0.02)		
		Erythromycin	0.9-8.5 (2.6)		
		Roxitromycin	nd-1.5 (0.38)		
		Azithromycin	nd-1.2 (0.14)		
		Clarithromycin	nd-0.82 (0.19)		
Huangpu River (Shanghai)	Surface water	Sulfadiazine	4.9-112.5 (53.6)	ng/L	(Chen and Zhou 2014)
		Sulfapyridine	nd-103.1 (24.1)		
		Sulfamethoxazole	2.2-764.9 (259.6)		
		Sulfathiazole	nd-121.1 (34.1)		
		Sulfamerazine	nd		
		Sulfamethazine	19.9-389.4 (188.9)		
		Sulfaquinoxaline	nd-64.2 (21.5)		
		Erythromycin	0.4-6.9 (3.9)		
		Roxithromycin	0.2-2.2 (0.9)		
		Norfloxacin	nd-2.6 (0.2)		
		Ciprofloxacin	nd-34.2 (2.7)		
		Enrofloxacin	nd-14.6 (2.8)		
		Ofloxacin	nd-28.5 (6.5)		
		Chloramphenicol	nd-3.9 (0.4)		
		Thiamphenicol	nd-0.6 (0.5)		
		Florfenicol	nd-241.1 (116.3)		
		Tetracycline	nd-54.3 (4.2)		
		Oxytetracycline	nd-219.8 (78.3)		
		Doxycycline	nd-112.3 (11.3)		
		Chlortetracycline	nd-46.7 (3.6)		
Yangtze Estuary	Surface water	Chloramphenicol	nd-8.63	ng/L	(Yan et al. 2013)
		Thiamphenicol	nd-86.6		
		Florfenicol	0.45-89.5		
		Sulfadiazine	0.55-71.8		
		Sulfapyridine	nd-219		
		Sulfamethoxazole	1.48-56.8		
		Sulfathiazole	nd-5.23		
		Sulfamerazine	nd		
		Sulfamethazine	0.53-89.1		
		Sulfaquinoxaline	nd-23.5		
		Norfloxacin	nd-14.2		
		Ciprofloxacin	nd-2.27		
		Enrofloxacin	nd-4.77		
		Ofloxacin	nd-12.4		
		Tetracycline	nd-2.37		
		Oxytetracycline	nd-22.5		
		Doxycyclinehyclate	nd-5.63		
		Chlortetracycline	nd-3.50		
		Erythromycin	nd-45.4		

		Roxithromycin	0.05-8.20		
Qingshan Lake	Surface water	Trimethoprim	nd-11.57	ng/L	(Zhu et al. 2013)
		Penicillin G	nd-1.68		
		Penicillin V	nd		
		Sulfamethoxazole	4.79-19.2		
Jianghan Plain	Surface water	Sulfadiazine	nd-37.4	ng/L	(Tong et al. 2014)
		Sulfathiazole	nd-3.7		
		Trimethoprim	nd-19.0		
		Sulfamethazine	nd-33.8		
		Sulfamethoxazole	nd-13.4		
		Sulfamerazine	nd-11.0		
		Ofloxacin	nd-135.1		
		Norfloxacin	nd-134.2		
		Ciprofloxacin	nd-18.0		
		Enrofloxacin	nd-53.1		
		Lomefloxacin	nd-13.1		
		Tetracycline	nd-137.4		
		Oxytetracycline	nd-61.8		
		Chlortetracycline	nd-122.3		
		Doxycycline	nd-66.5		
		Erythromycin-H_2O	nd-381.5		
		Clarithromycin	nd-15.8		
		Azithromycin	nd-5.6		
		Roxithromycin	nd-3.7		
Pearl River Delta	Surface water	Sulfadiazine	nd-18	ng/L	(Liang et al. 2013)
		Sulfamethazine	nd-218		
		Sulfamethoxazole	nd-37.6		
		Norfloxacin	nd-136		
		Ofloxacin	nd-15.8		
		Enrofloxacin	nd		
		Tetracycline	nd-13.1		
		Erythromycin-H_2O	nd-121		
		Roxithromycin	nd		
Pearl River Delta and Pearl River Estuary	Surface water	Sulfadiazine	nd-22.3	ng/L	(Xu et al. 2013)
		Sulfadimidine	nd-23.5		
		Sulfamethoxazole	nd-40.6		
		Norfloxacin	nd-34.2		
		Ofloxacin	2.5-127		
		Ciprofloxacin	nd-33.6		
		Enrofloxacin	nd-21.5		

		Erythromycin	nd-52.3		
		Roxithromycin	nd-12.0		
Pearl River	Surface water	Sulfadiazine	nd-726	ng/L	(Yang et al. 2011)
		Sulfamethoxazole	nd-616		
		Sulfamethazine	nd-1080		
		Sulfapyridine	nd-74.6		
		Trimethoprim	nd-605		
		Norfloxacin	nd-124		
		Erythromycin-H_2O	nd-1540		
		Roxithromycin	nd-2260		
Jiulong River	Surface water	Florfenicol	nd-20.8	ng/L	(Zheng et al. 2011)
		Sulfadiazine	nd-60.5		
		Sulfamethanzine	nd-124.4		
		Sulfamonomethoxine	nd-46		
		Sulfamethoxazole	nd-84.4		
		Ofloxacin	nd-49		
		Enrofloxacin	nd-60.8		
		Sulfapyridine	nd-1.8		
		Sulfameter	nd-5.2		
Other countries			1		
Korea	Surface water	Erythromycin	1.8-4.8 (3.4)		(Kim et al. 2007)
		Sulfamethoxazole	1.7-36 (20)		
		Trimethoprim	3.2-5.3 (4.0)		
US	Surface water	Sulfamethoxazole	5-7 (6)		(Arikan et al. 2008)
		Chlortetracycline	1-180 (20)		
		Oxytetracycline	5-84 (53)		
		Tetracycline	1-3 (2)		
		Doxycycline	13-146 (66)		
US	Surface water	Tetracycline	10-30 (20)		(Kim and Carlson 2007)
		Chlortetracycline	10-210 (80)		
		Oxytetracycline	10-1210 (180)		
		Doxycycline	10-50 (20)		
		Sulfamerazine	10-60 (20)		
		Sulfamethazine	20-20 (20)		
		Sulfamethoxazole	40-320 (110)		
		Erythromycin-H_2O	20-450 (120)		
		Tylosin	50-50 (50)		
UK	Surface water	Trimethoprim	nd-90 (19)		(Kasprzyk-Hordern et al. 2009)
		Sulfamethoxazole	nd-1		

