Health risk from veterinary antimicrobial use in China’s food animal production and its reduction

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ABSTRACT

The overuse and misuse of veterinary drugs, particularly antimicrobials, in food animal production in China cause environmental pollution and wide food safety concerns, and pose public health risk with the selection of antimicrobial resistance (AMR) that can spread from animal populations to humans. Elevated abundance and diversity of antimicrobial resistance genes (ARGs) and resistant bacteria (including multi-drug resistant strains) in food-producing animals, food products of animal origin, microbiota of human gut, and environmental media impacted by intensive animal farming have been reported. To rein in drug use in food animal production and protect public health, the government made a total of 227 veterinary drugs, including 150 antimicrobial products, available only by prescription from licensed veterinarians for curing, controlling, and preventing animal diseases in March 2014. So far the regulatory ban on non-therapeutic use has failed to bring major changes to the long-standing practice of drug overuse and misuse in animal husbandry and aquaculture, and significant improvement in its implementation and enforcement is necessary. A range of measures, including improving access to veterinary services, strengthening supervision on veterinary drug production and distribution, increasing research and development efforts, and enhancing animal health management, are recommended to facilitate transition toward rational use of veterinary drugs, particularly antimicrobials, and to reduce the public health risk arising from AMR development in animal agriculture.

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1. Introduction

To meet the growing demand for animal products in China, food animal production is increasingly dominated by concentrated animal feeding operations (CAFOs), which are more efficient and economically more competitive compared to the traditional family farming and “free-range” farming. However, pigs, chickens, cows, and fishes raised at high stocking densities in close confinement have high levels of stress, and such conditions favor occurrence and spread of infectious diseases. Consequently, antimicrobials are routinely administered to animals, via feed or drinking water, or by injection, for treatment and prevention of diseases. In addition, antimicrobials at low and sub-therapeutic doses are often used as growth promoters to improve feed efficiency and promote animal growth (Clark et al., 2012; Marshall and Levy, 2011; Mole, 2013). Along with the expansion of CAFOs, the consumption of veterinary drugs has also been growing fast. The global market value of veterinary drugs (including antimicrobials) increased from 8.65 to 20.1 billion US dollar between 1992 and 2010, and was projected to reach 42.9 billion US dollar by 2018 (Hao et al., 2014). In China, the gross value of domestically produced veterinary pharmaceuticals increased from 20 to 35 billion Chinese Yuan over the period of 2009–2011, with three-quarters contributed by chemical drugs (Ministry of Agriculture, 2013a).

Although several laws and regulations on drug use in animal agriculture, such as the Administrative Regulations on Feed and Feed Additives and the Regulation on Veterinary Drug Administration, had been issued (Hu and Cheng, 2015), overuse and misuse of veterinary drugs was prevalent in China (Ellis and Turner, 2007; Hvistendahl, 2012; Larson, 2015). It was estimated that the average dose of antimicrobials used on farmed animals in China had jumped from approximately 50 to 703 mg/kg biomass between 2001 and 2007, with the usage in 2007 much greater than those reported...
in the developed countries at the same period (Hu and Cheng, 2015). Starting in the late 1990s, European countries, led by Denmark, had gradually phased out the use of antimicrobial growth promoters (AGPs) in food-producing animals (Clark et al., 2012; Marshall and Levy, 2011). In contrast, with antimicrobials available at low costs and poor regulatory control, antimicrobial usage in food animal production in China could well be among the highest in the world.

The absorption, distribution, metabolism, and excretion of veterinary drugs in animal bodies are determined by their pharmacokinetic properties. Depending on the type and dosage of the drug, and the species and age of the animal, only a fraction of the administered drug can be metabolized, while the rest ends up in the urine and feces (Sarmah et al., 2006). Large variations have been reported for the excretion rates of common antimicrobials in livestock and poultry, e.g., 17–75% for chlorotetracycline and 28–100% for tylosin (Kim et al., 2011; Sarmah et al., 2006). The excreted drugs, and their metabolites, some of which can be transformed back to the active forms in the environment, can pollute surface water, soils, and groundwater through wastewater discharge from animal farms and land application of manures (Kim et al., 2011; Sarmah et al., 2006). Besides disrupting the structures of microbiological communities, cycling of antimicrobials, and their metabolites in the environment can function as selective pressures for antimicrobial-resistant bacteria (Gullberg et al., 2011; Mole, 2013).

