Developing a Methodology for and Better Understanding of Impacts from Antimicrobial Use in Aquaculture

Antimicrobial Assessment on Global Aquaculture Production (AGAP)

Review of global antibiotic use, impacts, solutions, and gaps in Aquaculture

Ibarra R., Norden W., Jimenez D., Farias D.R., Canales A., Isaac T.

Table of Contents

Summary

Aquaculture production is projected to increase rapidly through 2030 and will play a key role in providing nutrition and food security to the growing human population. The growth and intensification of aquaculture in the context of climate change will likely lead to an increase in the occurrence and virulence of existing and emerging infectious diseases, and in turn, continue to drive antibiotic consumption across the aquaculture sector. Asian countries lead global consumption, with China consuming over half of the world's antibiotics (57.9%) in 2017, of which half were administered to animals.

The current body of literature demonstrates negative short- and long-term impacts of antibiotics in marine and freshwater environments. In many countries, there is an apparent lack of adequate governance over the sale, distribution, and use of these drugs in the aquaculture sector. The availability of detailed data on the use of antibiotics in aquaculture is highly variable by sector. As a result, challenges persist in assessing the underlying drivers of and risks associated with their use. Importantly, there is a need to align governance, sociocultural, ecological, and economic frameworks with monitoring antibiotics sales, distribution, and use, alongside their discharges and environmental impacts.

In this context, this review aims to facilitate the discussion by providing an overview of the state of affairs and existing knowledge regarding the governance, environmental impact, and volume of

antibiotics use in aquaculture. We have focused on producer countries where antibiotics use is often described as excessive consumption, such as the salmon industry in Chile, and shrimp, pangasius, and tilapia production across East, South, and Southeast Asia, including China, India, Indonesia, Thailand, and Vietnam.

Introduction

Aquaculture production is projected to increase rapidly through 2030 and will play a key role in providing nutrition and food security to the growing human population (Schar et al., 2020). The growth and intensification of aquaculture in a warming climate will likely increase the occurrence and virulence of existing and emergent diseases and, in turn, continue to drive antibiotic consumption across the aquaculture sector. Antibiotics are the most commonly used chemicals in aquaculture, among other products, and their use is estimated to increase in the coming years (Lulijwa et al., 2020).

Among 15 of the major global aquaculture-producing countries, 6 are Asian countries that produce shrimp, pangasius, and tilapia (China, Bangladesh, India, Indonesia, Thailand, and Vietnam), and 3 are salmon producers (e.g., Chile) (Lulijwa et al., 2020). These countries used, on average, 15 antibiotic compounds; Vietnam and China lead in the number of antibiotic compounds used (Lulijwa et al., 2020). China consumed half of the world’s antibiotics (162,000 t in 2013), of which half were administered to animals (Yuan et al., 2019; Zhang et al., 2015). From an aquaculture systems perspective, antibiotic consumption in Asian countries occurs mostly in freshwater, but in the salmon industry, it occurs significantly at the marine phase, as is the case with Chile.

Many studies have demonstrated the potential adverse effects and ecological risks associated with antibiotic use in aquaculture. Antibiotics can be directly released into the environment through runoff, flow-through, and discharged water; sediment; feces; and uneaten feed particles, resulting in adverse effects on ecological systems (Capone et al., 1996; Soto y Norambuena, 2004; Fortt et al., 2007; Buschmann et al., 2012; Rico et al., 2013; Rico and Van den Brink, 2014; Andrieu et al., 2015; Muziasari et al., 2017; Kovalakova et al., 2020). It is estimated that 80% of the antibiotics used in aquaculture are released into the environment, and the presence of antibiotics in the environment has been widely documented, originating from human and terrestrial livestock systems as well (Cabello et al., 2013; Liu et al., 2019; Xu et al., 2021). Though it has been generally accepted that the use of antibiotics in aquaculture is at a smaller scale than in other terrestrial livestock systems, toxicological data have shown that use in aquaculture can be toxic to microorganism communities, particularly algal communities (Rico et al., 2018b). Risk assessment based on individual compound exposure merits further study and evaluation of the impact of current chemotherapeutic pollution on nontarget organisms. The presence of multiple antibiotics may act synergistically to cause a more significant effect, even though the amount of each compound may be below the maximum regulatory limits (Carvalho and Santos, 2016; Shi, 2016).

In a growing aquaculture sector, antibiotics transmission, dissemination, and persistence in natural environments are particular concerns (Thornber et al., 2020). Antibiotics are used in larger concentrations, but such information is not always correctly conveyed to or accessible to the public (Burridge et al., 2010; Carballeria et al., 2021). There is a lack of information about adequate governance over the sale, distribution, and use of these drugs in the aquaculture sector, and data quantifying the use of antibiotics are highly variable by sector. As a result, challenges persist in assessing the underlying drivers of and risks associated with their use. Importantly, there is a need to align governance, sociocultural, ecological, and economic frameworks to monitor antibiotics sales, distribution, and use, alongside their discharges and environmental impacts. Under this context, the Monterey Aquarium Seafood Watch® program and the World Bank established a collaboration to address the state of antibiotics used in aquaculture in Chile, China, India, Indonesia, Thailand, and Vietnam.

In this study, we reviewed the antibiotic use and impacts in aquaculture, focusing on producer countries where antibiotics use is often described as excessive, such as the salmon industry in Chile, and shrimp, pangasius, and tilapia production across East, South, and Southeast Asia, including China, India, Indonesia, Thailand, and Vietnam (Figure 1). This review's objective is to provide an overview of the state of affairs and the knowledge gaps regarding areas with common agreements; the governance; the use and misuse; the potential side effects in some organisms (bacteria, cyanobacteria, and vertebrates); and the environmental impact of antibiotics in aquaculture, to provide a baseline of information for discussion. A literature review was conducted to develop standardized risk assessment protocols under the One Health approach, and regarding effective antimicrobial use governance, socioeconomic considerations, approaches to monitoring, knowledge gaps, and the establishment of ecological impact indicators.

Figure 1. Map of country case studies where antibiotics use is described as excessive, such as Chile (salmon aquaculture) and the East, South, and Southeast Asian countries, including India (shrimp, tilapia, and pangasius). Details are shown about the amount of antibiotics used by two of the biggest consumers, Chile (t) and China (t).

Antibiotic use

In this section, we review the use of antibiotics in aquaculture in significant producer countries where the use is considered excessive. The majority of these countries have regulatory frameworks that govern antibiotics use in aquaculture and monitor residues in the final product (Lulijwa et al., 2020). This section has been divided into the salmon-producing country (Chile) and the East, South, and Southeast Asian countries (China, India, Indonesia, Thailand, and Vietnam).

1.1 Chile

Antibiotics use in the Chilean salmon industry increased from 2005 (239.2 t) to 2017 (393.9 t) (SERNAPESCA, 2020; Miranda et al., 2018). Consequently, antibiotic resistance has increased in direct proportion to the rise in antibiotics use (Millanao et al., 2011; Cabello et al., 2013; Millanao et al., 2018). Nevertheless, a slight decrease in their use has been observed, with 379.6 t used in 2020 and 1,078,896 t of salmon production reported (SERNAPESCA, 2020). The majority of use (98%) occurred in the seawater grow-out phase, in which 98.6% corresponds to florfenicol, 0.83% to oxytetracycline, and less than 0.1% to others, including erythromycin and tilmicosin (SERNAPESCA, 2020). Florfenicol is the dominant antibiotic used in marine-based salmon farming to treat *Salmo salar*, mainly for *Piscirikettsia salmonis* (Miranda et al., 2018; SERNAPESCA, 2020). Treatments may only be administered with a veterinary prescription and are almost entirely (99%) given as medicated feed pellets formulated by feed manufacturers (Miranda et al., 2018; Cravedi et al., 1987; Kemper, 2008). Between 40% and 90% of antibiotics applied are released to the sea bottom by fish excretion or urine (Kemper, 2008) and as uneaten feed, as demonstrated with oxytetracycline (Capone et al., 1996; Miranda et al., 2018). Both producers and feed manufacturers are obligated to register and separately report their antibiotics usage to authorities. This information is aggregated and published in an annual report and submitted to the World Organization for Animal Health (OIE).

Chile has seen a massive increase in fish biomass because of intensive farming, resulting in an increase in fish susceptibility to diseases. Based on available data, Chile reached the highest antibiotic consumption per harvested ton worldwide in 2014, at 563.2 tons (Miranda et al., 2018). Until 2016, six antibiotics were approved for use in the Chilean salmon industry; after quinolones were prohibited, four antibiotics remained: florfenicol, oxytetracycline, erythromycin, and tilmicosin (Miranda et al., 2018). In addition, in 2016 the Chilean National Fisheries and Aquaculture Service (SERNAPESCA) began a program to certify marine salmon farms as antibiotic-free, to reduce their environmental impacts (Quiñones et al., 2019). The Chilean Salmon Antibiotic Reduction Program (CSARP) is a broader collaboration initiative to improve practices, by which the salmon industry aims to reduce antibiotic use by 50% by 2025 (https://www.csarp.cl/). It is important to highlight that salmon farmers in Chile count on formal education, training in aquaculture production and epidemiology, a strong network with veterinary professionals, and specialized diagnostic laboratories in aquaculture. Consequently, although the country's antibiotic consumption is high, its management and regulations are complemented by the farmers' training.

Regulations in Chile include prohibiting the use of specific antibiotics (e.g., cloramphenicol and its derivatives) in aquaculture and requiring the registration and approval of new antibiotic drugs through the Aquaculture and Livestock Authority (SAG), after environmental risk assessments are completed. A mandatory national program tests salmon products for antibiotics residues before commercialization in domestic or external markets. Besides the regulations and control over antibiotics usage, Miranda et al. (2018) concluded that, until 2015, the number of antibiotics used was higher than the amount reported.

1.2 East, South, and Southeast Asia

Global aquaculture production totaled 114.2 million metric tons (mt) in 2018, of which 82.1 million mt corresponded to aquatic animals (FAO, 2020). Roughly 90% of the total volume is produced in Asia, with major producer countries including China (64.5 million mt; 61% of global production), India, Indonesia, Thailand, and Vietnam, plus Bangladesh (FAO, 2020; Lulijwa et al., 2020; Schar et al., 2020).

Among the Asian aquaculture-producing countries, Vietnam and China lead in the amount of antibiotics compounds used in aquaculture with 39 and 33 compounds, respectively; most of the antibiotics were associated with shrimp aquaculture (Lulijwa et al., 2020). Bangladesh is the third major antibiotics consumer, with 21 compounds used mainly for carp aquaculture. The Vietnam government has applied strict regulations on antibiotics since 2002 (Lulijwa et al., 2020), and forbade antibiotics use for growth promotion in 2018 (Coyne et al., 2019). In terms of production, China produced 210,000 t of antibiotics that finished up in animal feed, with 13 compounds authorized by the government; however, the information about amounts of antibiotics and their types remains limited (Rico et al., 2013; Liu et al., 2017; Lulijwa et al., 2020). But, worldwide, it is projected that antibiotics consumption will increase until 2030 (Schar et al., 2020) (Figure 2).

