Diseases and Antimicrobial Use in Aquaculture

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Contents

Abstract

Farming of finfish and shellfish is a growing industry in the developing world, owing to the increasing global demand for food fish. The artificial rearing conditions are stressful to fish, making them susceptible to infections by opportunistic microorganisms that inhabit the farm environment. Among the limited options available to prevent and control disease outbreaks in fish farms is the

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application of antibiotics. Unregulated and excessive use of antibiotics can be counterproductive, leading to the development of antibiotic resistance in bacteria in fish farms and the surrounding environments, transfer of resistance mechanisms to zoonotic bacterial pathogens, and the presence of antibiotic residues in fish. The application of antibiotics that are important in the treatment of human infections can diminish the clinical efficacy of these antibiotics when bacteria that develop resistance in the farm environment eventually spread in the community through food fish, farm workers, and the environmental contamination of farm effluents. Several countries have adopted stringent measures to reduce or end the use of antibiotics without affecting the economic prospects of fish farming, while also being able to gradually alleviate the bacterial resistance to clinically important antibiotics. With the scientific management of fish farms, use of vaccines, immune-stimulants, and biocontrol measures involving bacteriophages for pathogen control, the growing industry of aquaculture can remain viable and sustain a harmonious association with the environment.

Keywords

Antibiotics · Resistance · Aquaculture · Genes · Environment · Pathogen · Fish

1 Introduction

Fish is an integral part of human diet, with a vast portion of it contributed from the natural sources. About 88% of 177.8 million metric ton fish produced globally is consumed directly. The demand for food fish is constantly on the rise, whereas the availability of fish from the natural sources is declining. The global demand for food fish has dramatically increased, and an estimated 232 million metric tons of fish is required to meet the demand for food fish by 2030. Due to overexploitation, the wild stock of fish has drastically decreased and cannot meet the demands of rising global population. On the other hand, the production of fish by aquaculture is increasing at a rapid pace and is expected to contribute to most of dietary fish in the near future. While capture fisheries have remained nearly constant in the last two decades, the production of farmed fish has increased by over 50 times. In 2018, aquaculture produced 82 million metric tons of food fish, and the sector continues to grow rapidly, especially in developing countries of Asia, Africa, and the Latin America. The world's aquaculture production of fish is expected to reach 109 million tons in 2030 from the current 82 million tons (FAO, 2020). The farmed fish will be a major component of human diet in the near future. Farming of fish and shellfish has evolved from the traditional extensive faming system in which little or no human interference is involved to the modern semi-intensive and intensive methods in which several inputs including fish seed, artificial feed, probiotics, vaccines, etc. are involved in addition to a high stocking density of animals per unit area. The intensive system aims at maximizing production and profit. However, high-intensive rearing creates unnatural living conditions for fish and tends to disturb the fragile balance between the host and the environment. Microorganisms, being an integral component of this biological system, can often present formidable problems as disease-causing agents when fish reared in crowded conditions are subjected to physiological stress that makes them vulnerable to disease outbreaks. Microbial diseases are a major problem affecting the aquaculture systems responsible for production and economic losses. Microorganisms cohabiting with fish in intensive aquaculture systems are opportunistic pathogens that can cause infections of varying intensities, from mild to acute, often leading to mass mortalities. Unlike in terrestrial animals, the spread of disease is rapid in aquatic systems, with little or no scope for diagnosis and implementation of treatment regimes. The emergence of new infectious agents causes considerable crop losses before they are identified and control measures are implemented. Diverse and multiple infectious agents combined with the appearance of new pathogens complicate the development of vaccines. The rapid growth of aquaculture of commercial scale has inadvertently prompted unscientific management approaches involving the application of antimicrobial chemicals including antibiotics to control pathogens. Here, we discuss the current global trends of antimicrobial use in aquaculture, its impact on the environment and human health in terms of antimicrobial resistance development, and the strategies to make aquaculture an eco-friendly and sustainable activity.