In addition to livestock and poultry, antimicrobials are also widely used in aquaculture, which is one of the fastest growing global food animal production industries, to treat diseases caused by bacteria, and more often to prevent occurrence of diseases (Alderman and Hastings, 1998). With total output of 4.11 million tonnes in 2012, China accounts for >60% of the global aquaculture production of fish, crustaceans, molluscs, and other aquatic animals (Food and Agriculture Organization (FAO), 2014). Significant quantities of antimicrobials are used in the country’s aquaculture sector, most frequently by water medication and medicated feed. Different from terrestrial-based livestock production, drugs and chemicals are administered directly or indirectly, into the culture water in aquafarming. As a result, the antimicrobials and their metabolites not only bring exposure of non-target organisms, such as algae and bacteria, which does not occur with direct administration of drugs in livestock husbandry, but also lead to selection of resistant bacteria in the impacted aquatic environments (Alderman and Hastings, 1998; Park et al., 2012).

2. Public health risk from veterinary drug use

The overuse and misuse of veterinary drugs in CAFOs not only cause pollution of the environmental media, but also pose health risk to the public through food-borne drug residues and selection of antimicrobial resistance (AMR) that can spread easily to humans. Residues of veterinary drugs, primarily antimicrobials and hormones, pose health hazard and risk to the consumers when exceeding the thresholds of toxicological concern in food products of animal origin, including meat, eggs, and milk. With pharmacological activity and/or toxicity, food-borne drug residues can cause acute and chronic health consequences, posing direct health risk to humans. To protect the health of consumers, the residues of veterinary drugs commonly used in food-producing animals, as well as those not approved for use, are regulated in the major categories of animal products and are monitored regularly (Table S1). National monitoring campaigns showed that the overall compliance rates for the residues of over 60 antimicrobials and 20 other veterinary drugs ranged from 99.37 to 99.96% in recent years (Ministry of Agriculture, 2014). Nonetheless, the excessive, and sometimes illegal, use of veterinary drugs had resulted in a few food safety incidents and caused significant public outcry (Table S2).

The selection and spread of resistant bacteria that can survive in the presence of one or more classes of antimicrobials probably represent the most serious public health risk from antimicrobial use in food animal production (Marshall and Levy, 2011; Mole, 2013). Although the causes of AMR are complex, there is a large scientific consensus that the antimicrobials used for treatment and prevention of bacterial infections and growth promotion in food-producing animals contribute to the emergence and spread of resistant bacteria (Marshall and Levy, 2011; Mole, 2013; Prudan et al., 2013). In particular, the non-therapeutic use of antimicrobials in CAFOs, where thousands to tens of thousands of animals are concentrated at high stocking rates under unnatural conditions, contributes significantly to the selection and propagation of resistant bacteria (Gullberg et al., 2011; Marshall and Levy, 2011; Mole, 2013). AMR can be transmitted readily among bacteria of the same or different species, and the resistant pathogens in food animals can infect humans directly or indirectly through a range of pathways, such as contact with the animals, animal products, and environmental media (e.g., water and soils) impacted by animal wastes (Mole, 2013; Smith et al., 2005). AMR developed in aquaculture also poses risk to humans through direct dissemination of the resistant bacteria fed in aquaculture products to people and transfer of the antimicrobial resistance genes (ARGs) from bacteria in aquatic environments to bacteria of terrestrial animals and human pathogens (Alderman and Hastings, 1998; Park et al., 2012). Modeling results suggest that agricultural antimicrobial use has important quantitative effects on the spread of AMR and the transmission from agriculture may even have a greater impact on human populations than hospital transmission (Smith et al., 2005). Because many antimicrobials used in food-producing animals are the same as or closely related to the medically important ones used in human health care, the emergence and spread of bacteria resistant to these drugs limit the therapeutic options for human diseases and can cause prolonged illness, serious disability, and even death (Marshall and Levy, 2011; Mole, 2013).

