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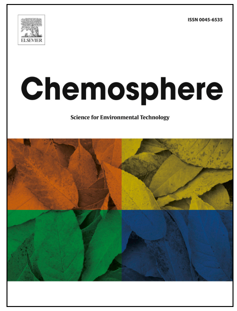

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Antibiotics in the aquatic environment of Vietnam: sources, concentrations, risk and control strategy

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Abstract

The presence of antibiotics in the aquatic environment is a serious concern because it may lead to the emergence of antibiotic resistance, thus lowering the therapeutic effect of antibiotics. In Vietnam, the problem is aggravated by the irrational use of antibiotics in different sectors of agriculture and human health service. Moreover, the residues of antibiotics in the aquatic environment can be spread widely due to the lack of proper wastewater treatment systems. In this paper, we aim to comprehensively review all relevant sources that discharge antibiotics to the aquatic environment in Vietnam. Apart from the common source of antibiotics from aquaculture, other activities that release considerable amounts of antibiotics into water environment are also included. Environmental concentrations of antibiotics related to those sources are studied to demonstrate their contributions to the presence of antibiotics in the aquatic environment in Vietnam. As antibiotic-contained water may be used as water supply for irrigation and even human consumption in rural areas, the essence of wastewater treatment is highlighted. Finally, we also discuss the new National Action plan from the Ministry of Health for controlling the issue of antibiotic resistance in Vietnam.

Keywords:

Antibiotic resistance; pharmaceutical manufacturing; veterinary antibiotics; wastewater treatment; antibiotic contamination; emergence of resistance;

List of abbreviation:

AZI: azithromycin, CEF: ceftazidime, CLA: clarithromycin, CIP: ciprofloxacin, DOX: Doxycycline, ENR: enrofloxacin, ERY: erythromycin, LIN: lincomycin, LOM: lomefloxacin, NOR: norfloxacin, OFX: ofloxacin, OTC: oxytetracycline, ROXI: roxithromycin, SDX sulfadimethoxine, SDZ: sulfadiazine, SMR sulfamerazine, SMT: sulfamethazine, SMX: sulfamethoxazole, SMZ sulfamethizole, SND: sulfanilamide, SPI: spiramycin, SPY: sulfapyridine; STZ sulfathiazole, TC: tetracycline, TRI: trimethoprim

1. Introduction

Antibiotics are effective medication for the treatment of infectious diseases in human and animals. Additionally, antibiotics can also be used as preventative medicine and more and more commonly as growth promoters in farming and husbandry (McEwen and Fedorka-Cray, 2002; Van Boeckel et al., 2015). The production and use of antibiotics for human and animals have resulted in significant reduction of mortality and morbidity rates, which were once inflicted by common infectious diseases. But the mass production and consumption of antibiotics also led to the situation that antibiotics are now ubiquitous in the environment (Kümmerer, 2009a). Antibiotics have been detected in aquatic environments such as lakes, rivers, water reservoirs, wastewater influents and effluents, groundwater and even drinking water even though drinking water was treated (Kolpin et al., 2004; Valcárcel et al., 2013; Sui et al., 2015). The most remarkable potential consequence of environmental antibiotics is the emergence of antibiotic resistance even at low antibiotic concentration (Kümmerer, 2009b; Gullberg et al., 2011). Therefore, antibiotics are considered emerging environmental pollutants of substantial consequence (Sui et al., 2015).

Antibiotics in environmental water originated from various sources: municipal (hospital and municipal sewage including a large part from household use and disposal) (Bound and Voulvoulis, 2005; Tong et al., 2011), agriculture (aquaculture, husbandry) (Hirsch et al., 1999; Lin et al., 2008), and pharmaceutical industry (Phillips et al., 2010). The degree of contribution of each source is different from country to country. For example, the veterinary contribution in Germany was minor while human contribution is a major source (Hirsch et al., 1999). Meanwhile in Taiwan, husbandries, hospitals and pharmaceutical manufacturers were the dominant sources of antibiotics in comparison to aquaculture and effluent of sewage treatment plants (Lin et al., 2008).

Vietnam's economy has been growing and so as the production and consumption of antibiotics, for both humans and livestock (Sy et al., 2017). Consequently, more antibiotic residues are expected to be discharged into the environment. However, information on the profile of antibiotics in aquatic environment on Vietnam was limited although the number of antibiotic groups and the quantity of antibiotics are considerably larger than other neighboring countries, including Indonesia and China (Andrieu et al., 2015). There are previous reviews on antibiotics in aquatic environment in Vietnam (Thuy et al., 2011; Sebesvari et al., 2012; Suzuki and Hoa, 2012; Thuy and Nguyen, 2013). However, they were focused mainly on the antibiotics discharged from aquaculture practice and did not look into the input side of the industries. Hence it does not provide enough information to understand all the potential sources of antibiotic contamination in aquatic environment in Vietnam. Apart from aquaculture, there are consumptions and discharges of antibiotics from other farming sectors (Dang et al., 2011; Kim et al., 2013), hospitals (Duong et al., 2008; Lien et al., 2016) and pharmaceutical manufacturer industry (Cardoso et al., 2014; Larsson, 2014; Binh et al., 2017) that could contribute substantially to the load of antibiotics measured in the aquatic environment of Vietnam (see Fig. 1) but so far they were not discussed in details in previous reviews.

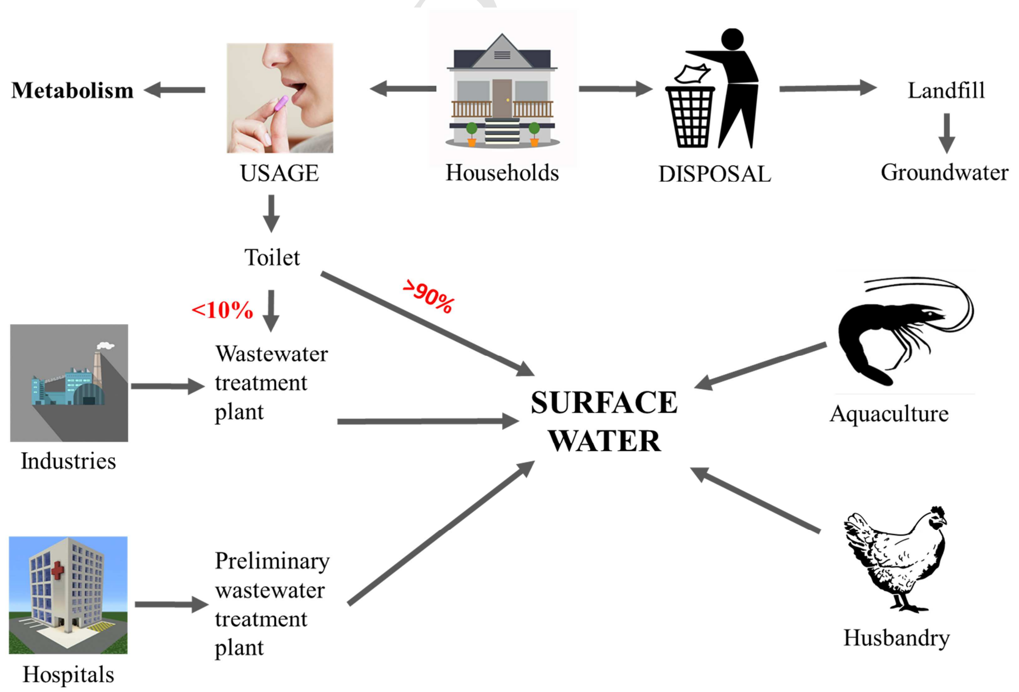

Figure 1. Pathways of antibiotics into the aquatic environment in Vietnam.

This review thus aims to provide a more comprehensive picture on the introduction of antibiotics in environmental waters in Vietnam from different sources (aquaculture, husbandry, hospital, and pharmaceutical manufacturer industry) in order to understand the profile of antibiotics in the aquatic environment and to provide the basis for any policy to control the antibiotic pollution in Vietnam.

2. Search approach

The relevant publications for this comprehensive review were collected by searching in the Web of Science database for published papers in all years using following key words: “antibiotic”, “water”, and “Vietnam”. The outcome was then screened using the title. This screening resulted in 34 peer-reviewed publications in English. Additionally, we also searched for relevant documents in Vietnamese including Government reports and guidelines on the topic of antibiotic residues and resistance. The documents in Vietnamese are the basis for our discussion on control strategy in Vietnam.

Our review covered 6 classes of antibiotics including beta-lactams, sulfonamides, macrolides, cyclines, lincosamides, quinolones with all potential sources, the first comprehensive review of this kind for Vietnam. A summary of the antibiotics found in the aquatic environment of Vietnam discussed in this review is presented in Table 1 below.