2 Aquaculture: The Global Scenario

With the increasing demand for fish, aquaculture meets almost 50% of the food fish need (Miao & Wang, 2020). Globally, the average per capita fish consumption is 20.5 kg as of 2017. The type of aquaculture practices carried out, being an intensive or extensive type of system, type of species cultured, and the technology used for aquaculture depend on various factors like agroclimatic conditions, economic status, social and spatial factors, etc. The aquaculture is dominated by culture of food fish like carps which caters to the domestic requirements. Though the quantity of carps produced is enormous, it has a feeble role in international trade. On the other hand, the shrimp culture system is designed to meet the international market demand, with *Litopenaeus vannamei* being a classic example (Miao & Wang, 2020).

3 Current Global Status

According to the United Nation's Food and Agriculture Organization (FAO), from 2004 to 2017, China's grass carp (white amur) ranked first among the farmed species, in value. In 2018, the red swamp crawfish (*Procambarus clarkii*) overtook the grass carp and became the number one commodity in value at 14.23 billion US dollars. In China, the average annual growth rate of red swamp crawfish is very high at 30.33% for over 15 years (2003–2018). In the ranking based on the aquaculture produce live weight, China and Indonesia are among the top countries in seaweed production. China's Japanese kelp and Indonesia's Eucheuma seaweed are competing for the top rank in terms of live weight of the aquaculture produce. Norway leads in the production of Atlantic salmon. Since the seaweed tops the chart in terms of quantity, the marine environment contributes the most to aquaculture production. As expected, the freshwater environment contributed most to aquaculture in terms of value realized since seven out of the top ten species belong to this environment.

4 Types of Aquaculture

The aquaculture systems can be classified based on the culture environment into freshwater, brackishwater, and marine aquaculture. Based on the organism cultured, it could be monoculture or polyculture. The structure used for the cultured organism confinement could be a pond, pen, cage, or raceway system. The traditional aquaculture systems are developed based on socio-environmental conditions. For example, in rural areas, where agriculture and animal husbandry practices are the predominant livelihood sources, aquaculture is integrated with them as in rice-cum-fish culture, integrated aquaculture with poultry, duckery, piggery, and cattle. Waste-fed fish culture in suburban setup and trash fish-fed aquaculture in coastal regions reflect the socio-environmental conditions behind the development of such traditional aquaculture systems. Modern aquaculture practices like recirculatory aquaculture and biofloc technology aim at making intensive aquaculture eco-friendlier (Edwards, 2015).

The system of aquaculture classification into intensive and extensive aquaculture is based on the stocking density and the input intensity. In extensive systems, the stocking density is low, and inputs like feed and fertilizers are not usually provided, leading to a low yield. Usually, low-value fish and carps for domestic consumption are cultured extensively. Filter-feeder silver carp is the most cultured fish in non-fed aquaculture system. The contribution of non-fed aquaculture to the total aquaculture production was 30.5% in 2018 and is facing a declining trend compared with fed aquaculture productions (FAO, 2020). Like in any other production system, aquaculture also requires intervention at different stages to increase the system's yield. Inputs, viz., fertilizer, feed, aeration, and prophylactics, are essential to sustain a high stocking density of intensive aquaculture systems. In extensive fish culture, however, there is a lesser requirement for the addition of chemicals.