		Chloramphenicol	nd		
		Erythromycin-H_2O	nd-2		
		Trimethoprim	10-183 (62)		
		Sulfamethoxazole	nd-4 (1)		
		Chloramphenicol	nd-40 (5)		
		Erythromycin-H_2O	nd-72 (15)		
Germany	Surface water	Erythromycin	4-190		(Christian et al. 2003)
		Roxythromycin	nd-14		
		Trimethoprim	nd-12		
		Sulfadimidine	nd-7		
		Sulfamethoxazole	nd-52		
		Ciprofloxacin	nd-9		
		Ofloxain	nd-20		
France	Surface water	Tylosin	nd-2.8		(Dinh et al. 2011)
		Erythromycin	nd-131		
		Tetracycline	nd-7.4		
		Trimethoprim	nd-254		
		Sulfamethoxazole	nd-1435		
		Ciprofloxacin	nd-135		
		Norfloxacin	nd-75		
		Ofloxacin	2.1-231		
Italy		Azithromycin	7		(Verlicchi et al. 2014)
		Ciprofloxacin	25		
		Trimethoprim	2		
Finland		Ciprofloxacin	nd-36		(Vieno et al. 2006)
		Ofloxacin	nd-5		
Dagu River	Sediment	Roxithromycin	21-5622	ng/g	(Hu et al. 2012)
		Ofloxacin	nd-634		
		Ciprofloxacin	9-7812		
		Enrofloxacin	nd-7708		
		Acetylspiramycin	16-7653		
		Sulfachloropyridazine	nd-6310		
		Trimethoprim	nd-3502		
		Sulfadiazine	nd-12300		
		Gentamicin	nd-11230		
		Rifampicin	nd-12370		
		Minocycline	nd-5622		
		Oxytetracycline	nd-8211		
Haihe River	Sediment	Trimethoprim	0.75-28	ng/g	(Luo et al. 2011)
		Sulfadiazine	3.4-34		
		Sulfamethoxazole	0.85-59		
		Sulfachloropyridazine	2.1-39		

		Ciprofloxacin	nd-55		
		Ofloxacin	nd-69		
		Tetracycline	nd-7.8		
		Oxytetracycline	nd-57		
		Erythromycin	nd-7.3		
		Roxithromycin	nd-7.2		
Yellow River	Sediment	Sulfadiazine	nd-22.0	ng/g	(Zhou et al. 2011)
		Trimethoprim	nd-2.86		
		Oxytetracycline	nd-7.42		
		Tetracycline	nd-18.0		
		Norfloxacin	nd-56.9		
		Ofloxacin	nd-63.04		
		Ciprofloxacin	nd-32.8		
		Erythromycin-H_2O	nd-49.8		
		Roxithromycin	nd-6.80		
Hai River	Sediment	Sulfadiazine	nd-1.71		
		Sulfapyridine	nd		
		Sulfamethazine	nd-5.69		
		Trimethoprim	nd-5.63		
		Oxytetracycline	nd-422		
		Tetracycline	1.19-135		
		Chlortetracycline	nd-10.9		
		Doxycycline	nd-7.00		
		Norfloxacin	5.95-5770		
		Ofloxacin	nd-59.5		
		Ciprofloxacin	2.05-1290		
		Lomefloxacin	nd-298		
		Enrofloxacin	nd-2.34		
		Erythromycin-H_2O	nd-67.2		
		Roxithromycin	nd-11.7		
Liao River	Sediment	Sulfadiazine	nd-11.0		
		Sulfamethoxazole	nd		
		Trimethoprim	nd-9.84		
		Oxytetracycline	nd-653		
		Tetracycline	nd-4.82		
		Chlortetracycline	nd-32.5		
		Doxycycline	nd-2.80		
		Norfloxacin	nd-177		
		Ofloxacin	nd-50.5		
		Ciprofloxacin	nd-28.7		
		Lomefloxacin	nd-5.82		
		Erythromycin-H_2O	nd-40.3		
		Roxithromycin	nd-29.6		
Huangpu River	Sediment	Sulfadiazine	0.07-0.71 (0.4)	ng/g	(Chen and Zhou 2014)

(Shanghai)					
		Sulfapyridine	nd-6.6 (1.7)		
		Sulfamethoxazole	0.05-0.6 (0.2)		
		Sulfathiazole	nd-0.6 (0.2)		
		Sulfamerazine	0.03-0.8 (0.2)		
		Sulfamethazine	0.2-2.7 (1.2)		
		Sulfaquinoxaline	0.08-0.9 (0.4)		
		Erythromycin	1.5-24.6 (10.2)		
		Roxithromycin	0.3-4.1 (1.9)		
		Enrofloxacin	nd-8.9 (3.2)		
		Ofloxacin	nd-12.4 (4.1)		
		Chloramphenicol	nd-0.7 (0.3)		
		Thiamphenicol	nd-1.3 (0.4)		
		Florfenicol	nd-1.3 (0.5)		
		Tetracycline	nd-21.7 (3.5)		
		Oxytetracycline	0.6-18.6 (6.9)		
		Doxycycline	nd-21.3 (7.0)		
		Chlortetracycline	nd-6.3 (2.4)		
Yongjiang River	Sediment	Sulfacetamide	nd-0.43 (0.039)	ng/g	(Xue et al. 2013)
Nanning City		Sulfadiazine	nd-0.07 (0.017)		
		Sulfathiazole	nd		
		Sulfadimidine	nd-0.81 (0.13)		
		Sulfamethoxazole	nd-0.20 (0.032)		
		Trimethoprim	nd-1.07 (0.32)		
		Roxithromycin	0.19-2.16 (0.93)		
		Erythromycin	0.30-2.58 (1.36)		
		Clarithromycin	0.09-0.89 (0.40)		
		Azithromycin	0.11-0.79 (0.35)		
Qingshan Lake	Sediment	Trimethoprim	42.0-130.3	ng/g	(Zhu et al. 2013)
		Penicillin G	nd		
		Penicillin V	nd		
		Sulfamethoxazole	2.1-7.9		
Pearl River Delta	Sediment	Sulfadiazine	nd	ng/g	(Liang et al. 2013)
		Sulfamethazine	0.44-3.24		
		Sulfamethoxazole	nd		
		Norfloxacin	2.61-20.5		
		Ofloxacin	0.74-13.7		
		Enrofloxacin	1.03-1.43		
		Tetracycline	0.61-7.13		
		Erythromycin-H_2O	0.70-14.0		
		Roxithromycin	6.07-13.5		
Gongdong province	Sediment	Sulfadiazine	nd-83.9	ng/g	(Yang et al. 2010)

(Pearl River Delta)					
		Sulfapyridine	nd		
		Sulfamethazin	nd-248		
		Sulfamethoxazole	nd		
		Oxytetracycline	nd-196		
		Tetracycline	nd-72.6		
		Norfloxacin	nd-1120		
		Ofloxacin	nd-1560		
		Ciprofloxacin	nd-87.5		
		Erythromycin-H_2O	nd-62.7		
		Roxithromycin	nd-133		
Other countries					
US	Sediment	Chlortetracycline	2.1-10 (4.6)	ng/g	(Arikan et al. 2008)
		Sulfamethoxazole	0.10-0.15 (0.10)		
US	Sediment	Tetracycline	1.1-102.7 (17.9)	ng/g	(Kim and Carlson 2007)
		Chlortetracycline	1.1-30.8 (10.8)		
		Oxytetracycline	2.4-56.1 (14.8)		
		Doxycycline	2.2-38.9 (15.7)		
		Sulfamerazine	2.3-6.8 (4.8)		
		Sulfamethazine	1.0-13.7 (4.7)		
		Sulfamethoxazole	1.2-1.9 (1.6)		
		Erythromycin-H_2O	1.3-25.6 (10)		
		Roxithromycin	1.1-5.9 (2.1)		
		Tylosin	1.1-9.3 (3.0)		
France	Sediment	Azithromycin	265.1 maximum	ng/g	(Feitosa-Felizzola and Chiron 2009)
		Clarithromycin	3.82 maximum		
Spain	Sediment	Carbamazepine	0.9		(Vazquez-Roig et al. 2012)
		Ciprofloxacin	1.1		
		Norfloxacin	0.4		
		Ofloxacin	0.1		
		Sulfamethoxazole	0.1		
		Tetracycline	0.7		
		Trimethoprim	0.2		
South Africa		Trimethoprim	87.55	ng/g	(Matongo et al. 2015)
Tianjin, Liaoning	Swine, chicken, and cattle manures	Ciprofloxacin	0.808	mg/kg	(Hou et al. 2015)
		Chlortetracycline	8.06		
		Oxytetracycline	2.875		
		Sulfamethoxazole	0.0189		
Tianjin	Swine	Ciprofloxacin	0.3-3	mg/kg	(Hu et al.

