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Usage, residue, and human health risk of antibiotics in Chinese aquaculture: A review

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ABSTRACT

Aquaculture is a booming industry in the world and China is the largest producer and exporter of aquatic products. To prevent and treat diseases occurred in aquaculture, antibiotics are widely applied. However, the information of antibiotics used in Chinese aquaculture is still limited. Based on peer-reviewed papers, documents, reports, and even farmer surveys, this review summarized antibiotics used in Chinese aquaculture. In 2014, more than 47.4 million tonnes of farmed aquatic products were produced in mainland China. The outputs in the east and south parts of China can reach as much as 600 times higher than those in the northwest areas, which is clearly separated by the “Hu Line” – a line that marks a striking difference in the distribution of population. A total of 20 antibiotics belonging to eight categories have been reported for use, mainly via oral administration. However, only 13 antibiotics have been authorized for application in Chinese aquaculture and 12 antibiotics used are not authorized. Totally, 234 cases on antibiotic residues in Chinese aquatic products were recorded, including 24 fish species, eight crustacean species, and four mollusk species. Thirty-two antibiotics have been detected in aquatic products; quinolones and sulfonamides were the dominated residual chemicals. For specific compound, ciprofloxacin, norfloxacin, and sulfisoxazole have the highest concentrations. Except for a few cases, all residual concentrations were lower than the maximum residue limits. Through the consumption of aquatic products tainted by antibiotics, humans may acquire adverse drug reactions or antibiotic-resistant bacteria. However, the risk of antimicrobial resistance in human body, when exposed to antibiotics at sub-inhibitory concentrations, has not been exhaustively considered in the risk assessment. In addition, a national comprehensive investigation on the amount of antibiotics used in Chinese aquaculture is still needed in future studies.

1. Introduction

Aquaculture is a booming industry around the world, providing one of the most sustainable forms of edible protein and nutrient production. According to a report by the Food and Agriculture Organization (FAO) in 2014, the global aquaculture production has doubled over the past decade, now accounting for ~50% of fishery products for human consumption. As the largest provider of aquaculture products, China yields 41.1 million tonnes of farmed food fish in 2012, contributing to ~61.7% of total world output (FAO, 2014). Driven by market forces, the aquaculture has been increasing rapidly and then suffering from overcrowding, diseases, and mortalities worldwide (FAO, 2013). For example, China loses 100–200 billion Yuan (approximately 15–30 billion USD) every year because of disease outbreak in aquaculture, and more than half of the diseases are caused by bacterial infections (Wang et al., 2015a).

To prevent and treat these diseases, antibiotics have been largely applied in aquaculture. Consequently, their residues in fishery products have occurred and raised wide concerns because dietary consumption is generally considered as a main way for unintentional human exposure to organic pollutants (Cabello, 2006; Wang

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et al., 2016). During 1995–2000, Japan frequently returned or disposed farmed eels and eel products imported from China as the levels of antibiotics contained exceed the standards established by Japanese government (FAO, 2005). Since 2002, the United States and European Union also have issued stringent regulations for antibiotic residues in aquatic products (Chen and Chen, 2002; Hvistendahl, 2012; Wang and Xiong, 2007).

China is the largest producer and user of antibiotics in the world (Zhu et al., 2013); approximately 162,000 tonnes of antibiotics were used in 2013, with animal consumption accounting for half of the total (Zhang et al., 2015). Hvistendahl (2012) presented similar data – nearly half of the 210,000 tonnes of antibiotics produced in China end up in animal feed. Despite the widespread use of antibiotics, the types and amounts of antibiotics used in Chinese aquaculture is still limited, and the contribution from aquaculture is generally overlooked when estimating non-human use of antibiotics. In addition, the antibiotic residues in aquatic products were not fully recognized. Here we conducted a systematic review on antibiotics in Chinese aquaculture, from the usage to the occurrence in aquatic products and to the human health risk caused. An extensive literature survey was performed, including studies from 1996 to early 2016. All targeted antibiotics in this review are listed in Table S1 ("S" indicates the Supporting Information), including common name, CAS number, full chemical name, and chemical formula and structure.

2. Aquaculture in China

Although the detailed history is unavailable, aquaculture in China can date back to 1100 B.C. (Pappalardo et al., 1992). Since the 1970s, Chinese aquaculture has undergone unprecedented development driven by economic benefits (Yuan and Chen, 2012). More than 47.4 million tonnes of farmed aquatic products were produced in mainland China in 2014 (except for Hong Kong and Macau), in which freshwater and saltwater (marine) aquaculture accounted for approximately 62% and 38%, respectively (NBSC, 2015). For freshwater species, fish (e.g., grass carp, silver carp, and bighead carp), contributed to ~89%, whereas mollusks (e.g., oysters, clams, and mussels) were the main categories (~75%) for saltwater species (FBMA, 2015).