5 Chemicals Used in Aquaculture

Aquaculture practices make use of an array of chemicals for various purposes. These chemicals can be broadly categorized into water and soil quality management chemicals, disinfectants, pesticides, fertilizers, antibiotics, feed additives, and probiotics. There has been a boom in the aqua chemical industry to cater to the needs of the farmers. More than 100 companies provide about 400 types of aquaculture chemicals in Bangladesh alone, including medicines (Alam & Rashid, 2014; Ali et al., 2016). In Mexico, nearly 106–134 different chemicals are used in shrimp aquaculture (Lyle-Fritch et al., 2006). In Bangladesh, aquaculture farms of various capacities were surveyed, and almost all the farmers used some type of chemicals in their farming practices (Ali et al., 2016). In Bangladesh, the extensive type of rice-cum-fish farming system uses chemicals like lime for water quality management, and the use of other chemicals is negligible (Ali et al., 2016). On the other hand, Mexico uses more of feed additives with negligible use of zeolite, pesticides, and malachite green, when compared to Asian countries (Lyle-Fritch et al., 2006). Although the use of chemicals in an intensive aquaculture system is inevitable, the farmers need to take into consideration their detrimental effects on the environment and, hence, adopt environmentally friendly substances (Lieke et al., 2020).

It is essential to understand the fate of the chemicals used and their bioaccumulative potentials. Use of self-degrading chemicals in food fish culture considerably reduces the threat to consumer health from bioaccumulation of such chemicals in food chain (Boyd & Massaut, 1999). However, certain chemicals like malachite green, methylene blue, and formalin are toxic to the cultured organism and the consumers as well (Lieke et al., 2020). Malachite green and its reduced form leucomalachite green are known carcinogens and mutagens (Henderson et al., 1997; Srivastava et al., 2004). Thus, the use of malachite green in aquaculture was banned in the EU from 2002 (Jennings et al., 2016). The use of manures could pose a food safety risk in terms of heavy metals and pathogens (Boyd & Massaut, 1999). Formalin is a frequently reported disinfectant in the aquaculture industry (Mishra et al., 2017; Akter et al., 2020). Formalin is toxic not only to microorganisms but also to fish and humans. Damage to fish gills, skin, liver, kidney, and spleen has been reported at higher concentrations (Ayuba et al., 2013; Andem et al., 2015; Tavares-Dias, 2021).

6 Microbial Problems in Aquaculture

6.1 Bacterial Diseases

Bacterial pathogens are among the most significant disease-causing organisms in farmed finfish and shellfish. A majority of the diseases reported from warm- and cold-water fisheries are influenced by poor water quality parameters, environmental stress, malnutrition, excess waste deposition, etc., and outbreaks can occur in nursery, nearing, or stocking ponds (Park, 2009). Some of the very common and important diseases caused by gram-negative bacteria in finfish are vibriosis (in both freshwater and seawater fish, shrimp, prawn, etc.), aeromoniasis (furunculosis), edwardsiellosis, pseudomonasis, flavobacteriosis (columnaris disease), eye disease, tail rot, fin rot, etc. (Austin, 2012). Gram-positive bacterial diseases include mycobacteriosis, streptococcosis, renibacteriosis (bacterial kidney disease), and infections with anaerobic bacteria like *Clostridium botulinum*, enterobacterium, *Catenibacterium*, etc. Some of the very prominent bacterial diseases reported from crustaceans are vibriosis, penaeid bacterial septicemia, luminescent vibriosis, gaffkemia, bacterial shell disease, etc. (Ibrahim et al., 2020).

6.2 Viral Diseases

Virus carried by wild fish readily transmits to a large number of hosts in intensive aquaculture system, where the presence of chronic stress triggers outbreak of the viral diseases. The outbreaks are also influenced by environmental factors, host animal factors, and viral factors (Kibenge, 2019). The important DNA viruses infecting teleost fish (carp, catfish, eel, grouper, salmon, trout, etc.) belong to the families of *Adenoviridae*, *Iridoviridae*, and *Herpesviridae*, while *Reoviridae*, *Picornaviridae*, *Aquareoviridae*, *Togaviridae*, *Nodaviridae*, *Paramyxoviridae*, *Rhabdoviridae*, and *Orthomyxoviridae* are the families of RNA viruses that infect grass carp, channel catfish, cyprinids, salmon, flounder, halibut, striped bass, milk-fish, ayu, grouper, and sea bass (Austin, 2012). Retroviruses belonging to the reverse transcriptase group infect Atlantic salmon, chinook salmon, and damsel fish (Lepa & Siwicki, 2011). Monodon baculovirus (MBV), baculoviral midgut gland necrosis virus (BMNV), hemocycte-infecting baculovirus (HB), type C baculovirus (TCBV), infectious hypodermal and hematopoietic necrosis virus (IHHNV), hepatopancreatic parvo-like virus (HPV), Taura syndrome virus (TSV), lymphoid parvo-like virus (LOPV), yellow head virus (YHV), lymphoid organ vacuolization virus (LOVV), and white spot syndrome virus (WSSV) are few of the important viruses that cause diseases in shrimp aquaculture (Murray, 2013).

