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Review

Veterinary antibiotics in animal manure and manure laden soil: Scenario and challenges in Asian countries

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ABSTRACT

The incidence of antibiotics in various environmental matrices is a major matter as the occurrence is linked to the emergence and prevalence of antibiotic resistance genes (ARGs). Country such as China holds the largest allotment of antibiotics utilization in food animal. Whereas, Asian countries such as Myanmar, Indonesia, and Vietnam are projected to obtain the most considerable percentage increment in antibiotics consumption. Decades old agricultural practise (animal manure fertilization), aquaculture, wastewater (untreated), sewage sludge are major routes that allowed antibiotics to enter and persist in environment. Most of the veterinary antibiotics are water soluble and are not fully absorbed by animals. High percentage of the veterinary antibiotics is excreted by animals in their wastes (manure and urine). Many studies have reported detection of antibiotics in various matrices including soil and are discussed in this paper, with special highlights on manure and manure laden soil in Asian countries. Increased adsorption of antibiotics in soil unswervingly raises the potential of antibiotics being taken up by crop. This review also revealed the current state of regulations in certain countries on antibiotics sales and consumption, which is important as an effort in mitigating the spread of antibiotics occurrence as well as the dissemination of ARGs in the environment.

Contents

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1. Introduction

In the past decades, worldwide utilization of antibiotics for both human and animals are on the climb. The production of total antibiotics in China in 2009 was nigh on 1.47 million tonnes (Yang et al., 2009), while in the US, veterinary antibiotics used in animal feeds solely was increased to 130,000 tons in 2009 from 9300 tons (FDA, 2012). Globally, the consumption of antibiotics in animal feeds was increased by 8% from 2009 to 2011 (FDA, 2009, 2011). Approximately 80.5% of the total antibiotics consumed in the US were used on farmed animals (FDA, 2011). Veterinary antibiotics are used on a regular basis for treatment and prevention of diseases in animals in commercial livestock farming. Substantial amount of antibiotics is used in livestock for prophylactic, metaphylactic and therapeutic purposes as well as feed addictives. Veterinary antibiotics are also extensively adopted for subtherapeutic use with the intention of preventing disease and promoting growth. Despite the fact that incorporation of antibiotics in animal feed for the purpose of growth promotion (as antimicrobial growth promoters) is fully banned in European Union under Regulation (Regulation 1831/2003/EC) (EC, 2005), nonetheless, many countries still permit such practice.

Animals are not able to effectively metabolize antibiotics. Depends on antibiotics, they may be either completely metabolized or a portion may be excreted via urine or feces in either its original state or as active/non-active metabolites. Incomplete metabolization will lead to the presence of high concentration of antibiotics in animal waste. In fact, up to 72% of the active principle in tetracycline, one of the most commonly used veterinary antibiotics is excreted via faeces and urine (Winckler and Grafe, 2001). Antibiotic residues were recurrently detected in animal manures such as swine and poultry (Awad et al., 2014; Chen et al., 2012; Geng et al., 2013; Hou et al., 2015; Zhao et al., 2010), as well as soil amended with animal manure for fertilizing purpose in Canada (Aust et al., 2008), China (An et al., 2015; Hou et al., 2015; Zhang et al., 2015), and Malaysia (Ho et al., 2014).

Wang and Tang (2010) had reported the total amount of antibiotic use annually including both medical and veterinary antibiotics has attained 100,000–200,000 tonnes worldwide. The quantity is in rising trend as the usage of VA guarantees the production outcome. This is not an all-inclusive review, but as an endeavour to present and add new information to previously published researches. Key questions that will be addressed in this paper are: 1) The prevalent occurrence of antibiotics in animal manure and manure laden agricultural soil in Asia region. 2) The current policy available (FDA and EC) and the lack of regulations controlling antibiotics used as animal growth promoter in other countries. Hence, the primary intention of this paper is to reveal the extent of antibiotics use on farm animals and its significant linkage to soil "pollution" attributable to common agriculture practise in selected countries, and at the same time, heightening awareness for the need of proper handling of antibiotics-containing manure.