Table 1. Antibiotics found in the aquatic environment of Vietnam

Antibiotic classes	**Compounds**	**Source of antibiotics (max concentration ng L^{-1})**				
		Aquaculture	Husbandry	Hospital	Pharmaceutical manufacturing	Household consumption
Quinolones	Enrofloxacin	√ (680) [1]				
	Ciprofloxacin	√ (250) [1]		√ (53300) [7]		
	Oxolinic acid	√ (2500000) [6]				
	Ofloxacin	√ 238.6 [11]	√ (191.2) [11]	√ (19800) [7]	√ (1184) [2]	

	Norfloxacin	√ (6060000) [6]	√ (15.2) [11]	√ (1500) [4]		
	Lomefloxacin		√ (35.9) [11]			
Sulfonamides	Sulfamethoxazole	√ (2390000) [6]	√ (897) [9]	√ (20300) [7]	√ (1089) [2]	√ (4330) [9]
	Sulfadiazine					
	Sulfamethazine	√ (2) [9]	√ (19153) [8, 9]			√ (351) [9]
	Sulfapyridine					√ (15) [3]
	Sulfamerazine					
Trimethoprim	Trimethoprim	√ (1040000) [6]	√ (96) [9]	√ (7100) [7]	√ (844.5) [2]	√ (1808) [9]
Macrolides	Azithromycin				√ (2768) [2]	
	Erythromycin	√ (4) [9]	√ (64) [9]	√ (1200) [12]		√ (2246) [9]
	Clarithromycin		√ (4) [9]		√ (2445) [2]	√ (778) [9]
	Roxithromycin					√ (125) [9]
	Oleandomycin					√ (27) [3]
	Spiramycin			√ (2200) [7]		
	Tylosin		√ (381) [9]			
Cyclines	Oxytetracycline	√ (18) [9]	√ (900) [9]			√ (316) [9]
	Tetracycline		√ (275) [9]	√ (100) [12]		√ (258) [9]
	Docycycline		√ (1) [9]			
Others	Lincomycin	√ (10) [9]	√ (503) [9]			√ (2666) [9]
	2-hydroxy-3-phenylpyrazine		√ (128.8) [10]			
	Metronidazol			√ (130400) [7]		
	Ceftazidim			√ (5000) [7]		
	Cefotaxime				√ (349.5) [2]	
	Cephalexin				√ (4137.5) [2]	
	Ceficime				√ (43.33) [2]	
	Ampicilin					

[1]Andrieu et al. (2015); [2] Binh et al. (2017); [3] Chau et al. (2015); [4] Duong et al. (2008); [5] Hoa et al. (2011); [6] Le and Munekage (2004); [7] Lien et al. (2016), [8] Managaki et al. (2007b); [9] Shimizu et al. (2013); [10] Sy et al. (2017); [11] Takasu et al. (2011); [12] Vo et al. (2016)

3. Sources of antibiotics to the aquatic environment

3.1. Aquaculture

3.1.1. Antibiotic use in aquaculture

Use of antibiotics in aquaculture is a common practice in Vietnam to treat or prevent infections, and to promote growth of the batches. The utilization of intensive farming method, which facilitates the development of several bacterial diseases, has consequently led to an increase in antimicrobial uses. This topic has been the focus of previous reviews about antibiotics in the aquatic environment of Vietnam (Thuy et al., 2011; Rico et al., 2013).

In Vietnam, a range of antibiotics are approved by the Ministry of Agriculture and Rural Development (MARD) to be used legally in aquaculture. More than 30 antibiotics belonging to sulfonamide, β-lactam, quinolones, macrolides, cyclines and some other antibiotic groups are allowed to be used in limited quantities (Table 2). At the same time, some broad spectrum-antibiotics such as chloramphenicol, most of fluoroquinolone and nitroimidazole groups are banned in aquaculture due to their potential impacts on human health upon consumption of the aquaculture products (MARD, 2014). The number of antibiotics that can be used in aquaculture in Vietnam is much higher than in other countries such as the United States, where only 4 antibiotics (oxytetracycline, florfenicol, sulfadimethoxine, and ormetoprim) can be used in aquaculture (Chuah et al., 2016). The large number of antibiotics allowed to be used in this industry makes it difficult to control their use and likely to increase the risk of irrational use and environmental pollution.

Table 2. Allowed and banned antibiotics in Vietnam aquaculture practices (MARD, 2014)

Allowed with limit use			Banned
Amoxicillin	Difloxacin	Oxytetracycline	Chloramphenicol
Ampicillin	Emamectin	Paromomycin	Dimetridazole
Benzylpenicillin	Erythromycin	Sarafloxacin	Enrofloxacin
Ciprofloxacin	Flumequine	Spectinomycin	Fluoroquinolones
Chlortetracycline	Lincomycin	Sulfonamides	Florfenicol
Cloxacillin	Neomycin	Tetracycline	Glycopeptides

Colistin	Ormetoprim	Tilmicosin	Metronidazole
Cypermethrim	Oxacillin	Trimethoprim	Ronidazole
Danofloxacin	Oxolinic acid	Tylosin	Ipronidazole
Dicloxacillin			

The use of antibiotic in aquaculture varies with the species and raising stages. According to Tai (2004) there were 138 antibiotic formulations among 376 products for aquaculture in Vietnam, accounting for 36.7 %. The numbers of antibiotic products are different for each species. For example, 39 in total of 98 products for production of shrimp larvae contained antibiotics (39.8%), while it is 14/29 (48.3%) for marine finfish, 41/74 (55.4%) for freshwater-caged fishes, and 31/67 (46.3%) for pond-cultured fishes used. Notably, a survey by Rico et al. (2013) reported 100% use of antibiotics in *Pangasius* farms while only 2.9% shrimp farms used this group of drugs. The percentage of fish farms using antibiotics in Vietnam is considerably higher than in other countries (tilapia farm in Thailand: 9.7%; in China: 16%). The *Pangasius* farms in Vietnam also used a wider variety of antibiotics covering 10 different classes (penicillins, aminoglycosides, cephalosporin, quinolones, tetracyclines, amphenicols, polymyxin, diaminopyrimidines, rifamycins and sulfonamides). The most common antibiotics are enrofloxacin (quinolones) (69% farmers used), florfenicol (amphenicols) (63%), sulfamethoxazole (sulfonamides) in combination with trimethoprim (44%), doxycycline (cyclines) (34%). On average, each farm used 3 different antibiotic products, with 10% used up to 5-6 antibiotic products. Some products even contained mixture of different antibiotics (sulfadimethoxine and ormetoprim; sulfamethoxazole and trimethoprim; apramycin and levofloxacin).

Quinolones, especially fluoroquinolones, have been the most widely used synthetic antibiotics because of their relative stability in water and sediment (Le and Munekage, 2004) although fluoroquinolones are now banned from used (MARD, 2014). Quinolones antibiotics are used in larvae stage (ciprofloxacin) and postlarvae to adult stage (norfloxacin, oxolinic acid) (Thuy et al., 2011) or all stages (enrofloxacin) (Pham et al., 2015). Cyclines are used for larvae such as oxytetracycline, doxycycline, chlortetracycline, tetracycline (Pham et al., 2015). Sulfonamides antibiotics are used in post-larvae to adult stage (sulfonamides, trimethoprim); sulfadiazine; sulfadimethoxine (Thuy et al., 2011; Pham et al., 2015).

3.1.2. Antibiotic residues from aquaculture

There were antibiotics of various groups detected in water bodies that receive wastewater from shrimp or fish farming due to their common use. According to Giang et al. (2015), 91,6% of surface water samples taken in the Mekong Delta that receives wastewater from aquaculture contains 1 antibiotic and 55,2% contains 3-4 antibiotics. Antibiotics found in aquaculture wastewater including sulfonamides, macrolides, cyclines and quinolones (Le and Munekage, 2004; Takasu et al., 2011; Shimizu et al., 2013; Andrieu et al., 2015; Giang et al., 2015) with details shown in Table S1.

Due to the wide use of fluoroquinolone antibiotics in aquaculture, they have been detected frequently in a variety of aquatic environments at different concentration levels. It is reasonable to see that enrofloxacin, the antibiotic consumed most frequently, was found at the highest concentration, up to 680 ng L^{-1} at the discharged point of the wastewater pipeline from a *Pangasius* catfish farm into the canal (Andrieu et al. 2015), higher than ofloxacin and norfloxacin (238.6 ng L^{-1} and 44.4 ng L^{-1}) in shrimp farm wastewater, respectively (Takasu et al. 2011).

It is noted that although fluoroquinolones, specifically enrofloxacin, are banned in aquaculture since 2009 (MARD, 2014), they were still reportedly used in catfish farming (Andrieu et al., 2015; Giang et al., 2015) as well as shrimp farming (Chi et al., 2017). And the intensive use of antibiotics in aquaculture not only contaminates the water but also the sediment phase because antibiotics accumulated in sediments along with the settling of unconsumed feed particles. The incorporation of fluoroquinolone antibiotics into the sediment probably increases their persistence in the environment and subsequently prolongs their adverse impact (Le and Munekage, 2004; Andrieu et al., 2015; Giang et al., 2015). Enrofloxacin was ubiquitous in the canals and rivers that received the aquaculture wastewater with concentrations up to 59 ng L^{-1} at a canal (Giang et al., 2015). Other quinolone antibiotics (NOR, LOM and CIP) were detected in surface water and wastewater collected in shrimp farms, fish farm sites, fishponds integrated with pig and duck farm. The integrated farming system may be economically beneficial but also pose the risk of contaminating antibiotics from husbandry to aquaculture (Hoa et al., 2011). Oxolinic acid and NOR concentrations in surface water in shrimp pond were from 0.01 to 2.5 mg L^{-1} and from 0.06 to 6.06 mg L^{-1}, similar to the levels measured in surface water in surrounding canals (Le and Munekage, 2004). LOM was detected in fishpond integrated with pig farms at concentrations up to 35.9 ng L^{-1} (Takasu et al., 2011). CIP and LOM was not detected in wastewater from shrimp farm (Takasu et al., 2011).