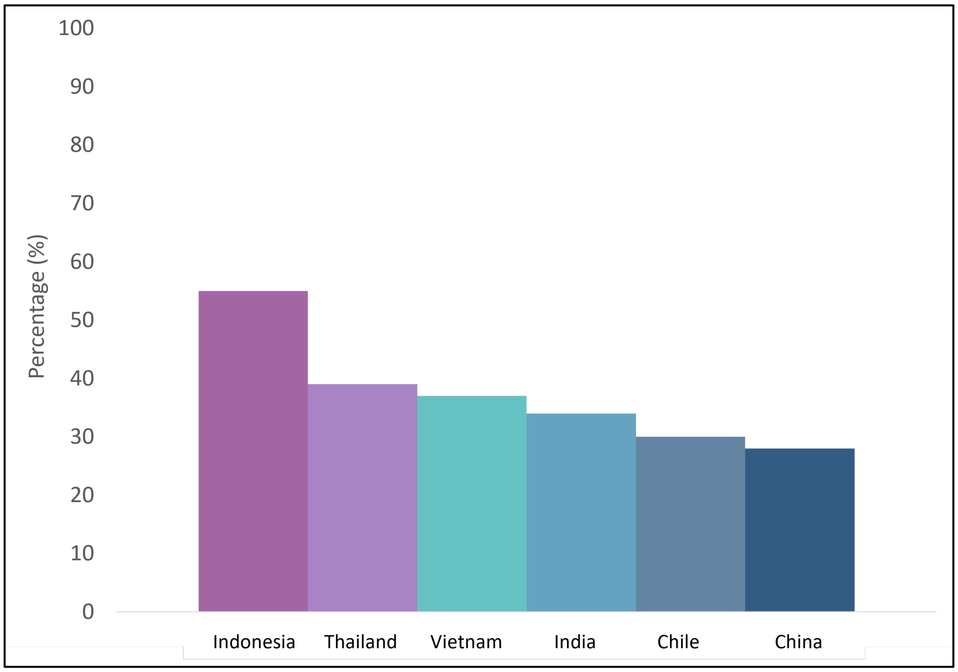


Figure 2. Estimation (%) of growth projected in antibiotics consumption between 2017 and 2030 by country considered in this review. Modified from Schar et al., 2020.

The East, South, and Southeast Asian regions have been considered a hot spot of antimicrobial resistance. Antibiotics are used in animal production (chicken and pig) as well as in aquaculture, and the most common antibiotic used there is amoxicillin (Nhung et al., 2016). The highest frequency of antibiotic use has been observed in pangasius farms in Vietnam (Rico et al., 2013).

As supply chains and markets have developed, aquaculture of freshwater fish, brackish finfish, and crustaceans in Asia has shifted toward semi-intensive and intensive production (Rico et al., 2013; Little et al., 2017). In turn, this has increased disease incidence and the use of antibiotics, which is often described as excessive and widespread—mainly because of limited effective governance (Coyne et al., 2019). Many antibiotics are used in South and Southeast Asia, where some studies have shown antibiotic prevalence and where weak governmental regulation still exists (Nhung et al., 2016; Coyne et al., 2019). Farmers often lack formal education and training in aquaculture production and epidemiology. Also, there is a need for expanding animal health support networks, including veterinary professionals and diagnostic laboratories specialized in aquaculture.

Most antibiotics are typically sourced without a veterinary prescription from private distributors and shops (Table 1), but this varies across sectors and regions. Antibiotics are sold in varying forms (e.g., isolated active ingredients, mixtures, and medicated feed) and may be sold without proper labeling or label use instructions. Farmers may manually mix antibiotic ingredient(s) with manufactured feed on-site, which risks inaccurate dosing, heterogeneous distribution across the target population, and leaching to the surrounding environment. Additional risks arise from traditional integrated fish-livestock systems and multiple industries operating in the same area, where antibiotics use may occur in terrestrial livestock, such as poultry, and enter the aquaculture environment through runoff, feces, or uneaten feed. Unfortunately, available data on antibiotic use are inconsistent and sparsely available, often only reported through relatively small-scale studies and surveys.

Table 1. Description of the use of antibiotics in the East, South, and Southeast Asia regions.

Country	**Species**	**Number of approved antibiotics**	**List of antibiotics****	**Production scale**	**Regulations**
China	90% of freshwaters are carp (domestic) and tilapia (international)	13 (reported use up to 20)	ERY, OXY, FLO, ENR, FLU, QUI (*2)	Small-scale, 50% earthen ponds	MRL residues (*2) ERA (*3)
India, Bangladesh	Freshwater carp, pangasius, pacu (*Piaractus brachypomus*), and brackishwater shrimp	No regulatory program in India. 7 in Bangladesh	India: CLO, CIP, FUR (*4) Bangladesh: OXY, CLO, AMO, SLD, SLX, TRI, DOX	Small-scale entrepreneurs with farm size less than 2 hectares	MRL residues (*1)
Indonesia	Shrimp and milkfish. Freshwater: tilapia, pangasius, carp, and grouper	3 classes	TET, MAC, FLU	80% small-scale. Extensive and semi-extensive cage systems and ponds	MRL residues (*1)
Thailand	Brackishwater: whiteleg shrimp, green mussel, bloodcockle, and oyster. Freshwater: Nile tilapia and pangasius	5	ENR, OXY, SLX, AMO	Improved extensive, semi-intensive, and intensive net and cage systems. Intensive systems dominate for shrimp production for export	MRL residues (*1)
Vietnam	Pangasius, whiteleg shrimp, and tiger shrimp	27 (variable, depending on species and production system)	Prohibited use ENR	Improved extensive, semi-intensive, and intensive cage systems	Residues

***1:** Poor compliance. ***2:** Two separate MRL programs for domestic and international markets. China claims inspection on domestic seafood commenced in 2013. ***3:** "Shining Sword" campaign to enforce environmental and regulatory compliance. ***4:** Significant use of antibiotics in aquaculture farming other than shrimp.

** The antibiotics listed by class include: **Phenicols (PHE):** FLO = florfenicol, CLO = chloramphenicol; **Tetracyclines (TET):** OXY = oxytetracycline, DOX = doxycycline, CLOT = chlortetracycline; **Macrolides (MAC):** TIL = tilmicosin, ERY = erythromycin; **Sulfonamides (SUL):** SLD = sulfadiazine, SLX = sulfamethoxine/ormethoprim; **Penicillins (PEN):** AMO = amoxicillin, amoxicillin trihydrate; **Quinolones (QUI):** FLU = fluoroquinolones; CIP = ciprofloxacin, ENR = enrofloxacin; **Nitrofurans (NF):** FUR = furazolidone; **Amphenicols (AMP):** CLO = chloramphenicol, DP = dihydropyrimidin, TRI = trimethoprim.

International trade has created incentives for some producers and governments to govern antibiotics more robustly. For example, most countries with export-oriented aquaculture industries now restrict some antibiotics through lists of compounds that are banned for aquaculture use. This has fostered some harmonization in the region, but it has not yet achieved full regional harmonization of regulations and governance, which still vary across sectors and countries. For example, Thailand has relatively strict regulations and forbids the use of antibiotics as growth promoters in livestock, and drugs that are listed as critically important by the World Health Organization are available only through veterinary prescription (Coyne et al., 2019; Lulijwa et al., 2020). The Thai government has also implemented a plan to control antibiotic residues in food exports, which dramatically reduced the number of product rejections at export destinations. India has implemented similar pre-export product testing strategies, yet its shrimp products are regularly rejected by the U.S. Food and Drug Administration (FDA) because of residues of banned antibiotics, such as nitrofurazone and furazolidone. Meanwhile, there are no data about antibiotics for Indonesia—probably due to a lack of records, among other reasons (Lulijwa et al., 2020). Broadly, most of these countries lack effective systems for the registration and reporting of antibiotics sales, distribution, and application, as well as systems to monitor their presence in the environment and assess their potential impact.

1.3 Summary of antibiotic use recorded in Seafood Watch (SFW) assessments

Seafood Watch Reports (https://www.seafoodwatch.org/) show that the majority of antibiotics used in aquaculture fall into one of several classes of antibiotics: tetracyclines, fluoroquinolones, amphenicols, and sulfas (Table 2). Tetracyclines appear to be the most common, while amphenicols are frequently the cause for import rejection. But, an import rejection due to contamination is not indicative of on-farm use, so using this metric as an indicator of aquaculture usage should be approached with caution.

Table 2. Major aquaculture species in selected producer countries and accompanying Seafood Watch (SFW) assessment status and types of antibiotics recorded.

Species group	System	Water	Country	Production volume (mt, total 2019)	Report	Date	Drugs
Tilapia	Ponds/cages	Fresh	China	1,641,662	YES	2018	oxytetracycline, florfenicol, amoxicillin, sulfadiazine, trimethoprim, sulfamethoxazole, malachite green, gentian violet
Pangasius	Ponds/cages	Fresh	Indonesia	1,400,458	NO		
Pangasius	Ponds/cages	Fresh	Vietnam	1,382,000	YES	2014	oxytetracycline, doxycycline, sulfadiazine, trimethoprim, thiamphenicol, chloramphenicol, nitrofurans, amoxicillin, ampicillin, colistin, apramycin, gentamycin, kanamycin, levofloxacin, rifampicin
Salmon	Net pens	Marine	Norway	1,364,042	YES	2021	florfenicol, oxolinic acid
Tilapia	Ponds/cages	Fresh/brackish	Indonesia	1,257,000	YES	2015	n/a
Vannamei	Ponds	Brackish	China	1,144,370	YES	2015	chloramphenicol, gentian violet, malachite green
Tilapia	Ponds/cages	Fresh/brackish	Egypt	1,081,202	NO		
Salmon	Net pens	Marine	Chile	906,541	YES	2021	florfenicol, oxytetracycline
Vannamei	Ponds	Brackish	India	724,267	YES	2021	nitrofurans, chloramphenicol, oxytetracycline
Vannamei	Ponds	Fresh	China	671,180	YES	2015	chloramphenicol, gentian violet, malachite green
Vannamei	Ponds	Brackish	Indonesia	670,000	YES	2015	chlortetracycline, oxytetracycline, chloramphenicol, nitrofurans, enrofloxacin
Pangasius	Ponds/cages	Fresh	India	637,000	NO		
Vannamei	Ponds	Brackish	Vietnam	577,000	YES	2017	oxytetracycline, ciprofloxacin, enrofloxacin, oxolinic acid, sulfamethazine, sulfadiazine
Pangasius	Ponds/cages	Fresh	Bangladesh	441,929	NO		