6.3 Fungal Diseases

Fungal diseases occur in fish and shellfish as secondary manifestations to infections caused by bacteria, virus, parasites, poor water quality, environmental stress, etc. Fungi can infect eggs, larvae, or adult fish. A majority of the infective fungi are multicellular and possess hyphae for infection. Some common fungal diseases include saprolegniasis, epizootic ulcerative syndrome (EUS), branchiomycosis, ichthyophoniasis, and infections caused by *Fusarium* sp. (Yanong, 2003). *Achlya*, *Calyptralegnia*, *Leptolegnia*, *Dictyuchus*, *Pythiopsis*, and *Thraustotheca* sp. are important fungi belonging to the *Saprolegniales* that infect eggs as well as adult fish. *Ichthyophonus gasterophilus* and *Ichthyophonus hoferi* have been reported to be the major causative agents of infections in salmonids (Austin, 2012). Marine oomycetes cause disease in marine abalones and shellfish. These include *Lagenidium*, *Halocrusticida*, *Haliphthoros*, *Halioticida*, *Pythium*, and *Atkinsiella*. *Fusarium*, *Ochroconis*, *Plectosporium*, *Exophiala*, etc. are mitosporic fungal species that infect marine fish and shellfish (Hatai, 2012).

6.4 Parasitic Diseases

Parasitic diseases are one of the major constraints in aquaculture systems of tropical and subtropical countries. Both ectoparasites (in direct contact with external environment) and endoparasites (no direct contact with the external environment) are reported to cause infections in cultured fish (Bellay et al., 2015). Parasitic groups such as Protista, Myxozoa, Monogenea, Digenea, Cestoda, Nematoda, Acanthocephala, Arthropoda (copepods, isopods, branchiurans) etc. constitute the major parasitic organisms infecting aquaculture systems across the world (Paladini et al., 2017). Protistans can translocate without an intermediate host, and *Amyloodinium ocellatum* (marine dinoflagellate), *Ichthyobodo necator*, and *Chilodonella cyprini* (freshwater flagellates) are some important species of this group that attach to host epithelial cells and feed on it causing focal erosion of the cell (Hoffman, 1999). Other members of this group affecting finfish are *Ichthyophthirius multifiliis*, *Trypanosoma* spp. (blood-borne), *Trichodina* spp., etc. *Perkinsus marinus*, *Bonamia ostreae*, etc. are some protistans affecting shellfish (bivalves) (Hine & Thorne, 2000). Myxozoans alternate between vertebrates and invertebrates in their lifecycle. Examples are *Tetracapsuloides bryosalmonae* (etiological agent of proliferative kidney disease (PKD)), *Myxobolus cerebralis* (etiological agent of whirling disease (WD)), *Ceratonova* spp., *Chloromyxum* spp., and *Thelohanellus* spp. which target cyprinids (carps, goldfish, etc.) along with other species like *Anabas*, etc. (Yokoyama et al., 2012).