SMX, SDZ and TRI were detected in high frequency (Le and Munekage, 2004; Hoa et al., 2011; Giang et al., 2015). This is in agreement with the prevalent use of sulfonamide – containing products. Other sulfonamides such as STZ, SMR, SMZ, SDX were not detected in any sample from shrimp farm and pig/fish farm (Hoa et al., 2011). Maximum SMX concentration in shrimp farm surface water was 2.39 mg L^{-1} (Le and Munekage, 2004), several times higher than in shrimp farm wastewater of 914 ng L^{-1} (Hoa et al., 2011; Shimizu et al., 2013). SMX at bottom layer in surrounding canals were as high as that in pond water (about 5.57 mg L^{-1}) (Le and Munekage, 2004). TRI concentration in shrimp farm water was up to 2.03 mg L^{-1}, about 1.2 mg L^{-1} at bottom water in surrounding canals (Le and Munekage, 2004) and in wastewater was up to 85 ng L^{-1} (Hoa et al., 2011). SMX and SDZ were detected at comparable concentration in canals receiving wastewater from the hatchery and *Pangasius* farms (135 and 108 ng L^{-1}, respectively) (Giang et al., 2015). However, in wastewater from fishponds integrated with pig farm, SDZ concentration can be 10 times higher than SMX, which were 6662 ng L^{-1} and 625 ng L^{-1} (Hoa et al., 2011). The difference in concentration of the two compounds was observed in case of fish/duck pond where SDZ concentration was 28 times larger than SMX (1966 ng

L^{-1} and 70 ng L^{-1}) (Shimizu et al., 2013). Therefore, it is concluded that SMX was mainly used in shrimp ponds while SDZ was more dominant in pig farm integrated with fish ponds (Hoa et al., 2011). However, in another study, SMX was not detected in wastewater samples of many shrimp farms (Shimizu et al., 2013).

Macrolides were detected in shrimp farms, fishponds integrated with pig farms in northern Vietnam, however, their concentration is far below those in city canals, which were believed to be severely impacted by human activities (Hoa et al., 2011). Erythromycin (ERY) was the most common macrolide detected. It was found in both kinds of wastewater samples from shrimp farms and pig/fish integrated farms at the concentration up to 0.28 ng L^{-1} and up to 63.9 ng L^{-1}, respectively. CLA concentration was low, maximum 0.4 ng L^{-1} at pig/fish farm. SPI, ROXI and AZI were not detected in these samples (Shimizu et al., 2013).

Although cyclines antibiotics were used widely, they were not detected in high frequency and high concentration probably because they degrade quickly and are not easy to analyze. Only one study has attempted to measure this antibiotic group in aquaculture in Vietnam (Shimizu et al., 2013). OTC was the most common cycline antibiotic and was the only one detected in wastewater of pig/fish farm with concentration up to 36 ng L^{-1}. Concentration of OTC, TC in shrimp farm wastewater were 18 ng L^{-1} and 17 ng L^{-1}, respectively. DOX was not detected in any sample.

LIN was the only lincosamide antibiotic under investigation in studies in Vietnam. It was found at concentration up to 416 ng L^{-1} in pig/fish farm (Shimizu et al., 2013).

3.2. Husbandry

3.2.1. Antibiotic use in husbandry

Similar to the case of aquaculture, antibiotics are used in husbandry in Vietnam in order to treat and prevent diseases as well as promote growth. Some antibiotics of high risk are banned while some are allowed to be used in limit quantities for veterinary purpose (MARD, 2014). Those banned are chloramphenicol, furazolidon, dimetridazole, metronidazole, eprofloxacin, ciprofloxacin, ofloxacin, carbadox, olaquidox, and bacitracin Zn while those with limited use are spiramycin, avoparcin, virginiamycin, meticlorpidol, flavophospholipol, salinomycin, avilamycin, monensin, tylosin phosphate. Additionally, there is a list of 15 antibiotics for growth promotion with specific dosages for each species including bambermycins, bacitracin methylene disalicylate, chlortetracycline, colistin sulphate, enramycin, kitasamycin, lasalocid sodium, lincomycin, monensin, narasin, neomycin sulphate, nosiheptide, salinomycin sodium, tylosin phosphate, virginiamycin (MARD, 2016) (Table 3).

It was reported that of 1174 commercial feed products available in the market, 43.7% contained at least 1 antibiotic with 5.4% and 21.5% of chicken and pig feed formulations contained 2 or more antibiotics, respectively (Cuong et al., 2016). Bacitracin and chlortetracyclines were the most common antibiotics used in feeds for both chicken and pig.

Table 3. Allowed and banned antibiotics in Vietnam aquaculture practices (MARD, 2016).

Allowed with limited use			**Forbidden**
General use	Growth promoters		
Avilamycin	Bacitracin methylene disalicylate	Monensin	Chloramphenicol
Avoparcin	Bambermycins	Narasin	Dimetridazole
Flavophospholipol	Chlortetracycline	Neomycin sulphate	Metronidazole
Monensin	Colistin sulphate	Nosiheptide	Eprofloxacin
Meticlorpidol	Enramycin	Salinomycin sodium	Ciprofloxacin
Salinomycin	Kitasamycin	Tylosin phosphate	Ofloxacin
Spiramycin	Lasalocid sodium	Virginiamycin	Carbadox

Tylosin phosphat	Lincomycin		Olaquidox
Virginiamycin			Bacitracin

Antibiotics used as growth promoters for pigs were much more common in industrial scale farms (up to 66.7%) than in semi-industrial scale (up to 43.3%) and household farms (up to 20.0%) in the North of Vietnam (Kim et al., 2013). Similarly, the percentage of farms using antibiotics for disease prevention for piglets, fattening pigs, breeding poultry and laying hens in household farms is less than in the corresponding industrial production systems. However, a number of farms used multiple (3-6) antibiotics for pig and chicken productions (26.7% and 16.7%, respectively). In the Mekong Delta, all chickens and pigs were administered antibiotics at least once in their life to prevent or treat diseases with 50% of the products contained 2 or more antibiotics (Nguyen et al., 2016).

Use of 10 antibiotic classes in the North were reported by (Kim et al., 2013) while 8 antibiotic classes were reported in the South (Cuong et al., 2016). Tylosin (TYL), gentamycin, colistin, enramycin, ampicillin, salinomycin and chlortetracycline were used in high frequency (Kim et al., 2013; Nguyen et al., 2016). Surprisingly, chloramphenicol, a fully-banned antibiotic was also found in use in a pig farm (Nguyen et al., 2016). There were concerns that some antibiotics like salinomycin and spiramycin were used in a large quantity despite being restricted by the legislation (MARD, 2014) as well as colistin, a critically important medicines for humans, had a widespread use for animal in Vietnam (Nguyen et al., 2016). A preliminary estimation indicated that the annual amounts of antibiotics used for chicken and pig production were 42.2 tons and 981.3 tons, respectively (Cuong et al., 2016).

3.2.2. Antibiotic residues from husbandry

Only three studies so far have monitored the residual antibiotics originated from husbandry in Vietnam (Managaki et al., 2007b; Hoa et al., 2011; Shimizu et al., 2013) but the findings of those studies are important because some antibiotics were found at extremely high concentrations. The targeted compounds were limited to four classes of sulfonamides, macrolides, lincosamides, and cyclines. It is noted that the antibiotic found with high frequency in use such as spiramycin (Kim et al., 2013) was not monitored in the above mentioned studies.

SMX and SMT were the prevalent sulfonamide antibiotics detected in wastewater from livestock farms. In most wastewater samples from pig farms, SMT was higher than SMX. In contrast, SMX was the dominant in wastewater from cow, chicken and duck farms. Very high concentrations of SMT (as high as 19153 ng L^{-1}) were detected near pig farms (Managaki et al., 2007a; Hoa et al., 2011) but lower concentrations were measured near other farms. The maximum concentration of SMX was lower than those of SMT but still very high (up to 2715 ng L^{-1}) near another pig farm. Trimethoprim, an antibiotic usually used in combination with SMT, was detected at concentration up to 96 ng L^{-1} (Shimizu et al., 2013). SDX was detected at low frequency, with maximum concentration of 4 ng L^{-1} (Shimizu et al., 2013). SPY, STZ and SMR were not detected in any samples (Managaki et al., 2007a).

