Chapter 9

Q3 Q1 Antimicrobial drugs in aquaculture: use and abuse

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Abstract

Aquaculture, the most dynamic food sector, is continuously growing to meet the challenge of the increasing demand for animal protein and health benefits of fish consumption. Intensification of production, introduction of new farmed species, and other unpredicted factors may create animal welfare problems, resulting inevitably in higher risks of disease outbreaks and thus increasing use of antimicrobials mainly in top-producing countries. Residues of antimicrobials in farmed animals have received much attention in recent years because of growing food safety and public health concerns, especially in regions where imports of aquatic food are necessary to cover unmet local demand. Development of antimicrobial drug resistance, hypersensitivity reaction, possible carcinogenicity, and disruption of normal intestinal flora are the most crucial concerns for consumers. Several legislative directives and control systems have been implemented to regulate use of antimicrobials and protect consumers from unwanted side effects. Along with the encouragement for modern husbandry and biosecurity practices, increased prevention and prudent chemical use at a farm level, international organizations and national governments should enforce rigid monitoring of antimicrobials and promote further measures to reduce potential human health risks.

Keywords: Aquaculture; antibacterials; drug; residues; veterinary; legislation; surveillance; hazard; resistance; public health; food safety

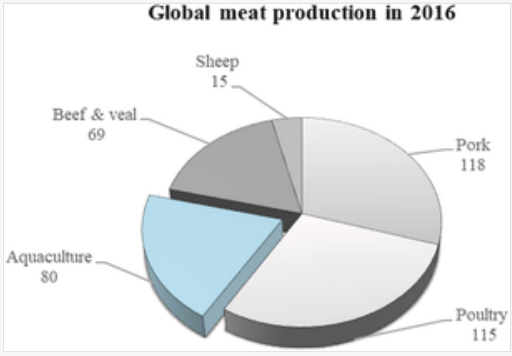
Q4 9.1 Introduction

9.1.1 Importance of aquaculture globally to meet consumer demand for fish

Human society must successfully meet the enormous challenge of producing food for a population reaching over 9 billion by the middle of the 21st century, without neglecting the necessity of moving to sustainable production and adapting to the adverse impacts of climate change.[1] Among the main animal farming sectors, fish production will play a leading role in facing this challenge, especially in developing regions, which suffer most from poverty and hunger. Global fish production peaked at about 171 million tons in 2016, with aquaculture representing almost half of its volume.[1] Forecasting for aquaculture production is being more optimistic for fish farming as opposed to fisheries, where stable or even reduced catches are expected. Indeed, aquaculture is the most dynamic food sector compared to other major food production industries, although it no longer enjoys the accelerated growth gained in the previous decades. Aquaculture displayed comparable production figures to the main land-based livestock sectors (Fig. 9.1). Global aquaculture production in 2016 included around 80 million tons of fish and 30 million tons of aquatic plants. Farmed/fish production is led by finfish production (54.1 million tons), followed by mollusks (17.1 million tons), crustaceans (7.9 million tons), and other aquatic animals (<1 million tons). Asia dominates aquaculture production, with China being by far the leading producer of farmed fish in 2016, providing more than 60% of global fish supply. Other major producers are also from Asia, including India, Indonesia, Vietnam, and Bangladesh (Fig. 9.2). Egypt and Chile

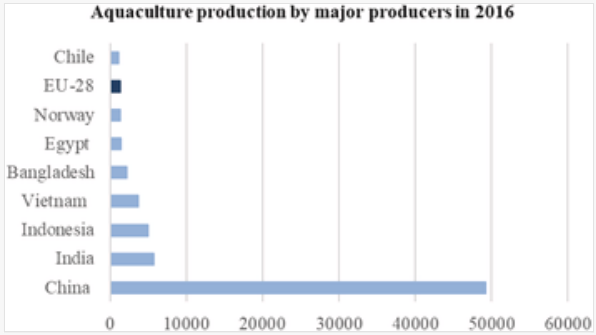
are the leading aquaculture producers in Africa and America, respectively, while Norwegian aquaculture alone slightly exceeds the respective European Union (EU)-28 production (Fig. 9.2).[1]

Figure 9.1



Q14 Global meat production (million tons) in 2016.
FAO. The State of World Fisheries and Aquaculture 2018 – Meeting the Sustainable Development Goals. Rome: FAO; 2018; https://www.statista.com/statistics/237632/production-of-meat-worldwide.

Figure 9.2



Aquaculture production (million tons) by major producers in 2016.
FAO. The State of World Fisheries and Aquaculture 2018 – Meeting the Sustainable Development Goals. Rome: FAO; 2018.

Global demand for fish products is continuously increasing as reflected by the average annual increase in global food fish consumption (3.2%), as compared to the corresponding meat from all terrestrial animals combined (2.8%).[1] Fish consumption nowadays accounts for almost 20% of the animal protein consumed globally. Annual per capita fish consumption is unequal, ranging from 2 to 50 kg, between different global regions, where developing countries have a higher share of fish protein in their diets compared to those in developed countries.

9.1.2 European Union—the world's biggest importer of aquaculture products

Although EU aquaculture sector production reached 1.4 million tons of seafood in 2016 (https://ec.europa.eu/fisheries/cfp/aquaculture_en), EU is by far the world's biggest importer of aquatic products (http://www.eumofa.eu/), with demand considerably exceeding local production. Consumption of seafood in the EU is estimated to be around 24 kg per capita in 2017 (https://www.seafoodsource.com/news/supply-trade/european-markets-importing-exporting-more-seafood-products). Given that seafood production has currently limited space for further regional growth, EU self-sufficiency for seafood has remained at values below 50% during the last decade, revealing a disappointing trade profile in fisheries and aquaculture products, and thus an increasing dependence on imported products. The EU imports of both fisheries and aquaculture products were dependent on nearly 150 countries around the world, although a majority of the total value was sourced from only few countries, such as Norway, China, and Ecuador (https://ec.europa.eu/fisheries/press/eu-fish-market-2019-edition-out-everything-you-wanted-know-about-eu-market-fish-and-seafood_en). Shrimps are currently the leading imported products in terms of value, ahead of salmon and cod whilst tuna, cod,
Q5 salmon, and pollack are now the main species consumed in the EU. Despite the EU market's global strength, following a strong period of growth in consumption in the last decade, consumption dropped by 5% between 2008 and 2010 and has since remained stable. Of the seafood consumed in the EU 75% is derived from fisheries, but consumption of

farmed products has been decreased by 5%. Concerning seafood trade trends, EU imports from third-countries increased by 4% in volume and 2% in value over the previous year, reaching an almost 6 million tons dependence (ec.eumofa.eu).

Import rules for these products are harmonized among EU countries. For non-EU countries the European Commission (EC) is the negotiating partner that defines import conditions and certification requirements. Also, for most countries with existing trade, the EC negotiates on behalf of the Member States. Moreover, EC has developed the European Market Observatory for Fisheries and Aquaculture (EUMOFA) as a market intelligence tool in the EU fisheries and aquaculture sector (https://www.eumofa.eu). Its tasks include increasing market transparency and efficiency, analyzing EU markets dynamics and supporting policy-making. The EUMOFA enables direct monitoring of volumes, values, and prices of fisheries and aquaculture products, from the first sale to retail stage, including imports and exports. General rules for fishery products imports into the EU are subjected to official certification, which is based on the recognition of the competent authority of the non-EU country by the EC. This formal recognition of the reliability of the competent authority is a prerequisite for a candidate country to be authorized for EU exports. All bilateral negotiations and other relevant aspects concerning imports of fishery products must be undertaken by the national competent authority (The EU fish market, 2017). The eligibility importing criteria selected for aquaculture edible products have been established by EC and stated below (https://ec.europa.eu/food/sites/food/files/safety/docs/ia_trade_import-cond-fish):

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- Exporting countries must have a competent authority, which is responsible for official controls throughout the production chain. The authorities must be empowered, structured, and resourced to implement effective inspection and guarantee credible public health and animal health attestations in the certificate to accompany fishery products that are destined for the EU.
- The national authorities must also guarantee that the relevant hygiene and public health requirements are met. The hygiene legislation contains specific requirements on the structure of vessels, landing sites, processing establishments, and on operational processes, freezing, and storage. These provisions are aimed at ensuring contamination of the product during processing.
- In the case of aquaculture products, a control plan on heavy metals, contaminants, residues of pesticides, and veterinary drugs must be in place to verify compliance with EU requirements. A suitable control plan must be designed by the competent authority and submitted to the EC high standards and at preventing any for initial approval and yearly renewal.
- Inspections by the Commission's Food and Veterinary Office are necessary to confirm compliance with the above requirements. Such an inspection mission is the basis of establishing confidence between the EC and the competent authority of the exporting country.