Vannamei	Ponds	Brackish	Thailand	365,503	YES	2020	oxytetracycline, enrofloxacin, nitrofurans
Macrobrachium	Ponds	Fresh	China	364,930	YES	2014	tetracyclines, nitrofurans
Tilapia	Ponds/cages	Fresh/brackish	Bangladesh	344,784	NO		
Tilapia	Ponds/cages	Fresh	Brazil	323,714	NO		
Channel catfish	Ponds/cages	Fresh	China	297,732	YES	2017	ciprofloxacin, enrofloxacin, chloramphenicol, gentian violet, malachite green
Tilapia	Ponds/cages	Fresh/brackish	Philippines	279,384	NO		
Tilapia	Ponds/cages	Fresh	Vietnam	263,107	NO		
Monodon	Ponds	Brackish	Vietnam	261,000	YES	2017	oxytetracycline, ciprofloxacin, enrofloxacin, oxolinic acid, sulfamethazine, sulfadiazine
Tilapia	Ponds/cages	Fresh	Thailand	213,981	NO		
Salmon	Net pens	Marine	Scotland	190,500	YES	2021	florfenicol, oxytetracycline
Monodon	Ponds	Brackish	Indonesia	189,000	YES	2015	none
Channel catfish	Ponds	Fresh	US	153,428	YES	2017	florfenicol, oxytetracycline, sulfadimethoxine-ormetoprim
Penaeus nei	Ponds	Brackish	China	132,196	YES	2015	chloramphenicol, gentian violet, malachite green
Salmon	Net pens	Marine	Canada (BC)	88,874	YES	2021	florfenicol, oxytetracycline
Monodon	Ponds	Brackish	China	84,066	NO		
Monodon	Ponds	Brackish	Bangladesh	63,171	YES	2017	chlortetracycline, oxytetracycline
Macrobrachium	Ponds	Fresh	Bangladesh	52,197	YES	2017	chlortetracycline, oxytetracycline
Monodon	Ponds	Brackish	Myanmar	51,796	YES	2018	none
Salmon	Net pens	Marine	NW Atlantic	46,246	YES	2021	florfenicol, oxytetracycline
Monodon	Ponds	Brackish	India	34,615	YES	2021	nitrofurans, chloramphenicol, oxytetracycline
Macrobrachium	Ponds	Fresh	Thailand	31,345	YES	2014	tetracyclines, nitrofurans
Vannamei	Ponds	Fresh	Indonesia	27,100	YES	2015	chlortetracycline, oxytetracycline, chloramphenicol, nitrofurans, enrofloxacin
Macrobrachium	Ponds	Fresh	Vietnam	20,129	YES	2014	tetracyclines, nitrofurans
Monodon	Ponds	Brackish	Thailand	17,364	NO		
Pangasius	Ponds/cages	Fresh	Thailand	13,889	NO		
Macrobrachium	Ponds	Fresh	India	8,702	YES	2014	tetracyclines, nitrofurans
Macrobrachium	Ponds	Fresh	Indonesia	4,600	YES	2014	tetracyclines, nitrofurans
Monodon	Ponds	Fresh	Indonesia	2,300	YES	2015	none

Drug registration and other regulations in aquaculture

The use and misuse of antibiotics in human and veterinary medicine have propelled an unprecedented global crisis of antibiotics resistance (AR) that poses a serious threat to human health. Antibiotic pollution in the environment presents acute and chronic toxicity risks, and it threatens natural habitats and functioning food webs. Therefore, drug registrations and regulations by governments are needed.

Advancements in research and technology have provided society with tools to understand, monitor, and eventually mitigate antibiotic pollution impacts. Governmental agencies, research institutions, and organizations, such as the Food and Agriculture Organization (FAO), World Health Organization (WHO), World Organization for Animal Health (OIE), and the World Bank, have generously invested time and resources in the knowledge, education, and recommendations of good practices as well as the risks of antibiotics use in aquaculture. WHO provides a list of critically important antibiotics for human health; although the majority are not used in the veterinary sector, the majority of those used in aquaculture are on this list. The FAO and OIE have provided extensive documentation and workshops regarding antimicrobial use, needs, and issues, recommendations on best management practices, and drug resistance risk (OIE, 2021).

Most countries follow standardized procedures for the registration and approval of drugs to use in veterinary medicine. These protocols include assessments to ensure animal safety, drug quality and efficacy, food safety, and environmental impacts. Two other international agencies provide standards for the application of pharmaceuticals in aquaculture. The Codex Alimentarius Commission (CAC) is a joint commission by FAO and WHO in charge of developing international food safety standards and tackling the food safety of antimicrobial use and residues (George, 2019), among other issues. Most countries in the world have regulatory agencies governing pharmaceutical products, or they are a signatory to one of the international organizations.

In Chile, authorization procedures, registration, and the use of antibiotics in aquaculture are heavily regulated and enforced by the different governing institutions, as reviewed by Miranda et al. (2018) and Alvarado-Flores et al. (2021). Aquaculture facilities in Chile must comply with relevant environmental regulations, such as the emission standard of associated contaminants to marine and continental surface waters (MINSEGPRES, 2021). Despite this, several governance shortcomings are apparent, including the lack of a system for monitoring the emission of aquaculture chemotherapeutics into the environment (Paredes and Martínez, 2018).

Major producer countries in East, South, and Southeast Asia also have regulations and guidelines for proper antibiotics use that are based on governmental agencies' standards (FAO, 2016). Thus, China, Bangladesh, India, Indonesia, Thailand, and Vietnam have aligned their regulations and the maximum residue limits (MRLs) to the standards of the European Commission (EC) and the U.S. Food and Drug Administration (FDA), to meet export requirements (Lulijwa et al., 2020). Despite this, scientific literature has shown the widespread use of antibiotics in aquaculture across the region, which some authors postulate is due to four primary causes (Pham, 2015; Founou, 2016):

1. A belief that antibiotics use is required for a successful harvest
2. Limited education, information, and knowledge of good practices and adverse effects among farmers and extension agencies
3. Easy and unrestricted access to antibiotics
4. Lack of proper controls and monitoring of antibiotics use, disposal, and impacts.

In developed and developing countries alike, there is a clear need to improve aquatic animal health and health management, such as stress management by reducing stock densities (Rico et al., 2014). There is also a need to enforce and improve existing regulations for the sale, distribution, and use of antibiotics in aquaculture (Alvarado-Flores et al., 2021), specifically in the following ways:

1. Ensure transparency in the collection and publication of antibiotics use data
2. Regulate quality at the manufacturing facility and label requirements throughout the value chain to reduce both on-farm misuse and the presence of residues in final products
3. Develop incentives and disseminate knowledge of best practices to reduce on-farm misuse and resulting ecological impacts.

Potential side effects

The quantities of antibiotics detected vary across regions and environments, and those used in aquaculture are fated to enter the receiving waterbody and sediments (Pan and Chu, 2016; Xu et al., 2021). The behavior of a drug in the environment depends on numerous factors, including the physicochemical properties of the compound, temperature, pH, light, oxygen levels, microbial community makeup, and the physical properties of water and soil. These factors dictate the half-life, diffusion rate, absorption, and reabsorption in water and soil compartments (García-Galán, 2011; Jechalke et al., 2014). Natural antibiotics are more biodegradable than synthetic drugs, which are more stable in the environment and can be refractory to biodegradation (Dantas et al., 2008). Despite this, it has been demonstrated that most antibiotic pollution is usually below detectable limits in the water column but stable upon absorption in sediments, due to antibiotics' physicochemical properties (Halling-Sorensen et al., 1998; Hirsch et al., 1999). Antibiotics have a dose-dependent effect on various microorganisms, including bacteria, archaea, and fungi. In the sub-sections below, we have summarized the known ecotoxicological effects on some organisms, such as bacteria, cyanobacteria, and vertebrates.

a) Bacteria

Lethal effects are rarely reached with bactericidal compounds at below therapeutic concentrations or with bacteriostatic compounds that do not kill but inhibit bacterial growth (Grenni et al., 2018). Furthermore, lethal effects depend on the dose, the class of antibiotics, the toxicological assay, and the target species. Several studies have demonstrated that antibiotics have a selective effect on nontarget bacterial groups by altering relative abundance and interfering in the interactions among population groups. These effects can be detrimental to enzymatic and growth functions and may ultimately affect critical ecological functions, such as biomass production and nutrient transformation. Literature on short-term effects (i.e., days) is extensive (Constanzo et al., 2005; Bressan et al., 2013; Katipoglu-Yazan et al., 2013; Hou et al., 2015) and can be contrasted with long-term effect studies (Fountoulakis et al., 2004; Alighardashi et al., 2009; Conkle and White, 2012; Ahmad et al., 2014).

For example, the relevant information is available on the acute toxicological effects of antibiotics, based on toxicity assays—particularly at the single species level. But, there is a need for standardized testing to better understand the long-term impacts in bacterial communities; the impacts to biochemical processes such as nitrification, denitrification, and respiration are poorly understood (Roose-Amsaleg & Laverman, 2016). Despite numerous studies demonstrating elevated antibiotic levels in soil, no such literature could be found analyzing the ecosystem-level impacts that may result. A recent review found that relevant concentrations of fluoroquinolones and sulfonamides could partly inhibit some of the biogeochemical processes (Roose-Amsaleg & Laverman, 2016), and that environments poor in oxygen promote blooms of harmful algae (Roose-Amsaleg & Laverman, 2016; Janeko et al., 2016; Kovalakova et al., 2020).

Nonlethal or subinhibitory concentrations of antibiotics can have long-term effects and act as selective forces toward AR in some microbial populations. The generation of AR is favored by the presence of other environmental pollutants, such as heavy metals (Norman et al., 2021). It has been speculated that the ecological impact of AR on bacteria could be from the generation of genotypic and phenotypic variability that alters the physiological and behavioral functions of the affected microbial communities, which in turn affect the function of the broader environmental microbiome (Yadad Kapley, 2021). But, information in this field is quite scarce.

Natural microbial communities are key factors regulating the fate (degradation) and transport (dispersal) of antibiotic pollutants in the environment (Hansen et al., 1992; Kerry et al., 1996; Burka et al., 1997; Sørum, 2000; Black, 2001; Cabello, 2003; Pillay, 2004). But, as noted, most synthetic antibiotics are designed to resist biodegradation. For example, quinolones, sulfonamides, and dianopyrimidine are highly persistent in soils, while ciprofloxacin and oxolinic acid persist in water. Degradation also depends on other abiotic factors, such as pH, salinity, sunlight, and the presence of other pollutants. Overall, the impacts of antibiotics are often underestimated, and their fate in the natural environment needs to be more comprehensively explored.

b) Cyanobacteria

Algae are sensitive to a wide variety of pollutants and are often considered useful ecotoxicological indicators. Freshwater algae species such as *Scenedesmus quadricauda*, *Selenastrum capricornutumor*, and *Chlorella* spp. are commonly cultured and used as a bioindicator of pollution, to assess the hazards of a chemical or a mixture of chemicals (Gomaa et al., 2020). Some studies have shown that 20%–40% of antibiotics are highly toxic to algae and other microinvertebrates, such as daphnids and Artemia (Migliore et al., 1997; Sanderson et al., 2003). For example, sulfonamides, tetracyclines, and macrolides are known to exert an adverse effect on the growth and development of algae (Pomati et al., 2004; Gao et al., 2013). Tetracyclines adversely affect the growth of *Microcystis aeruginosa* (Shang et al., 2015).