ERY was the most commonly detected macrolide in water related to husbandry activities with concentration up to 64 ng L^{-1}. Tylosin was not detected as frequently as ERY but its maximum concentration was much higher, up to 381 ng L^{-1}. This prevalence was in accordance with the survey of Kim et al. (2013). CLA was only detected at cow and duck farm at concentration below 0.4 ng L^{-1} (Shimizu et al., 2013). AZI, ROX were not detected at any site (Managaki et al., 2007a; Shimizu et al., 2013).

LIN was detected in all samples taken from pig farm, cow farm, chicken farm, and duck farm. Maximum concentration of this antibiotic was 503 ng L^{-1} near a chicken farm (Shimizu et al., 2013).

OTC was detected at the highest frequency with concentration up to 900 ng L^{-1} in pig farm in Can Tho (Shimizu et al., 2013) but not detected in pig farms in Ho Chi Minh city (Managaki et al., 2007a; Shimizu et al., 2013). It was also detected in wastewater of a cow farm with concentration up to 726 ng L^{-1}. TC was detected at lower frequency and lower concentration than OTC with concentration up to 275 ng L^{-1} in pig farm, 7 ng L^{-1} in cow farm. And both of them were not detected in chicken and duck farms (Shimizu et al., 2013). DOX was detected only one time at concentration of 1 ng L^{-1} in a pig farm in Can Tho (Shimizu et al., 2013).

In an attempt to figure out the presence of β-lactam antibiotics in the environment, a degradation product of ampicillin and other β-lactam antibiotics with similar structure - 2-hydroxy-3-phenylpyrazine was suggested as a marker for β-lactam antibiotics in the environment. It was found in household ponds in Hanoi and Thaibinh, which located closed to livestock farms at concentration 4.5 – 128.4 ng L^{-1} and 10 – 128.8 ng L^{-1} (Sy et al., 2017).

3.3. Hospitals

3.3.1. Antibiotic use in the hospitals

Vietnam has almost 1200 hospitals, most of them public ones, with about 200,000 beds (Anonymous, 2012; Thu et al., 2012). Pharmaceuticals used in all hospitals are regulated by the Ministry of Health, Vietnam and provided through a bidding system. Table 4 presents the 2016 pharmaceutical bidding list. There are 8 groups in total. The beta lactam with 36 antibiotics is the most common followed by the sulfonamide group (9 antibiotics). The quinolone, macrolide and aminoglycoside groups share similar number of antibiotics listed (7, 6 and 6, respectively). From our literature search, there are 7 studies, 1 review (Nguyen et al., 2013) and 1 report (Anonymous, 2016) on the use of antibiotics in hospitals in Vietnam, indicating the increasing attention on the issue of appropriate use of antibiotics. The surveys were done in 15 hospitals (national and provincial levels) by (Nguyen et al., 2013), 36 hospitals by Thu et al. (2012), 14 hospitals (7 tertiary and 7 provincial hospitals) by Phu et al. (2016) and 3 studies in 3 national hospitals (articles in Vietnamese) (Hiền et al., 2011; Huế et al., 2013; Thắng, 2013).

309 **Table 4.** Pharmaceutical bidding list issued in Circular 09/2016/TT-BYT, Ministry of Health

β-lactam group	**β-lactam group (cont.)**	**Sulfonamide group**	**Tetracycline group**
Amoxicillin	Doripenem	Sodium sulfacetamide	Doxycycline
Ampicillin	Ertapenem	Sulfadiazinbạc	Minocycline
Benzathinbenzylpenicillin	Imipenem	Sulfadimidin	Tetracycline
Benzylpenicillin	Meropenem	Sulfadoxin	
Cefaclor	Oxacilin	Sulfaguanidin	**Nitroimidazole group**
Cefadroxil	Piperacilin	Sulfamethoxazole	Metronidazole
Cefalexin	Phenoxymethylpenicilin	Sulfasalazin	Secnidazole
Cefalothin	Procainbenzylpenicilin	Pyrimethamin	Tinidazole
Cefamandol	Sultamicillin	Pernamidin	
Cefazolin	Ticarcillin		**Others**
Cefdinir		**Phenicol group**	Clindamycin
Cefepim	**Aminoglycoside group**	Chloramphenicol	Colistin
Cefmetazol	Amikacin	Triamphenicol	Daptomycin
Cefoperazon	Gentamicin		Fosfomycin
Cefotaxim	Neomycin	**Quinolone**	Fusafungine
Cefotiam	Netilmicinsulfat	Ciprofloxacin	Linezolid
Cefoxitin	Tobramycin	Levofloxacin	Nitrofurantoin
Cefpirom	Spectinomycin	Moxifloxacin	Nitroxolin
Cefpodoxim		Nalidixic acid	Rifampicin
Cefradin	**Macrolide**	Norfloxacin	Teicoplanin
Ceftazidim	Azithromycin	Ofloxacin	Vancomycin
Ceftezol	Clarithromycin	Perfloxacin	
Ceftibuten	Erythromycin		
Ceftizoxim	Roxithromycin		
Cefuroxim	Spiramycin		
Cloxacilin	Telithromycin		

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A research carried out across 36 general hospitals (2 national level, 18 provincial level, and 16 district level) in Vietnam in 2008 pointed out that 67.4% inpatients were prescribed antibiotic (Thu et al., 2012). However this percentage in outpatient prescription was much lower (29% in Bach Mai Hospital, a national general hospital in Vietnam) (Thắng, 2013). The use of antibiotics also varied depending on the departments. For examples, in most cases, the antibiotics were prescribed in the departments with high risk of infections such as surgery wards (93.2%), Odonto-stomatology department (92.8 %). In 2012, in pediatric department of Hospital Central Thai Nguyen, 100% children aged from 2 months to 5 years old with apparently acute respiratory infections were prescribed antibiotics although only 54,9% patients has clinical infectious expression and positive to infectious test (Huế et al., 2013).

Among the 8 antibiotic groups in the hospital-bidding list, six have been reported to be prescribed in the hospitals (β-lactam, aminoglycoside, macrolide, quinolone, imidazole and sulfonamide groups) (Thu et al., 2012; Nguyen et al., 2013; Phu et al., 2016). The phenicol group such as chloramphenicol was considered the “older” antibiotics and mainly sold in pharmacy retailers (Nguyen et al., 2013). Tetracycline group was not specifically mentioned in those studies. However, there were a group called “other antibiotics” in those studies that may contain this antibiotic group and the rest of the antibiotics in the Table 2. The most common prescribed antibiotic group was β-lactam. Second and third generation cephalosporins and carbapenems were the most common used antibiotics at all hospitals, followed by fluoroquinolones, broad-spectrum penicillins, aminoglycosides, and macrolides. Expenditure of carbapenems has contributed a remarkable part in the treatment budget (12.3%) indicated that this group is been increasingly used in treatment in all hospitals. Older antibiotics such as phenicols, betalactamase sensitive penicillins, lincosamides are used little in treatment. Colistin only accounted for a small faction (about 3.3%) of general use but was frequently used agent for specific indications such as hospital-acquired infections (Phu et al., 2016). In many cases, combination of antibiotics was prescribed. 37,1% outpatients in Bach Mai hospital and 66,3% children in pediatric department of Hospital Central Thai Nguyen were treated with more than one type of antibiotics. In particular, 20% cases of antibiotic combination prescription for children were composed of 4 antibiotics (Huế et al., 2013; Thắng, 2013).

The inappropriate antibiotic prescription appears to be common in Vietnam (Mao et al., 2015). This can lead to the development of antibiotic resistant bacteria. Approximately one third of the patients in 36 general hospitals in Vietnam received inappropriate antibiotic prescription. Antibiotics such as carbapenems that were considered as the last choice in treating multi-drug resistant bacteria were used extensively at Department of Anesthesiology and Reanimation, Viet duc Hospital (24.9% patients in 2010). Carbapenems were selected as empiric schemes in 12.5% of patients although *Acinetobacter spp* and *Pseudomonas aeruginosa* were highly resistant to imipenem and meropenem (Hiền et al., 2011). Due to the easy access to drugs in retailed pharmacy stores, a number of patients used antibiotics without prescription. In a study, 71.0% of patients had used antibiotics before admission into the hospital, of which, the rate of using β-lactam family was 76.2%. Notably, these patients are children and their parents give them the drugs (Huế et al., 2013). The fact that people can purchase antibiotics without prescription in pharmaceutical retailers makes the difficulties in controlling the actual use of this drug.

3.3.2. Antibiotic residues from hospitals

Despite an extensive use of antibiotics with large potential of irrational use in the hospital system in Vietnam, there have been only three studies published, two in Hanoi (Duong et al., 2008; Lien et al., 2016) and one in Ho Chi Minh city (Vo et al., 2016). The hospitals covered in the studies were operated either with a wastewater treatment plant (18 hospital and 24 healthcare facilities) or without a wastewater treatment plant (5 hospitals). However, only in 3 hospitals, residual antibiotics were measured in wastewater samples before and after treatment (Duong et al., 2008; Lien et al., 2016).