AMR is a growing global public health threat, and a particularly serious problem in China due to the historic overuse and misuse of antimicrobials in human health care and animal agriculture (Hvistendahl, 2012; Larson, 2015; Zhang et al., 2006). Although the Ministry of Agriculture has started to conduct surveillance on drug resistance in bacteria of animal origin since 2009, the results are not publicly available (Ministry of Agriculture, 2013a). Meanwhile, many small-scale investigations have found relatively high abundance of resistant bacteria, including multi-drug resistant strains, in animal meat products, livestock, poultry, and fish on the markets and in animal farms throughout the country (e.g., Broughton and Walker, 2009; Jiang et al., 2011, 2012; Jiang and Shi, 2013; Lai et al., 2014). Spread readily through the food chain, the AMR carried by food-borne bacteria constitutes a direct public health threat. Besides elevated occurrence of AMR in the pathogens responsible for hospital- and community-acquired infections (Hvistendahl, 2012), Chinese individuals have been found to harbor far more ARGs in their gut microbiota compared to the Europeans (Hu et al., 2013). The ARGs in human gut probably came from both the adaption of bacteria strains after antimicrobial exposure in the gastrointestinal tract and the antimicrobial-resistant bacteria and ARGs spread from food animals to humans (Forslund et al., 2013).

In addition to direct spreading of resistant bacteria and ARGs with the handling and disposal of animal wastes, the synthetic antimicrobials contained in them can also contribute significantly to the development of AMR in the environment, as enrichment and maintenance of AMR in bacterial populations can occur in the presence of antimicrobials even at low concentrations (Gullberg et al., 2011; Mole, 2013). It has been found that the diversity and
abundance of ARGs in the manure from Chinese swine farms, which used all major classes of antimicrobials except vancomycins, and in the soils fertilized by the manure were both drastically higher than those in the antimicrobial-free manure and soils (Zhu et al., 2013). The occurrence of ARGs in the Escherichia coli isolates from surface water bodies impacted by intensive livestock and poultry production was as high as or higher than those in fecal, wastewater, and clinical isolates (Chen et al., 2011). Resistance to multiple antimicrobials and multi-drug resistance were detected at high frequencies in the Enterobacteriaceae isolates from fish farms in southern China (Su et al., 2011). Oxytetracycline-resistant bacteria were found to be abundant in mariculture waters of northern China, and multi-drug resistance was also common, indicating ARGs were potentially widespread in the mariculture environments (Dang et al., 2007, 2008). Together, these findings indicate that the intensive animal farms with frequent antimicrobial use constitute an environmental reservoir of highly diverse and abundant ARGs and pose potentially significant public health risk (Alderman and Hastings, 1998; Park et al., 2012; Su et al., 2011).

The health risk from transmission of AMR developed in animal husbandry to humans is well recognized. It has been demonstrated that significant proportion of Escherichia coli infections in humans, plated with the strains resistant to antimicrobials, were transferred from food animals (Johnson et al., 2007; Zhang et al., 2009). Strong and significant correlations were found between the prevalence of AMR in Escherichia coli isolates from blood stream of human infections and the resistance in Escherichia coli isolates from food animals (particularly poultry and pigs) from analysis of surveillance data in 11 European countries over the period of 2005 and 2008 (Vieira et al., 2011). A systematic review of peer-reviewed publications also revealed that a proportion of human extraintestinal expanded-spectrum cephalosporin-resistant Escherichia coli infections originated from food-producing animals (especially poultry), primarily through whole bacterium transmission and transmission of resistance via mobile genetic elements (Lazarus et al., 2015). Overall, link between ARGs in strains from food animals, animal farms, and the clinic has been established, although continuing research is needed to develop a deeper understanding on the transfer of AMR from animals to humans.

