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Review

# Veterinary antibiotics (VAs) contamination as a global agro-ecological issue: A critical view

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ABSTRACT

Veterinary antibiotics (VAs) are used worldwide in animal farming as drugs to treat or prevent diseases and serve as feed additives. VAs are usually poorly sorbed in the animal gut, and the majority are excreted unchanged or as their recalcitrant metabolites in feces and urine. More importantly, animal wastes are frequently employed in agriculture as a supplement to fertilizer, raising a major international concern about the potential impacts of VAs on agro-ecosystems. Increasing use of these manures in agriculture is thus posing a threat in the form of rapid increase in antibiotic resistance. The current review critically summarizes available literature on the global consumption, exposure pathways, occurrence, fate and environmental effects of VAs in manure-fertilized agricultural soils. Recognizing the importance of the issue of VA resistance in the environment, we focused on the increased abundance and transferability of VA resistance determinants, highlighting details as to how they contribute to the change in human microbiome. Notably, existing regulations and research gaps in association with the spread of VAs and their resistance due to manure application in agricultural fields are also outlined. Finally, we highlight the areas that future research should prioritize and propose certain strategies that could help curtail VAs occurrence and the danger they pose to agro-ecosystems.

## 1. Introduction

'Antibiotics' are organic substances synthesized either naturally by microorganisms through secondary metabolism or artificially from industries that may kill or inhibit growth or metabolic activity of other microorganisms (Kim et al., 2011). Antibiotics have been utilized in industrial production, agriculture and medicine for over 60 years (Knapp et al., 2009). Many antibiotics are used worldwide extensively, and have been approved for use as drugs for preventing plant, animal and human infections, growth promotion, and as feed additives for animals to prevent or treat diseases (Kumar et al., 2005). Notably, the largest amounts of antibiotics serve to treat animals rather than treat human diseases (Gelband et al., 2015). The main groups of antibiotics used in animal husbandry (and their examples) include: aminoglycosides (apramycin, kanamycin and spectinomycin), β-lactams (amoxicillin, ampicillin, benzylpenicillin, cloxacilin, dicloxacilin and oxacillin); ionophores (monensin); peptides (virginiamycin); peptidomimetics (bacitracin); cephalosporines (ceftiofur and cefquinom); fluorochinolones (enrofloxacin and marbofloxacin); lincosamides (lincomycin); macrolides (erythromycin, spiramycin and tylosin); sulphonamides (sulphadimethoxine, sulphadimidine and sulfapyridine); tetracyclines (oxytetracycline, chlortetracycline, tetracycline and doxycycline); and trimethoprim (Kemper, 2008; Tasho and Cho, 2016a, 2016b).

Rapid developments in animal farming have led to an unprecedented increment in the usage of VAs (O'Neill, 2015). Both unaltered VAs together with their recalcitrant metabolites are released into the agricultural systems as excreta via different pathways (Winckler and Grafe, 2001; Jjemba, 2002; Heuer et al., 2008; Lamshöft et al., 2010). Additionally, the overuse and abuse of VAs worldwide has led to substantial increases in their excretion rates and environmental release (Smith et al., 2005; Zhang et al., 2008; Sukul et al., 2009). In recent times, VA contamination has been recorded in different environmental settings including soil (Li et al., 2015; Wei et al., 2016;

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Yang et al., 2016; Sun et al., 2017), plants (Boonsaner and Hawker, 2015; Hussain et al., 2016; Bartrons and Peñuelas, 2017), water (Dong et al., 2016; Chen et al., 2017; Ding et al., 2017; Li et al., 2017; Zhang et al., 2018) and air (McEachran et al., 2015) along with the emergence and spread of resistant microorganisms. Consequently, this represents a daunting ecological and human health risk (Jechalke et al., 2014). Even very low concentrations of VAs encourage the selection of resistant microbes in the environment, and may even cause serious allergies or toxicity to plants and humans (Kim et al., 2011). Research on the transfer of genes that confer resistance to VAs from an agricultural system to the environment has only made progress in the past few years, and still requires more thorough investigation (Heuer et al., 2011). The main sources of VAs and their resistance at field-level are the manure fertilizers, run-off and aerial transport (Poulsen et al., 2013). Notably, the pollution of farmlands through repeated manure fertilization has become inevitable. VAs accumulated via manure may pose a serious threat to soil ecosystems when bioaccumulation occurs (Ding et al., 2014).

Much of the currently published information on the development of VAs-resistant genes relates mostly to the aquatic environments, however, corresponding data on ecological health in manure-fertilized agro-ecosystems is very limited (Sarmah et al., 2006). Research publications collating the regulations and strategies required to limit persistence and spread of VAs in the manure-fertilized agro-ecosystems are unavailable. Explaining the migration pathways, together with ecological impacts in manure-fertilized lands is a key to understanding the fates and environmental risks of VAs from animal farms to soil-crop plant systems. Monitoring and controlling the spread of VA contaminants in agricultural fields and to their crops is critical for preventing damage to agro-ecosystems and ultimately, consumers who purchase foodstuffs derived from them (Du and Liu, 2012). In view of the above, the current review discusses the following: (1) the amount of VAs used worldwide in agriculture, (2) exposure pathways, occurrence, fate and impacts of VAs in manure-fertilized agro-ecosystems, (3) international regulations and voluntary measures that aid in limiting the use and spread of VAs from animal farms to the environment, (4) existing knowledge gaps with priority areas for future research in manure-fertilized fields, and (5) strategies that can be adopted to limit VAs in agricultural farms.