	manure, chicken manure				2008)
		Chlortetracycline	0.6-24.3		
		Oxytetracycline	9.7-173.2		
		Tetracycline	10.2-41.5		
		Doxycycline	8.6-59.8		
		Sulfamethoxazole	2.3;5.2		
		Sulfadiazine	4.5-18.7		
Tianjin	Manure	Ciprofloxacin	0.1-4.3	mg/kg	(Hu et al. 2010)
		Ofloxacin	0.23-15.7		
		Chlortetracycline	0.14-26.8		
		Oxytetracycline	0.08-183.2		
		Tetracycline	0.11-43.5		
		Sulfamethoxazole	0.23-5.7		
Liaoning	Swine, chicken and cattle manure	Tylosin	0.23-0.35	mg/kg	(Li et al. 2012)
		Enrofloxacin	1.77		
		Ciprofloxacin	0.78		
		Norflxacin	2.28		
Heilongjiang, Jilin and Liaoning provinces	Cattle manure	Tylosin	0.22-0.28 (0.25)	mg/kg	(Li et al. 2013b)
		Enrofloxacin	0.46-4.17 (1.18)		
		Ciprofloxacin	0.28-0.84 (0.53)		
		Norflxacin	0.43-1.76 (0.85)		
		Chlortetracycline	0.61-1.94 (1.04)		
		Oxytetracycline	0.21-10.37 (5.1)		
		Tetracycline	0.43-2.69 (1.08)		
		Sulfamethoxazole	0.22-1.02 (0.46)		
	Chicken manure	Tylosin	0.23-0.34 (0.28)		
		Enrofloxacin	0.33-15.43 (3.33)		
		Ciprofloxacin	0.33-2.94 (1.03)		
		Norflxacin	0.5-9.52 (2.72)		
		Chlortetracycline	0.57-3.11 (1.29)		
		Oxytetracycline	0.96-13.39 (6.45)		
		Tetracycline	0.54-4.57 (1.83)		
		Sulfamethoxazole	0.25-7.11 (2.23)		
	Swine manure	Tylosin	0.23-1.88 (0.69)		
		Enrofloxacin	0.36-2.22 (0.87)		
		Ciprofloxacin	0.31-0.96 (0.49)		
		Norflxacin	0.41-3.18 (1.1)		
		Chlortetracycline	0.68-22.34 (3.19)		
		Oxytetracycline	0.73-56.81 (11.81)		
		Tetracycline	0.32-30.55 (5.29)		
		Sulfamethoxazole	0.21-2.16 (1.07)		

Beijing, Jiaxing (Zhejiang province) and Putian (Fujian province)	Swine manure	Chlortetracycline	0.0079;0.0674;0.127	mg/kg	(Qiao et al. 2012)
		Oxytetracycline	0.0749;2.544;0.0392		
		Tetracycline	0.0022;0.122;1.21		
Shandong	Swine manure	Chlortetracycline	2.6 Median	mg/kg	(Pan et al. 2011)
	Winter and Summer	Oxytetracycline	0.4 Median		
		Tetracycline	0.4 Median		
		Sulfamethoxazole	0.3 Median		
Shandong,Jiangsu,Shanghai,Zhejiang, Anhui,Sichuan and Yunnan	Chicken manure	Enrofloxacin	0.0106-8.575 (0.1028)	mg/kg	(Zhang et al. 2015b)
		Ofloxacin	0.0179-4.99 (0.232)		
		Norflxacin	0.0102-4.54 (0.114)		
		Chlortetracycline	0.0139-0.1295 (0.0227)		
		Oxytetracycline	0.019-416.75 (0.7153)		
		Tetracycline	0.0214-8.675 (0.1102)		
		Doxycycline	0.0198-8.3 (0.1049)		
		Sulfamethoxazole	0.0041-0.0288 (0.0067)		
		Sulfamethazine	0.0059-0.0227 (0.0097)		
		Sulfadiazine	0.0055-1.845 (0.0282)		
	Duck manure	Enrofloxacin	0.0201-0.0287 (0.024)		
		Ofloxacin	0.0735-0.595 (0.209)		
		Norflxacin	0.0162-0.384 (0.0789)		
		Chlortetracycline	0.0191-0.0443 (0.0291)		
		Oxytetracycline	0.0205-7.15 (0.3829)		
		Tetracycline	0.132-0.52 (0.262)		
		Doxycycline	0.1225-0.505 (0.2487)		
		Sulfamethoxazole	0.0049-0.0081 (0.0063)		
		Sulfamethazine	0.0074-0.011 (0.009)		

		Sulfadiazine	0.0053-0.0055 (0.0054)		
	Swine manure	Enrofloxacin	0.0125-0.089 (0.0388)		
		Ofloxacin	0.012-0.124 (0.038)		
		Norflxacin	0.0138-0.107 (0.0409)		
		Chlortetracycline	0.0206-215.346 (1.0407)		
		Oxytetracycline	0.0215-43.429 (1.1)		
		Tetracycline	0.0159-30.941 (0.6027)		
		Doxycycline	0.0151-30.718 (0.6379)		
		Sulfamethoxazole	0.0041-0.0143 (0.0065)		
		Sulfamethazine	0.0057-0.0337 (0.0117)		
		Sulfadiazine	0.0051-6.792 (0.1195)		
	Cattle manure	Enrofloxacin	0.0101-0.74 (0.0561)		
		Ofloxacin	0.0212-0.1895 (0.0642)		
		Norflxacin	0.0184-0.227 (0.0624)		
		Chlortetracycline	0.0151-0.0655 (0.0302)		
		Oxytetracycline	0.13-1.94 (0.532)		
		Tetracycline	0.0173-2.495 (0.074)		
		Doxycycline	0.0153-2.495 (0.0745)		
		Sulfamethoxazole	0.0042-0.00785 (0.0052)		
		Sulfamethazine	0.0047-0.034 (0.0106)		
		Sulfadiazine	0.0052-0.065 (0.0125)		
Shandong, Jiangsu, Shanghai, Zhejiang, Jiangxi, Hubei, Hunan and Guangxi	Swine manure	Enrofloxacin	0.48-33.26 (2.09)	mg/kg	(Zhao et al. 2010)
		Ciprofloxacin	0.64-33.98 (2.01)		
		Norflxacin	0.56-5.5 (2.09)		
		Chlortetracycline	0.16-21.06 (1.15)		
		Oxytetracycline	0.15-59.06 (2.69)		
		Doxycycline	0.23-13.5 (0.79)		
		Sulfamethoxazole	0.23-0.84 (0.51)		