9.1.3 Strategies to reduce import dependence of aquaculture products in European Union: farming of new fish species

The EU self-sufficiency ratio in seafood products, which measures the capacity of EU Member States to meet demand from their own production, showed a decreasing profile from 47.4% to 46.0% (2015), reflecting that more of the consumed fisheries and aquaculture products were supplied through imports from non-EU countries than through EU catches or aquaculture production. It furthered declined to 43% in 2017 (https://ec.europa.eu/fisheries/press/eu-fish-market-2019-edition-out-everything-you-wanted-know-about-eu-market-fish-and-seafood). Imported volumes of seafood are thus increased approaching 6 million tones. In 2016 the volume increase was only 3%, while the growth observed in value terms was 9% (The EU fish market, 2017). The EU trade balance deficit reached a negative peak of more than €20 billion. In 2017 aquaculture production in the EU reached a 10-year high of 1.37 million tons with a value of more than €5 billion. Its value almost doubled in those 10 years, due to the increased production of high value species, such as salmon, European seabass, and bluefin tuna, and to the strong price increase of some major species, including salmon, European seabass, gilthead seabream, oyster, and clams. Although slightly less than in 2016, the 2017 consumption of farmed products in the EU was 2% above its decade average. Consumption of fish and seafood in the EU was estimated at 24.4 kg per capita in 2017. On average, EU citizens ate 0.5 kg less compared to the previous year.

More than 25% of fish and seafood products imported in the EU originate from Norway, Sweden, and Denmark; the main entry points for Norwegian products into the internal market allow the imports to reach other Member States' markets.

One of the potential strategies to reduce import dependence of aquaculture products in EU is the farming of new fish species. This direction may compensate for increased import dependence of seafood of often questionable quality, in parallel with market stagnation of some established farmed fish species in the EU. European aquaculture constitutes a safe, healthy, and potentially sustainable source of aquatic products and increase in local farmed fish production will be a partial solution to create independence to a certain degree from seafood imports. This strategy could be of special importance since fisheries production, as in other areas of the world, is not expected to enjoy its increasing pattern in the EU. Culture of fast grower species such as greater amberjack and meager with increased commercial value and tremendous potential production could be pioneers in raising seafood production in the EU (http://www.diversifyfish.eu). Both species are still considered as niche products, although European meager production has already reached several thousand tons.[2] Greater amberjack on the other hand has been baptized as the "Mediterranean salmon" and it could soon easily be one of the leaders in EU aquaculture production if specific barriers (diseases, survival, etc.) are solved.

9.1.4 Disease a limiting factor for aquaculture necessitates the use of more and new drugs

Diseases are functional disruptions which can have serious effects on living organisms especially if numerous individuals are confined in small areas, such as the environments of intensive production systems. Treatment of ill-farmed animals is essential to confront disease and return the production enterprises to a profitable pattern. During the 20th century, the use of veterinary drugs in farm animals was rapidly expanded and included nontherapeutic applications. By the turn of the 21st century it was estimated that half of the global production of antibiotics was being used in farm animals (http://www.who.int/mediacentre/news/releases/2011), while more recently, global antibiotic use for animal farming even exceeded that of human consumption.[3] Antimicrobials play a major role in modern livestock production for prevention and treatment of diseases and even growth promotion. Administration of antibiotics in food animals has been uncontrolled in many countries due to weak regulations and poor management practices.[4] Alarming projections stressed that growing meat consumption, mainly in developing countries, will be associated with an almost 70% increase of antibiotic use in livestock in the coming decades.[3] Nowadays, increase in animal production has largely been accomplished through modernization of the farming practices but also via intensification of existing systems, resulting inevitably in higher risks of disease outbreaks and, thus, increased use of antimicrobials.

In aquaculture medicine, use of therapeutics for prevention is not recommended and is actually prohibited for growth stimulation. The global rise in production and demand for aquaculture products has been paralleled with the promotion of several microbial diseases, resulting, thus, in increasing dependence on antimicrobials with often undesired impacts. Human welfare mainly related to the accumulation of drug residues in the products directed for consumption as well as environmental pollution are the main associated concerns.[5] The economic cost due to the incidence of diseases in aquaculture has been catastrophic on some occasions, and thus the need of effective therapeutic tools is paramount. It has been estimated that the annual cost solely due to parasites in aquaculture is >US$ 1 billion[6] and US$ 6 billion due to all diseases.[7] For example, sea lice infestations generate average damage of almost US$ 0.5 per kilogram of harvested Atlantic salmon in Norwegian farms.[8] Salmonid rickettsial septicemia, one of the most important disease problems in the Chilean salmon farming industry, has caused serious losses (>US$ 100 million) in the past.[9] The same industry has suffered a 30% production crash during the last decade, mainly attributed to infectious salmon anemia and to the sea lice.[10] In Bangladesh, one of the major aquaculture producers globally, the overall average economic loss due to fish diseases has been yearly calculated as high as BDT 24,870 (US$ 293) per ha.[11] In China, the leader in the aquaculture industry, it is estimated that diseases are responsible for losses accounting to 15%–20% of production annually, which implies an economic loss of 5–7 billion Yuan (~US$ 0.7–1 billion).[12]

Pharmaceuticals in aquatic medicine are represented by a wide range of compounds used mainly for therapeutic purposes such antibiotics, antivirals, antifungals, and antiparasitic substances. Unfortunately, pharmaceuticals have not always been used in a responsible manner in the aquaculture industry. The urgency of the farmer's response to an outbreak often results in ill-informed decision-making based on a rushed diagnosis and possible use of inappropriate drugs. Chemicals have been used in fish farming for more than 100 years; however, intensive efforts to register fish toxicants only commenced in the 1950s to late 1970s.[13] Misuse of drugs has been associated with increased microbial

resistance, thus necessitating the application of new therapeutics. Novel diseases have been also emerged. Sadly, in most cases, the battle in intensive fish farming appears to be in favor of the pathogen.

Current levels of antimicrobial use in aquaculture worldwide are not easy to monitor because different countries have different distribution and registration systems.[4] In developed countries, the effective use of vaccines, better management and implementation of biosecurity programs has led to a substantial reduction to the use of antibacterial compounds against bacterial pathogens. In Norway for example, consumption of antibacterials has been reduced to 0.36 mg/kg fish produced in 2014, which during the 1990s ranged from 1.2 to 11 mg/kg fish produced.[14] The impact, however, of sea lice on salmonid aquaculture has led to the search for additional therapeutic tools mainly in Norway and the total use of antiparasitics is not in accordance with the reduced pattern of antibacterial use.[15] Indeed, although in recent years, several strategies involving physical and biological measures have been employed in addition to chemical approaches, the amount of chemical antisea lice agents used has been actually increased from 1992 to 2015 but decreased in 2016 and 2017.[15]

Detailed and accurate information on the use of aquaculture chemotherapeutics in Asian aquaculture, where the leading producing counties exist, is relatively limited and in most cases is based on surveys rather than official governmental monitoring.[16] The latter survey reports the outcomes on the use of chemical products in numerous grow-out aquaculture farms in four major producer countries such as China, Thailand, Bangladesh, and Vietnam. Sixty different veterinary medicinal ingredients were recorded, including 26 antibiotics, 19 disinfectants, and 15 parasiticides, a much larger list in comparison with those registered in EU (Table 9.1). Interestingly, shrimp farms in China, Thailand, and Vietnam showed an overall decrease in the use of antibiotic treatments. The amount of total chemical use was estimated to be close to <19 kg per average ton of harvested shrimp in China and Thailand,[16] with parasiticides contributed a considerable portion of the total therapeutics applied.

Table 9.1

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List of registered antimicrobials for use in aquaculture (European Union and Norway).