The remaining hospitals had antibiotics measured only in raw wastewater even though many hospitals had the wastewater treatment plants.

Antibiotics belonging to quinolone, sulfonamide, macrolide, cycline and β-lactam classes were detected in wastewater from all studied hospitals in Vietnam. This finding confirmed the widespread use of antibiotics in the hospitals. However, the number of antibiotics as targeted compounds was limited. For example, β-lactam antibiotics, the most prescribed ones, were not included in all studies. And only one study measured ceftazidim (CEF), a third generation cephalosporin (Lien et al., 2016).

CEF was detected only in 2 samples in wastewater of a rural hospital while it was not detected in any sample from an urban hospital (Lien et al., 2016). The low detection frequency of this new generation antibiotic is probably a good sign that it has been overused yet.

In contrast, concentrations of quinolone antibiotics were relatively high. CIP was detected in all samples collected from wastewater discharged from all studied hospitals (15 in Ho Chi Minh City and 8 in Hanoi) with the highest concentration of CIP of 87.3 μg L^{-1} in influent and 53.3 μg L^{-1} in effluent of a rural hospital treatment plant (Lien et al., 2016). NOR and OFL were also detected in most wastewater samples in Ho Chi Minh City (Vo et al., 2016) and in Hanoi (Duong et al., 2008) in comparable range of several μg L^{-1}, respectively. Only one influent sample from an urban hospital in Hanoi has a very high concentration of OFL of 111 μg L^{-1} (Lien et al., 2016).

Wastewater treatment reduced concentrations of quinolone antibiotics but CIP, NOR and OFL were still detectable in most effluent samples, e.g. from 1.2 – 1.8 μg L^{-1} for NOR (Duong et al., 2008) or from 0.8 – 19.8 μg L^{-1} for OFL (Lien et al., 2016). The levels of reduction varied among the quinolones and varied between studies, which might be due to the different treatment methods and sampling uncertainties.

Only one sulfonamide, SMX, was monitored in hospital wastewaters in Vietnam. It was detected in all raw wastewater samples in Ho Chi Minh City (0.6 to 4.4 μg L^{-1}) (Vo et al., 2016) and in Hanoi (0.2 –

31.4 μg L^{-1}) (Lien et al., 2016). TRI was found in samples containing SMX because these two active ingredients were commonly used in combination. TRI concentration in raw wastewater was lower than SMX, ranging from 1.0 ± 0.9 μg L^{-1} in Ho Chi Minh City and from 0.1 – 22.4 μg L^{-1} in Hanoi respectively. Both SMX and TRI remained in the effluent of the treatment plants in most of samples even in relatively high concentration of 20.3 μg L^{-1} for SMX (Lien et al., 2016).

A macrolide antibiotic, spiramycin was found in about 45% to 75% samples from 2 hospitals in Hanoi with concentrations ranging from 0.2 – 2.2 μg L^{-1} (Lien et al., 2016). Erythromycin was found in 80% wastewater samples collected in Ho Chi Minh City (1.2 μg L^{-1}) while tetracycline was also detected at average concentration of 0.1 μg L^{-1} but at lower frequency (20%) (Vo et al., 2016).

3.4. Pharmaceutical manufacturers

3.4.1. Antibiotics from pharmaceutical manufacturers

Vietnam has a fast growing pharmaceutical industry to meet the demand of the population, which was recently reviewed by Angelino et al. (2017). In brief, there are 189 pharmaceutical facilities that are allowed to manufacture in 2017 (Drug Administration of Vietnam - 3/2017), compared to 131 in 2014 and 101 in 2010 (Angelino et al., 2017). Drug spending per capita doubled from 22.25 USD in 2010 to 44 USD in 2015, and estimated to double again every five years. However, the pharmaceutical industry in Vietnam depends largely on imported active ingredients and excipients (90%) from other countries and is characterized mainly as producers of simple dosage/generic forms with low values (Angelino et al., 2017). With widespread use of antibiotics as described in previous section, the industry is likely to have a very good market for their antibiotic products.

For this review, we attempted to collect the actual production data of the pharmaceutical manufacturers. However, it is not feasible through the Drug Administration of Vietnam because the

Administration only controls the registration of antibiotics or drugs in general, not the amount of production (MoH, 2013). To overcome this lack of information, we attempted to estimate the drug production of through the importation data, as most of the active ingredients, particularly antibiotics, were imported from other countries (Nguyen and Roughead, 2015).

The amount of imported raw materials for production of antibiotics can be extracted from the database of the Vietnam Customs Department. Figure 1 presents the amounts of antibiotics imported into Vietnam from 2014-2016. Overall the amount of imported antibiotics increased over the time. β-lactam antibiotics, especially amoxicillin, ampicillin, the 2nd generation cephalosporin (e.g. cefuroxime), and the 3rd generation cephalosporin (e.g. cefixim) antibiotics were imported in higher quantities than the others. Quinolones antibiotics were also imported in considerable amount, in which ciprofloxacin was the quinolone antibiotic imported in largest quantity. Erythromycin, neomycin and doxycycline were the most imported macrolide, aminoglycoside and cycline antibiotics.

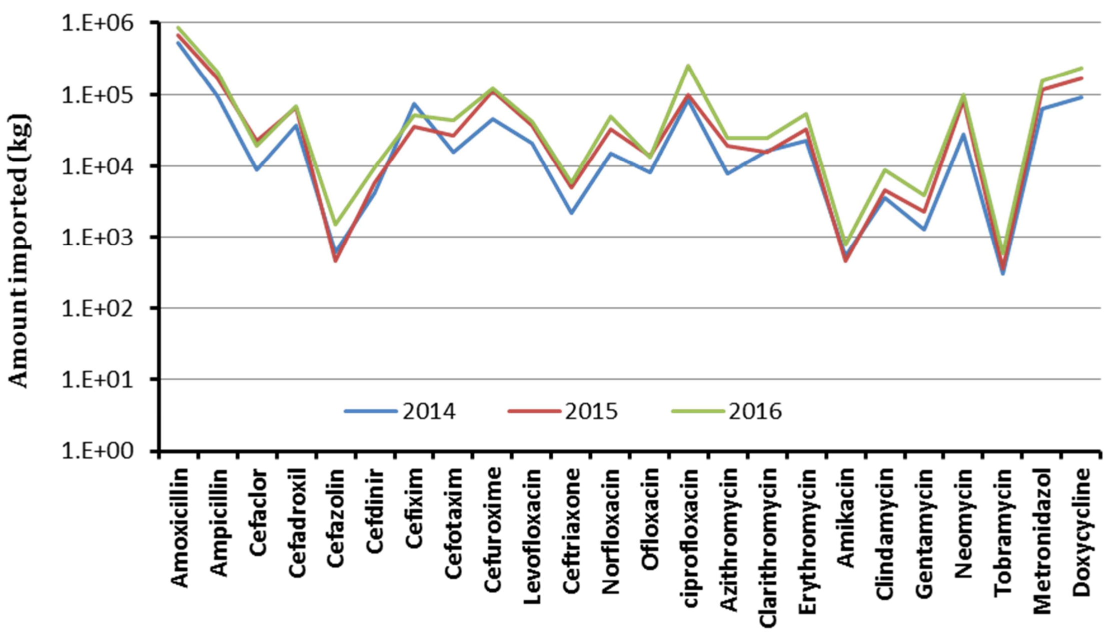

Figure 2. The amounts of antibiotics imported into Vietnam during 2014-2016

3.4.2. Residual antibiotics discharged from pharmaceutical manufacturers

Pharmaceutical manufacturers have been identified as a potential source of pharmaceuticals including antibiotics in the environment (Caldwell, 2016). A recent review reported that in China and India, where most of the generic antibiotics are produced, the concentrations of popular antibiotics like OTC or CIP in effluent from pharmaceutical facilities could be more than several mg L^{-1} (Cardoso et al., 2014). As Vietnam produced a large number of antibiotic products in its factories this industry might also be an important source of antibiotics in the aquatic environment in Vietnam. However, our search did not result in any publication on this topic in Vietnam except those from our own group. The first study in this area in 2014 only analysed a group of 4 cephalosporins in effluent samples from pharmaceutical factories and reported the concentrations of cefixime ranging from 19.24 to 43.33 μg L^{-1} (Hue et al., 2014). A more recent study has found high concentrations of quinolones, macrolides and sulfonamides in canals downstream from the discharge points of the pharmaceutical factories (Binh et al., 2017). Popular antibiotics measured were OFL (1.2 μg L^{-1}), cefotaxime (1.3 μg L^{-1}), AZI (2.8 μg L^{-1}), CLA (2.4 μg L^{-1}), SMX (1.1 μg L^{-1}), and TRI (0.9 μg L^{-1}). Cephalexin is the only β-lactam antibiotic detected at high concentration in downstream samples (4.1 μg L^{-1}). These preliminary findings suggested that wastewater from pharmaceutical manufacturers could be an important source of antibiotics in the environment of Vietnam and a more systemic research in this area is needed.