province		Sulfadiazine	0.09-0.8 (0.21)		
	Chicken manure	Enrofloxacin	0.33-1420.76 (4.65)		
		Ciprofloxacin	0.68-45.59 (3.78)		
		Norflxacin	0.85-225.45 (4.68)		
		Chlortetracycline	0.16-17.68 (1.09)		
		Oxytetracycline	0.27-10.56 (1.55)		
		Doxycycline	0.92-10.91 (3.39)		
		Sulfamethoxazole	0.12-2.8 (0.78)		
		Sulfadiazine	0.03-3.12 (0.15)		
	Cattle manure	Enrofloxacin	1.72-46.7 (6.79)		
		Ciprofloxacin	0.49-29.59 (3.44)		
		Norflxacin	1.23-2.76 (1.84)		
		Chlortetracycline	0.24-27.59 (2.22)		
		Oxytetracycline	0.32-59.59 (1.24)		
		Doxycycline	0.44-1.05 (0.68)		
Nanjing	Chicken manure	Enrofloxacin	0.0036-7 (1.2425)	mg/kg	(Huang et al. 2013b)
		Ciprofloxacin	0.0205-0.52 (0.1501)		
		Ofloxacin	0.072-1.0525 (0.2895)		
		Norflxacin	0.0765-1.285 (0.4028)		
		Chlortetracycline	0.0144-0.02551 (0.0182)		
		Oxytetracycline	0.1925-3.0775 (0.7566)		
		Tetracycline	0.0223-0.117 (0.0696)		
		Doxycycline	0.0256-0.1172 (0.0664)		
		Sulfamethoxazole	0.0048-0.0288 (0.012)		
		Sulfamethazine	0.0096-0.0227 (0.015)		
		Sulfadiazine	0.0058-1.04 (0.2126)		
Shanghai	Swine, poultry and cattle manure	Oxytetracycline	18.7;21.36;21.96	mg/kg	(Ji et al. 2012)
		Tetracycline	12.27;12.01;10.31		
		Sulfamethoxazole	7.56;9.36;8.62		
		Sulfamethazine	6.17;6.39;8.01		
		Sulfadiazine	4.87;4.57;8.03		
Guangxi	Swine manure	Ofloxacin	0.00815	mg/kg	(Zhou et al. 2012)

		Chlortetracycline	35.5		
		Oxytetracycline	0.661		
		Tetracycline	0.821		
Bobai county(swine) and Nanning city in Guangxi province	Swine manure	Enrofloxacin	nd-0.0165	mg/kg	(Zhou et al. 2013a)
		Ciprofloxacin	nd-0.00908		
		Ofloxacin	0.0053-2.97		
		Norflxacin	0.0102-0.0479		
		Chlortetracycline	2.36-97.6		
		Oxytetracycline	0.235-1.7		
		Tetracycline	0.0671-9.26		
		Doxycycline	0.0177-2.24		
		Sulfamethazine	0.00675-0.25		
		Sulfadiazine	0.00463-0.254		
Bobai County of Guangxi province	Swine manure	Ofloxacin	nd-0.00444	mg/kg	(Zhou et al. 2013c)
		Norflxacin	nd-0.00645		
		Chlortetracycline	0.464-141		
		Oxytetracycline	0.0108-0.636		
		Tetracycline	0.00738-17.7		
		Doxycycline	0.199-0.814		
		Sulfamethazine	nd-0.00177		
Other countries					
Korea	Swine, poultry and cattle manure	Macrolides	0.07-0.14,1.05-2.1,0.62-1.24	mg/kg	(Kim et al. 2011)
		Sulfanomides	0.49,8.44,1.39		
		Tetracyclines	1.65,16.56,15.62		
US	Slurry manure	Sulfamethazine	0.00225-0.00506	mg/L	(Shelver et al. 2010)
		Sulfamethoxazole	0.000108-1.47	mg/L	
		Sulfathiazole	0.000785-0.0017	mg/L	
Canada	Cattle manure	Sulfamethazine	9.9	mg/kg	(Aust et al. 2008)
		Chlortetracycline	0.4		
Germany	Swine manure	Tetracycline	0.1-46	mg/kg	(Holzel et al. 2010)
		Chlortetracycline	0.1-50.8		
		Oxytetracycline	0.1-0.9		
		Doxycycline	0.1-0.7		

		Sulfonamides	0.05-38.4		
Turkey	Swine, poultry and cattle manure	Oxytetracycline	0.06-0.48	mg/kg	(Karci and Balcioglu 2009)
		Chlortetracycline	0.24-0.38		
		Sulfamethazine	0.1-3.76		
		Enrofloxacin	0.06		
		Sulfadiazine	1.2		
Austria	Swine, chicken and turkey manure	Tetracycline	0.36-23	mg/kg	(Martinez-Carballo et al. 2007)
		Oxytetracycline	0.21-29		
		Enrofloxacin	0.13-0.75,2.8-8.3		
		Chlortetracycline	0.1-46;1.7		
		Sulfadiazine	51,91		
		Sulfadimidine	20		
		Trimethoprim	17		
Beijing and Tianjin	Soil	Chlortetracycline	0.8-5.2	ng/g	(Chen et al. 2014)
		Oxytetracycline	2.6-111.8		
		Sulfamethoxazole	0.8-90		
		Sulfadiazine	0.8-97.2		
Ninghe, Dongli, and Jinnan in Tianjin and from Shenyang, Fushun, and Tieling in Liaoning province	Soil	Tylosin	1.8-44.6	ng/g	(Hou et al. 2015)
		Enrofloxacin	9.2-96.4		
		Ciprofloxacin	6.2-83.2		
		Ofloxacin	4.9-115.1		
		Chlortetracycline	4.9-10967		
		Oxytetracycline	0.3-571.4		
		Tetracycline	2.3-152.9		
		Doxycycline	14.8-494.7		
		Sulfamethoxazole	2.2-58.1		
Tianjin	Soil	Ciprofloxacin	0.8-30.1	ng/g	(Hu et al. 2010)
		Ofloxacin	0.6-1.6		
		Chlortetracycline	33.1-1079		
		Oxytetracycline	124-2683		
		Tetracycline	2.5-105		
		Sulfamethoxazole	0.03-0.9		
		Chloramphenicol	0.1-1.1		
Beijing, Jiaxing (Zhejiang province) and Putian (Fujian province)	Soil	Chlortetracycline	1.6-239.4	ng/g	(Qiao et al. 2012)

		Oxytetracycline	1.6-12.3		
		Tetracycline	nd-90		
		Doxycycline	nd-8.6		
Beijing, Shijiazhuang, Wuhan, Kunming, Baotou and Urumqi	Soil	Ciprofloxacin	8.12-13.74	ng/g	(Wang et al. 2014b)
		Ofloxacin	7.54-25.23		
		Norflxacin	9.32-14.54		
		Chlortetracycline	0.36-62.61		
		Oxytetracycline	0.29-33.21		
		Tetracycline	1.32-95.28		
		Doxycycline	0.16-107.10		
Beijing, Tianjin, and Jiaxing	Soil	Chlortetracycline	0.36-33.2	ng/g	(Wu et al. 2010)
		Oxytetracycline	0.29-33.21		
		Tetracycline	1.32-95.28		
		Doxycycline	0.16-5.01		
Shandong province	Soil	Enrofloxacin	0.1-166.9 (18.6)	ng/g	(Li et al. 2014b)
		Ciprofloxacin	2.4-651.6 (104.4)		
		Ofloxacin	0.4-288.3 (55.7)		
Nanjing	Soil	Enrofloxacin	nd-20.6 (7.7)	ng/g	(Huang et al. 2013b)
		Ciprofloxacin	nd-17.1 (8.1)		
		Ofloxacin	nd-25.85 (8.1)		
		Norflxacin	nd-13.7 (4.0)		
		Oxytetracycline	nd-19.3 (7.3)		
		Sulfachinoxalin	20.3-33.1 (26.6)		
		Sulfaclozine	nd-10.2 (3.6)		
Shanghai	Soil	Oxytetracycline	3410-4240	ng/g	(Ji et al. 2012)
		Tetracycline	1870-2450		
		Sulfamethoxazole	1320-2210		
		Sulfamethazine	1290-1630		
		Sulfadiazine	1930-2450		
Fuyang city in Zhejiang provience	Soil	Chlortetracycline	0.22-18.2	ng/g	(Wu et al. 2013)
		Oxytetracycline	0.48-6.72		
		Tetracycline	0.28-2.75		
		Doxycycline	0.21-16.4		
Fujian	Soil	Enrofloxacin	nd-637.3 (15.3)	ng/g	(Huang et al. 2013a)
		Ciprofloxacin	nd-237.3 (29.3)		
		Ofloxacin	nd-205.7 (4.7)		
		Chlortetracycline	nd-2668.9 (55.6)		
		Oxytetracycline	7.2-613.2 (28.5)		
		Tetracycline	nd-189.8		