Compound	Dosing schedule	MRL (μg/kg edible tissue)	Source
Antibacterials			
Oxytetracycline, chlortetracycline	75 mg/kg, 10 days	100	17
Flumequine	12 mg/kg, 5 days	600	18
Oxolinic acid	10–30 mg/kg, 5–7 days	100	19
Sulfadiazine, sulfamethazine	25 mg/kg, 5 days	100	20
Trimethoprim	5 mg/kg, 5 days	50	21
Amoxicillin, ampicillin	80 mg/kg, 10 days	50	22
Florfenicol	10–15 mg/kg, 10 days	1000	23
Parasiticides			
Formalin	100–200 ppm, 60 min	0	http://mri.cts-mrp.eu/, ES/V/0184/001/MR
Emamectin benzoate	50 μg/kg/d, 7 days	100	24
Azamethiphos	0.1–0.2 ppm, 60 min	0	25
Cypermethrin	5 ppm, 60 min	50	26

Deltamethrin	2–10 ppm, 30 min	10	27
Diflubenzuron	3 mg/kg/d, 14 days	1000	28
Teflubenzuron	10 mg/kg/d, 7 days	500	29
Hydrogen peroxide	30–100 ppm, 30–60 min	0	Nonchemical
Lufenuron	10 mg/kg/day, 7 days	1350	under EMA consideration
Hexaflumuron	2 ppm, 60–120 min	500	under EMA consideration

EMA, European Medicines Agency; *MRL*, maximum residue limit.

9.1.5 General use of veterinary drugs

9.1.5.1 Global and aquaculture levels

Livestock production is one of the fastest growing agricultural sectors, and for health and productivity to be maintained, the use of veterinary drugs is inevitable. The pharmaceuticals used globally in food animals comprise a broad variety of chemical compounds' classes including vaccines, antimicrobials, antiparasitics, and β-agonists. Specifically, the common antibacterials used in livestock production include tetracyclines, penicillins, streptomycin, sulfonamides, tylosin, aminoglycosides, β-lactams, macrolides, lincosamides, and quinolones.

Until recently, the global average annual consumption of antimicrobials per kilogram of animal produced was estimated at >100 mg/kg[30] and this consumption was surprisingly twice that of humans.[31] In detail, according to the study of Van Boeckel et al.,[32] in 2013, the global consumption of all antimicrobials in food animals was estimated at 131,109 tons (100,812 to 190,492 tons) and is projected to almost double in volume by 2030 (from 150,848 to 297,034 tons). Globally, China is by far the largest user of veterinary drugs in livestock production (318 mg/population correction unit —PCU—which takes into account the animal population as well as the weight of each particular animal at the time of treatment with antibiotics), followed by United States and Brazil. On the other hand, considerably low consumption levels were found for Norway (8 mg/PCU).[3]

In United States, the key observations of Food and Drug Administration (FDA)'s recently published report regarding antimicrobial use[33] include:

Domestic sales and distribution of medically important antimicrobials approved for use in food-producing animals is:

- increased by 9% from 2017 through 2018
- decreased by 38% from 2015 (the year of peak sales) through 2018
- decreased by 21% from 2009 (the first year of reported sales) through 2018
- tetracyclines increased by 12% from 2017 through 2018.

Of the 2018 domestic sales and distribution of medically important antimicrobials approved for use in food-producing animals, tetracyclines accounted for 66%, penicillins for 12%, macrolides for 8%, sulfas for 5%, aminoglycosides for 5%, lincosamides for 2%, cephalosporins for 1%, and fluoroquinolones for >1%. The highest percent of chemicals (42%) was intended for use in cattle, 39% in swine, 11% in turkeys, 4% in chickens, and 4% in other species

In the EU, in the recently published ninth European Surveillance of Veterinary Antimicrobial Consumption report, data on the sales of veterinary antimicrobial agents from 31 European countries in 2017 were presented.[34] The main observations of the aforementioned report are summarized below:

- A large difference in the sales for 2017, expressed as mg/PCU, was observed between the countries with the highest and lowest sales (range: 3.1–423.1 mg/PCU).
- Of the overall sales of antimicrobials in the 31 countries in 2017, the largest amounts, expressed as mg/PCU, were accounted for by tetracyclines (30.4%), penicillins (26.9%), and sulfonamides (9.2%). Overall, these three classes accounted for 66.5% of total sales in the 31 countries.

- Pharmaceutical forms suitable for group treatment, that is, premixes accounted for 28.8%; oral powders for 9.9%; and oral solutions for 50.7%, accounted for 89.4% of the total sales.
- For the 25 countries which provided sales for all years between 2011 and 2017, an overall decline in sales (mg/PCU) of 32.5% was observed (from 162.0 mg/PCU in 2011 to 109.3 mg/PCU in 2017).

In the aquaculture sector, as a consequence of the intensification of the culture systems and of the diversification of both the species cultured and the culture methods employed, that pathogens will flourish is inevitable. Disease agents such as viruses, bacteria, fungi, and parasites have caused serious problems in major producing countries in the past.

A variety of compounds is used in aquaculture and categorized as antimicrobials, disinfectants, pesticides, hormones, anesthetics, probiotics and prebiotics, pigments, minerals, and vitamins. Similar to livestock production sector, the aforementioned compounds are used in aquatic animal health management, soil and water management, improvement of natural aquatic productivity, live transportation, feed formulation, manipulation of reproduction, growth promotion, and so on.

In aquaculture, the ideal approach to maintain fish health and welfare would be to prevent the introduction of disease agents so vaccine usage would seem preferable compared to chemical agents; however, this is not always the case. Therefore the use of chemotherapeutics is inevitable to control the impact of a disease. Unfortunately, statistical data regarding the use of chemicals in global aquaculture is relatively limited with a few exceptions (e.g., Norway, United Kingdom, United States, Chile, etc.). This is due for several reasons: (1) different countries have different distribution and registration systems,[4] and thus the requirement for the use of veterinary drugs among countries differs; (2) the scarcity of them specifically developed for use in aquaculture,[35] (3) the diversity of species and culture systems, (4) the unconsolidated nature of production in many regions, and (5) the often unregulated use of chemicals that are labeled and registered for use in aquaculture production.[36]

Q7 9.2 Main text

9.2.1 Aquatic animal diseases

9.2.1.1 OIE database in aquatic animal diseases

The need to combat animal diseases at global level has led to the creation of the Office International des Epizooties (OIE) almost a century ago (https://www.oie.int/). In the turn of the 21st century, OIE was renamed as the World Organization for Animal Health, keeping though its historical acronym. The OIE is the intergovernmental organization responsible for improving animal health that has been recognized as a reference organization by the World Trade Organization (WTO), having currently a total of 182 Member Countries (https://www.oie.int/). Among other production systems, OIE has produced the Aquatic Animal Health Code (Aquatic Code) which provides standards for the improvement of aquatic animal health worldwide as well as for the welfare of farmed fish and the use of antimicrobials. The sanitary measures in the Aquatic Code should be used by the Competent Authorities of importing and exporting countries for the prevention, early detection, reporting, and control of pathogenic agents in aquatic animals (amphibians, crustaceans, fish, and mollusks) and to prevent their spread via international trade in aquatic animals and their products, while avoiding unjustified sanitary barriers to trades. The objective of listing notifiable diseases (Table 9.2) is to support Member Countries by providing information needed to take appropriate action to prevent the transboundary spread of important diseases of aquatic animals.

Table 9.2

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OIE-listed diseases for aquatic farmed animals.

Disease	Infectious agent	Susceptible species
1.		