It is known that antibiotics can inhibit protein biosynthesis, thus altering critical metabolic functions such as photosynthesis and the ability to produce oxygen (Pomati et al., 2004; Guo et al., 2016). The toxicological effects can be amplified under certain conditions, such as UV light exposure. The interactions with other compounds and conditions are challenging to assess in both the field and laboratory, and extrapolation to real-world conditions is difficult. Similar to the case of bacteria, there is little knowledge about the long-term impacts of antibiotics on cyanobacteria communities in the natural environment (do Santos et al., 2021; Desbiolles et al., 2018). Cyanobacteria (blue-green algae) are primary producers that play a relevant role in aquatic ecosystems that contribute oxygen, nitrogen fixation, and carbon production (do Santos et al., 2021). Current research conducted by Gomaa et al. (2020) demonstrated that cyanobacteria were negatively affected by ciprofloxacin and tetracycline and were suggested as the most sensitive phytoplankton group.

c) Vertebrates

Antibiotics are considered to be less toxic to mammals and other vertebrates; results from experimental studies suggest that fish can recover from short-term exposure to antibiotics and that adverse effects in the aquatic environment are typically expected under chronic exposure (Lepage et al., 2007). But, exposure under experimental conditions has demonstrated negative effects on vertebrates through developmental, metabolic, and behavioral changes, where the most common marine organism studied is zebrafish (Cunha et al., 2018; Kreamer et al., 2019). Although amphibians are less investigated, they show adverse effects from tetracycline (Liu et al., 2018; Kreamer et al., 2019).

Another study has shown a high incidence of antibiotic resistance in marine mammals (e.g., *Halichoerus gryphus*) and seabirds (e.g., *Larus argentatus*, *L. marinus*, and *Phalacrocorax gryphus*) that are from areas close to human populations, where 16 antibiotics were examined (Rose et al., 2009). Blackurn et al. (2010) demonstrated the presence of antibiotic-resistant bacteria in nonvertebrate, top-predator fishes (mainly sharks), and their long lives and slow growth may provide information about long-term exposure to antibiotics in the marine environment. More recently, novel research on two marine mammals (*Phoca vitulina* and *Phocoena phocoena*) that inhabit urban marine ecosystems discovered a relatively high level (37%) of antibiotic resistance, where 15 antibiotics were tested (Norman et al., 2021). The relatively high occurrence of AR in these animals may reflect a large environmental reservoir of AR organisms in marine ecosystems; therefore, engaging animal, environment, and human in a collaborative One Health approach for monitoring antibiotics resistance will bring benefits to the ecosystems (Norman et al., 2021).

Environmental risk assessment framework

The widespread use of antibiotics across industries in regions of aquaculture importance is well known. Improper usage, incomplete removal, and slow degradation of these compounds have become common in water bodies. Residual antibiotics such as fluoroquinolones, macrolideas, and tetracyclines in natural environments are highly persistent and accumulate in higher concentrations (Grenni et al., 2019). Thus, some studies have shown that oxytetracycline remains in sediments for a couple of months or even a year, depending on the concentration, chemical structure, and half-life of the compound (Capone et al., 1996; Kerry et al., 1996; Coyne et al., 2001; Cabello et al., 2013). Other research has shown florfenicol concentrations ranging from 30 ug L^{-1} to 11 mg L^{-1} in water samples from salmon farming areas (Zong et al., 2010). Antibiotic pollution may cause ecotoxicological impacts to aquatic microorganisms and ecosystems. There is an urgent need to determine the methodology to quantify these risks and establish adequate standards and guidelines that define safe limits of antibiotic concentrations.

a) Surveillance of environmental antibiotics

Monitoring methods to control the environmental impacts of anthropogenic activity are widely used in aquaculture, where the most common design is the Before and After Control Impact (BACI). Although the monitoring programs are effective, they are expensive and, depending on the aquatic system, could be quite complex in their application (Carballeria et al., 2021). Antibiotic use data are lacking in many parts of the world due to insufficient data collection and the use of unregistered medicines (WHO, 2018). Digital transformation of animal health and surveillance data is critical to address the absence of near real-time data.

Despite many countries introducing legislation to evaluate potential environmental threats, a lack of monitoring data prevents the ability to robustly assess the risks posed by antibiotic use in aquaculture (and beyond). Some data regarding antibiotic usage in aquaculture and their impacts on the environment have been published using relatively small-scale surveys and/or field studies, enabling the classification and measurement of antibiotics in the environment. Many studies have recorded the concentrations of antibiotics in a variety of settings, including wastewater (Lindberg et al., 2005; ter Laak et al., 2010; Tran et al., 2017; Huang et al., 2021), urban lakes and canals (Tran et al., 2019), rivers (Zuccato et al., 2010), and seawater associated with aquaculture (Buschmann et al., 2012; Choi et al., 2020).

To our knowledge, none of the major aquaculture-producing countries reviewed in this document have a surveillance system to continuously monitor the presence of antibiotics in water. The European Union (EU) has recently developed a watch list of substances to monitor in water, including antibiotics such as amoxicillin, ciprofloxacin, and three macrolides (erythromycin, clarithromycin, and azithromycin) (EU Decision, 2015/495 of March 20, 2015; EU Decision, 2018/840 of June 5, 2018).

b) Environmental Risk Assessment (ERA) procedures, protection goals, and standards

In several countries, ERA is conducted under the framework set by the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH) (VICH, 2000; 2004a; 2004b). VICH is a guidance document to harmonize data requirements for the registration of new medicinal compounds in Australia, New Zealand, Canada, Europe, Japan, and the United States (Rico et al., 2018a). It follows a two-tiered approach. For VICH phase I guidance (VICH, 2000), the ERA stops when environmental concentration is expected to be below 1 ug L^{-1}. If the concentration is exceeded, the ERA proceeds to phase II (VICH, 2004b) and calculates a Risk Quotient (RQ). The RQ determines whether the Predicted Environmental Concentration (PEC) of a chemotherapeutic exceeds the Predicted No-Effect Concentration (PNEC) for a series of standard toxicity tests (Figure 3).

Toxicity data for calculation of the PNEC are determined through testing on algae, crustaceans, and fish species, following standard test protocols provided by the Organization of Economic Cooperation and Development (OECD) or the International Organization for Standardization (ISO). ERA considers the risk in worst-case scenarios or for the most sensitive species. Recommendations have been provided for testing other nontarget bacteria and other microorganisms (archaea and fungi) (Brandt et al., 2016) that have essential ecosystem functions. Furthermore, the PNEC has been derived from accounting for the risk of acquiring antimicrobial resistance (Bengtsson-Palme and Larsson, 2016).

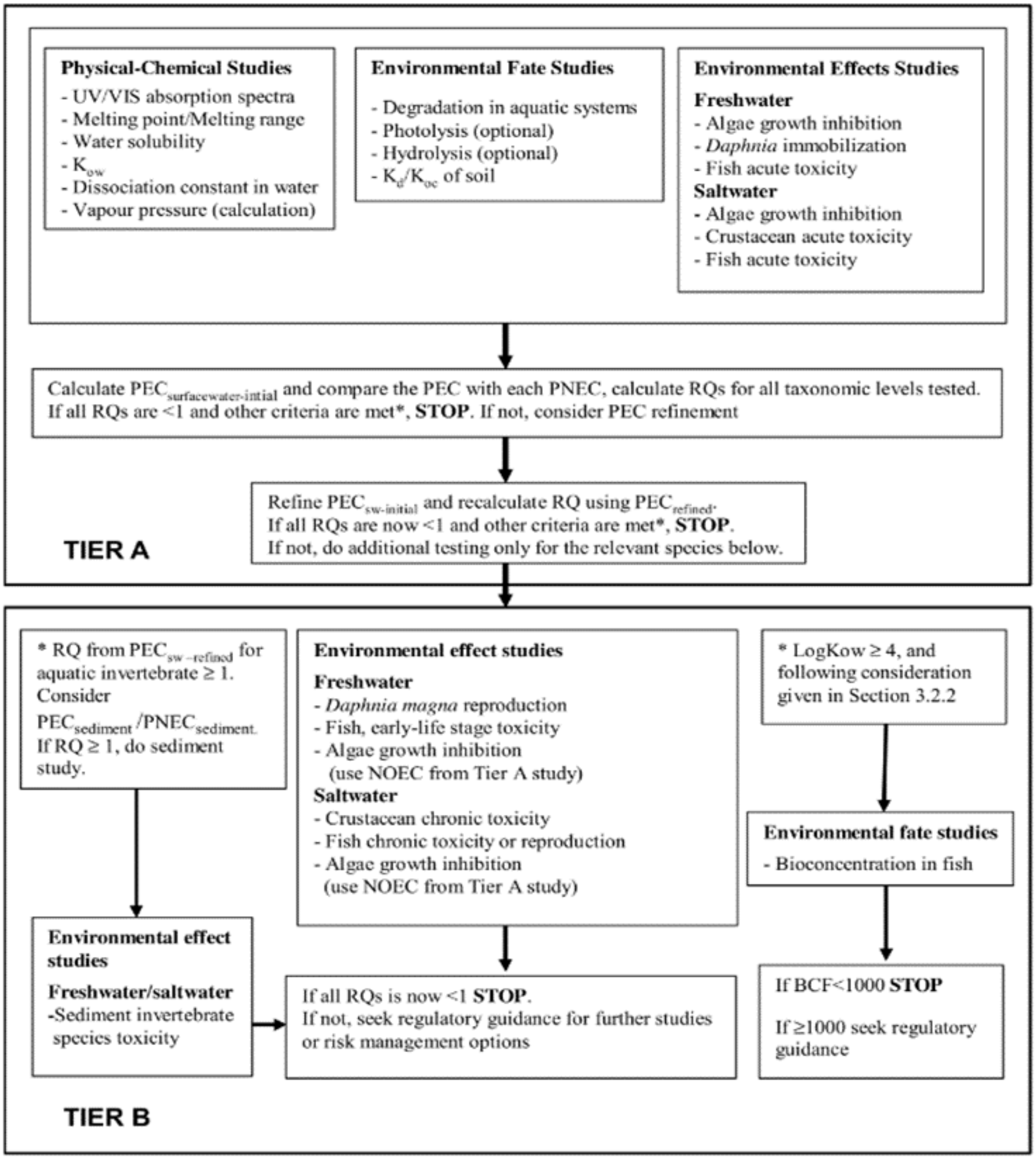


Figure 3. VICH phase II decision tree for the Environmental Risk Assessment of aquaculture veterinary products. VICH phase II decision tree for the Environmental Risk Assessment of aquaculture veterinary medicines (Source: VICH 2004b). K_{ow}: octanol-water partitioning coefficient; K_d: sorption coefficient to soil; K_{oc}: organic carbon sorption coefficient; PEC: predicted environmental concentration; PNEC: predicted no-effect concentration; RQ: risk quotient; NOEC: no observed effect concentration.