### 3. Recommendations for improving control of veterinary drug use beyond the regulatory ban

Given the scale of China’s food animal production and the volumes of antimicrobials consumed by the animal agriculture, AMR development in animal husbandry and aquaculture is a major threat to public health. To stop the overuse and misuse of veterinary drugs in food animal production and safeguard food safety, the Ministry of Agriculture recently set the requirement of prescription from licensed veterinarians for using a total of 227 drugs, including 150 antimicrobial products, in the treatment, control, and prevention of animal diseases after March 1, 2014 (Ministry of Agriculture, 2013b, 2013c). This ban targets the end users by restricting the access of medically important drugs, and its full implementation can greatly reduce the food safety concern and the potential for AMR development in animal agriculture. Unfortunately, there is little indication that the ban has impacted the availability and use patterns of veterinary drugs in food animal production after taking effect for two years. Like previously issued regulations, lack of transparency and accountability, along with the challenges associated with compliance monitoring, resulted in poor implementation and enforcement. To help reduce the health risk from the use of veterinary drugs, particularly antimicrobials, in food animal production, a range of measures that can facilitate effective and efficient implementation of the ban and promote their rational use, are recommended:

#### 3.1. Improving access to veterinary services

The shortage of veterinary professionals emerged as an immediate challenge after the regulatory ban became effective, as only approximately 25,000 veterinarians had been licensed since the launch of the licensing program in 2009. To alleviate the pressure for veterinary supervision, a provision was made to allow qualified assistant veterinarians ordering prescriptions by 2017 (Ministry of Agriculture, 2013d). Nonetheless, the small-scale animal farms and family farms, which are responsible for producing large portions of animal products yet cannot compete economically with CAFOs, are disproportionately affected by the restricted drug access. It is particularly problematic in the underdeveloped provinces and remote areas, where small producers often struggle to access regular and affordable veterinary services.

A critical component missing in China’s push toward veterinary oversight is measures on fostering veterinary services, particularly in the underserved areas. Veterinary programs in universities and colleges should be expanded in anticipation of the significant rise in demand, while special support should be provided to encourage graduates to practice in rural and remote areas. Meanwhile, the role of para-veterinarians, or “barefoot vets” in China, should be increasingly recognized. They largely complement public and private veterinarians by providing services at affordable prices to small producers or those located in remote areas (Hadrill et al., 2002). Professional training programs and more supportive policies should be developed to enhance the capacity of para-professionals. Meanwhile, to minimize potential drug misuse and sub-standard services, they should be required to operate under the supervision of licensed veterinarians. Such a two-tiered veterinary system is expected to greatly increase the availability and quality of animal health services in rural China.

#### 3.2. Strengthening supervision on veterinary drug production and distribution

Besides the end uses, the production and distribution of veterinary drugs should also be properly regulated and supervised. Cooperation from the pharmaceutical and animal feed industries is of paramount importance for full and prompt implementation of the regulatory ban, as they are responsible for producing the veterinary drugs and the commercial feed containing such additives, respectively. Compliance monitoring through regular on-site inspections and record reviews, along with stringent enforcement, can prevent corner-cutting or illegal activities in the production and distribution of veterinary drugs that would counteract the ban.

The lack of data on veterinary use of antimicrobials in China makes it difficult to assess the extent of overuse and misuse and its contribution to AMR development (Mole, 2013). Therefore, programs should be initiated to track domestic production and sale of important veterinary drugs, particularly antimicrobials, and their consumption rates in CAFOs and even smaller animal farms. Transparency of such data is also important for the public to verify the effectiveness of regulatory ban. These efforts will greatly improve the control on the use of prescription veterinary drugs in food animal production, and facilitate evaluation of the relationship between antimicrobial use and AMR development in food animals and the impact of AGP phase-out on AMR reduction.

