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Review article

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.

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)

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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 (normalized 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% 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 dropped 10% 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 (Fig. 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 remain 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 Hong Kong. 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 Hong Kong (7900 ng/L, 5430 ng/