At the time of publication of this report, the most recent and comprehensive study on the PNEC for discharge concentrations of majority antibiotics according to standard risk methodologies is the one published by (https://www.amrindustryalliance.org/) (Brandt et al., 2015; Le Page et al., 2017). It calculates two PNEC values based on ecotoxicity (PNEC-ENV) and antimicrobial resistance (PNEC-MIC) and recommends targeting the lower of these two values (Le Page et al., 2017).

c) Selective markers to assess functional community responses to pollutants

Recommendations have been developed to include microbial community-based testing in the aquatic risk assessment of antibiotics, in order to provide more comprehensive protection of key ecosystem functions and services (Brandt et al., 2015). Therefore, the combination of antibiotic assays complemented with environmental information will provide a better understanding of bacteria susceptibility, sensitive species and responses, and the antibiotic effects on the environment.

An understanding of microbial taxonomic and functional genetic diversity can be helpful in the assessment of the ecological effects. Environmental selection pressure from antibiotics has been shown to reduce bacterial diversity (Proia et al., 2013; Laverman et al., 2015) and produce changes in the abundance of different functional genes. These alterations may result in a long-term impact on ecosystem functionality (Yang et al., 2017). But, available studies have also shown that taxonomic microbial diversity is only moderately affected by high antibiotic levels (Kristiansson et al., 2011; Brandt et al., 2015; Lundström et al., 2016).

Other alternative risk measures include pollution-induced community tolerance (PICT) (Blanck, 2002). This short-term test challenges microbial communities with pollutants, and samples are taken from exposed and non-exposed communities. Some have argued that this test is not ideal because it has several limitations (Lundström et al., 2016): it cannot distinguish between taxonomic shifts, species selection, and phenotypic adaptation of individuals (Blanck, 2002).

d) Sites for environmental surveillance

Surveillance of antibiotics through environmental sampling should also be conducted as close as possible to the population of interest. The concentration and form of the compound should be assessed and calculated from a range of sites and points in time, and cross-referenced with independently derived usage data. It may be challenging to obtain good data for antibiotics that are prone to rapid degradation in some cases.

Several models are available to determine the fate and transport, based on both the compound and the environmental characteristics. Details on these tools are provided in the following section.

e) Spatio-temporal surveillance

The United Kingdom has set site-specific risk assessment requirements for chemotherapeutics used to treat sea lice infestations, based on the carrying capacity of receiving waters (SEPA, 2014). The environmental quality standards are derived from dispersal characteristics, toxicological information, and appropriate safety factors. These standards include spatial and temporal components to define different maximum allowable concentrations, following periods, and seabed distances from the farm (allowable zone of effect). Before applying a treatment, the farm must prove to authorities that treatment will not exceed standards.

f) Models for the ERA of chemotherapeutics used in aquaculture

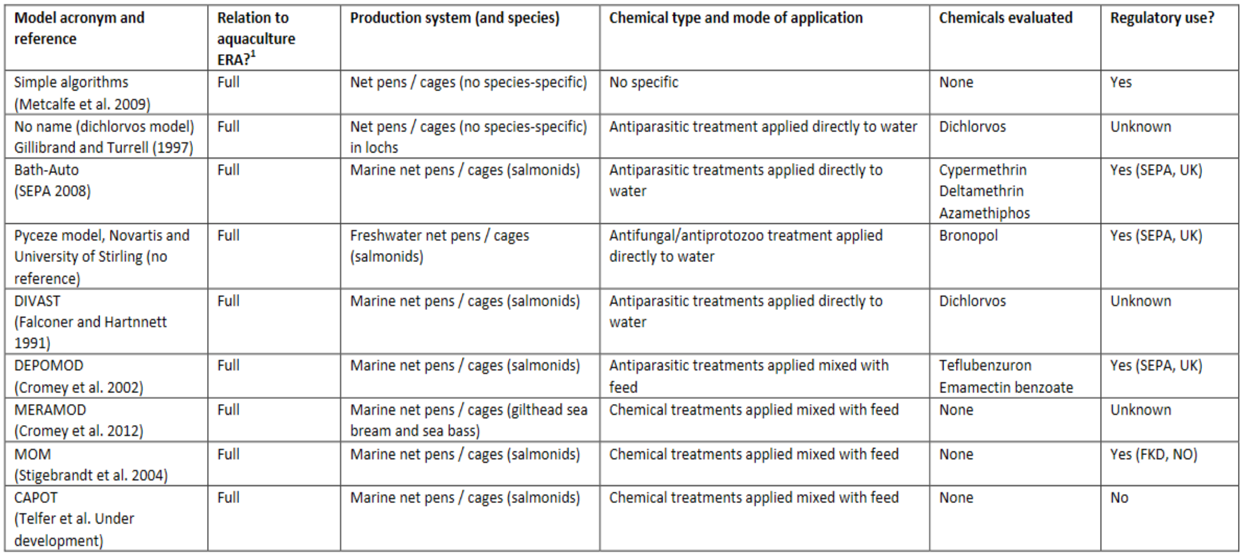
A recent study provides a detailed review of modeling tools available to perform ERA in aquaculture (Rico et al., 2018a). These models predict the dispersal of chemotherapeutics in space (local/farm-scale) and time (hours to months) but cannot assess the ecotoxicological risks. Model outputs (antibiotics concentration from emission or in the environment) can then be compared to the Environmental Quality Standards (EQS) and PNEC values to determine the environmental risk, define the toxicological limits, and predict the distribution and persistence over time (Rico et al., 2018a; Kalantzi et al., 2020; Carballeira Braña et al., 2021).

But, as mentioned, PNECs or EQS have not been validated at the community or ecosystem level; however, according to the authors, PNECs or EQS could be adapted to be suitable at these scales (Rico et al., 2018a). Significantly, these models can be adapted to test different scenarios, depending on the species produced and on regional contexts and settings (Henderson et al., 2001; Cromey and Black, 2005; Rico et al., 2018a). For example, models have been developed to predict the fate and transport of chemotherapeutics (including antibiotics) discharged from inland and flow-through aquaculture systems for various species in Asia (Table 1). Models for marine aquaculture systems are typically based on hydrodynamics and/or marine particle tracking, to enable site-specific results for the predicted dispersal of organic matter or chemotherapeutics (e.g., sea lice treatments) (Table 2). Due to the variety of scenarios and complexity in this field, models can be a handy tool for predicting effects in the field (Tables 3 and 4). It must be cautioned that, regarding antibiotics and their toxicity, the chemicals' application and environmental contexts are key determinants.

Table 3. Models to assess the environmental fate and risk of chemotherapeutics used in inland production systems. Full: explicitly developed for aquaculture production systems; Moderate: not explicitly developed for aquaculture production systems but has been used for aquaculture environmental impact assessments at least once; Low: not explicitly developed for aquaculture production systems and not used yet for aquaculture environmental impact assessment.

Model acronym and reference	**Relation to aquaculture ERA?[1]**	**Production system (and species)**	**Chemical type and mode of application**	**Chemicals evaluated**	**Regulatory use?**
Simple algorithms (Metcalfe et al. 2009)	Full	Ponds, net pens, cages, or flow-through systems (no species-specific)	No specific	None	Yes
ERA-AQUA (Rico et al., 2012 and 2013a)	Full	Ponds or tanks (tilapia, pangasius catfish, shrimp, prawn). Can be parameterized for a wide range of finfish and crustacean species	All kind of veterinary medicines applied mixed with feed or directly to water	A wide range of antibiotics and antiparasitic substances used in Asian aquaculture	No
VDC (Phong et al., 2009)	Full	Ponds (no species-specific)	Antibiotics applied mixed with fed	Oxytetracycline and oxolinic acid	No
Chloramine-T dilution models (Gaikowski et al. 2004)	Full	Flow-through hatchery (no species-specific)	Disinfectant applied directly to water	Chloramine-T	Unknown
WASP (Ambrose et al. 1993) used by Rose and Pedersen (2005)	Moderate	Hatcheries (no species-specific)	Antibiotic applied mixed with feed	Oxytetracycline	Unknown
TOXSWA (Adriaanse, 1997, Adriaanse et al., 2013)	Low	No specific. Diffuse and point source discharges into ponds, streams, ditches.	All kind of veterinary medicines released in farm effluents or veterinary medicines applied directly to water in ponds	None	No
GREAT-ER (Koormann et al. 2005)	Low	No specific. Point source discharges into rivers.	All kind of veterinary medicines released in farm effluents.	None	No
GEMCO (Baart et al. 2003)	Low	No specific. Point source discharges into estuaries and marine open waters.	All kind of veterinary medicines released in farm effluents.	None	No
AQUATOX (Park et al. 2008)	Low	No specific. Diffuse and point source discharges into rivers.	All kind of veterinary medicines released in farm effluents.	None	No
MASTEP (Van den Brink et al., 2008)	Low	No specific. Diffuse and point source discharges into rivers.	All kind of veterinary medicines released in farm effluents.	None	Few times

Table 4. Models to assess the environmental fate and risk of chemotherapeutics used in marine aquaculture systems. Full: explicitly developed for aquaculture production systems; Moderate: not explicitly developed for aquaculture production systems but has been used for aquaculture environmental impact assessments at least once; Low: not explicitly developed for aquaculture production systems and not used yet for aquaculture environmental impact assessment.