Guangxi	Soil	Enrofloxacin	6.22	ng/g	(Zhou et al. 2012)
		Ofloxacin	1.85		
		Norflxacin	9.35		
		Chlortetracycline	33.3		
		Oxytetracycline	8.59		
		Tetracycline	3.09		
Bobai county(swine) and Nanning city in Guangxi province	Soil	Enrofloxacin	nd-95.8	ng/g	(Zhou et al. 2013a)
		Ciprofloxacin	nd-14.0		
		Ofloxacin	nd-108		
		Norflxacin	nd-58.8		
		Chlortetracycline	nd-12900		
		Oxytetracycline	nd-1410		
		Tetracycline	nd-1010		
		Doxycycline	nd-499		
		Sulfamethazine	nd-3.69		
		Sulfadiazine	nd-4.95		
		Sulfamononmethoxine	nd-5.37		
Bobai County of Guangxi province	Soil	Ofloxacin	1.04	ng/g	(Zhou et al. 2013c)
		Chlortetracycline	116		
		Oxytetracycline	13.1		
		Tetracycline	4.06		
		Doxycycline	13.5		
		Sulfamethazine	11.9		
		Sulfamononmethoxine	5.74		
Other countries					
Korea	Soil	Chlortetracycline	0.31-0.89	ng/g	(Ok et al. 2011)
		Oxytetracycline	1.68-3.77		
		Tetracycline	0.82-2.94		
		Sulfamethoxazole	0.77-5.43		
		Sulfamethazine	20.30-28.38		
Malaysia	Soil	Doxycycline	63-728	ng/g	(Ho et al. 2014)
		Tylosin	8-679		
		Norfloxacin	18-96		
		Enrofloxacin	36-378		
Turkey	Soil	Oxytetracycline	20-510	ng/g	(Karci and Balcioglu 2009)
		Chlortetracycline	80-120		
		Sulfamethazine	40-110		
		Enrofloxacin	20-50		
US	Soil	Sulfamethazine	0.0345-0.663	ng/g	(Shelver et al.

					2010)
		Sulfadimethoxine	15	ng/g	(Watanabe et al. 2010)
		Sulfamethoxazole	11		
		Tetracycline	30		
Canada	Soil	Sulfamethazine	10.4-72	ng/g	(Aust et al. 2008)
UK	Soil	Oxytetracycline	322-1691	ng/g	(Kay et al. 2004)
		sulfachloropyridazine	212-365		
Spain	Soil	Sulfisomidin	0.11	ng/g	(Garcia-Galan et al. 2013)
		Sulfadiazine	2.59		
		Sulfamethoxazole	1.01		
		Sulfamethoxypyridazine	5.13		
		Sulfadimethoxine	0.18		
Denmark	Soil	Tylosin A	1-50	ng/g	(Halling-Sørensen et al. 2005)
		Chlortetracycline	20-30		
Germany	Soil	Tetracycline	295	ng/g	(Hamscher et al. 2005)
		Sulfamethazine	2		
		Chlortetracycline	39		

Table S2 Abundance of antibiotic resistant genes (ARGs) in different environment media in China

Location	Media	ARGs	Abundance Rang/mean	Unit	Reference
Hebei	STP Effluent & Sludge	*tetA, tetC, tetG, tetL, tetM, tetO, tetQ, tetW, tetX*	$1.2 \times 10^{-4} – 1.3$	copies/16SrRNA	(Liu et al. 2012)
Northern China	STP Effluent	*sul*	6.7×10^{5}	copies/mL	(Mao et al. 2015)
		erm	7.0×10^{5}		
		tet	8.4×10^{4}		
		qnr	7.3×10^{3}		
	STP Sludge	*sul*	2.2×10^{11}	copies/g	
		erm	1.2×10^{10}		
		tet	1.3×10^{10}		
		qnr	1.5×10^{9}		
Northern China	STP Influent	*sul*, *sul2, tetM, tetW, tetQ, tetO, tetT, blaOXA-1, blaOXA-10*	$1.46 \times 10^{2} – 1.78 \times 10^{8}$	copies/mL	(Wang et al. 2015)
	STP Effluent	*sul*, *sul2, tetM, tetW, tetQ, tetO, tetT, blaOXA-1, blaOXA-10*	$2.08 \times 10^{3} – 3.68 \times 10^{6}$	copies/mL	
	STP Sludge	*sul*, *sul2, tetM, tetW, tetQ, tetO, tetT, blaOXA-1, blaOXA-10*	$9.38 \times 10^{7} – 4.3 \times 10^{10}$	copies/g	
Harbin	STP Influent	*tetW*	2.63×10^{6}	copies/mL	(Wen et al. 2016)
		tetA	2.82×10^{4}		
		tetO	4.57×10^{4}		
	STP Effluent	*tetW*	1.0×10^{7}		
		tetA	2.19×10^{5}		
		tetO	2.82×10^{5}		
Hangzhou	STP Influent	*tet*	6.91×10^{7}	copies/mL	(Chen and Zhang 2013a)
		sul	3.06×10^{7}		
		intI1	8.44×10^{7}		
	STP Effluent	*tet*	1.21×10^{6}		
		sul	3.31×10^{6}		
		intI1	2.82×10^{6}		
Hangzhou	STP Influent	*tetM*	3.78×10^{-3}	copies/16SrRNA	(Chen and Zhang 2013b)