Fish		
Viral		
Epizootic hematopoietic necrosis	Ranavirus	Redfin perch (*Perca fluviatilis*) and rainbow trout (*Oncorhynchus mykiss*)
Infectious hematopoietic necrosis	Rhabdovirus	Pacific salmons including chinook (*Oncorhynchus tshawytscha*), sockeye (*Oncorhynchus nerka*), chum (*Oncorhynchus keta*), pink (*Oncorhynchus* gorbuscha), amago (*Oncorhynchus rhodurus*), masou (*Oncorhynchus masou*), and coho (*Oncorhynchus kisutch*), and Atlantic salmon (*Salmo salar*)
Spring viremia of carp	Rhabdovirus	Common carp (*Cyprinus carpio carpio*) and koi carp (*C. carpio koi*), crucian carp (*Carassius carassius*), silver carp (*Hypophthalmichthys molitrix*), bighead carp (*Aristichthys nobilis*), grass carp, *white amur* (*Ctenopharyngodon idella*), goldfish (*Carassius auratus*), ide (*Leuciscus idus*), and tench (*Tinca tinca*)
Viral hemorrhagic septicemia	Novirhabdovirus	Isolated from 82 different fish species. Most susceptible is rainbow trout
Infectious salmon anemia	Orthomyxovirus	Atlantic salmon
Red sea bream iridoviral disease	Iridovirus	41 fish species
Koi herpesvirus disease	Herpesvirus	Common carp, koi carp, ghost carp (*C. carpio goi*), and hybrids of these varieties
Parasitic		
Gyrodactylosis	*Gyrodactylus salaris*	Mainly Atlantic salmon
Oomycetic		
Epizootic ulcerative syndrome	*Aphanomyces invadans*	76 fish species
2. Mollusks		
Viral		
Withering syndrome	Xenohaliotis californiensis	Abalone (*Haliotis* spp.)
Viral ganglioneuritis	Herpesvirus	Abalone
Parasitic		
Bonamiosis	*Bonamia exitiosa*	*Ostrea chilensis*, *Ostrea angasi*, and *Ostrea edulis*
	Bonamia ostreae	Oysters such as European flat oyster (*O. edulis*), *Argentinian oyster* (*Ostrea puelchana*), *southern mud oyster* (*O. angasi*), and dredge oyster (*O. chilensis*)
Marteliosis	*Marteilia refringens*	European flat oyster, blue mussel (*Mytilus edulis*), and Mediterranean mussel (*Mytilus galloprovincialis*)
Perkinsosis	*Perkinsus marinus*	Eastern oyster (*Crassostrea virginica*), Pacific oyster (*Crassostrea gigas*), suminoe oyster (*Crassostrea ariakensis*), mangrove oyster (*Crassostrea rhizophorae*), Cortez oyster (*Crassostrea corteziensis*), soft-shell clam (*Mya arenaria*), and Baltic macoma (*Macoma balthica*)
	Perkinsosis olseni	Sydney cockle (*Anadara trapezia*), New Zealand cockle (*Austrovenus stutchburyi*), Palourde clam (*Tapes decussates*), Japanese cockle (*Tapes philippinarum*), maxima clam (*Tridacna maxima*), crocus clam (*Tridanca crocea*), clam (*Pitar rostrata*), Pacific oyster

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		(*C. gigas*), Suminoe oyster (*C. ariakensis*), *C. sikamea*, black-lip pearl oyster (*Pinctada margaritifera*), Akoya pearl oyster (*Pinctada martensii*), black-lip abalone (*Haliotis rubra*), smooth Australian abalone (*Haliotis laevigata*), staircase abalone (*Haliotis scalaris*), and whirling abalone (*Haliotis cyclobates*)
3. Crustaceans		
Viral		
Taura syndrome	Taura syndrome virus (Dicistroviridae)	Pacific white shrimp (*Penaeus vannamei*) and Pacific blue shrimp (*Penaeus stylirostris*)
White spot disease	Nimaviridae viruses	All decapod crustaceans from marine and brackish or freshwater sources
Yellowhead disease	Yellowhead virus (*Roniviridae*)	Black tiger prawn (*Penaeus monodon*), white Pacific shrimp (*P. vannamei*), kuruma prawn (*Penaeus japonicus*), white banana prawn (*Penaeus merguiensis*), Pacific blue prawn (*P. stylirostris*), white prawn (*Penaeus setiferus*), red endeavor prawn (*Metapenaeus ensis*), mysid shrimp (*Palaemon styliferus*), and Antarctic krill (*Euphausia superba*)
Infectious hypodermal and hematopoietic necrosis	Infectious hypodermal and hematopoietic necrosis virus	Black tiger prawn, Pacific white shrimp, Pacific blue shrimp (*P. stylirostris*) and Pacific blue prawn
Infectious myonecrosis	Infectious myonecrosis virus (totivirus)	Pacific white shrimp
White tail disease	RNA virus	Giant freshwater prawn (*Macrobrachium rosenbergii*)
Oomycetic		
Crayfish plague	*Aphanomyces astaci*	Noble crayfish (*Astacus astacus*), white clawed crayfish (*Austropotamobius pallipes*), stone crayfish (*Austropotamobius torrentium*), and the Turkish crayfish (*Astacus leptodactylus*)
Bacterial		
Necrotizing hepatopancreatitis	Intracellular rickettsia-like organism (α-proteobacterium)	Pacific white shrimp (*Litopenaeus vannamei*), western blue shrimp (*Litopenaeus stylirostris*), Atlantic white shrimp (*Litopenaeus setiferus*), northern brown shrimp (*Farfantepenaeus aztecus*), and yellowleg shrimp (*Farfantepenaeus californiensis*)

9.2.1.2 Alien farmed fish species may result in new pathogens being introduced locally

Aquatic diseases can emerge from established farmed animals, but also might be triggered by novel pathogens being introduced by alien farmed fish species. As many as 27 alien species, of which 20 are freshwater, have been intentionally introduced into Europe for aquaculture and related activities.[37] Accordingly, three variables have been considered to assess their negative ecological impacts: (1) their distribution across Europe (including non-EU Member States), (2) evidence of their environmental impact in the wild and lastly and more importantly, and (3) evidence of being vectors of nontarget alien species pathogens. Alien crayfish have been blamed, for example, for the spread of crayfish plague in local crustaceans.[37] Peeler et al.[38] have reviewed the effects of nonnative aquatic animals' introductions on disease emergence in Europe. They stressed that enteric red mouth disease and infectious hematopoietic necrosis of salmonids have invaded European aquaculture with the import of live fish and eggs, respectively. Oysters have been also affected by diseases introduced with nonnative species.

The movement of alien aquaculture species across Europe and the possible dispersal of alien pathogens from introduction of nonendemic fish species in the region is mainly controlled by EU Regulation 304/2011, amending Council Regulation 708/2007, which concerns the use of alien species in aquaculture. Aquaculture animals and products, from both the EU and from non-EU countries, must fulfill similar health requirements before they can be

moved across national borders. The animal health conditions governing the placing on the market of aquaculture animals and products are defined in Council Directive 2006/88/EC. This Directive has been regularly amended to update the current legislation from new scientific knowledge. Due to the fact that fish health status varies across the territory of the EU, the movement regulations are based on the concept of approved disease-free zones for nonexotic diseases (Table 9.3) listed in Part II of Annex IV to Directive 2006/88/EC. The Directive describes the criteria for the granting, suspension, restoration, and withdrawal of approval of such zones and farms as well as certification requirements for movement into disease-free zones and farms. It also contains rules governing import from non-EU countries. Based on the Directive, aquatic diseases are divided into exotic and nonexotic diseases. The first group is considered exotic in the EU and animals infected are destroyed as soon as possible to prevent transmission of the disease. Nonexotic diseases are important endemic diseases that should be eradicated in the long term. Where aquatic animals are suspected of being infected or are actually infected with an exotic disease, movement of the animals is allowed only with authorization from the authorities.

Table 9.3

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Aquatic diseases listed as exotic in Annex IV to Directive 2006/88/EC.

Animals	Diseases	Susceptible species
Fish	Epizootic hematopoietic necrosis	Rainbow trout and redfin perch
	Epizootic ulcerative syndrome	Genera: *Catla*, *Channa*, *Labeo*, *Mastacembelus*, *Mugil*, *Puntius*, and *Trichogaster*
Mollusks	*Bonamia exitiosa*	Australian mud oyster and Chilean flat oyster
	Perkinsus marinus	Pacific oyster and Eastern oyster
	Mikrocytos mackini	Pacific oyster, Eastern oyster, Olympia flat oyster, and European flat oyster
Crustaceans	Taura syndrome	Gulf white shrimp, Pacific blue shrimp, and Pacific white shrimp
	Yellowhead disease	Gulf brown shrimp, Gulf pink shrimp, Kuruma prawn, black tiger shrimp, Gulf white shrimp, Pacific blue shrimp, and Pacific white shrimp

9.2.2 Legislation governing use of veterinary chemicals in aquaculture in European Union, United States, and elsewhere

9.2.2.1 Concepts of acceptable daily intake, maximum residue limit and withdrawal time

After various pharmacological, toxicological, microbiological, and other tests undertaken to demonstrate the safety of the substance are completed, the first major stage in the process of safety evaluation is the establishment of the acceptable daily intake (ADI). ADI is an estimate by the joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (JECFA) of the amount of a veterinary drug, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable health risk. The basis ADI calculation is the no observed (adverse) effect level (NO(A)EL) or, in certain cases the lowest observed (adverse) effect level with respect to the most sensitive parameter in the most sensitive appropriate test species, or in some cases, in humans. An uncertainty factor—often called a safety factor—is then applied to take into account the inherent uncertainties in extrapolating animal toxicity data to human beings and to take account of variations within the human species. The ADI concept is not applicable to Q8 substances for which it is not possible to determine a NOEL because they demonstrate nonthreshold effects (such as genotoxicity and delayed neurotoxicity). In such cases, an alternative approach to safety evaluation may be applied on a case by case basis, having regard to all the data available. Since the ADI is related to body weight, an arbitrary average human BW is defined at 60 kg (average value for all age groups in the European population). The ADI expressed on a

μg or mg per kg body weight basis is therefore multiplied by 60 to give the total amount of residue, which can be ingested by an individual. The safe concentration for each edible tissue using the ADI will be calculated by FDA as follows: Safe concentration=[ADI (μg/kg/day)×60 kg]/(grams consumed/day). Since accurate consumption profiles are difficult to be estimated, and there are substantial variations between individual consumers and between groups of consumers, arbitrarily high fixed values are used to ensure the protection of the majority of consumers. Alternatively, the Temporary ADI (TADI) is used by JECFA when data are sufficient to conclude that use of the substance is safe over the relatively short period of time required to generate and evaluate further safety data, but are insufficient to conclude that use of the substance is safe over a lifetime. A higher-than-normal safety factor is used when establishing a TADI and an expiration date is established by which time appropriate data to resolve the safety issue should be submitted to JECFA.