2. Veterinary antibiotics

Prevalence of antibiotic consumption in livestock production, in correlation to the rising pervasiveness of antibiotic resistance in

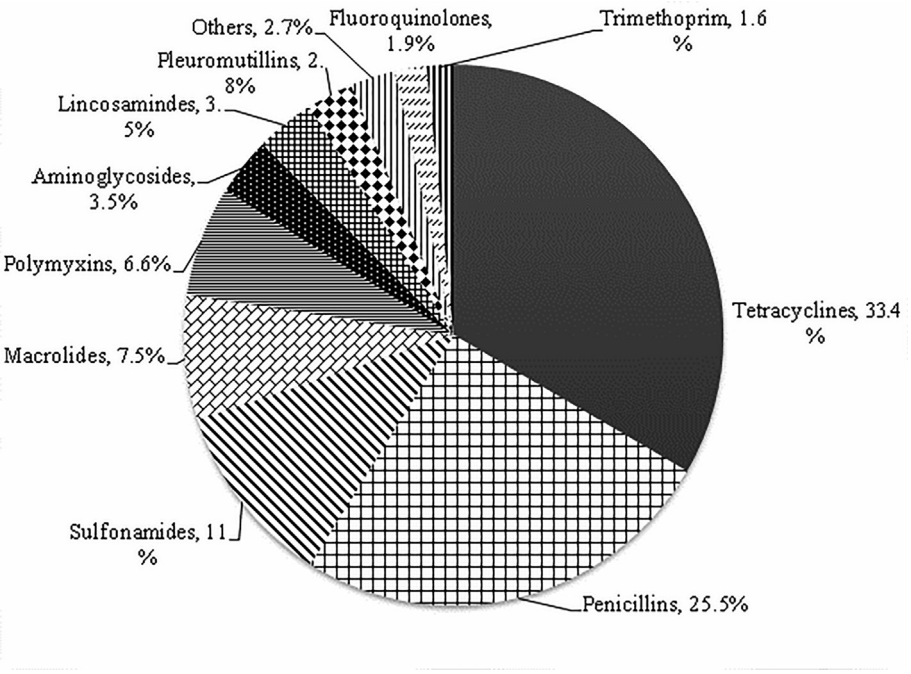

Fig. 1. Consumption of antibiotics for food producing animals by classes in 29 European countries (EMA, 2012).

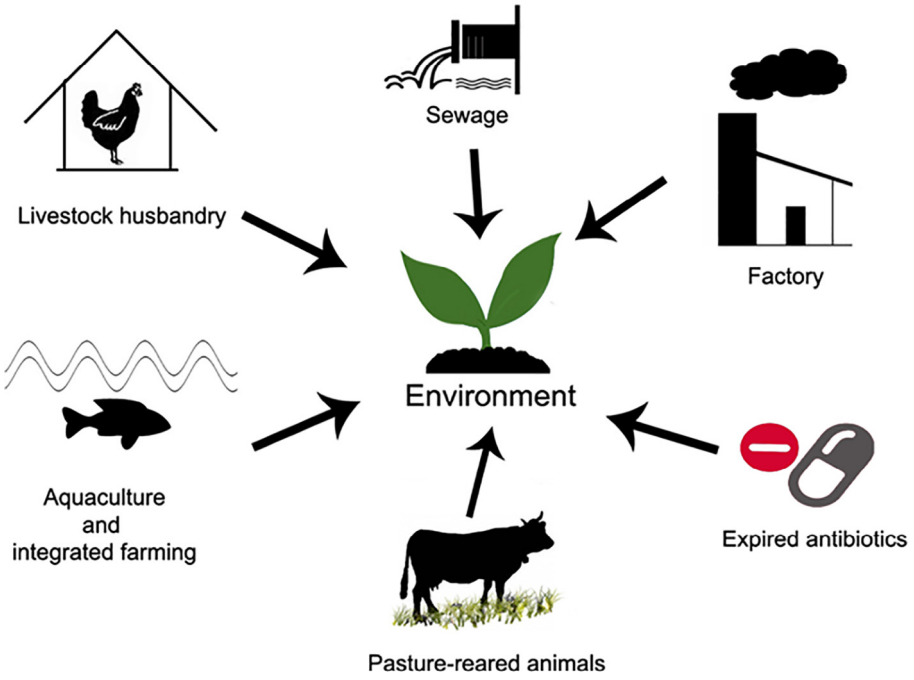

Fig. 2. Multiple entry pathways of antibiotics into environment.

Table 1
Excretion rate of selected antibiotics in animal.