Model acronym and reference	Relation to aquaculture ERA?[1]	Production system (and species)	Chemical type and mode of application	Chemicals evaluated	Regulatory use?
Simple algorithms (Metcalfe et al. 2009)	Full	Net pens / cages (no species-specific)	No specific	None	Yes
No name (dichlorvos model) Gillibrand and Turrell (1997)	Full	Net pens / cages (no species-specific) in lochs	Antiparasitic treatment applied directly to water	Dichlorvos	Unknown
Bath-Auto (SEPA 2008)	Full	Marine net pens / cages (salmonids)	Antiparasitic treatments applied directly to water	Cypermethrin Deltamethrin Azamethiphos	Yes (SEPA, UK)
Pyceze model, Novartis and University of Stirling (no reference)	Full	Freshwater net pens / cages (salmonids)	Antifungal/antiprotozoo treatment applied directly to water	Bronopol	Yes (SEPA, UK)
DIVAST (Falconer and Hartnnett 1991)	Full	Marine net pens / cages (salmonids)	Antiparasitic treatments applied directly to water	Dichlorvos	Unknown
DEPOMOD (Cromey et al. 2002)	Full	Marine net pens / cages (salmonids)	Antiparasitic treatments applied mixed with feed	Teflubenzuron Emamectin benzoate	Yes (SEPA, UK)
MERAMOD (Cromey et al. 2012)	Full	Marine net pens / cages (gilthead sea bream and sea bass)	Chemical treatments applied mixed with feed	None	Unknown
MOM (Stigebrandt et al. 2004)	Full	Marine net pens / cages (salmonids)	Chemical treatments applied mixed with feed	None	Yes (FKD, NO)
CAPOT (Telfer et al. Under development)	Full	Marine net pens / cages (salmonids)	Chemical treatments applied mixed with feed	None	No

Antibiotics impact assessments: methodological and technical gaps

The bibliographic review can deduce the following knowledge gaps in the methodological and technical areas in Table 5.

Table 5. Methodological and technical knowledge gaps identified on antibiotics impact assessments.

Identified gap	**Possible solution**
Predicted No-Effect Concentration (PNECs) or Environmental Quality Standards (EQS) have not been validated at the community or ecosystem level	▪ Provide toxicological information for the development of EQS for critical compounds ▪ Develop EQS for antibiotics ecotoxicological and antimicrobial resistance
Field monitoring of antibiotics (emission and environment)	▪ Identification and classification of regions/areas according to environmental characteristics (e.g., current and bathymetry characteristics), and main aquaculture production practices
Definition and selection of aquaculture scenarios (integrated fish and livestock farming)	▪ Select worst-case scenarios at the regional and local level that include climate, production systems, and management practices ▪ Propose a research plan for the development and test of country/region-oriented EQS
Select and optimize available modeling tools to test for multiple present and future scenarios	▪ Produce a set of ready-to-use model scenarios representing the main production areas, species, and production systems ▪ Model and scenario validation: - Test and validate new modeling approaches and scenarios based on several case studies. - Test and validate EQS based on field experiments

	▪ Upscaling models from farms to a larger scale (water body) ▪ Coupling hydrodynamic/particle tracking models to exposure and environmental effects ▪ Coupling chemical exposure to ecological community-level models ▪ Test and validate improved modeling approaches and scenarios based on several case studies
Scientific proof that exceeding standards has nonreversible ecological consequences	▪ Stakeholders to use these tools are regulators, assessors, and farmers

Antibiotics impact assessments: regulatory gaps

The bibliographic review can deduce the following knowledge gaps in the regulatory framework identified in Table 6.

Table 6. Identified regulatory gaps/needs and possible solutions on the regulatory framework of antibiotics impacts assessments.

Identified gaps/needs	**Possible solution**
Improved regulatory frameworks for adoption of ERA framework	▪ Evaluate, review, and improve current ERA schemes
Available information for policy, licensing, and regulations that consider environmental protection	▪ Identify sustainability requirements set by existing regulation and environmental approaches ▪ Identify possible bottlenecks hampering cost-effective regulatory and licensing practices ▪ Identify gaps between needs and available tools and framework for aquaculture management and monitoring
Improved tools for quantification of environmental services	▪ Improved spatial planning linked to site selection, carrying capacity, and sustainability indicators (carrying capacity models) ▪ Improved, more efficient tools for licensing and aquaculture development ▪ Assess environmental services provided by different countries
Strengthen management practices and develop cost-effective management tools	▪ Evaluate available tools and approaches available to predict and monitor environmental impacts ▪ Significantly enhanced real-time *in-situ* monitoring linked to early warning and sustainability

Conclusions

Although some progress has been made regarding the governance, potential side effects, and environmental impacts of antibiotics use in aquaculture, there are still gaps in these themes. In this review, we provided a baseline of information for opening discussion and facilitating decision-making, in order to develop standardized risk assessment protocols under the One Health approach in relevant aquaculture producers' countries.

Chile and the East, South, and Southeast Asian countries reviewed (China, India, Indonesia, Thailand, and Vietnam) have listed authorized and banned antibiotics used in aquaculture, and some of them have to meet export requirements. Little is known about Indonesia's antibiotics consumption. However, based on this review, gaps remain regarding antibiotic uses and the methodology and regulations that are listed and described in this review.

From the perspective of potential side effects, an ecological risk has been associated with antibiotic use in aquaculture. Bacteria and cyanobacteria are the most affected organisms in the sediments. In the column water, this ecological impact can cause disruption of critical ecological processes (e.g., nitrogen and carbon cycles). Environmental monitoring plans could be a useful solution but are difficult at highly dispersed sites. EQS thresholds could be defined to improve aquaculture sustainability and reduce ecological impacts.

As suggested by some authors, there is an urgent need to standardize antibiotic consumption surveillance in the aquaculture industry. Robust surveillance information will facilitate understanding of aquaculture sectors, productions, monitoring consumptions, and antibiotics resistance trends. Freshwater aquaculture systems are quite different from marine systems, so they should be treated and analyzed separately.

Based on the information gathered in this review and the current literature, although some gaps were detected, it is expected to provide adequate information for opening discussion about the use of antibiotics in aquaculture in the selected countries where antibiotics use is considerably high. The consolidation of an initial risk assessment framework to be utilized by aquaculture stakeholders will be useful to better estimate the potential environmental impacts associated with antibiotic use at the farm(s) under assessment. In this way, assessments of the type and degree of impact(s) expected from using antibiotics in a specific ecological and farm context may be established. This will enable the SFW Aquaculture Standard to assess the risk of chemical use more robustly by including the outputs of the developed risk framework (e.g., impact to indicator X shall not exceed threshold Y) in its scoring methodology and criteria. In addition, the risk framework and accompanying standardized sampling protocols may be used on the ground in projects where SFW is engaged, such as Indian shrimp and Chilean salmon, to establish baselines of current impacts and roadmaps for improvement toward sustainability targets.

References

Ahmad M, Vithanage M, Kim K, Cho J-S, Lee YH, Joo YK, Lee SS, Ok YS (2014) Inhibitory effect of veterinary antibiotics on denitrification in groundwater: a microcosm approach. Sci. World J. DOI:10.1155/2014/879831

Alighardashi A, Pandolfi D, Potier O, Pons MN (2009) Acute sensitivity of activated sludge bacteria to erythromycin. J Hazard Mater 172: 685–692. DOI: 10.1016/j.jhazmat.2009.07.051

Alvarado-Flores C, Encina-Montoya F, Tucca F, Vega-Aguayo R, Nimptsch J, Oberti C, Carmona ER, Lüders C (2021) Assessing the ecological risk of active principles used currently by freshwater fish farms. Sci. Total Environ. 775, 144716. DOI: 10.1016/j.scitotenv.2020.144716

Andrieu M, Rico A, Minh Phu T, Thi Thanh Huong D, Thanh Phuong N, Van den Brink PJ (2015) Ecological risk assessment of the antibiotic enrofloxacin applied to Pangasius catfish farms in the Mekong Delta, Vietnam. Chemosphere 119, 407-414.

Bengtsson-Palme J, Larsson DJ (2016) Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. Environ. Int. 86: 140–149.

Blanck H (2002) A critical review of procedures and approaches used for assessing pollution-induced community tolerance (PICT) in biotic communities. Hum. Ecol. Risk Assess. 8: 1003–1034.

Brandt KK, Amézquita A, Backhaus T, Boxall A, Coors A, Heberer T (2015) Ecotoxicological assessment of antibiotics: a call for improved consideration of microorganisms. Environ. Int. 85: 189–205.

Bressan CR, Kunz A, Schmidell W, Soares HM (2013) Toxicity of the colistin sulfate antibiotic used in animal farming to mixed cultures of nitrifying organisms. Water Air Soil Pollut 224(3):1–9. DOI:10.1007/ s11270-013-1441-4

Burka JF, Hammell KL, Horsberg TE, Johnson GR, Rainnie DJ, Speare DJ (1997) Drugs in salmonid aquaculture – a review. J Vet Pharmacol Ther 20: 333-349.

Burridge L, Weis JS, Cabello F, Pizarro J, Bostick K (2010) Chemical use in salmon aquaculture: a review of current practices and possible environmental effects. Aquaculture 306: 7-23.

Buschmann AH, Tomova A, López A, Maldonado MA, Henríquez LA, Ivanova L, Cabello F (2012) Salmon aquaculture and antimicrobial resistance in the marine environment. PLoS ONE 7: e42724

Buschmann AH, Tomova A, López A, Maldonado MA, Henríquez LA, Ivanova L, Cabello F (2012) Salmon aquaculture and antimicrobial resistance in the marine environment. PLoS ONE 7: e42724

Cabello FC (2003) Antibiotics and aquaculture. An analysis of their potential impact upon the environment, human and animal health in Chile. Fundación Terram. Análisis de Políticas Públicas No. 17, pp. 1–16.

Cabello FC, Godfrey HP, Tomotova A, Ivanova L, Dölz H, Millanao A, Buschmann A (2013) Antimicrobial use in aquaculture re-examined: its relevance to antimicrobial resistance and to animal and human health. Environ. Microbiol. 15 (7): 1917-1942. DOI: 10.1111/1462-2920.12134.

Capone DG, Weston DP, Miller V, Shoemaker, C (1996) Antibacterial residues in marine sediments and invertebrates following chemotherapy in aquaculture. Aquaculture 145: 55-75.

Carballeira Braña CB, Cerbule K, Senff P, Stolz IK (2021) Towards Environmental Sustainability in Marine Finfish Aquaculture. Front. Mar. Sci. 8:666662. DOI: 10.3389/fmars.2021.666662

Carvalho IT & Santos L (2016) Antibiotics in the aquatic environments: a review of the European scenario, Environ. Int. 94: 736–757.

Choi S, Sim W, Jang D, Yoon Y, Ryu J, Oh J, Woo JS, Mo Kim Y, Lee, Y (2020) Antibiotics in coastal aquaculture waters: Occurrence and elimination efficiency in oxidative water treatment processes. Journal of Hazardous Materials, 122585. DOI: 10.1016/j.jhazmat.2020.122585

Cravedi JP, Choubert G, Delous G (1987) Digestibility of chloramphenicol, oxolinic acid, and oxytetracycline in rainbow trout and influence of these antibiotics on lipid digestibility. Aquaculture 60, 133–141. DOI: 10.1016/0044-8486(87)90305-X

Conkle JL & White JR (2012) An initial screening of antibiotic effects on microbial respiration in wetland soils, J. Environ. Sci. Health A. 47: 1381–1390.

Costanzo SD, Murby J, Bates J, (2005) Ecosystem response to antibiotics entering the aquatic environment. Mar. Pollut. Bull. 51, 218e223. DOI: 10.1016/ j.marpolbul.2004.10.038.