3.5. Residual antibiotics from household consumption in urban drainage, city canals, suburban canals and rivers

In Vietnam, wastewater from the above-mentioned sources and wastewater from household were discharged into suburban canals, city canals, and rivers. In many cities and rural areas, this water is not treated by any wastewater treatment plant. Only recently that centralized wastewater treatment plants have been constructed, starting in large cities such as Hanoi, Da Nang and Ho Chi Minh City. By 2013, a total of 20 urban wastewater treatment systems were in operation, covering less than 10% of the total wastewater generated in Vietnam (World-Bank, 2013). Subsequently, water from these bodies could be used as supply water for agricultural practices and in some rural areas it could be used for human use purpose (Giang et al., 2015), which can pose a very high risk of exposure to antibiotics and even antibiotic resistant bacteria. As such, there were two studies specifically monitoring of antibiotics in lakes (Yên et al., 2016), canals and river water (Chau et al., 2015) besides other studies that measured antibiotics among sampling sites near the various sources mentioned above. Yên et al. (2016) measured quinolones, sulfonamides and trimethoprim in water of two important lakes in Hanoi. Chau et al. (2015) monitored ampicillin, CLA, ERY, griseofulvin, lincomycin, oleandomycin, ROXI, SPI, SDZ, SMX, sulfanolamide, SPY, and TRI in main rivers in big cities in the North, Central and South part in Vietnam. The concentration of antibiotics in canals is commonly higher than lakes and rivers, all of which ranged from ng L^{-1} to some μg L^{-1}.

Sulfonamide antibiotics were commonly detected in canal and river water. SMX was detected in all samples collected in urban drainage in 3 big cities in both North and South of Vietnam (Hanoi, Cantho, and Ho Chi Minh City) with concentration ranging from hundreds to thousands ng L^{-1}. However, SMX was not detected in any urban samples collected in Hue and Danang, 2 big cities in central area of Vietnam (Chau et al., 2015). The concentration was high in Hanoi 612 – 4330 ng L^{-1} (Hoa et al., 2011) and Cantho 103-4030 ng L^{-1} (Shimizu et al., 2013) and lower in Ho Chi Minh City 190 – 1008 ng L^{-1} (Managaki et al., 2007b; Shimizu et al., 2013; Giang et al., 2015). In Hanoi, rivers that received wastewater from industrial and domestic activities, SMX was found at concentration from 623 – 2159 ng L^{-1} (Chau et al., 2015). In 2 big lakes in Hanoi, which received directed household wastewater, SMX was detected in high frequency, however, at concentration lower than city canals (104.3 ng L^{-1}) (Yên et al., 2016). The concentration of SMX in the urban canals of Cantho was even higher than the wastewater from pig farm in Cantho, indicating that those canals could be highly contaminated from different sources (Shimizu et al., 2013). In main city canals in Mekong delta affected by industrial and domestic sources, SMX was found with maximum concentration of 239 ng L^{-1}, while in canals affected by aquaculture and domestic sources, the maximum concentration was 185 ng L^{-1} (Giang et al., 2015). In city canals in Mekong delta, SMX concentration was from 75 to 131 ng L^{-1} and from 25 to 313 ng L^{-1} (Managaki et al., 2007b) (Shimizu et al., 2013), comparable to suburban canals (11 – 308 ng L^{-1}) (Shimizu et al., 2013), 63 – 313 ng L^{-1} (Chau et al., 2015). From these observations, it is suggested that human consumption could also contribute substantially to the load of SMX in the environment (Hoa et al., 2011) although we lacked the import data of sulfonamide group to support this proposition.

The detection frequency of SMX was different among places. While the detection frequency was 100% in the Mekong delta (Shimizu et al., 2013), it was detected only in 1/14 samples in the Red river (Chau et al., 2015). Fortunately, there was no detection of SMX in ground/piped water (Giang et al., 2015).

SMT was another sulfonamide antibiotic detected in all samples in urban drainage but at concentration approximately 3-10 times lower than SMX: 18 – 88 ng L^{-1} in Hanoi (Hoa et al., 2011); 7 to 351 ng L^{-1} in Cantho (Shimizu et al., 2013), 67 - 251 ng L^{-1} in Ho Chi Minh City (Managaki et al., 2007b; Shimizu et al., 2013). It is suggested that the main source of SMT in the environment was pig farms (Managaki et al., 2007b; Hoa et al., 2011; Shimizu et al., 2013); therefore it was not detected in high concentration in urban drainage. In West Lake and Truc Bach Lake in Hanoi, which were polluted by wastewater from household discharge, SMT was still detected but at concentration up to only 34.8 ng L^{-1} (Yên et al., 2016). Calculation based on the SMT/SMX ratio also suggested that both sewage (urban drainage) and livestock waste contributed comparable amount of SMT in city canals (ratio 0.1), suburban canals (0.4) and Mekong river (0.17 - 0.97) (Shimizu et al., 2013).

A less prevalent sulfonamide, SDZ, was detected in main city canals in the Mekong delta affected by industrial and domestic sources (63 ng L^{-1}) and in the city canals affected by aquaculture and domestic sources (26 ng L^{-1}). More importantly, the river that located a pumping station for human use contained SDZ at concentration comparable to the main canal (48 ng L^{-1}) (Giang et al., 2015). However, it was not detected in any samples in other research (Chau et al., 2015). SND was found in waste canals in Ho Chi Minh city at concentration up to 593 ng L^{-1}, much higher than almost all other sulfonamides, however, it was not detected in other canal and river samples (Chau et al., 2015). SMR was detected in 2 big lakes in Hanoi (16.3 ng L^{-1}) (Yên et al., 2016) but not detected in urban drainage, city canals and river samples in other studies (Managaki et al., 2007a; Hoa et al., 2011; Shimizu et al., 2013). Other sulfonamide antibiotics such as STZ, SMZ, SDX were not either included or detected at any site (Managaki et al., 2007b; Hoa et al., 2011; Shimizu et al., 2013; Chau et al., 2015).

TRI is normally used in combination with SMX. Therefore, it was not surprised when TRI was detected in urban drainage with similar pattern like SMX. The distribution of TRI concentration to some extent shared common trend with SMX: comparably high in Hanoi (91 – 1808 ng L^{-1}) (Hoa et al., 2011); high in Cantho (7 – 466 ng L^{-1}) (Shimizu et al., 2013), and lower in Ho Chi Minh City (42 - 140 ng L^{-1}) (Managaki et al., 2007b; Shimizu et al., 2013; Giang et al., 2015) and not present in any urban water samples from Hue and Danang City (Chau et al., 2015). In closed lakes in Hanoi, TRI was found at concentration up to 69 ng L^{-1} (Yên et al., 2016). Main city canals in Mekong delta that was affected by industrial and domestic sources and by aquaculture and domestic sources contained TRI at concentration 111 ng L^{-1} and 163 ng L^{-1}, respectively (Giang et al., 2015). Rivers in Hanoi contained TRI at concentration from 28 – 176 ng L^{-1} (Chau et al., 2015). Its concentrations were lower in Hau river (1-10 ng L^{-1}) (Shimizu et al., 2013) and Mekong river (Managaki et al., 2007b) and was not detectable in Red riverand Saigon river (Chau et al., 2015). However, at a pumping station located in Hau River, TRI concentration was high (144 ng L^{-1}). Fortunately, there was no detection of these sulfonamide antibiotics and TRI in ground/piped water (Giang et al., 2015).

The second antibiotic group that was prevalent in urban drainage, city canals and rivers was macrolide. Among the studied macrolide antibiotics, ERY is the most prevalent and detected in highest concentration. It was detected in all urban drainage samples collected in three big cities in Northern and Southern region of Vietnam: higher in Hanoi 61-2264 ng L^{-1}, lower in Cantho 28 – 231 ng L^{-1} and Ho Chi Minh city 104 – 600 ng L^{-1} (Shimizu et al., 2013), 29 – 39 ng L^{-1} (Managaki et al., 2007b). However, a lower detection frequency was reported by Chau et al. (2015), in which only 1/4 waste canal in Ho Chi Minh City contained ERY at concentration 86 ng L^{-1}. The distribution of ERY in city canals shares the same pattern: highest in Hanoi 61.1 – 2246 ng L^{-1} (Hoa et al., 2011), lower in Mekong delta 31 – 41 ng L^{-1} (Managaki et al., 2007b) and not detected in Ho Chi Minh City (Chau et al., 2015). ERY was not detected in suburban canals (Chau et al., 2015) or detected at low concentration 2-10 ng L^{-1} (Shimizu et al., 2013). Despite the high detection rate in urban drainage and city canals in Hanoi, ERY was not detected in 5 rivers receiving waste in this city and Red River (Chau et al., 2015). On the other hand, ERY was found in rivers in South of Vietnam at low concentration and frequency: Hau river 1 – 12 ng L^{-1} (Shimizu et al., 2013) and Mekong river (9 – 12 ng L^{-1}) (Managaki et al., 2007b). The considerably higher ERY concentration in urban drainage in comparison to husbandry and aquaculture wastewater (section 3.1.2 and 3.2.2) suggested that human was a major source releasing ERY into water. The possible explanation was that ERY was imported in considerable amount in 3 consecutive years 2014 – 2016 for drug production (Figure 2) and macrolide antibiotics were used at high consumption rate in hospitals (section 3.3.1.), while it was not enlisted as the common antibiotic used in aquaculture and husbandry (section 3.1.1 and 3.2.1). Therefore the urban drainage was polluted from this antibiotic more severely than the wastewater from aquaculture and husbandry farms were.