Antibiotics	Excretion rate in animal
Tetracycline	75–80%
Lincosomides	60%
Macrolides	50–90%
Sulfamethazine	90%
Chlortetracyclie	65%
Tylosin	50–100%
Norfloxacin	30%
Ofloxacin	90%
Sulfonamide	90%
Sulphamethoxazole	85%
Amoxicillin	10–20%

(EMEA, 1997; Halling-Sørensen et al., 2001;, Kumar et al., 2005; Kümmerer and Henninger, 2003).

our environment, points towards the call for the strict directive on antibiotic usance in agriculture.

Fig. 1 shows the utilization of antibiotics in food producing animals in 29 European countries (EMA, 2012), with tetracyclines, penicillin and sulphonamides as the top three most consumed antibiotics. Prevalence studies of antibiotics in manure laden soil are also in line with the consumption as reported in Fig. 1. As stated by Van Boeckel et al. (2015), top five countries with largest shares of antibiotics consumption in food animal in 2010 were China (23%), United States (13%), Brazil (9%), India (3%) and Germany (3%). However, the projected ranking by 2030 has revealed increment; estimated China will remain possessing the highest share of global antibiotics consumption (30%), following by United States (10%), Brazil (8%), India (4%) and Mexico (2%). Projected findings also revealed three out of the top five countries that are expected to have greatest percentage increases in antibiotics consumption by 2030 are from Asia. Each year, estimated more than 20,000 tonnes of sulphonamides, with bacteriostatic properties, are introduced into biosphere, exclusive of drugs that introduced to the environment as herbicides (Baran et al., 2011). Regardless of the above-mentioned findings, data on antibiotics used on animal farming in these developing countries are still not widely available. Antibiotics can enter the environment via multiple routes (Fig. 2), encompassing emission from factory, disposal of unused medicine and container, pharmaceutical manufacturing effluents, livestock husbandry effluents and animal waste, excretory products from pasture-reared animals, aquaculture and sewage treatment plant. Fig. 2 illustrated the major entry pathways for antibiotics to enter our environment.

Fig. 1 Utilization of antibiotics for food producing animals by classes in 29 European countries (EMA, 2012)

These antibiotics are added into livestock feed for three core purposes: to treat disease (therapeutic levels), to preclude disease (subtherapeutic levels), and to boost growth (subtherapeutic levels). Morton (1989) defined "subtherapeutic" use of antibiotics as concentration less than 2 gt^{-1} feed for a period longer than two weeks, or as mentioned by Cohen (1998), lower than 0.2 g kg^{-1}. Yet, in most countries, antibiotics are used as prophylactic measures (for example in extenuating infection and disease widespread), and for growth boosting (WHO, 2014). In general, antibiotics are presented to livestock via feed or water, nonetheless, a faction are administered by intramammary, oral, or direct application (Van Epps and Blaney, 2016) (Table 1).

3. Occurrence of veterinary antibiotics in soil animal manure and soil in selected Asian countries.

3.1. China

Concentrated animal feeding operations (CAFOs) and animal husbandry are widely distributed in Northern China. Agricultural soils adjacent to CAFOs are often fertilized with animal manure. Hou et al. (2015) collected samples to identify veterinary antibiotics distribution in Tianjin and Liaoning Province (Northern China). Results indicated tetracyclines group as the most frequently detected antibiotics in manure laden soils, particularly chlortetracycline, (highest concentration detected was 10,967.1 μg kg^{-1}). Huang et al. (2013) found that up to 2668.9 μg kg^{-1} of chlortetracycline was detected in soils around swine feedlots in Fujian Province of China. Tang et al. (2015) had investigated the