Coyne R, Smith P, Moriarty C (2001) The fate of oxytetracycline in the marine environment of a salmon cage farm. Mar Environ Health 3: i-24.

Coyne L, Arief R, Benigno C, Ngan Giang V, Quynh Huong L, Jeamsripong S, Kalpravidh W, McGrane J, Padungtod P, Patrick I, Schoonman L, Setyawan E, Harja Sukarno A, Srisamran J, Thi Ngoc P, Rushton J (2019) Characterizing Antimicrobial Use in the Livestock Sector in Three South East Asian Countries (Indonesia, Thailand, and Vietnam). Antibiotics 8, 33. DOI: 10.3390/antibiotics8010033

Cromey CJ & Black KD (2005) Modelling the impacts of finfish aquaculture. In: Hargrave BT (ed.) Environmental Effects of Marine Finfish Aquaculture, pp. 129–155. Springer Verlag, Berlin.

Cunha D, Mendes M, Marques M (2018) Environmental risk assessment of psychoactive drugs in the aquatic environment. Environ. Sci. Poll. Res. DOI: 10.1007/s11356-018-3556-z

Dantas G, Sommer MOA, Oluwasegun RD, Church GM (2008) Bacteria subsisting on antibiotics, Science 320: 100–103.

Desbiolles F, Malleret L, Tiliacos C, Wong-Wah-Chung P, Laffont-Schwob I (2018) Occurrence and ecotoxicological assessment of pharmaceuticals: is there a risk for the Mediterranean aquatic environment? Sci Total Environ 639:1334–1348. DOI: 10. 1016/j.scitotenv.2018.04.351

Dolliver HA, Kumar K, Gupta SC (2007) Sulfamethazine uptake by plants from manure-amended soil. J. Environ. Qual. 36, 1224–1230.

dos Santos Costa R, Rabelo Quadra G, de Oliveira Souza H, Souza de Amaral, Viviane, Navonia JA (2021) The link between pharmaceuticals and cyanobacteria: a review regarding ecotoxicological, ecological and sanitary aspects. Environ. Sci. Poll. Res. DOI: 10.1007/s11356-021-14698-5

FAO, Food and Agriculture Organization of the United Nations (2016). The State of World Fisheries and Aquaculture 2016. Contributing to Food Security and Nutrition for all, pp. 200. Food and Agricultural Organization of the United Nations, Rome.

Fortt ZA, Cabello CF, Buschmann RA (2007) Residues of tetracycline and quinolones in wild fish living around a salmon aquaculture center in Chile. Rev Chilena Infectol. 24: 14–18.

FAO (2020) The State of World Fisheries and Aquaculture 2020. Sustainability in action. Rome. DOI: 10.4060/ca9229en

Founou LL, Founou RC, Essack SY (2016) Antibiotic resistance in the food chain: a developing country perspective. Front. Microbiol. 7(1881), (2016).

Fountoulakis M, Drillia P, Stamatelatou K, Lyberatos G (2004) Toxic effect of pharmaceuticals on methanogenesis. Water Sci. Technol. 50, 335–440.

Gao L, Shi L J, Yuan T (2013) Growth inhibitive effect of typical antibiotics and their mixtures on *Selenastrum capricornutum*. J. Environ. Health 30 (6): 475-478

García-Galán, M. J., Díaz-Cruz, M. S., & Barceló, D. (2012). Occurrence and Fate of Sulfonamide Antibiotics in Surface Waters: Climatic Effects on Their Presence in the Mediterranean Region and Aquatic Ecosystem Vulnerability. The Llobregat, 167–192. doi:10.1007/698_2011_140

Guo J, Selby K, Boxall BA (2016) Comparing the sensitivity of chlorophytes, cyanobacteria, and diatoms to major-use antibiotics. Environ. Tox. Chem. 35 (10): 2587-2596

George A, (2019) Antimicrobial resistance (AMR) in the food chain: Trade, one health, and codex. Tropical medicine and Infectious Disease. Trop. Med. Infect. Dis. 2019, 4: 54. DOI: 10.3390/tropicalmed4010054

Gomaa M, Zien-Elabdeen A, Hifney A, Adam M (2020) Environmental risk analysis of pharmaceuticals on freshwater phytoplankton assemblage: effects on alpha, beta, and taxonomic diversity. Environ. Sci. Poll. Res. DOI: 10.1007/s11356-020-11542-0

Grenni P, Ancona V, Barra Caracciolo A (2018) Ecological effects of antibiotics on natural systems: A review. Microchem. J. 136: 25-39. DOI: 10.1016/j.microc.2017.02.006.

Hansen PK, Lunestad BT, Samuelsen OB (1992) Effects of oxytetracycline, oxolinic acid, and flumequine on bacteria in an artificial marine fish farm sediment. Can. J. Microbiol. 38: 1307–1312.

Henderson A, Gamito S, Karakassis I, Pederson P, Smaal A (2001) Use of hydrodynamic and benthic models for managing environmental impacts of marine aquaculture. J. Appl. Ichthyol. 17: 163–172.

Halling-Sørensen B, Nors Nielsen S, Lansky PF, Ingerslev F, Holten Lützhøft HC, Jørgensen SE (1998) Occurrence, fate and effects of pharmaceutical substances in the environment - a review, Chemosphere. 36, 357–393.

Hirsch (1999) Occurrence of antibiotics in the aquatic environment. Sci. Total Environ. 225 (1-2) 109-118.

Hou L, Yin G, Liu M, Zhou J, Zheng Y, Gao J, Zong H, Yang Y, Gao L, Tong C (2015) Effects of sulfamethazine on denitrification and the associated N2O release in estuarine and coastal sediments. Environ. Sci. Technol. 49: 326-333

Huang A, Yan M, Lin J, Xu l, Gong H, Gong H (2021) A Review of Processes for Removing Antibiotics from Breeding Wastewater. Int. J. Environ. Res. Public Health. 18: 4909. DOI: 10.3390/ ijerph18094909

Jechalke S, Heuer H, Siemens J, Amelung W, Smalla K (2014) Fate and effects of veterinary antibiotics in soil. Trends Microbiol. 22(9): 536–545.

Kalantzi I, Rico A, Mylona K, Pergantis SA, Tsapakis M (2021) Fish farming, metals and antibiotics in the eastern Mediterranean Sea: Is there a threat to sediment wildlife? Sci. Total Environ. 764: 142843. DOI: 10.1016/j.scitotenv.2020.142843

Katipoglu-Yazan T, Pala-Ozkok I, Ubay-Cokgor E, Orhon D (2013) Acute impact of erythromycin and tetracycline on the kinetics of nitrification and organic carbon removal in mixed microbial culture. Bioresour. Technol. 144, 410–419.

Kemper N (2008) Veterinary antibiotics in the aquatic and terrestrial environment. Ecol. Indic. 8, 1-13.

Kerry J, Coyne R, Gilroy D, Hiney M, Smith P (1996) Spatial distribution of oxytetracycline and elevated frequencies of oxytetracycline resistance in sediments beneath a marine salmon farm following oxytetracycline therapy. Aquaculture 145: 31-39

Kreamer S, Ramachandran A, Perron G (2019) Antibiotic pollution in the environment: from microbial ecology to public policy. Microorganism. 7, 180. DOI: 019, 7, 180; doi:10.3390/microorganisms7060180

Kristiansson E, Fick J, Janzon A, Grabic R, Rutgersson C, Weijdegard, B (2011) Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. PLoS One 6: e17038.

Kovalakova (2020) Occurrence and toxicity of antibiotics in the aquatic environment: A review. Chemosphere 251: 126351. DOI: 10.1016/j.chemosphere.2020.126351

Kuppusamy S, Kakarla D, Venkateswarlu K, Megharaj M, Yoon YE, Lee YB (2018) Veterinary antibiotics (Vas) contamination as a global agro-ecological issue: a critical review. Agric. Ecosyst. Environ. 257, 47-59.

Kümmerer K (2009) Antibiotics in the aquatic environment – A review – Part I. Chemosphere. 75: 417-434.

Laverman AM, Cazier T, Yan C, Roose-Amsaleg C, Petit F, Garnier J, Berthe T (2015) Exposure to vancomycin causes a shift in the microbial community structure without affecting nitrate reduction rates in river sediments, Environ. Sci. Pollut. Res. Int. 22: 13702–13709.

Le Page (2017) Integrating human and environmental health in antibiotic risk assessment: A critical analysis of protection goals, species sensitivity, and antimicrobial resistance. Environ. Int. 109, 155-169.

Lindberg R, Wennberg P, Johansson M, Tysklind M, Andersson B (2005) Screening of Human Antibiotic Substances and Determination of Weekly Mass Flows in Five Sewage Treatment Plants in Sweden- Environ. Sci. Technol. 39 (10): 3421-3429

Little DC, Young JA, Zhang W, Newton R, Al Mamum A, Murray FJ (2017) Sustainable intensification of aquaculture value chains between Asia and Europe: A framework for understanding impacts and challenges. Aquaculture.

Liu (2017) Usage, residue, and human health risk of antibiotics in Chinese aquaculture: A review. Environ. Poll. 223: 161-169.

Liu L, Wu W, Zhang J, Lv P, Xu L, Yan Y (2018) Progress of research on the toxicology of antibiotic pollution in aquatic organisms. Acta Ecol. Sin. 38: 36–41

Liu X, Zhang G, Liu Y, Lu S, Qin P, Guo X, Bi B, Wang L, Xi B, Wu F, Wang W, Zhang T (2019) Occurrence and the fate of antibiotics and antibiotic resistance genes in typical urban water of Beijing, China. Environ. Pollut. 246: 163–173.

Lundström Sara V, Marcus Östman, Johan Bengtsson-Palme, Carolin Rutgersson, Malin Thoudal, Triranta Sircar, Hans Blanck, K. Martin Eriksson, Mats Tysklind, Carl-Fredrik Flach, D.G. Joakim Larsson (2016) Minimal selective concentrations of tetracycline in complex aquatic bacterial biofilms. Sci. Total Environ. 553, 587:595. DOI: 10.1016/j.scitotenv.2016.02.103.

Lulijwa R, Rupia EJ, Alfaro AC (2020) Antibiotic use in aquaculture, policies and regulation, health and environmental risks: a review of the top 15 major producers. Rev. Aq. 1-24.