		tetO	5.81×10^{-4}		
		tetQ	1.23×10^{-3}		
		tetW	9.27×10^{-3}		
		sul	4.76×10^{-2}		
Zhejiang	STP Influent	*tetA, tetB, tetC, tetG, tetL, tetM, tetO, tetQ, tetW, tetX, sul1, sul2, and intI*	$1.38 \times 10^{11} – 1.49 \times 10^{11}$	copies/mL	(Li et al. 2016b)
	STP Sludge	*tetA, tetB, tetC, tetG, tetL, tetM, tetO, tetQ, tetW, tetX, sul1, sul2, and intI*	$3.24 \times 10^{10} – 9.68 \times 10^{10}$	copies/g	
Jiangsu, Shanghai	STP Influent	*tetG*	$2.34 \times 10^{2} – 4.37 \times 10^{5}$	copies/mL	(Du et al. 2014)
		tetW	$1.74 \times 10^{3} – 5.62 \times 10^{5}$		
		tetX	$9.77 \times 10^{2} – 1.95 \times 10^{6}$		
		sul1	$1.29 \times 10^{5} – 1.1 \times 10^{7}$		
		intI1	$1.58 \times 10^{5} – 2.04 \times 10^{7}$		
	STP Effluent	*tetG*	$2.45 \times 10^{3} – 3.8 \times 10^{4}$		
		tetW	$5.89 \times 10^{1} – 3.55 \times 10^{3}$		
		tetX	$5.01 \times 10^{3} – 2.09 \times 10^{5}$		
		sul1	$9.33 \times 10^{4} – 1.05 \times 10^{6}$		
		intI1	$8.71 \times 10^{4} – 9.12 \times 10^{6}$		
Nanjing	STP Influent	*tetA*	4.96×10^{7}	copies/mL	(Zhang et al. 2009b)
		tetC	8.06×10^{7}		
		intI1	2.04×10^{7}		
	STP Effluent	*tetA*	1.41×10^{6}		
		tetC	1.37×10^{6}		
		intI1	1.20×10^{6}		
Xinjiang	STP Influent	*sul1*	$1.79 \times 10^{-1} – 6.67 \times 10^{-1}$	copies/16SrRNA	(Li et al. 2016a)
		sul2	$7.33 \times 10^{-2} – 3.38 \times 10^{-1}$		
		sul3	$9.22 \times 10^{-2} – 5.9 \times 10^{-1}$		
		intI1	$8.07 \times 10^{-3} – 3.02 \times 10^{-2}$		
Hongkong	STP Influent	*tetA*	1.59×10^{8}	copies/mL	(Zhang et al. 2009a)
		tetC	1.90×10^{8}		
	STP Effluent	*tetA*	6.5×10^{4}		
		tetC	3.68×10^{5}		
South China	STP Effluent	*tetA, tetB, tetC, tetE, tetM, tetO, tetS,tetX,*	$7.11 \times 10^{-9} – 1.53 \times 10^{-4}$	copies/16SrRNA	(Huang et al. 2015)
Harbin,	STP Sludge	*tetA*	1.06×10^{-2}	copies/16SrRNA	(Zhang and

Beijing, Qingdao, Wuhan, Nanjing, Shanghai, Guangzhou, Hongkong					Zhang 2011)
		tetB	7.66×10^{-6}		
		tetC	1.31×10^{-2}		
		tetD	2.20×10^{-6}		
		tetE	2.20×10^{-6}		
		tetG	1.38×10^{-2}		
		tetK	2.68×10^{-5}		
		tetL	6.29×10^{-6}		
		tetM	5.15×10^{-5}		
		tetO	2.53×10^{-3}		
		tetA/P	1.30×10^{-4}		
		tetS	8.52×10^{-3}		
		tetX	1.62×10^{-3}		
Beijing River, South China	Surface water	*sul1*	$2.62 \times 10^{-3} – 4.16 \times 10^{-2}$ (1.41×10^{-2})	copies/ 16SrDNA	(Ling et al. 2013)
		sul2	$2.60 \times 10^{-4} – 7.09 \times 10^{-3}$ (1.58×10^{-3})		
		tetC	$8.30 \times 10^{-2} – 13.20$		
		tetA	$1.38 \times 10^{-2} – 1.37 \times 10^{-1}$		
		tetX	$2.69 \times 10^{-4} – 6.73 \times 10^{-2}$		
		tetG	$9.65 \times 10^{-7} – 3.76 \times 10^{-2}$		
		tetQ	$8.53 \times 10^{-5} – 1.53 \times 10^{-3}$		
		tetM	$4.30 \times 10^{-6} – 8.77 \times 10^{-4}$		
		tetO	$5.51 \times 10^{-6} – 8.23 \times 10^{-4}$		
Haihe River	Surface water	*sul1*	$9.3 \times 10^{4} – 1.8 \times 10^{6}$	copies/mL	(Luo et al. 2010)
		sul2	$3.9 \times 10^{5} – 3.6 \times 10^{7}$		
Northern Yellow Sea	Surface water	*sul1, sul2*	$33 \times 10^{4} – 3.55 \times 10^{4}$	copies/mL	(Na et al. 2014)
Urban River, Beijing	Surface water	*sul1, sul2, tetA, tetB, tetE, tetM, tetZ*	$7.0 \times 10^{1} – 5.9 \times 10^{6}$	copies/mL	(Xu et al. 2016)
		intI1	1.2×10^{6}	copies/mL	
Huangpu River	Surface water	*sul1*	$0.32 \times 10^{5} – 1.84 \times 10^{5}$	copies/mL	(Jiang et al. 2013)
		sul2	$0.43 \times 10^{5} – 4.19 \times 10^{5}$		
		tetA	$0.28 \times 10^{3} – 3.16 \times 10^{3}$		
		tetB	$2.92 \times 10^{1} – 4.30 \times 10^{1}$		
		tetC	$1.03 \times 10^{3} – 4.08 \times 10^{3}$		
		tetG	$0.06 \times 10^{4} – 3.18 \times 10^{4}$		
		tetM	$2.30 \times 10^{1} – 31.0 \times 10^{1}$		
		tetO	$1.95 \times 10^{1} – 22.7 \times 10^{1}$		
		tetW	$1.61 \times 10^{1} – 38.4 \times 10^{1}$		
		tetX	$1.76 \times 10^{2} – 7.83 \times 10^{2}$		

		TEM	$1.36 \times 10^3 – 20.0 \times 10^3$		
Taihu Lake	Surface water	*tetA*	$10^4 – 10^5$	copies/mL	(Zhang et al. 2009b)
		tetC	10^5		
		intI1	10^3		
Jiulongjiang River	Surface water	*ami*	$2.78 \times 10^{10} – 3.66 \times 10^{10}$	copies/L	(Ouyang et al. 2015)
		sul	$2.55 \times 10^9 – 2.66 \times 10^9$		
		van	$6.00 \times 10^8 – 1.69 \times 10^9$		
Haihe River	Sediment	*sul1,sul2*	$2.6 \times 10^{-5} – 5.1 \times 10^{-2}$	copies/g	(Luo et al. 2010)
Northern Yellow Sea	Sediment	*sul1,sul2*	$8.3 \times 10^3 – 5.9 \times 10^7$	copies/g	(Na et al. 2014)
Urban River,Beijing	Sediment	*sul1, sul2, tetA, tetB, tetE, tetM, tetZ*	$4.2 \times 10^2 – 2.0 \times 10^8$	copies/g	(Xu et al. 2016)
		intI1	4.4×10^7	copies/g	
Dongjiang River	Sediment	*intI1*	1.84×10^8	copies/g	(Su et al. 2014)
		intI2	6.04×10^5		
		sul1	3.63×10^8		
		sul2	6.97×10^8		
		sul3	3.67×10^8		
		tetA	1.59×10^8		
		tetB	6.31×10^5		
		tetM	5.42×10^7		
		tetO	2.01×10^7		
		tetQ	2.68×10^7		
		tetS	1.87×10^7		
		tetW	1.99×10^7		
		tetX	1.04×10^8		
		ermB	1.29×10^8		
		ermC	8.27×10^6		
		ermF	4.37×10^8		
Yangtze River Estuary	Sediment	*intI1*	3.7×10^6	copies/g	(Lin et al. 2015)
Taihu Lake	Sediment	*tetA*	$10^8 – 10^9$	copies/mL	(Zhang et al. 2009b)
		tetC	$10^8 – 10^{10}$		
		intI1	$10^6 – 10^8$		
Liaoning	Manure	*tetM*	$(1.99 \pm 0.16) \times 10^6 – (1.85 \pm 0.13) \times 10^9$	copies/g	(Mu et al. 2015)
		tetO	$(3.53 \pm 0.26) \times 10^5 –$		