occurrence of antibiotics and effect of continuous manure application in paddy soils across couth of China. The results showed chlortetracycline concentration of 10 times higher in the top soil (344.74 ± 88.03 μg kg^{-1} dw) compared to non-manure soil samples collected in Jiaxing city, Zhejiang experimental sites. Up to 38.49 ± 9.28 μg kg^{-1} dw of chlortetracycline was also detected in manured soil in Changsha city, Hunan. For manured soil samples collected from Yingtan city and Nanchang city in Jiangxi, up to 31.35 ± 3.80 μg kg^{-1} dw and 107.86 ± 18.81 μg kg^{-1} dw of chlortetracycline were detected whereas chlortetracycline was not detected in non-manure soils in these two sampling sites. Range between 11.66 ± 2.44 to 40.27 ± 1.58 μg kg^{-1} dw of oxytetracycline were reported from manured soil samples in Jiaxing, Changsha and Nanchang. Tetracycline was detected in both manured and non-manure soil in Jiaxing city, but not detected in non-manure soil samples collected from Changsha, Yingtan and Nanchang city. As stated by Wei et al. (2016), the detection rates for the five classes of drugs in manure laden soils exhibited the rank order of cyromazine (insect growth regulator) > tetracyclines > sulfonamides > fluoroquinolones > florfenical. Findings also revealed high concentration of antibiotics in deeper soil layers (20–40 cm and 40–60 cm). Wei et al. (2016) results revealed highest maximum concentrations range of sulfonamides in soil layers laden with poultry manure (20–40 cm) were 682–1784 μg kg^{-1}. Sulfonamides were not detected in 0–20 and 20–40 cm layer of cow manure laden soil but were detected in 40–60 cm layer with maximum concentration of 1692 μg kg^{-1} (sulfamethezine) The most notable finding was the concentrations of tetracycline group in poultry manure laden soil, cow manure laden soil and swine manure laden soil. Floroquinolones were mostly detected in soil applied with poultry manure and in deeper soil layer but not in other manures laden soil. This coincides with Dheilly et al. (2011) which stated floroquinolones are more regularly used in poultry industry for controlling and preventing respiratory diseases as feed additive. Meanwhile, previous studies that carried out at the same sites back in year 2009 and 2011 revealed the fact that veterinary antibiotics (tetracyclines) accumulated easily and showed higher persistence in deeper soil layers (Wei et al., 2016). Application of contaminated in agriculture practise follows with ploughing further encourages antibiotics accumulation in deeper soil layers and increase their persistence in soil.

Corresponding to results reported by Zhang et al. (2015) Oxytetracycline achieved highest mean concentration in four out of seven protected vegetable farms tested and detection frequency of 100% in six of the selected farms. Tongshan in Xuzhou exhibited highest maximum concentration (8,400 μg kg^{-1}) and the findings were also in consonance with the highest organic loading rate (approximately 150 t/ ha yr^{-1}) of livestock manure amongst all sites investigated. Tetracyclines and fluoroquinolones are predominantly detected in soil amended in livestock manures. In addition, sulfonamides were higher in poultry manure in cow manure.

Thus, tetracyclines, fluoroquinolones and sulphonamides are indisputably the most widely used VA groups in China with direct correlation to occurrence and detection frequency of antibiotics in manure laden soil.

3.2. Korea

In Korea, approximately 600 tons of tetracyclines and sulphonamides were used feed addictives. This amount was close to 20-fold higher in total consumption of antibiotics in United Kingdom in year 2004 (Kim et al., 2008). Chlortetracycline, oxytetracycline, sulfamethazine, sulfathiazole, and tylosin are in the top priority group of VAs in Korea (Seo et al., 2007).

Soil samples collected in close proximity to swine manure composting facilities revealed elevated concentration of veterinary antibiotics in September compared to samples collected in June. Highest maximum concentration was reported for tetracycline in soil sample, reaching 177.64 μg kg^{-1} (Awad et al., 2014). Findings from Awad et al. (2014) also showed that both tetracyclines and sulfonamides were detected with higher concentrations in sediment and soil samples compared to water samples.