CLA was another macrolide antibiotic commonly detected in urban drainage and canals in Vietnam. CLA distribution in urban drainage in big cities was the same as ERY but at lower concentration range: higher in Hanoi 2 - 778 ng L^{-1}; lower in Cantho 5 - 256 ng L^{-1}, (Shimizu et al., 2013), Danang 110 ng L^{-1} (Chau et al., 2015) and lowest in Ho Chi Minh City 9 - 92 ng L^{-1} (Shimizu et al., 2013), 13 – 66 ng L^{-1} (Chau et al., 2015). However, in contrast to ERY, CLA was found all samples collected in rivers in Hanoi at concentration 29-169 ng L^{-1} (Chau et al., 2015). This is difficult to explain due to the lack of dissipation properties of the two antibiotics. City canals also contained CLA at different concentration: as high as 1.6-778 ng L^{-1} in Hanoi (Hoa et al., 2011) and as low as 3-16 ng L^{-1} in Ho Chi Minh city (Managaki et al., 2007b; Shimizu et al., 2013). Suburban canals in Mekong delta also contained CLA at very low concentration 1 - 8.7 ng L^{-1} (Shimizu et al., 2013; Chau et al., 2015). In main rivers such as Red River, Hau River, CLA was detect at low frequency (1/14 samples in Red River, 3/25 samples in Hau River) at low concentration 16 ng L^{-1} in Red River (Chau et al., 2015) and 1 ng L^{-1} in Hau river (Shimizu et al., 2013). In other rivers such as Saigon River, Dongnai River, and Mekong River, CLA was not detected. The high concentration of CLA in urban drainage and low concentration from agriculture wastewater led to the preposition that CLA is mainly originated from human consumption. The possible explanation is similar to ERY case in the previous part.

A less prevalent macrolide antibiotic is ROXI. it was detected in urban drainage at concentration 1 – 125 ng L^{-1} in Hanoi (Hoa et al., 2011); 23 to 32 ng L^{-1} in Cantho and 2 – 55 ng L^{-1} in Ho Chi Minh City (Shimizu et al., 2013; Chau et al., 2015). Surprisingly, ROXI was detected in city canals in Hanoi at very high concentration 726.9 ng L^{-1} and lower in Mekong delta at concentration 7 -87 ng L^{-1} (Hoa et al., 2011; Shimizu et al., 2013) and in rivers that received wastewater in Hanoi 22 – 48 ng L^{-1} (Chau et al., 2015). Main rivers such as Red River, Mekong River did not contain ROXI at detectable amount. Similar to ERY and CLA, ROXI origination was believed to be from human consumption.

Other macrolides were detected in city canals in Hanoi such as AZI 90.8 ng L^{-1} (Hoa et al., 2011) or rivers that received wastewater in Hanoi such as spiramycin, oleandomycin (concentration 134 -621 ng L^{-1} and 369 – 530 ng L^{-1}) (Chau et al., 2015), They were not detected in suburban canals and main rivers such as Red River, Mekong river (Chau et al., 2015).

Another antibiotic group that was monitored and detected in city canals and rivers is quinolone. Although the detection rate is lower than sulfonamide and macrolide antibiotics, it is still worrisome that ENR, a quinolone antibiotic was detected at a pumping station located in a river at concentration 49 ng L^{-1} (Giang et al., 2015). In lakes, ENR, CIP, OFL and NOR were detected at concentration higher than the sulfonamides (73, 98.6, 211.7 and 79 ng L^{-1}). CIP, OFL, NOR and LOM were detected in a city canal and lakes at concentration considerably higher than in aquaculture wastewater (162, 255, 41.1 and 25.3 ng L^{-1} in canals, respectively) (Takasu et al., 2011; Yên et al., 2016). A different trend was observed in case of ENR where it was detected at lower concentration in main canals that were affected by industrial and domestic activities (22 ng L^{-1}) than those affected by aquacultural and domestic activities (55 ng L^{-1}). In lakes, ENR was detected at concentration 73 ng L^{-1}. As mentioned earlier, ENR is banned in aquaculture practice. The higher concentration in canals affected by aquaculture practice could reflect a violation in using this antibiotic. The overall concentration of quinolone in the water did not correlate with the high consumption rate and import amount of this group (see previous section 3.3.1 and 3.4.1). This could be due to the quick absorption of quinolone antibiotics into sediments and soil. This was observed in a case reported by Yên et al. (2016), the quinolone antibiotics were detected in in sediment with high frequency and at higher concentration than the sulfonamide antibiotics in West Lake and Truc Bach Lake in Hanoi.

Lincomycin was the only lincosamides studied but it was detected in all urban drainage and canals at remarkable concentration. LIN was found in urban drainage at equally extremely high concentration in all 4 big cities in Vietnam (from North to South): 1481 ng L^{-1} in Hanoi, 748 ng L^{-1} in Danang, 132-

2666 ng L^{-1} in Cantho, and 470-2661 ng L^{-1} in Ho Chi Minh City (Shimizu et al., 2013; Chau et al., 2015). In 5 rivers that receive wastewater in Hanoi, LIN was detected in highest concentration in comparison to the rest of all studied antibiotics: 667-1375 ng L^{-1}. In suburban canal in Ho Chi Minh City, LIN was also detected at concentration 111-1301 ng L^{-1} (Chau et al., 2015). In city canals and suburban canals in Mekong delta, the concentration of LIN was lower, 9-188 ng L^{-1} and 1-48 ng L^{-1} respectively, however the detection rate was 100% (Shimizu et al., 2013). The ubiquitous detection and high concentration of LIN in canals led to the prevalence of this antibiotic in rivers. It was the only antibiotic detected in Saigon River and Saigon-Dongnai River downstream (Chau et al., 2015). The detected concentration in Hau River and Red River was 1-15 ng L^{-1} (Shimizu et al., 2013) and 120 ng L^{-1} (Chau et al., 2015). Interestingly, in wastewater from shrimp and pig/fish farm LIN was detected but in much lower concentration (see previous section 3.1.2 and 3.2.2). This led to an assumption that other sources than this aquaculture and husbandry is responsible for LIN emission.

Cyclines were detected in urban drainage, city canal, suburban canal and river but in considerably less frequency than the above-mentioned antibiotics. In urban drainage, TC and OTC were detected in only 2 samples at concentration 258 ng L^{-1} (in Hanoi) and 316 ng L^{-1} (in Cantho), respectively. In city canal, suburban canal and rivers, only OTC was detected at concentration less than 5 ng L^{-1}, 226 ng L^{-1} and 7 ng L^{-1} (Shimizu et al., 2013).

Only one β-lactam antibiotic, ampicillin was studied and it was detected in rivers in Hanoi city at concentration 425 - 643 ng L^{-1} while it was not detected in any urban canals, suburban canals and rivers (Chau et al., 2015). This is a surprising observation since ampicillin is unstable in the environment (Sy et al., 2017). As mentioned before, 2-hydroxy-3-phenylpyrazine was suggested as a marker for ampicillin and other β-lactam antibiotics in the environment. It was detected in Thai Binh River (located in Red River Delta region) and Mekong River in Cantho (Mekong Delta region) at concentration 1-8 – 413.3 ng L^{-1} and 1.3 – 6.8 ng L^{-1}, respectively. The higher concentration was detected in locations near hospitals (Sy et al., 2017). This is also in accordance with the spread use of this antibiotic in hospital (see section 3.3.1).

3.6. Comparison with the situations in other countries

Comparing to the concentrations of antibiotics reported in surface water all over the world (Kümmerer, 2009a), the concentration of those in urbane drainage and canals in Vietnam as described above, i.e. sulfonamides (SMX 1900 ng L^{-1}, SMT 220 ng L^{-1}), macrolides (AZI 20 ng L^{-1}; ERY 1700 ng L^{-1}, CLA 37 ng L^{-1}, ROXI 560 ng L^{-1}), quinolones (CIP 30 ng L^{-1}, NOR 120 ng L^{-1}, OFX 20 ng L^{-1}) and cyclines (TC 110 ng L^{-1}, chlortetracycline 690 ng L^{-1}, OTC 340 ng L^{-1}), are comparable or slightly higher. However, comparing to surface water polluted with antibiotics from drug manufacturers in China, India and Pakistan, the concentration of antibiotics in surface water in Vietnam is considerably lower (OTC 721 000 ng L^{-1} in China, CIP 6500000 ng L^{-1} in India, SMX 49 000 ng L^{-1} in Pakistan) (Larsson, 2014).