Several parameters have been globally established to regulate the use of antimicrobials in animal production including aquaculture. Maximum Residue Limit for veterinary drugs (MRL or MRLVD) is the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or μg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food. The MRLs for veterinary drugs are established through the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) in Codex Alimentarius last amended in 2018.[39] MRL establishment is based upon a risk assessment of the joint FAO/WHO JECFA. Albeit efforts have been made to harmonize MRL worldwide under the aegis of WTO and the Codex Alimentarius, MRLs still vary between geographical locations which might be related to the differences found in risk assessment. In fact, MRLs in a particular animal product may differ from one country to another depending on the local food safety regulatory agencies and drug usage patterns but most developing countries have yet to develop their own MRLs. In Europe, the main legislative documents regarding veterinary chemicals are Regulation 726/2004 and Directive 2001/82. Directive 2001/82/EC,[40] amended by Commission Directive 2009/9/EC[41] and by Regulation 470/2009,[42] is the safety net that foodstuffs of animal origin do not contain drug residues which can induce undesirable effects on human health from a toxicological, pharmacological, or microbiological point of view. The primary purpose of this law is the safeguarding of public health. Furthermore, Regulation 726/2004[43] lays down the procedures for the authorization and supervision of medicinal products for human and veterinary use as well as the Q9 structure and mission of the EMEA. The European Medicines Agency's (EMA), Committee for Medicinal Products for Veterinary Use is responsible for preparing the opinion of the Agency on issues concerning the evaluation of the quality, safety, and efficacy of veterinary drugs and the recommendation of the MRL of veterinary chemicals that can be accepted in foodstuffs of animal origin. Regulation 470/2009[42] lays down the Community rules and procedures for the establishment of MRLs of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation No 2377/90[44] and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation 726/2004 of the European Parliament and of the Council.[43] In Article 14 of the aforementioned legislation, the pharmacologically active substances are classified into (1) substances with a defined MRL, (2) substances with a provisional MRL, (3) substances that do not require MRL, and (4) substances whose use is forbidden in food-producing animals. Finally, in the Commission Regulation 37/2010[45] the classified pharmacologically active substances with respect to MRL, for reasons of ease of use, are listed in one Annex in alphabetical order. In the United States, the FDA under the Federal Food, Drug, and Cosmetic Act (FFDCA) is the responsible agent who establishes tolerances for veterinary drugs. Limitations are published in the Code of Federal Regulation.[46] The FDA also prohibits the usage of some drugs under the 21 Code of Federal Regulation for extra-label animal and human uses in food-producing animals. In Canada, the Health Canada's Veterinary Drugs Directorate sets the limits for veterinary drugs residues found in foods and also prohibits the use of specific chemicals in animals intended for human consumption.[47,48] In China, the Ministry of Agriculture issued a National Food Safety Standard on Maximum Residue Limits for Veterinary Drugs in Foods (GB 31650-2019), which took effect on April 1, 2020.[49] The aforementioned standard replaces portions from Announcement No. 235 of the Ministry of Agriculture and Rural Affairs, published in December 2002. Additionally, the prohibited veterinary drugs and other chemicals in food animals are listed in the National Standard No 193.[50]

Another parameter regulating the use of antimicrobials is withdrawal time (WT) or withholding time. WT is defined as the period of time between the last administration of a drug and the collection of edible tissue or products from a treated animal that ensures the contents of residues in food comply with the MRL for this veterinary drug. The establishment of an MRL allows the setting of a withdrawal period of the drug. In most food-animal species withdrawal periods are defined in days, but with fish the EU requires data to be presented from trials conducted at least two water temperatures

relevant to the proposed conditions of use. If depletion of residues is found to be temperature-dependent, then a withdrawal period in degree-days will be set, making the withdrawal period a function of temperature and time. If the data do not indicate a temperature effect on depletion, then a day-based withdrawal can be accepted.[51] Additionally, for meat of fish, when no specific withdrawal period is defined, a withdrawal period of 500-degree days has to be respected. According to the FDA "the WT is determined when the tolerance limit on the residue concentration is at or below the permitted concentration. A tolerance limit provides an interval within which a given percentile of the population lies, with a given confidence that the interval does contain that percentile of the population. FDA will use the 99th percentile of the population and the 95% confidence level."[52] In Europe, EMA recently issued documentation that provides a standard approach to be used across the EU in the analysis of residue depletion data for the purpose of establishing withdrawal periods for edible tissues.[53]

Admittedly, the number of medicines that can be used "on label" in aquaculture is extremely low and only very few pharmaceutical antibacterial-based products have been licensed at different national level for specific use against fish diseases. The differences between countries (even at EU country-level) regarding licensed products are also an add-on problem. If no licensed medicine for fish are available in a country but available in other EU countries, then it is also possible to use another legal mechanism known as "importation and use of veterinary medicines under exceptional circumstances." In these cases, it is possible to apply to the responsible national authorities for a particular import authorization. Unfortunately, given the lack of specific licensed medicines for finfish, this mechanism becomes common instead of exceptional and requires additional bureaucratic efforts.

The scarcity of specific "on label" medicines, also problematic for other animal species, such as the so-called "minor species," has also been alleviated by the "prescribing cascade" mechanism. EU regulations (90/676; 19/6; 19/4) provide a "prescribing cascade" to support the use of medicines authorized for other farmed animals, when no suitable compound has been licensed to treat diseases in fish. In such cases, a minimum standard withdrawal period is imposed, corresponding to 500-degree days in fish in order to ensure consumer safety, and is enforced by an established MRL, which is derived from toxicity testing data.

9.2.2.2 Hazard analysis and critical control point approaches

The hazard analysis and critical control point (HACCP) system, which is science-based and systematic, identifies specific hazards and measures for their control to ensure the safety of food. HACCP is a tool used to assess hazards and establish control systems that focus on prevention rather than relying mainly on end-product testing. This tool can be applied throughout the food chain from primary production to final consumption and its implementation should be guided by scientific evidence of risks to human health. As well as enhancing food safety, implementation of HACCP can provide other significant benefits. In addition, the application of HACCP systems can aid inspection by regulatory authorities and promote international trade by increasing confidence in food safety.

Agriculture experts believed that the application of HACCP would have been difficult at the "farm level." On the contrary, HACCP system has been proven suitable and has been applied for almost 30 years in aquaculture sector. According to Jensen and Martin,[54] the first exposure of the US aquaculture community to HACCP occurred during 1989 and 1990 when three Aquaculture Application Workshops were conducted by the National Fisheries Institute in cooperation with the National Marine Fisheries Service (NMFS). The first HACCP Regulatory Model for Aquaculture was published and released by NMFS in 1991. There, participants of the International Conference on Quality Assurance in the Fish Industry held in Denmark agreed that HACCP was a superior method of fish inspection and that the HACCP concept should be applied in the fish industry to cover food safety, plant/ food hygiene, and economic fraud issues.[55] During the Second International Conference on Fish Inspection and Quality Control held in Washington, DC, United States, in 1996, participants affirmed that HACCP-based programs were in the process of being implemented on a global scale. Urged on by this International Conference, governments as well as the aquaculture industry alike continued their efforts to give a high priority to the full implementation of HACCP-based systems.[56]

The development of an HACCP plan for an aquaculture facility requires the collaboration of a team of experts from several disciplines related to public health and aquaculture, for example, public health specialists, veterinarians (food inspectors and fish pathologists), aquaculturists, and fishery extension workers. Such HACCP plans and HACCP-based regulations, regarding the safety of fish and fish products, including products from aquaculture, are applied by a large number of countries globally. Specifically, HACCP systems are being put into practice in aquaculture at various

levels but mainly in the sectors of high-valued farmed species such as salmon in Norway, Canada, Ireland, United States, New Zealand, United Kingdom, and Chile; shrimp in Thailand, Ecuador, Australia, Cuba, Brazil, and Central American countries, and United States; trout in European countries, Argentina, Peru, and Brazil; catfish in United States; crawfish in United States; and bullfrogs in Brazil.