Fig. 1 illustrates the spatial profile of aquaculture volumes in China. Clearly, a large variation by region was observed – the volumes in the east and south parts can reach as much as 600 times higher than those in the north and west areas. The distribution of aquaculture production is consistent with that of population, which can be separated geographically into two sections by the "Hu Line" (also known as the "Heihe-Tengchong Line"). Guangdong, Shandong, Fujian, Jiangsu, and Hubei are the top five provinces of production with annual output of 6.68, 6.26, 4.63, 4.29, and 4.13 million tonnes, respectively, together contributing over half of the total production nationwide (NBSC, 2015). The first four provinces are located in coastal areas, where saltwater species are heavily cultured in cages suspended in water (pie chart in Fig. 1A). The aquaculture density, expressed as the ratio of output to the culture area, reflects the production capacity per unit area of aquaculture (Fig. 1B). By comparison, the distribution of density is more in conformity with the "Hu Line". Fujian, Guangdong, and Guangxi are the top three provinces with density as high as 17.7, 11.8, and 10.7 tonnes/ha, respectively.

3. Usage of antibiotics in Chinese aquaculture

High-density aquaculture provides big opportunities for disease-causing organisms to grow rapidly (Yang and Zheng, 2007). To control these diseases in aquaculture, antibiotics have been largely applied in China since the 1980s for their low cost, convenience of use and remarkable curative effect (Yuan and Chen, 2012). Prior to the 1990s, antibiotics were mainly used to treat aquatic species with high values (e.g., larval shrimps, eels, and soft-shell turtles) (Jiang, 1996), and then their applications have been largely expanded, including both freshwater and saltwater species in recent years. The information on antibiotic use in Chinese aquaculture is very limited (Rico et al., 2013; WHO, 1998), therefore we summarized data available from peer-reviewed papers, documents, reports, and even farmer surveys.

As shown in Table 1, a total of 20 antibiotics belonging to eight categories (i.e., aminoglycosides, β-lactams, chloramphenicols, macrolides, nitrofurans, quinolones, sulfonamides, and tetracyclines) have been reported in use during 1996–2013. All antibiotics used were developed between 1928 and 1996, almost two thirds of which are broad-spectrum bacteriostatic agents active against both Gram-positive and Gram-negative bacteria (Zhang, 2004). It should be noted that some antibiotics were designed only for humans, e.g., chloramphenicol, ciprofloxacin, erythromycin, and furazolidone. However, their applications in aquaculture were often reported in China, which may cause severe bacterial resistance on human clinical medication (Van Doorslaer et al., 2014). Moreover, as shown in Table 2, 13 antibiotics have been authorized for use in Chinese aquaculture (doxycycline, enrofloxacin, florfenicol, flumequine, neomycin, norfloxacin, oxolinic acid, sulfadiazine, sulfamethazine, sulfamethoxazole, sulfamonomethoxine, thiamphenicol, and trimethoprim), whereas only five (amoxicillin, oxolinic acid, oxytetracycline, sarafloxacin, and trimethoprim-sulfadiazine) were authorized for use by the United Kingdom and FAO (Alderman and Hastings, 1998; FAO, 2005). Furthermore, 12 antibiotics used in aquaculture are not authorized, i.e., amoxicillin, chloramphenicol, chlortetracycline, ciprofloxacin, erythromycin, furazolidone, gentamycin S, oxytetracycline, penicillin G, streptomycin, sulfamerazine S, and sulfisoxazole. Some antibiotics have been banned but they were still used occasionally. For example, usage of erythromycin was banned in 2002, but usage was reported in 2012 (Yuan and Chen, 2012). On the contrary, some antibiotics (i.e., flumequine, sulfamethazine, sulfamonomethoxine, thiamphenicol, and trimethoprim) were authorized whereas no case of usage was reported (Table 2).

Natural antibiotics, e.g., chloramphenicol, chlortetracycline, and erythromycin, were mainly used before 1996 (Jiang, 1996), and then some were banned for use due to bacterial resistance or severe adverse reactions, and replaced by chemically modified derivatives, semi-synthetic and synthetic antibiotics. For example, chloramphenicol and oxytetracycline were substituted by florfenicol, a second-class veterinary drug approved by the Ministry of Agriculture of China in 1999 (Xu et al., 2005; Yuan and Chen, 2012). A synthetic category of antibiotics – quinolones – is heavily used in aquaculture for the strong antibacterial activity on Gram-negative bacteria – the main bacterial pathogens in aquaculture (Ling et al., 2010). Besides, the action mechanism of quinolones is different with other antibiotics, which is inhibiting and interdicting DNA gyrase (Yu et al., 2005). However, the usage of quinolones should decrease because the Chinese government regulated the use of quinolones (e.g., lomefloxacin, norfloxacin and ofloxacin) in food-animals in 2016 (MAPRC, 2015).

Oral administration, usually mixed with feed, is the common route to apply antibiotics, especially for intestinal parasites and systemic diseases in aquaculture. Dosages of antibiotics administrated in this method varied greatly. Generally, less than 30 mg antibiotics were used for per kg fish (body weight; BW), but some antibiotics were applied with over 50 mg/kg BW. The antibiotics that were employed earlier have relatively larger dosage (Table 1). For example, chloramphenicol and furazolidone's usage limit was