3.3. Vietnam

Only limited data is available with regards to the antimicrobials usage in animal farms (swine and poultry) in Vietnam. With Vietnamese government actively encouraging the integrated agriculture-aquaculture farming system, the situation of antimicrobial use in the country is really in need offurther studies toprecisely portray actual condition. Antibiotics are the most universally indexed drugs (70% of all veterinary drugs) used on animal in Vietnam (An, 2009). Findings reported by Dang et al. (2013) has revealed the recent situation in Vietnam, which include lacking of systematic monitoring and regulation to control antimicrobials use in food animal, as well as limited information available for reference. Dang et al. (2013) discovered at least 45 antibiotics from 10 classes of antibiotic groups were used in pig and poultry production, for treatment and prevention of disease, and growth promoting. Up to 31 and 25 different antibiotics were used in disease prevention in poultry and pig production respectively. Antibiotics such as aminoglycosides, tetracyclines, fenicols, beta-lactams and fluoroquinolones group are most widely used for disease treatment in swine production. Whereas in poultry production, sulphonamides, beta-lactams, tetracyclines, aminoglycosides and ionophores are used extensively. Among all 45 antibiotics identified in Dang et al. (2013) study, colistin, chlortetracycline and oxytetracyline are the most commonly used antibiotics in the region (Red River Delta). Problems arise when farmers who utilized the antibiotics for prophylactic or therapeutic purposes did not follow the advised dosage, length of treatment and withdrawal time as indicated on the label. An interesting finding revealed was that antibiotics are used equally for therapy of poultry and broiler breeding, but less used for therapy of laying hens. The survey unearthed the basis of choice for antibiotics used were largely based on farmers' experience and pharmaceutical company's representatives' advices. Only a handful of samples of ill animals were sent to laboratories for diagnosis before treatment was proposed. Even though the comprehensive survey has managed to provide an overview on antibiotics usage situation in Red Delta Region of Vietnam, yet, the lack of studies to establish the occurrence of antibiotics residues in animal manures, especially those under integrated farming system is still one of the most important limitations.

3.4. Malaysia

Agriculture sector remains imperative in Malaysia. Continuous extension of agriculture sector contributed 8.9% to the country's Gross Domestic Product (GDP) in year 2015. With oil palm remained as the major contributor (46.9%), followed by other agriculture (17.7%), livestock (10.7%) and fishing (10.7%) in 2015 (Department of Statistics, Malaysia, 2016).

Occurrences of pharmaceuticals and personal care products (PPCPs) in different environmental matrices have been reported in Malaysia, though number of studies is still scarce. Occurrence of PPCPs was reported by Al-Odaini et al. (2010) in surface water, veterinary antibiotics was detected in swine farm effluent as stated by Malintan and Mohd, (2006) and in broiler muck and different farming soil (Ho et al., 2014). Manure application in Malaysian agriculture sector is a common practise. Recent attention has been developed on investigating antibiotics pollution in soil amended

Table 2
Approved antibiotics for food producing animals that are critically and highly important to human medicine.

Antibiotics	Importance to human medicine	Animal used
Aminoglycosides	Critically important	Swine, poultry
Lincosamides	Highly important	Swine, poultry
Macrolides	Critically important	Cattle, swine, poultry
Penicillins	Critically important	NA
Streptogramins	Highly important	Cattle, swine, poultry
Sulfonamides	Highly important	Cattle, swine, poultry
Tetracyclines	Highly important	Cattle, swine, poultry

Refs.: FDA, 2011; WHO, 2017.

with animal manure. Animal manure becomes one of the major sources of precarious unmetabolized veterinary antibiotics to our environment via common, decades old manuring practise, and poses threat to the environment. Ho et al. (2014) stated maximum concentration of doxycycline in broiler manure sample of 78,516 μg kg^{-1} dry weight, and 1331 μg kg^{-1} dry weight of flumequine in manure amended soil. Apart from that, doxycycline and enrofloxacin remnant were also detected in all manure amended soil samples.

4. Policy on veterinary antibiotics use on animal and aquaculture production

Despite the banning of antibiotics use in animal growth, the usage of antibiotics in livestock industries is still on the rise globally. Currently, only Food and Drug Administration (FDA) and EU have clear regulations on prohibiting the application of selected antibiotics as growth promoter. According to FDA, 18 classes of antimicrobials are authorizedto be employed in livestock (FDA, 2011). China follows agricultural industry standards (NY525-2012) which only control and regulate pH, worm mortality, the number of fecal coliforms of manure-based commercial organic fertilizers. However, antibiotics uses on animal are presently not regulated under any standards in China (Zhou et al., 2017).