Migliore L, Civitareale C, Brambilla G, Dojmi Di Delupis G (1997) Toxicity of several important agricultural antibiotics to Artemia. Water Res. 31: 1801–1806

Millanao AB, Barrientos H M, Gómez C, Tomova A, Buschmann A, Dölz H J (2011) Uso inadecuado y excesivo de antibióticos: Salud pública y salmonicultura en Chile. Rev Med Chile, 139: 107-108. Review. PubMed PMID: 21526325

Millanao AB, Barrientos-Schaffeld, Siegel-Tike CD, Tomotova A, Ivanova L (2018) Antimicrobial resistance in Chile and the one health paradigm: dealing with threats to human and veterinary health resulting from antimicrobial use in salmon aquaculture and the clinic. Rev. Chilena. Infectol. 35 (3), 299-308. DOI: 10.4067/s0716-10182018000300299

Miranda CD, Godoy FA, Lee MR (2018) Current Status of the Use of Antibiotics and the Antimicrobial Resistance in the Chilean Salmon Farms. DOI: 10.3389/ fmicb.2018.01284.

MINSEGPRES (2021). Revisión de la norma de emisión de descargas residuos líquidos a aguas marinas y continentales superficiales (d.s. 90/2000) https://consultasciudadanas.mma.gob.cl/storage/act/102/08-04-21_Revisi%C3%B3nDS90.pdf

Muziasari WI, Pitka¨nen LK, Sørum H, Stedtfeld RD (2017) The resistome of farmed fish feces contribute to the enrichment of antibiotic resistance genes in sediments below Baltic Sea Fish Farms. Front Microbiol 7:1–10. https://doi.org/10.3389/fmicb. 2016.02137

Nhung NT, Cuong NV, Thwaites, G, Carrique-Mas, J (2016) Antimicrobial Usage and Antimicrobial Resistance in Animal Production in Southeast Asia: A Review. Antibiotics 5- 37. DOI: 10.3390/antibiotics5040037.

Norman SA, Lambourn DM, Huggins JL, Gaydos JK, Dubpernell S, Berta S, Olson JK, Souze V, Evans A, Carlson B, Johnson M, Mayer R, King Cathy, Scott A (2021) Antibiotic Resistance of Bacteria in Two Marine Mammal Species, Harbor Seals and Harbor Porpoises, Living in an Urban Marine Ecosystem, the Salish Sea, Washington State, USA. Oceans 2: 86–10

OIE (2021) annual report on antimicrobial agents intended for use in animals. Better understanding of the global situation. Fifth Report. World Organisation for Animal Health. 136pp.

Pan M & Chu LM (2016) Adsorption and degradation of five selected antibiotics in agriculture soil. Sci. Total Environ. 545-546: 48-56

Paredes C & Martines I (2018) “La regulación ambiental aplicable a la salmonicultura y los principios jurídico - ambientales que la inspiran”. Fundación Terram, 45pp.

Pham DK, J Chu, NT Do, F Brose, G Degand, P Delahaut, E De Pauw, C Douny, K Van Nguyen, TD Vu, ML Scippo, and HFL Wertheim (2015) Monitoring antibiotic use and residue in freshwater aquaculture for domestic use in Vietnam. EcoHealth 12:480–489

Pillay, TVR (2004) Aquaculture and the environment. Second edition Blackwell Scientific Publications.

Pomati F, Netting AG, Calamari D, Neilan BA (2004) Effects of erythromycin, tetracycline and ibuprofen on the growth of *Synechocystis* sp. and *Lemna minor*. Aquatic toxicology 67: 387-396

Proia L, Lupini G, Osorio V, Pérez S, Barceló S, Schwartz T, Amalfitano S, Fazi S, Romaní AM, Sabater S (2013) Response of biofilm bacterial communities to antibiotic pollutants in a Mediterranean river. Chemosphere. 92: 1126–1135.

Quiñones R, Fuentes M, Montes RM, Soto D, León-Muñoz (2019) Environmental issues in Chilean salmon farming: a review. Rev. Aquac. 11: 375-402.

Rose JM, Gast RJ, Bogomolni A, Ellis JC, Lentell BJ, Touhey K, Moore Michael (2009) Occurrence and patterns of antibiotic resistance invertebrates off the Northeastern United States coast. FEMS Microbiol Ecol 67: 421-431

Roose-Amsaleg C & Laverman AM (2016) Do antibiotics have environmental side-effects? Impact of synthetic antibiotics on biogeochemical processes, Environ. Sci. Pollut. Res. 23: 4000–4012.

Rico A, Phu TM, Satapornvanit K, Jiang K, Shahabuddin M, Henriksson AM, Murray PJG, Little FJ, Dalsgaard DC, Brink PJ (2013) Use of veterinary medicines, feed additives and probiotics in four major internationally traded aquaculture species farmed in Asia. Aquaculture 412-413: 213-243.

Rico A & Van den Brink PJ (2014) Probabilistic risk assessment of veterinary medicines applied to four major aquaculture species produced in Asia. Sci. Total. Environ. 468–469: 630–641. DOI: 10.1016/j.scitotenv.2013.08.063

Rico A, Vighi M, Van den Brink PJ, Mechteldter H, Macken A, Lillicrap A, Falconer L, Telfer TC (2018) Use of models for the environmental risk assessment of veterinary medicines in European aquaculture: current situation and future perspectives. Rev. Aquac. 1-20. DOI: 10.1111/raq.12274

Rico A, Zhao W, Gillissen F, Lürling M, Van de Brink P (2018b) Effects of temperature, genetic variation and species competition on the sensitivity of algae populations to the antibiotic enrofloxacin. Ecotox. Environ. Safety. 148: 228-236. DOI: 10.1016/j.ecoenv.2017.10.010.

Sanderson H, Johnson DJ, Wilson CJ, Brain RA, Solomon KR (2003) Probabilistic hazard assessment of environmentally occurring pharmaceuticals toxicity to fish, daphnids and algae by ECOSAR screening. Toxicol Lett. 144:383–395. DOI: 10.1016/s0378- 4274(03)00257-1

Schar D, Klien EY, Laxminarayan R, Gilbert M, Van Boeckel T (2020) Global trends in antimicrobial use in aquaculture. Scientific Reports, Nature 10:21878. DOI: 10.1038/s41598-020-78849-

SEPA, Scottish Environmental Protection Agency (2014) Supporting guidance (WAT-SG-53), pp. 34. Environmental quality standards and standards for discharges to surface waters. V5.1.

SERNAPESCA (2020) Antimicrobial uses in the salmon Chilean industry. Aquaculture Sub-direction, Animal Health Department, Valparaíso. Ministry of Economy, Development, and Tourism, Chile. 13pp.

Shang AH, Ye J, Chen DH, Lu XX, Lu HD, Liu CN, Wang LM (2015) Physiological effects of tetracycline antibiotic pollutants on non-target aquatic Microcystis aeruginosa. J Environ Sci Health B 50: 809–818. https://doi.org/10.1080/03601234.2015.1058100

Shi J, Zheng GJS, Wong MH, Liang H, Li Y, Wu Y, Li P, Liu W (2016) Health risks of polycyclic aromatic hydrocarbons via fish consumption in Haimen bay (China), downstream of an e-waste recycling site (Guiyu). Environmental Research 147, 233e240.

Soto D & Norambuena F (2004) Evaluation of salmon farming effects on marine systems in the inner seas of southern Chile: a large-scale mensurating experiment. J. App. Ichthyol. 20: 493-501.

Sørum H. (2000) Farming of Atlantic salmon - an experience from Norway. Acta Vet Scand. Suppl. 93: 129-134, and 149-157.

ter Laak TL, van ser Aa M, Houtman CJ, Stoks PG, van Wezel AP (2010) Relating environmental concentrations of pharmaceuticals to consumption: A mass balance approach for the river Rhine. Environ. Int. 36 (5): 403-409. DOI: 10.1016/j.envint.2010.02.009

Thornber K, Verner-Jeffreys D, Hinchiffle S, Meezanur Rahman M, Bass D, Tyler CR (2020) evaluating antimicrobial resistance in the global shrimp industry. Rev. Aquac. 12: 966-986

Tran NH, Reinhard M, Yew-Hoong Gin K (2017) Occurrence and the fate of emerging contaminants in municipal wastewater treatment plants from different geographical regions-a review. Water Res. 133: 182-207.

Tran NH, Hoang L, Nghiem LD, Nguyen NMH, Ngo HH, Guo W, Trinh QT, Mai NH, Chen H, Nguyen DD, Ta TT, Gin KY (2019) Occurrence and risk assessment of multiple classes of antibiotics in urban canals and lakes in Hanoi, Vietnam. Sci Total Environ. 20, 692: 157-174. DOI: 10.1016/j.scitotenv.2019.07.092.

VICH (2000) International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products. Topic GL6: Environmental Impact Assessments (EIAs) for Veterinary Medicinal Products (VMPs) – Phase I. VICH, London, UK. CVMP/VICH/592/98.

VICH (2004a) International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products. Topic GL38: Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products (VMPs) – Phase II. VICH, London, UK. CVMP/VICH/790/03.

VICH (2004b) Environmental Impact Assessment for Veterinary Medicinal Products- Phase II. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

Wei R, Ge F, Zhang L, Hou X, Cao Y, Gong L, Chen M, Wang R, Bao E (2016) Occurrence of 13 veterinary drugs in animal manure-amended soils in Eastern China. Chemosphere. 144: 2377-2383. DOI: 10.1016/j.chemosphere.2015.10.126

WHO (2018) Antimicrobial resistance and primary health care- technical series on primary health care. Department of Service Delivery and Safety, World Health Organization (WHO) headquarters, Geneva, Switzerland. 62pp.

Xu L, Zhang H, Xiong P, Zhu Q, Liao C, Jiang G (2021) Occurrence, fate, and risk assessment of typical tetracycline antibiotics in the aquatic environment: A review. Science of The Total Environment, 753, 141975. DOI: 10.1016/j.scitotenv.2020.1419

Yang Y, Xie J, Li H, Tan S, Chen Y, Yu H (2017) Prevalence, antibiotic susceptibility and diversity of *Vibrio parahaemolyticus* isolates in seafood from South China. Frontiers in Microbiology 8: 2566.

Yuang L, Wang L, Li ZH, Zhang MQ, Shao W, Sheng GP (2019) Antibiotics resistance and microbiota in the gut of Chinese four major freshwater carp from retail markets. Environ. Poll 255 (2): 113327. doi:10.1016/j.envpol.2019.113327

Zhang QQ, Ying GG, Pan CG, Liu YZ, Zhao JL (2015) A comprehensive evaluation of antibiotics emission and fate in the river basins of China: source analysis, multimedia modeling, and linkage to bacterial resistance. Environ. Sci. Technol. 49: 6772-6782

Zong H, Ma D, Wang J, Hu J (2010) Research on florfenicol residue in the coastal area of Dalian (northern China) and analysis of functional diversity of the microbial community in marine sediment. Bull. Environ. Contam. Toxicol. 84, 245e249.DOI: 10.1007/s00128-009-9923

Zuccato E, Castiglioni S, Bagnati R, Melis M, Fanelli R (2010) Source, occurrence and fate of antibiotics in the Italian aquatic environment. J. Hazardous Materials 179: 1042-1048. DOI: 10.1016/j.jhazmat.2010.03.110