HACCP-based system can be apparently applied without difficulty to intensive cultural commercial aquaculture ventures; however, in small-scale, subsistence aquaculture systems, where fish are mainly farmed for domestic consumption under minimal inputs, knowledge, and assistance, application of an effective HACCP-based system poses considerable difficulties. Therefore the design and implementation of HACCP systems should be considered following careful evaluation of the feasibility of applying such a control system to a particular aquaculture system, the risks associated with the systems components and procedures, and the identification of the correct and appropriate critical control points.[57]

As mentioned above, the HACCP system has for years been widely adopted in the fisheries sector. EU rules on food safety and food standards are complex and subject to regular changes as International and European standards, commercial factors, scientific knowledge, food and food inspection technology, and known hazards are all in constant development. New hygiene rules were adopted in April 2004 (providing for primary responsibility for food safety on the food business operator, registration or approval for certain food establishments, and general implementation of procedures based on the HACCP principles) which have generally been welcomed by the aquaculture industry.[58] Additionally, both the General and Fisheries Directives[59,60] have a requirement for the use of HACCP or HACCP-based principles. In the United States, HACCP has been mandatory for the fisheries sector by 1997. Specifically, on December 18, 1995, FDA published as a final rule 21 CFR 123, “Procedures for the Safe and Sanitary Processing and Importing of Fish and Fishery Products” that requires processors of fish and fishery products to develop and implement Q10 Hazard Analysis Critical Control Point (HACCP) systems for their operations.”–The regulation became effective on December 18, 1997. The agency also published the “Fish and Fishery Products Hazards and Controls Guide” (“the Guide”) in September, 1996, to assist processors in the development of their HACCP plans, and to provide information to help them identify hazards that may be associated with their products and formulate control strategies for those hazards. The guide was developed to coincide with the issuance of the final regulation.

9.2.2.3 Surveillance programs and national control systems

One of the major health concerns in addition to the presence of harmful veterinary residues in aquaculture products is the development of antimicrobial resistance. Admittedly, the relationship between antibiotic use in food animals and antibiotic resistance in human and animal pathogens has been postulated as a contributing not causative factor (Feiyang et al., 2020). In the aquaculture sector, development of antimicrobial resistance is more pronounced in countries where aquaculture medicine is heavy and uncontrolled, since bacteria in the aquatic environment share a large assortment of mobile genetic elements and antimicrobial resistance genes with a wide range of terrestrial bacteria.[61]

To monitor trends in resistance and allow for timely corrective action and evaluation of interventions, WHO[62] suggested:

- a surveillance system for the usage of antibiotics in people and food animals and
- an integrated (among the public health, food, and veterinary sectors) surveillance system to monitor antibiotic resistance in selected food-borne bacteria.

A surveillance system for the usage of antibiotics in aquaculture requires data to be collected on a regularly and reported as weight of active substance per animal species and antibiotic class. In addition the data should be further assorted regarding their therapeutic use and reported by route of administration. Typically, the data on overall use could be obtained from the pharmaceutical industry, wholesalers, pharmacies, and tariff declarations, for countries without a pharmaceutical industry or wholesalers, which depend on the distribution system for antibiotics used in animals in each country.[62] In cases where collecting detailed data for an entire country is difficult, they could be collected through surveys in a representative area by a statistically robust sampling scheme probably from sources such as the records of veterinary practitioners and producers. The usage data should be combined with data on animal population size and ideally with data on animal health status in order to reflect the need for using different kinds of antibiotics.

As an example, the US cage salmon aquaculture industry was the first food animal industry to report monthly antimicrobial use at the farm level to the government.[63] Norway, Chile, Canada, and Scotland have also produced comprehensive reports on salmon production and veterinary drug use.[64–67] To date most countries, however, do not have a surveillance system of antibiotic use and different methodologies are used for presenting those data. This could explain the variability of information and lack of reliable data; therefore EMA has worked on the development of a harmonized approach to surveillance of antibiotic usage in animals in the EU.[62] The surveillance of antibiotic resistance in zoonotic and commensal bacteria in different food animal reservoirs and aquaculture products is a prerequisite for understanding the development and dissemination of antibiotic resistance, providing relevant risk assessment data, and implementing and evaluating targeted interventions. This surveillance entails specific and continuous data collection, analysis, and reporting that quantitatively monitor temporal trends in the occurrence and distribution of resistance to antibiotics.[62]

As in most regions, EU Member States have a responsibility to monitor the use of veterinary medicines in food-producing animals, to ensure that produce from these animals do not contain residues that could be harmful to consumers. It is a requirement to implement surveillance monitoring in accordance with the Residues Directive (Directive 96/23/EC) and to have in place national plans for the monitoring of certain chemical substances and residues in a range of all food producing species and related products. The specifications for the harmonized surveillance of antibiotic resistance in food animals have been recently documented by EFSA.[68] Other agencies such as European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), European Centre for Disease Prevention and Control (ECDC), and EMA are also part of the European Surveillance System (TESSy) in order that the EU Commission can manage the public health risk of antimicrobial resistance and to evaluate the impact of interventions.[69]

A policy publication has evaluated EU sampling strategies for the detection of veterinary drug residues in aquaculture species.[70] This communication examined the existing EU sampling schedule for aquaculture products and evaluated its possible application in a global context. The UK statutory sampling data were the main subject of evaluation in the study and the findings confirmed the effectiveness of the directive; however, it was mentioned that the methodology might lead to unnecessary sampling. Concerning examination of aquaculture imports, evaluation of the Rapid Alert System for Food and Feed database using process control charts and statistical modeling suggested that the sampling protocol is effective but not sufficiently flexible for the range of existed aquaculture practices.

Indeed, as aquaculture enterprises and markets continue to develop, the challenge will be to develop efficient sampling strategies for residue surveillance that are flexible, reactive, and relevant to different farm animals and practices. Presently there is no consensus agreement regarding sampling regimens for veterinary residues for countries exporting to the EU. While Directive 96/23/EC may be applied within the EU region, it does not entertain global acceptance. Therefore Directive 96/23/EC should not be considered a suitable replacement for CODEX sampling protocols, which provide alternative global sampling strategies for food animals.

In addition to surveillance programs, national food control systems (NFCS) are a group of elements organized and arranged in a way that they can act as a whole to protect consumers' health. The principal objectives of NFCS have Q11 been determined by FAO and WHO[71] and Codex Alimentarius.[72] Food control systems need to be up-to-date, which means that they need to adapt to today's food production and distribution practices. Thus principles and guidelines for NFCS should focus on the entire chain, that is, production, packing, storage, transport, handling, and sale of foods within national borders. Since a great part of food products is intended to be consumed outside a country, properly designed import and export control systems, as part of the overall NFCS, are essential. Principles and Guidelines for National Food Control Systems are published by Codex Alimentarius (CAC/GL 82-2013), serving as guidance to countries. This document allows countries to be flexible on how to best design their food control system and implement specific control measures; therefore identical NFCS cannot be found. According to Lupin,[73] the EU has adopted the most comprehensive food safety control system in the world with the most stringent legislation and regulation toward food safety. Furthermore, the EC regulations No. 178/2002[74] and No. 854/2004,[75] and No. 882/2004,[76] set the objectives of a general food law and give the conditions required for an effective national implementation.