Veterinary feed directive (VFD) regulations were pronounced by Food and Drug Administration (FDA) in 2015, altering classification of certain antimicrobial drugs and banning animal production application of VFD drugs (CFR, 2015, FDA, 2015). An order of VDF has to be issued by a licensed veterinarian before being fed to animal. This system helps in governing the distribution and use of certain drugs (VFD drugs) that can be only used in animal feed with explicit approval of a licensed veterinarian. The more detailed breakdown of these regulations summarized into five major points on tackling antibiotic usage. First, it requires of several previously approved antimicrobial drugs into VFD drugs which will require order in black and white issued by licensed veterinarian. Second, medicated feeds that carry VFD drug can no longer be used for improving weight fain and feed efficiency. Third, a VFD order can only be issued if anofficial veterinarian-client-patient relationship with the animal and the customer (owner of animal) is established. Fourth, acknowledgment and the administering of all medicated animal feeds that carry VFD listed drug must be properly recorded for two years. Fifth, veterinarian may be charged with adulterating or misbranding the VDF drug if a VFD is issued without complying with regulations (CFR, 2015).

Regulation of antibiotics application in aquaculture is broadly regulated, with great differences from country to country, and little to no enforcement in many countries of major aquaculture production (Pruden et al., 2013). Discrepancies between regulations on antibiotics usage in both agriculture and aquaculture have led to frequent detection of antibiotics occurrences in Asia region. Aquaculture is mentioned here as the practise of integrated farming is also common in Asia region (reusing of aquaculture water on farmland), hence indirectly affects the situation at some point. Table 2 supported the importance of antibiotics that shared between animal and human health. The prevalence of veterinary antibiotics in agricultural soil revealed the objective of this work as the effectiveness of such antibiotics in human health industry may be affected in long term.

5. Conclusion

Reusing animal manures in agriculture industry is not a brand new practise and it has been carried out for a very long time. However, this only came under spot light of researchers after the raising concern on antibiotics usage hike in food animals and its risk, particularly associated with occurrences of antibiotic resistance gene in the environment and its potential fallout. This manuscript has brought out the major findings on veterinary antibiotics detected in agricultural soil, as well as in the environment. Even though findings mentioned above are mainly focused on Asia region (as Asia is the region with rising veterinary antibiotics use), but be cognizant that these findings are actually reflecting a worldwide scenario. Some results reported on antibiotics concentration detected were said to be argumentatively low (not high enough to pose any current threat), but the major point of this review lies towards the long term usage and the accumulation potential of such recalcitrant and hazardous environmental pollutant, especially when veterinary antibiotics usage is still unavoidable for now.

Veterinary antibiotics from few groups (tetracyclines and sulphonamids) of antibiotics were commonly detected in the environment. Though other groups of veterinary antibiotics are also widely used and detected. Different regions may have different practises in selecting which veterinary antibiotics to be used. Apart from that, elimination mechanism of tetracyclines, which have been widely in used for the past decades are mainly via urine, unlike the newer derivatives such as doxycycline, which is excreted via feces (Szatmári et al., 2012). Hence, with the shift from older antibiotics to newer veterinary antibiotics for greater effectiveness, risk in reutilising animal waste for food crops fertilisation is ever-increasing. It is apparent that policies on controlling veterinary antibiotics usage on food animals still need to be strengthened in many countries, as well as be introduced in countries in Asia. Chung et al. (2017) revealed that EU (European Union) has set maximum residue limits (MRL) for antibiotics (tetracyclines and fluoroquinolones) in foods of animal origin (EU Commission, 2010), but there was no MRL set for food crops. Antibiotics sales and usage are not regulated in India (Ganguly et al., 2011; NICD, 2011), and there is no current regulation to regulate the antibiotics usage on animals in China (Zhou et al., 2017). It is important to understand that antibiotics sales do not always represent the antibiotic usage as most of the information regarding antibiotic usage is not readily available. Antibiotics are prone to be more persistent once released into soil and sediment (Wang and Yates, 2008) and this observable fact was in a manner corresponding to soil characteristics, antibiotics sorption capacity, distribution coefficient and hydrophobicity (Tolls, 2001). Apart from that, antibiotics are also likely to stay in soil with high acidity and clay content (Awad et al., 2014) and soil pH also play an important role in determining sorption capacity of antibiotics in soil (Sassman and Lee, 2005).

Risk assessment on veterinary antibiotics towards soil microbial communities is still in lacking. Available data and results from current available research are often too vague to have definitive conclusion, hence, leading to the lack of regulations and control of antibiotics usage in many countries, especially in Asia. More research attention should be focus on such issue to bring greater understanding on current antibiotics "pollution" scenario. If such

heavy veterinary antibiotic usage trend continues, no doubt we are to face the severe consequences in near future, and environment is the one paying the price.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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