#### 3.3. Increasing research and development efforts

More research and development efforts are needed to reduce the reliance on veterinary drugs in food animal production and the
impact of intensive animal farming on the environment and public health. Development of new therapeutic drugs, safe and effective vaccines, alternatives to antimicrobials for growth promotion and disease prevention, and rapid and convenient diagnostic technologies for epidemic diseases can help safeguard the health of farmed animals (Clark et al., 2012). In particular, signiﬁcances for epidemic diseases can help safeguard the health of farmed disease prevention, and rapid and convenient diagnostic technologies for animal wastes, and disinfection technologies for animal wastes can help minimize the selection and spread of AMR in the environment (Hu and Cheng, 2014; Pruden et al., 2013). Close collaboration with pharmaceutical companies and animal producers can maximize the impact of academic research on animal health and AMR control.

The impact of veterinary antimicrobial use on human health in China, including the development of AMR in animal husbandry and aquaculture, and the transfer of such resistance to humans, remains largely unknown. National surveillance systems on antimicrobial-resistant bacteria in humans, retail meats, and food animals need to be established to track the emergence and spread of AMR, and ﬁll the data and knowledge gaps. Such information is critically needed for developing measures to reduce the spread of AMR and supporting relevant regulatory decision-making.

3.4. Enhancing animal health management

Besides diagnosing, treating, and preventing diseases in farmed animals, veterinarians need to supervise the proper use of prescribed veterinary drugs. Outreach effort should be made to train animal producers on the safe and effective use of drugs, with special attention paid on administering antimicrobials to individual animals, when possible, to avoid dosing a whole herd/flock of mostly healthy animals or the culture water. Being in close contact with animal producers, veterinary staff can also offer practical guides on alternatives to antimicrobial use for growth promotion, and prevention of animal diseases with safe, cost-effective, and hygienic production techniques (Clark et al., 2012).

Animal producers are eventually responsible for the overuse and misuse of antimicrobials. Feeding antimicrobials constantly to animals is a cheap solution to prevent disease and promote their growth under crowded, unsanitary, and stressful conditions in CAFOs. Preventive medication is not needed for animals raised with good nutrition and in clean environment with adequate space, as they have low levels of stress and the spread of infectious diseases is reduced. Thus, it is particularly important to improve the sanitation and hygiene conditions for animals raised in close conﬁnement, while reducing animal overcrowding, controlling facility temperature, and facility ventilation can all help improve the health and well-being of the animals (Clark et al., 2012; Marshall and Levy, 2011).

4. Perspective

Effective control of veterinary drug use, particularly phasing out AGPs, is expected to remove substantial amounts of drug residues from the food chain and thereby greatly improve the safety of food products of animal origin. Furthermore, by reducing the loadings of antimicrobials in animal husbandry and aquaculture, gradual decline of AMR in farmed animals, food chain, and the environment, and correspondingly reduction in public health risk, are expected. Improved animal health management can signiﬁcantly reduce the occurrence and spread of infectious diseases, and consequently the need for veterinary antimicrobials. Smooth transition toward veterinary oversight of drug use in China requires joint efforts of the government, industry, academia, veterinary professionals, and animal producers on protecting animal health and welfare and improving the health management practices of intensive animal farming. Meanwhile, the experience of international initiatives, such as the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) and the Antimicrobial Consumption and Resistance in Animals (AMCRA), can provide valuable insights and lessons for developing monitoring programs and guidelines to facilitate such transition. Ultimately, rational use of veterinary antimicrobials can greatly reduce the public health risk from AMR in China while providing adequate protection for the well-being of farmed animals.

Acknowledgments

The constructive comments of the anonymous reviewers on an earlier version of this manuscript are greatly appreciated. This study was supported in parts by the Natural Science Foundation of China (Grant Nos. 41322024 and 41472324) and the National Program for Support of Top-notch Young Professionals.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2016.04.099.

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