Different inspection programs in imported aquatic products have in most cases revealed residues of registered antibacterials above legal levels or the presences of banned compounds. For example, national statutory surveillance schemes on residues of veterinary medicines in food carried out annually in the United Kingdom (http://www.gov.uk/government/statistics/residues-of-veterinary-medicines-in-food), have shown the illegal use of antimicrobials. These

included increased levels of emamectin and presence leucomalachite green (biotransformation product of banned malachite green) in local farmed salmon. An earlier Canadian surveillance study revealed that Canadian consumers during the period of 1993–2004 were exposed to low concentrations of some prohibited veterinary drugs via the consumption of certain imported farmed fish and shrimp.[77] Sadly, metabolites of furazolidone, nitrofurazone and furaltadone, leucomalachite green, and even chloramphenicol were found in the examined aquatic products. In a Japanese survey, it was reported that the number of violations regarding veterinary drugs in imported food has increased largely, and most of them were attributed to chloramphenicol and nitrofurans in seafood from Asian countries.[78] Lastly, Love et al.[79] presented veterinary drug violations among four inspecting bodies (EU, United States, Canada, and Japan), using government-collected data from the period of 2000 to 2009. Most drug violations were detected in species that are commonly farm-raised in Asian such as shrimp and prawns, catfish, crab, tilapia, and eel. Chilean salmon was also among the most commonly found violated aquatic products. Vietnam had the greatest number of violations among exporting countries. Nitrofurans and chloramphenicol represented the dominant drug violations in farmed crustacean tested, while in farmed fish, top illegal findings consisted of malachite green, nitrofurans, and chloramphenicol.

9.2.3 Public/consumer health issues

Antimicrobials used in aquaculture are commonly applied to combat aquatic microbial pathogens via the feed or less frequently directly to the water (baths in cages, tanks, raceways) and seldom by injection (broodstock). These practices are inevitably responsible for chemical pollution into the environment due to released antimicrobials after the completion of the therapy as well as from metabolic and fecal products and uneaten medicated feed particles. Such chemical releases from aquaculture facilities can contribute to increased risk of antibacterial resistance development in environmental compartments which at the end may affect human welfare. More importantly as related to consumer health and irrespective of the route or purpose of administration, antimicrobials can accumulate as residues in tissues of the aquaculture products, before they are being excreted from the fish body compartment. The occurrence of residues in farmed aquatic organisms is most likely when these animals are harvested for human consumption after medication, before the necessary withdrawal period elapses. Antimicrobial residues can also occur in fish when the drugs are administered outside of the labeled recommendations or suggested dosing schedules. Extra-label usage of antimicrobials in aquaculture is practicing though the “cascade” system mentioned above but is required to be supervised by veterinarians to minimize risk. Illegal chemotherapeutics can be also found as fish residues. Consumption of such “polluted” products may result in many health problems in humans including allergic reactions, toxicity side effects, disruption of normal intestinal flora, and lastly and perhaps more importantly, development and propagation of antimicrobial resistance.

1. Allergic reactions could also arise in sensitive consumers when the aquaculture products have increased levels of antimicrobials (above MRL). A notable proportion of the general population may have allergic sensitivity to these substances mainly due to prior medical treatments rather than being exposed to dietary residues. Indeed, cases of proven allergy to such substances in food are extremely rare, based on clinical and laboratory proof of an immunological reaction, whereas there are less well-substantiated reports blaming antibiotics. Clearly, any exposure to a chemical will carry at least a notional risk of causing harm, which could be a reversible functional deviation, or a permanent and rarely even life-threatening disease.[80] The factors ~~mentioned~~ ~~that~~to determine the nature and magnitude of the risk, are the properties of the substances, the level of exposure and the constitution of the exposed individual as related to the genetic background. ~~The extend that some abnormality is induced and whether it remains subelinical, thus representing a demonstrable risk, depends on the aforementioned factors.~~ Such cases are usually related to high medications along with short exposure, whereas any risk from residues in food would probably represent prolonged ingestion of small amounts. However, it is still worth analyzing the evidence from recorded medical cases if dietary veterinary residues were associated with a possible disorder.

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2. Possible carcinogenic and mutagenic effects to consumers may be linked to the presence of illegal toxic compounds, occasionally detected in aquacultured products. Perhaps the most hazardous agent is chloramphenicol, which has been banned for use in livestock, but its detection through monitoring programs in farmed aquatic products from Asia is not uncommon.[81] Chloramphenicol has been extensively used in human medicine in the past such as eye drops and topical cream due to its powerful

broad spectrum antimicrobial activity.[81] However, chloramphenicol is known to exert many side effects in humans such as allergic reactions and gastrointestinal disorders,[82] but more importantly, may lead to an increased risk of developing cancer and in very low concentrations may trigger aplastic anemia, a disease that causes bone marrow to stop producing red and white blood cells and could be fatal. Chloramphenicol is thus not allowed for use in the treatment of animals for food production in the EU and elsewhere and may not be used in the production of food of animal origin, which is imported into the EU. Actually, in 2002, the EU imposed a 30-month ban on shrimp imports from China because of illegal chloramphenicol antibiotic use, and in 2006 the United States rejected shrimp imports from China because of repeated chloramphenicol contamination,[83] both of which caused a huge economic impact on China's aquatic production industry. The Chinese government also has banned the use of chloramphenicol in aquatic species, but chloramphenicol residues are frequently detected in aquatic products by the government enforcement departments.

Monitoring programs carried out in EU or in North America on imported aquaculture products have also indicated the presence of other illegal drugs. Particularly, a Canadian survey revealed that local consumers are exposed to low concentrations of banned veterinary residues via the consumption of certain fish and shrimp.[77] Nitrofurans (e.g., furazolidone, furaltadone), another group of hazardous antimicrobials for consumers, were included in the detected drugs in addition to chloramphenicol. Nitrofurans belong to a family of antibacterials, which have broad-spectrum antimicrobial activities and can be used in both human and veterinary medicine. Due to concerns about potential carcinogenicity of the drug residues and their potential to cause harmful effects on human health, the EU banned their use in food-producing animals in 1995,[84] but residues continue to be found in imported shrimp because of their ready availability and high efficacy in veterinary therapy.

3. Disruption of the normal intestinal flora could be associated to antibacterial consumption in humans.[85] The bacteria that usually live in the intestine act continuously to protect against pathogen infection, which could cause diseases. Antibacterials might reduce the total number of these beneficial bacterial communities or selectively kill some important species. Consequently, antimicrobials might adversely affect a wide range of intestinal flora and subsequently cause gastrointestinal disturbance and imbalance. This disturbance can cause bacterial overgrowth and emergence of resistant microorganisms, which may lead to serious infections and encourage transfer of resistance factors among bacteria. As in the case of allergic reactions, this abnormality mainly refers to high and prolonged medication for therapeutic reasons rather than to residues resulting from food consumption. There is little scientific information on the effect of antimicrobial residues on the bacterial flora of the human intestinal tract, because human studies have mainly been carried out at therapeutic dose levels and not at the residue range concentrations.[86]

4. Chiefly, among the major health concerns related to the presence of veterinary residues in aquacultured products, is the potential development of antimicrobial resistance. Antibacterial resistance, especially that induced by use of chemicals in livestock production, poses a global challenge with serious economic damage and devastating effects on public health.[69] There is increasing evidence for a direct relationship between antibacterial use in farmed animals and the emergence of resistance both in human and animal pathogens (Feiyang et al., 2020). Even more, there are alarming signs that antibacterial use in aquaculture has also a potential to select for antimicrobial-resistant bacteria in the aquatic environment.[61,87,88] Particularly, aquaculture systems contain high numbers of diverse bacteria, which exist in combination with the current and past use of different antibacterials. Such production systems have been actually blamed as genetic hotspots for gene transfer.[89] The associated risk for development and transfer of antimicrobial resistance via the measures of aquatic medicine is mainly related to the release of uneaten medicated diet, undigested food, and fish excreta containing unabsorbed and secreted drug metabolites, which can remain in the water and sediment near farming sites for an extensive period. Development of antimicrobial resistance could be more apparent in farming sites in countries where aquaculture medicine usage is heavy, prophylactic, and uncontrolled, since bacteria in the aquatic environment share a large assortment of mobile genetic element and antimicrobial resistance genes with a wide range of terrestrial bacteria.[61] Indeed, there is strong laboratory proof of horizontal gene transfer

between bacteria in the aquatic environment and human pathogens.[90] As a result of horizontal gene transfer, the genetic materials originating from the aquatic ecosystem may be inserted into the genome of terrestrial bacteria, bridging the aquatic and land counterparts and eventually affecting the treatment of human diseases in some cases.[61] Indeed, many aquatic bacteria harbor a large variety of mobile genetic elements and resistance determinants such as plasmids, integrons, and transposons that can readily recombine and promote the emergence of new genetic combinations.[61,91]