## 2. Global usage of antibiotics in agriculture and animal farming

Estimates of total annual global antibiotics consumption in agriculture vary considerably (63,000–240,000 tons) due to poor surveillance and data collection in many countries. Over 50% of the antibiotics deemed medically important for human health and sold in most countries throughout the world are used in animal farming (O'Neill, 2015). Van Boeckel et al. (2015) estimated that the global average annual consumption of antibiotics per kg of animal produced was 45, 148 and 172 mg $kg^{-1}$ for cattle, chicken and pigs, respectively. Starting from this baseline, they estimated that the global consumption of antibiotics in agriculture will rise by 67% between 2010 and 2030 due to a projected increase in the number of animals required for food production and intensive farming systems. Indeed, consumption in Brazil, Russia, India, China and South Africa is expected to double by 2030 as the human population is expected to increase by 13%. In the US, an estimated 80% of antibiotics sold are used in animals, primarily to promote growth and prevent infection (Ventola, 2015). The US Food and Drug Administration (FDA) estimates that 14,600 tons of antibiotics were sold for use in animals in 2012, more than four times the 3290 tons of antibiotics sold for human use in 2011 (Teillant and Laxminarayan, 2015). In 2015, China – which is the largest meat producer in the world exceeding the US – deployed nearly half of the 210,000 tons of antibiotics it produced in food animals (Collignon and Voss, 2015). VAs usage in Australia, Norway, Sweden and the UK accounts for 932, 6, 16 and 308 tons, respectively (Kim et al., 2011). Gelband et al. (2015) estimated consumption of most antibiotics in animal farming in Brazil (5600 tons), Germany (1900 tons) and India (1890 tons). DANMAP (2005) recorded 11, 93 and 0.4 tons of VAs use in cattle, pig and poultry farming, respectively, in Denmark. Of the total 1278 tons of VAs used every year in South Korea, the consumption in piggery, poultry and cattle farming was 831, 335 and 112 tons, respectively (KFDA, 2006). Kim et al. (2011) have asserted that antibiotics usage in animal farming is of the following order: piggery > poultry > cattle. Among the VAs, tetracyclines were the most commonly used followed by sulfonamides and macrolides (Du and Liu, 2012). In fact, these three VAs accounted for approximately 90% of the total antibiotics used in the UK (VMD, 2006), and more than 50% in South Korea (KFDA, 2006) as well as in Denmark (DANMAP, 2005).

## 3. Exposure pathways for VAs in agro-ecosystems

The majority of VAs causing environmental concern are solely of anthropogenic origin. The primary causes of VAs being released into agro-ecosystems are: firstly, fertilization with animal urine/manure containing antibiotics (direct application from medicated animals or application after composting), sewage sludge, sediment or biosolid; secondly, irrigation with antibiotics-contaminated waste/surface/groundwater (Du and Liu, 2012) and thirdly, aerial transport (McEachran et al., 2015). Depending on pharmacokinetics and specific transformation processes in animals, large proportions of the administered antibiotics are usually poorly adsorbed in animal gut and are excreted with urine and feces in the form of parent compounds or their metabolites, which may also still be active, within a few days of medication (Sarmah et al., 2006; Kim et al., 2016a, 2016b). The animal excretion rate varies depending on the type of VAs used (Table 1) – 65% for tetracyclines (Winckler and Grafe, 2001), 90% for sulfonamides (Halling-Sørensen et al., 2001), and 50–100% for macrolides (Arikan et al., 2009). In manure sampled within 2 days after oral application of tetracyclines, more than 72% of the drug was excreted unaltered (Winckler and Grafe, 2001). Similar findings were reported for fluoroquinolones wherein more than 90% was excreted by pigs after oral administration, predominantly as the parent compound (Sukul et al., 2009).

The amounts of antibiotics excreted may also vary with the dosage level, type and age of the animal (Sarmah et al., 2006). In excreta, concentrations of antibiotics can even increase due to retransformation of metabolites back to the parent compound (Heuer et al., 2008; Lamshöft et al., 2010). Many investigations have been conducted to examine the residual levels of antibiotics in feces and manures from animal farms (Table 2). Zhang et al. (2008) showed that the residual levels of VAs were in the order: pig manure > poultry manure > cattle manure, with generally higher amounts of VA residues in manures from industrial-scale farms compared to those belonging to farmers' households. Apart from animal excreta, dust from animal farming zones is also one of the notable routes of entry of VAs into the environment. In

**Table 1**
Excretion rate of some commonly used VAs.

| VA | Excretion rate (%) | References |
|---|---|---|
| Amoxicillin | 90 | Park and Choi (2008) |
| Ampicillin | 60 | Hirsch et al. (1999) |
| Chlortetracycline | 65 | Arikan et al. (2009) |
| Difloxacin | 90 | Sukul et al. (2009) |
| Erythromycin | 5–10 | McArdell et al. (2003) |
| Ivermectin | 40–75 | Jjemba (2002) |
| Oxytetracycline | 21 | Montforts (1999) |
| Streptomycin | 66 | Jjemba (2002) |
| Sulfamethazine | 90 | Halling-Sørensen et al. (2001) |
| Sulfamethoxine | 15 | Jjemba (2002) |
| Tetracycline | 72 | Winckler and Grafe (2001) |
| Tylosin | 28–76 | Halling-Sørensen et al. (2001) |
| Virginiamycin | 0–31 | Jjemba (2002) |