			$(1.69\pm0.14)\times10^{9}$		
		tetQ	$(3.10\pm0.33)\times10^{6}$ – $(1.66\pm0.09)\times10^{9}$		
		tetW	$(1.05\pm0.09)\times10^{7}$ – $(6.84\pm0.65)\times10^{8}$		
		sul1	$(9.35\pm0.87)\times10^{7}$ – $(2.05\pm0.19)\times10^{10}$		
		sul2	$(7.40\pm0.56)\times10^{7}$ – $(1.48\pm0.17)\times10^{10}$		
		qnrS	$(2.68\pm0.15)\times10^{6}$ – $(8.42\pm0.78)\times10^{7}$		
		oqxB	$(4.42\pm0.33)\times10^{8}$ – $(2.02\pm0.12)\times10^{10}$		
		ermB	$(1.70\pm0.14)\times10^{7}$ – $(1.31\pm0.10)\times10^{9}$		
		ermC	$(6.52\pm0.44)\times10^{5}$ – $(4.45\pm0.26)\times10^{7}$		
Tianjin	Manure	*tetM*	$(2.60\pm0.18)\times10^{7}$ – $(1.41\pm0.11)\times10^{9}$	copies/g	(Mu et al. 2015)
		tetO	$(5.41\pm0.46)\times10^{7}$ – $(8.26\pm0.81)\times10^{8}$		
		tetQ	$(2.25\pm0.14)\times10^{8}$ – $(2.96\pm0.25)\times10^{9}$		
		tetW	$(1.89\pm0.15)\times10^{8}$ – $(1.43\pm0.12)\times10^{9}$		
		sul1	$(1.46\pm0.08)\times10^{9}$ – $(2.89\pm0.26)\times10^{10}$		
		sul2	$(4.41\pm0.31)\times10^{8}$ – $(7.48\pm0.52)\times10^{9}$		
		qnrS	$(3.01\pm0.22)\times10^{8}$ – $(2.72\pm0.14)\times10^{9}$		
		oqxB	$(5.16\pm0.42)\times10^{8}$ – $(7.05\pm0.54)\times10^{10}$		
		ermB	$(9.31\pm0.86)\times10^{7}$ – $(2.06\pm0.16)\times10^{9}$		
		ermC	$(9.33\pm0.85)\times10^{6}$ – $(7.65\pm0.52)\times10^{7}$		
Beijing	Manure	*tet*M	1.47×10^{-3} – 1.95×10^{-2}	copies/16SrRNA	(Wang et al. 2016a)
		*tet*O	9.23×10^{-2} – 1.19×10^{0}		
		*tet*Q	1.77×10^{-2} – 1.54×10^{-1}		
		*tet*W	1.70×10^{-2} – 1.11×10^{-1}		
		*tet*A	1.56×10^{-4} – 1.87×10^{-3}		
		*tet*C	4.48×10^{-4} – 2.48×10^{-3}		
		*tet*G	7.44×10^{-6} – 1.59×10^{-3}		
		*tet*L	9.33×10^{-4} – 2.81×10^{-1}		
		*tet*A/P	2.50×10^{-3} – 2.70×10^{-2}		
		*tet*X	7.04×10^{-4} – 1.48×10^{-1}		
		*sul*1	1.80×10^{-3} – 2.53×10^{-2}		
		*sul*2	7.05×10^{-4} – 3.34×10^{-2}		
		*int*I1	1.85×10^{-5} – 3.45×10^{-3}		
		*int*I2	1.03×10^{-4} – 1.08×10^{-3}		

Hangzhou	Manure	*tet*A	$3.28 \times 10^6 – 2.48 \times 10^8$	copies/g	(Cheng et al. 2013)
		*tet*B	$7.29 \times 10^6 – 3.03 \times 10^8$		
		*tet*C	$1.47 \times 10^6 – 2.34 \times 10^7$		
		*tet*G	$1.68 \times 10^8 – 2.66 \times 10^9$		
		*tet*L	$3.74 \times 10^7 – 7.38 \times 10^8$		
		*tet*M	$6.63 \times 10^8 – 1.33 \times 10^9$		
		*tet*O	$2.23 \times 10^8 – 3.11 \times 10^9$		
		*tet*Q	$1.45 \times 10^9 – 3.18 \times 10^9$		
		*tet*W	$2.25 \times 10^8 – 1.64 \times 10^9$		
		*tet*X	$2.71 \times 10^7 – 1.65 \times 10^9$		
		*sul*I	$3.59 \times 10^8 – 3.66 \times 10^9$		
		*sul*II	$7.14 \times 10^8 – 4.27 \times 10^9$		
		*intI*1	$8.27 \times 10^8 – 3.15 \times 10^{10}$		
Hangzhou	Manure	*tet*A	4.7×10^9	copies/g	(Cheng et al. 2016)
		*tet*B	1.44×10^8		
		*tet*C	3.94×10^7		
		*tet*G	2.30×10^{10}		
		*tet*L	1.18×10^9		
		*tet*M	5.15×10^9		
		*tet*O	1.01×10^{11}		
		*tet*Q	6.60×10^{11}		
		*tet*W	2.98×10^{11}		
		*tet*X	1.13×10^{10}		
		*sul*I	1.14×10^{11}		
		*sul*II	4.90×10^{10}		
		*intI*1	4.53×10^{10}		
Shanghai	Manure & soil	*sul1, sul2, sul3, sulA*	$2.37 \times 10^{-5} – 4.23 \times 10^{-2}$	copies/16SrRNA	(Ji et al. 2012)
		tetM, tetW, tetO, tetBP	$2.23 \times 10^{-8} – 3.96 \times 10^{-3}$		
Jiangsu	Manure	*tet*A	$10^4 – 10^9$	copies/g	(Wang et al. 2016b)
		*tet*C	$10^5 – 10^8$		
		*tet*E	$10^5 – 10^8$		
		*tet*G	$10^5 – 10^9$		
		*tet*M	$10^5 – 10^{11}$		
		*tet*O	$10^6 – 10^{10}$		
		*tet*Q	$10^6 – 10^{10}$		
		*tet*T	$10^5 – 10^9$		
		*tet*W	$10^4 – 10^{10}$		
		*sul*1	$10^6 – 10^{10}$		
		*sul*2	$10^6 – 10^{11}$		
		*sul*3	$10^4 – 10^9$		