In addition to dissemination of antimicrobial-resistant bacteria via the aquatic environment, excessive use of antimicrobials in aquaculture may affect human health via the dietary route if residues exceed certain levels.[87] Specifically, contamination of fish products for human consumption with antimicrobial residues at doses higher than MRL, are often. When such products are accidentally and repeatedly eaten, they can potentially select for antimicrobial-resistant bacteria.[87,88] Furthermore, bacterial strains carrying resistance determinants in aquaculture products, which may include human pathogenic bacteria, could eventually spread resistance genes, thereby increasing the risk of spreading antimicrobial resistance from aquaculture to the consumer.[92–94]

In addition to the farmed aquatic products, caution should be also paid to the consumption of wild animals from the vicinity of aquaculture sites with possible chemical pollution,[95] since antimicrobials can reach these animals via uneaten medicated feed, metabolic products, and excreta of farmed fish. The potential bridging of aquatic and human pathogen genetic backgrounds leads to emergence of new antimicrobial-resistant bacteria, resulting to a possible dissemination of antimicrobial resistance genes into human populations. Efforts to prevent antimicrobial overuse and ensure prudent use in aquaculture must include education of all stakeholders about its detrimental effects on the welfare of fish, aquatic ecosystem, and consumers. The absolute contribution of aquaculture to the emergence of antimicrobial-resistant human infections needs to be fully determined and clarified as to its past occurrence. For example, the cholera pandemic in Ecuador during the 1990s, which was characterized by the emergence of multiresistance strains of *Vibrio cholerae*, was blamed on the use of antimicrobials in Ecuadorian shrimp farms. However, this hypothesis was finally rejected based on the available knowledge concerning the epidemic and the emergence of resistance (Smith, 2007). In the absence of thorough prophylaxis, even increase in the list of new antimicrobials will not be possibly sufficient alone to prevent a crisis in the treatment of bacterial infectious diseases in both human and veterinary populations.[96]

9.2.4 Analytical techniques to identify drug residues

The need of sensitive and rapid advanced analytical techniques to detect and quantify drug residues of pharmacologically active compounds, in foodstuffs of animal origin, has become mandatory. Admittedly, there is also an urgent need for cheap, portable, and fast analytical methods enabling screening followed by confirmatory analysis.

The Commission Decision 2002/657/EC[97] reported the technical guidelines and performance criteria for method validation for the control of the different residues. According to EU guidelines, screening methods should be used to detect the presence of a substance or class of substances at the level of interest prior to confirmatory analysis. Screening analysis allows testing of large number of samples faster, thus excluding compliant samples from further analysis. Additionally, according to 2002/657/EC, the confirmatory methods for organic residues or contaminants should provide information on the chemical structure of the analyte suggesting that only chromatographic separation coupled with spectrometric detection is suitable as confirmatory methods. It should be noted, however, that under certain conditions, fluorescence and ultraviolet-visible detectors might also be used for confirmation.[97]

The decision limit (CCα) and the detection capability (CCβ) were introduced to 2002/657/EC, having replaced the formerly used limits of detection and quantification.[97] CCα is the concentration at and above which can be concluded with an error probability of α (5%) that a sample is noncompliant (positive), while CCβ is the smallest content of the substance that may be detected, identified, and/or quantified in a sample with an error probability of β. The concept of the minimum required performance limit for banned substances, which corresponds to the minimum content of an analyte in a sample that has to be detected and confirmed and constitutes the lowest level that can be reliably considered nonzero, was also introduced to this legislation document. Furthermore, 2002/657/EC introduced a system of identification points (IPs) for Ms detection.[97] In detail for confirmation of substances belong to A group, a minimum of four IPs are needed, while for substances belong to B group, a minimum of three.[97]

For years, the applied analytical methods mainly focused on the extraction and determination of a single class of analyte, which apparently was not time- and cost-efficient. When food safety issues are concerned, designing methods

that allows increased number of samples tested per day and multiresidue analysis are of high importance.

In recent years, analytical instrumentation has been significantly advanced. In particular, fast scanning and sensitive high resolution mass spectrometry (HRMR) instruments (resolution ≥20,000 FWHM, full width at half maximum), for example, (Q)TOF-Ms, FT ion cyclotron resonance-Ms, and FT Orbitrap-Ms combined with recent developments in chromatographic systems like ultra-high-performance liquid chromatography and columns allow the introduction of new analytical methods. Therefore the residue testing laboratories can now apply considerable faster, multiresidue and multiclass screening and confirmatory methods that include simplified sample preparation procedures, which offer advantages such as simplicity, high sample throughput, and reduced costs. These methodologies, also called dilute-and-shoot or QuEChERS which stands for quick, easy, cheap, effective, rugged, and safe, are being used for some time now; however, the criteria for performance assessment has not been established yet.

Due to the progress in the analytical methodologies, more detailed criteria should be introduced than those documented in 2002/657/EC in order to define clearly the requirements for a reliable confirmation with LC-HRMS technologies.[98] Therefore it has been proposed that the performance and validation criteria should be revised on a regular basis, for example, every 5 years (Vanhaecke et al., 2011).

9.3 Research gaps and future directions

Aquaculture has become an increasingly important industry for production of finfish, crustaceans, and shellfish for human consumption. Relative to the livestock sector, aquaculture is, however, highly diverse involving the farming of some hundred species. The big diversity of farmed aquaculture species translates into a greater number of pathogens, which may cause disease. The use of antimicrobials in aquaculture to confront disease outbreaks, even as a last resort, is inevitable and may result in deposition of residues in edible portions of aquaculture products. Registered antibacterials at concentrations above legal limits and illegal presence of banned compounds may pose an unacceptable risk to public health. To minimize the risk, strict procedures should be enforced locally, including prudent and responsible use of antimicrobials under veterinary supervision, provided that prevention has failed and proper diagnostic management was undertaken. Optimization of treatment regimens using modern pharmacokinetic data is advised to reduce total antibacterial use and enhance efficacy, safety, and risk of selecting resistant organisms.

Several preventive strategies, including genetic selection, dietary manipulation, functional diets, vaccination, probiotics, immune-stimulants, and phage therapy, should be applied when possible to reduce therapeutic use. Biosecurity measures and high level of husbandry practices at the farm level must also be mandatory to eliminate disease outbreaks. Alternative strategies and preventive compounds mentioned above are gaining increasing interest because of their safe status, ease of application, lack of authorization in most cases, and wide acceptance. Although the application of these alternatives to aquaculture medicine is very promising mainly at small scale, further clinical studies are needed to gain more insight about their mechanisms of actions and to evaluate their impact on the environment and host welfare. Vaccination covers only a small list of aquaculture pathogens and thus new research effort should be devoted to this direction.

At the farm level, record keeping of antimicrobial use is still poor in most top producing countries, thus limiting the ability to establish a comprehensive antimicrobial database for aquaculture at regional or country level. Such databases are vital to identify local sources in which antimicrobials are improperly used and to direct the necessary management efforts. Specific guidelines on prudent antibacterial use should be developed and communicated. Risk assessment approaches for preventing diseases and spread of antibacterial resistance in farming sites need to be established. Identifying the potential link between antimicrobial use in aquaculture and antimicrobial resistance in the terrestrial environment is also of critical importance for both environments. Also, at regional level, governments should ensure the appropriate production and sale of antimicrobials in a controlled manner. Government controls on drug use and compliance with both legislation and agreed codes of practice are important factors if appropriate antimicrobial use is to be permitted. However, the lack of strict regulations or law enforcement in many low income, top-aquaculture-producing countries has induced reductions of drug residues in seafood exported to high-income countries because of the latter's governmental controls. Even though this is an important mechanism to control drug use, it only applies to internationally traded products and occasionally leaves production directed for domestic consumption largely unregulated. Communication and education strategies that emphasize the multibeneficial aspect of prudent drug use by all stakeholders, but with main emphasis on farmers, should be established. Eventually, a thorough global mapping of

drug use in aquaculture enterprises would be the ideal accomplishment for controlling safety in and from aquatic farmed products.

To avoid the necessity of importing high volumes of seafood with unknown or questionable safety, new research should be directed toward fast grower species and close farming systems, in order to increase local aquaculture production in conditions where environmental and chemical control is well regulated. This increased local aquaculture production will not only reduce dependence on imports and thereby minimize the risk of consuming unsafe products, it would also allow government inspection resources to be more focused at those areas of higher risk to protect public health and allow increased surveillance programs, with improvements in sampling methodology, to be applied. Ensuring the same high levels of food safety in imported aquaculture products compared to those domestically produced is paramount for consumer confidence, public health, and efficient and effective use of governmental resources.

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The corrections made in this section will be reviewed and approved by master copier.

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