In rivers and lakes in Vietnam, antibiotics were common (18/25 antibiotics were detected, comparing to 14/22 antibiotics in streams susceptible to contamination in the United State) (Kolpin et al., 2002). The concentration of some antibiotics, except ERY (12 ng L^{-1} in Vietnam vs 1700 ng L^{-1} in the US), especially in rivers impacted by the aforementioned pollution sources in Vietnam exceeded the one in the US (e.g. CIP: 98.6 ng L^{-1} in Vietnam vs 30 ng L^{-1} in the US, LIN: 1373 ng L^{-1} vs 730 ng L^{-1}, SMX 2159 ng L^{-1} vs 1900 ng L^{-1} (Kolpin et al., 2002). In Europe, the maximum concentration of antibiotics reported in river water samples considerably larger than in those in Vietnam (except SMX – 1500 ng L^{-1} in comparison to 2159 ng L^{-1} in Vietnam) (macrolides such as AZI 16633 ng L^{-1}, CLA 2330 ng L^{-1}, ERY 3847 ng L^{-1}, quinolones such as CIP 9660 ng L^{-1}, OFX 1903.6 ng L^{-1}, NOR 442.8 ng L^{-1}, sulfonamides such as SDZ 5000 ng L^{-1}; SMT 5000 ng L^{-1}; sulfapyridine 5000 ng L^{-1}…) (Carvalho and

Santos, 2016). However, the contamination sources influenced on these rivers were not mentioned clearly. There were also rivers with substantially lower concentrations of antibiotics than others.

4. Environmental risk of antibiotic residues

The antibiotic residues in aquatic environment as described above can be taken up by plants or organisms/animals in the environment and trigger unintended effect. Like most of other active pharmaceuticals found in the environment, antibiotic residues can pose some risks to human and animal health.

The general potential effect of antibiotic residues is on the function of ecosystems. Because antibiotics are compounds that can kill or inhibit the growth of microorganisms, they are likely to tip the balance of micro-organisms in the ecosystem. For example, agricultural farms irrigated by wastewater contaminated with antibiotic residues can lose the important bacteria group for nitrogen fixation due to the effect of residual antibiotics. Or similarly, antibiotic residues in wastewater can disrupt the activities of microorganisms involved in the treatment of both household wastewater (septic tanks) and community/industrial wastewater (wastewater treatment plants). A recent review about the impact of antibiotics in the aquatic environment has reported that laboratory tests have shown antibiotics can be toxic to non-target organisms, including a range of algae and bacteria (Carvalho and Santos, 2016). But further studies using real scenarios are needed in order to taking into account the complexity of chemical mixture in the real environment.

However, the greatest concern about antibiotic residues in the environment is their capacity to develop resistance to those very antibiotics in the micro-organisms. Most importantly, environmental residues of antibiotics can initiate resistance even at low concentration (Kümmerer, 2009b; Gullberg et al., 2011). The novel resistance gene or resistance vector can be then transferred to a human or an animal for further dissemination thereafter.

Although there is no study on risk assessment of antibiotics in the aquatic environment of Vietnam, there are several studies identifying the presence of antibiotic resistance in locations with antibiotic pollution issues, many of them have been tabulated in reviews by (Suzuki and Hoa, 2012; Thanh Thuy and Nguyen, 2013; Nhung et al., 2016).

For example, (Le et al., 2005) found evidence of bacteria resistance in mud and water samples near shrimp farms to NOR, oxolinic acid, TMP and SMX at concentration of 0.1 μg/mL. Among individual antibiotics, the incidence of resistance to TMP and SMX was higher than the others. However, the relation between concentration of antibiotic residues and incidence of antibiotic resistance was not clearly established. Other study reported chloramphenicol-resistant (CmR) isolates in samples near fish and shrimp farms in Vietnam were higher than in Thailand and Malaysia (Huys et al., 2007). Meanwhile, sulfonamide resistant bacteria were isolated from aquatic environment of northern Vietnam (Hoa et al., 2008). Due to the frequent detection of antibiotic resistance bacteria and gene in Vietnam and other countries in Asia, waters in this region were described as a hot spot of antibiotic resistance gene development (Suzuki, 2017).

In water samples collected in canals, shrimp ponds and pig farm integrated with fish pond where SMX concentration was higher than ERY, SMX^r occurrence rate was also higher than ERY^r (maximum 94.44% in comparision to 38.80%**)** (Hoa et al., 2011). There was significantly positive correlation between SMX^r bacteria and SMX concentration. However, there was no statistically significant correlation between ERY concentration and the occurrence rate of ERY^r bacteria.

Flouroquinolone (NOR, CIP) resistant bacteria occurred at all sites in Vietnam with rate of resistance varied from 0.1 to 15%. In general, Vietnam had higher rate of resistance than Thailand but no relationship was found between contamination and the occurrence of FQr bacteria (Takasu et al., 2011).

In bacteria strain isolated from 15 hospitals in Vietnam in 2009, 30-70% of the gram-negative bacteria were resistant to 3rd and 4th generation cephalosporins, approximately 40-60% to aminoglycosides and fluoroquinolones. Almost 40% of *Acinetobacter* species showed decreased susceptibility to imipenem (GARP-VN, 2010). At the same time, (Duong et al., 2008) reported that wastewater treatment facilities at hospitals may be an effective barrier to reduce the residual FQ levels and the number of resistant bacteria entering the public aquatic environment.

5. Strategy to control the risk of antibiotic resistance in the aquatic environment

Nowadays in Vietnam, the Government understands the seriousness of antibiotic resistance issue. It has set up a National Action Plan (NAP) against Drug Resistance, which involved the Ministry of Health and the Ministry of Agriculture and Rural Development (MARD) with the support of WHO, FAO and other organisations for the period from 2013 – 2020.

The NAP aims to review, amend and implement regulations and policies to promote proper use of antibiotics and the establishment of microbial resistance monitoring system in order to understand the extent and reduce antibiotic resistance. It also focuses on raising the awareness of antimicrobial use and the risk of antimicrobial resistance infections among all stakeholders including doctors, patients, and farmers in the agricultural and food industries.

While the NAP of Vietnam shares many common strategies with the Global Action Plan on antimicrobial resistance established by World Health Organization (World Health Organization 2015), it lacks the aspect of monitoring the antibiotic residues in the environment, especially in water, wastewater (to identify the sources and develop standards), which was mentioned in Objectives 8 of the WHO Global Action Plan. Additionally, European Commission’s Action Plan against the raising threats from antimicrobial resistance also urges the reduction of environmental pollution by antimicrobial medicines particularly from production facilities (European Commission 2011). At the same time, an important review has indicated that water (or the aquatic environment) can be the dissemination route for antibiotic resistance (Finley et al., 2013). Thus, the understanding of the prevalence of antibiotics in the aquatic environment in Vietnam is essential for the overall NAP to fight against antibiotic resistance.

Vietnam lacks a good wastewater treatment system to reduce the level of antibiotic residues in the aquatic environment (Kookana et al., 2014). This situation increases the risk of antibiotic resistance emergence because even simple wastewater treatment system can considerably reduce the number of bacteria and level of antibiotic residues to reach the open environment (Duong et al., 2008; Kookana et al., 2014; Lundborg and Tamhankar, 2017). As described in previous sections, releases of antibiotics from human consumption, agricultural uses and pharmaceutical manufacturing without proper treatment have caused high level of antibiotic residues in the aquatic environment. Pruden et al. (2013) recommended that limiting antibiotic use and release in agriculture, proper treatment of household, hospital, and drug manufacturer wastewater and promoting a healthy stock in aquaculture were management options to reduce the spread of antibiotics and antibiotic resistance genes to the environment.

Therefore, it is important for Vietnamese Government to consider antibiotic resistance within the "One Health" concept, which supports interdisciplinary approach for better management of the issue. The expansion of the NAP to include support for better wastewater treatment in around the country, or initially at main point sources such as hospitals and pharmaceutical manufacturing factories will certainly lead to better control of the emergence of antibiotic resistance.

6. Conclusions

This review has provided the most up-to-date information on antibiotic uses and the resulting antibiotic concentrations in all relevant sources in Vietnam. Besides the high concentrations of many antibiotics reported in the aquatic environment of Vietnam, we also found that many antibiotics which are in use with high frequency were not included in any monitoring study. Our review also indicates that antibiotic residues discharged from pharmaceutical production facilities in Vietnam, which has not been reviewed before, can be a significant source comparable to other sources such as aquaculture or husbandry. The presence of antibiotic residues from all sources, sometimes in high concentration, means that the Government has to pay more attention to control these sources in order to prevent the emergence of antibiotic resistant bacteria in Vietnam.

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Highlight

- Review of all sources of antibiotics discharged to the aquatic environment in Vietnam.
- Both input and output (residues in the environment) of each source were reviewed.
- Pharmaceutical manufacturing could be an important source of antibiotics in open waters
- Lack of wastewater treatment system in Vietnam may increase the emergence antibiotic resistance.
- Government should pay more attention to controlling discharges of antibiotics to the environment.