		*qnr*D	$10^4 – 10^8$		
		*qnr*S	$10^4 – 10^8$		
		*oqx*B	$10^4 – 10^9$		
		*erm*B	$10^6 – 10^{11}$		
		*erm*C	$10^5 – 10^{10}$		
		*acr*A	$10^5 – 10^9$		
		*acr*B	$10^4 – 10^9$		
		*aad*D	$10^5 – 10^{10}$		
		aph	$10^5 – 10^9$		
		aac	$10^5 – 10^{10}$		
Jiangsu	Manure	*sul*1	2.2×10^{-2}	copies/16SrRNA	(Zhang et al. 2015c)
		*sul*2	8.99×10^{-3}		
		*sul*3	6.09×10^{-3}		
		sulA	0.2×10^{-3}		
		qnrA	32×10^{-3}		
		*qnr*S	0.12×10^{-3}		
		*tet*A	2.03×10^{-3}		
		tetE	2.45×10^{-3}		
		tetB	1.02×10^{-3}		
		tetO	2×10^{-2}		
Beijing, Tianjin	Soil	*tet*A	$1.6 \times 10^{-5} – 1.2 \times 10^{-2}$	copies/16SrRNA	(Chen et al. 2014)
		*tet*B	nd – 2.1×10^{-5}		
		*tet*C	$2.4 \times 10^{-6} – 1.2 \times 10^{-1}$		
		*tet*D	nd – 2.6×10^{-5}		
		*tet*E	nd – 1.5×10^{-2}		
		*tet*G	$1.4 \times 10^{-5} – 4.3 \times 10^{-1}$		
		*tet*K	nd – 1.7×10^{-4}		
		*tet*L	nd – 3.1×10^{-4}		
		*tet*M	nd – 1.1×10^{-4}		
		*tet*O	$2.2 \times 10^{-6} – 8.2 \times 10^{-2}$		
		*tet*S	$1.4 \times 10^{-5} – 4.2 \times 10^{-1}$		
		*tet*Q	nd – 4.2×10^{-6}		
		*tet*X	nd – 1.2×10^{-3}		
		*sul*1	$4.9 \times 10^{-6} – 1.7$		
		*sul*2	$5.8 \times 10^{-7} – 1.7 \times 10^{-1}$		
		*sul*3	$1.4 \times 10^{-6} – 5.5 \times 10^{-3}$		
Liaoning	Soil	*tetM*	$(2.67\pm0.19)\times10^5$ – $(3.31\pm0.27)\times10^7$	copies/g	(Mu et al. 2015)
		tetO	$(1.92\pm0.08)\times10^5$ – $(3.68\pm0.34)\times10^7$		
		tetQ	$(1.91\pm0.14)\times10^5$ – $(1.24\pm0.07)\times10^7$		
		tetW	$(1.04\pm0.08)\times10^5$ – $(7.17\pm0.66)\times10^6$		

		sul1	$(4.89\pm0.37)\times10^{6}$ – $(5.98\pm0.58)\times10^{8}$		
		sul2	$(9.86\pm0.84)\times10^{6}$ – $(1.72\pm0.13)\times10^{9}$		
		qnrS	$(3.76\pm0.24)\times10^{4}$ – $(2.92\pm0.21)\times10^{6}$		
		oqxB	$(3.45\pm0.21)\times10^{7}$ – $(1.53\pm0.09)\times10^{8}$		
		ermB	$(1.79\pm0.15)\times10^{5}$ – $(1.79\pm0.11)\times10^{7}$		
		ermC	$(1.64\pm0.13)\times10^{4}$ – $(4.00\pm0.37)\times10^{5}$		
Tianjin	Soil	*tetM*	$(7.40\pm0.72)\times10^{6}$ – $(2.31\pm0.22)\times10^{7}$	copies/g	(Mu et al. 2015)
		tetO	$(2.08\pm0.12)\times10^{7}$ – $(1.82\pm0.14)\times10^{8}$		
		tetQ	$(1.13\pm0.09)\times10^{7}$ – $(5.06\pm0.41)\times10^{7}$		
		tetW	$(2.69\pm0.21)\times10^{6}$ – $(2.38\pm0.17)\times10^{7}$		
		sul1	$(4.84\pm0.33)\times10^{6}$ – $(1.83\pm0.15)\times10^{8}$		
		sul2	$(3.09\pm0.24)\times10^{6}$ – $(1.74\pm0.14)\times10^{8}$		
		qnrS	$(6.99\pm0.62)\times10^{5}$ – $(1.30\pm0.11)\times10^{7}$		
		oqxB	$(3.52\pm0.28)\times10^{7}$ – $(5.30\pm0.45)\times10^{8}$		
		ermB	$(6.81\pm0.54)\times10^{6}$ – $(1.05\pm0.07)\times10^{7}$		
		ermC	$(1.99\pm0.18)\times10^{5}$ – $(4.20\pm0.33)\times10^{5}$		
Beijing	Soil	*tet*M	1.18×10^{-4} – 6.44×10^{-4}	copies/16SrRNA	(Wang et al. 2016a)
		*tet*O	7.39×10^{-5} – 5.34×10^{-4}		
		*tet*Q	2.86×10^{-5} – 1.82×10^{-3}		
		*tet*W	5.98×10^{-5} – 3.68×10^{-4}		
		*tet*A	2.46×10^{-4} – 4.96×10^{-4}		
		*tet*C	1.48×10^{-3} – 4.37×10^{-3}		
		*tet*G	1.80×10^{-4} – 1.75×10^{-3}		
		*tet*L	4.38×10^{-4} – 2.80×10^{-3}		
		*tet*A/P	8.88×10^{-5} – 8.63×10^{-4}		
		*tet*X	3.62×10^{-6} – 1.08×10^{-2}		
		*sul*1	2.04×10^{-3} – 1.82×10^{-2}		
		*sul*2	4.44×10^{-4} – 1.52×10^{-2}		
		*int*I1	5.15×10^{-4} – 3.80×10^{-3}		
		*int*I2	4.39×10^{-5} – 7.08×10^{-4}		

Beijing, Tianjin, Jiaxing	Soil	*tet*M	$2.96 \times 10^5 – 1.43 \times 10^9$	copies/g	(Wu et al. 2010)
		*tet*O	$3.68 \times 10^5 – 4.09 \times 10^8$		
		*tet*Q	$6.63 \times 10^5 – 4.30 \times 10^8$		
		*tet*W	$1.38 \times 10^5 – 3.48 \times 10^8$		
		*tet*T	$7.86 \times 10^4 – 1.41 \times 10^7$		
Hangzhou	Soil	*tet*A	4.7×10^6	copies/g	(Cheng et al. 2016)
		*tet*B	1.38×10^5		
		*tet*C	4.16×10^6		
		*tet*G	5.36×10^7		
		*tet*L	2.51×10^6		
		*tet*M	4.89×10^7		
		*tet*O	1.50×10^8		
		*tet*Q	2.83×10^8		
		*tet*W	3.15×10^8		
		*tet*X	6.15×10^6		
		*sul*I	9.66×10^7		
		*sul*II	2.22×10^7		
		*intI*1	42.03×10^8		
Jiangsu	Soil	*tet*	$10^6 – 10^8$	copies/g	(Wang et al. 2016b)
		sul	$10^6 – 10^9$		
		qnr	$10^4 – 10^6$		
		erm	$10^4 – 10^7$		
		acr	$10^4 – 10^7$		
		ami	$10^4 – 10^7$		
Jiangsu	Soil	*sul*1	39.19×10^{-2}	copies/16SrRNA	(Zhang et al. 2015c)
		*sul*2	0.42×10^{-3}		
		*sul*3	0.48×10^{-3}		
		sulA	0.71×10^{-3}		
		*qnr*S	0.08×10^{-3}		
		*tet*A	0.02×10^{-3}		
		tetE	1.35×10^{-3}		
		tetB	0.44×10^{-3}		
		tetO	10.55×10^{-2}		

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