Dactylogyrus spp. (gill fluke), *Gyrodactylus* spp. (skin fluke), and *Lamellodiscus* spp. are important monogeneans with hyper-parasitic activity (Reed et al., 2012). Prime examples of Digenea affecting finfish include *Clonorchis sinensis*, *Opisthorchis viverrini*, and *Opisthorchis felineus* (dos Santos & Howgate, 2011). *Paragonimus* and *Metagonimus* target shellfish (mollusks and crustaceans). Helminths of other families are found in tropical countries in among 2400 families of fish, and some of them act as biological markers (Pakdee et al., 2018). Some significant examples of helminth group are *Anisakis* spp., *Diplostomum* spp., *Bothriocephalus* spp., *Haplorchis* spp., *Anguillicola* spp., *Gnathostoma* spp., and *Acanthocephalus* spp. Crustacean parasites include *Ergasilus*, *Argulus* (carp lice), and *Lernaea* which cause severe morbidity and mortality in the culture stock (Sahoo et al., 2013). These parasites cause hyperplasia in fish and trigger inflammation and erosions on the skin and gills. Table 1 summarizes the most common diseases encountered in farmed fish and shellfish.

7 Antibiotic Use in Livestock

The global use of antibiotics in agriculture exceeds that of human use (Van Boeckel et al., 2015). According to an estimate, 105,600 tons of antibiotics will be used annually in livestock by 2030, which is a 67% increase from 2010 (Van Boeckel et al., 2015). The drastic increase in the consumption of antibiotics is due to the

Table 1 Diseases of farmed fish and shellfish and their causative agents

Category	Disease	Etiological agent	Susceptible species
Bacterial diseases	Furunculosis	*Aeromonas salmonicida*	Freshwater salmon, rohu
	Columnaris	*Flavobacterium columnare*	Ayu, tilapia, carp, gold fish, channel catfish
	Eye disease	*Staphylococcus aureus*, *Aeromonas liquefaciens*	Rainbow trout, carps
	Edwardsiellosis	*Edwardsiella tarda*	Tilapia, channel catfish, mullet, carps
	Mycobacteriosis (piscine tuberculosis)	*Mycobacterium marinum* *Mycobacterium piscium*	Siamese fighting fish, bettas, piranhas, barbs
	Brown/black spot (shell disease)	*Vibrio, Aeromonas*, and *Pseudomonas* groups	*Penaeus monodon*, *P. merguiensis*, *P. indicus*
	Luminous bacterial disease	*Vibrio harveyi, Vibrio splendidus*	*P. monodon, P. merguiensis, P. indicus*
Viral diseases	Infectious pancreatic necrosis virus (IPNV)	Birnavirus (*Birnaviridae*)	Salmonids (rainbow trout, brook trout)
	Infectious spleen and kidney necrosis virus (ISKNV)	*Megalocytivirus* (*Iridoviridae*)	Freshwater fish
	Infectious hematopoietic necrosis (IHN)	*Novirhabdovirus* (*Rhabdoviridae*)	Salmonids (Atlantic chum, chinook, sockeye, rainbow trout)
	Viral hemorrhagic septicemia (VHS)	*Novirhabdovirus* (*Rhabdoviridae*)	Lake, brook, and rainbow trout, brown and golden trout, Atlantic salmon, pike turbot, sea bass
	White spot syndrome virus (WSSV)	*Whispovirus* (*Nimaviridae*)	Penaeid shrimps (specially *Penaeus monodon*)
	Monodon baculovirus (MBV)	*Baculoviridae*	Shrimps and freshwater prawns
	Taura syndrome virus (TSV)	Picornaviridae	Penaeid shrimps (specifically white leg shrimp)
	Yellowhead virus (YHV)	*Okavirus* (*Roniviridae*)	Penaeid shrimps and prawns, Antarctic krill, mysis shrimps, etc.
Fungal diseases	Saprolegniasis	*Saprolegnia* spp., *Achlya* spp., *Aphanomyces* spp.	Freshwater fish (carps and goldfish)
	Branchiomycosis (gill rot)	*Branchiomyces* spp.	Carps, gold fish, eels

(continued)

Table 1 (continued)

Category	Disease	Etiological agent	Susceptible species
	Epizootic ulcerative syndrome (EUS)	*Aphanomyces invadans* (along with rhabdovirus and *Aeromonas hydrophila*)	Catfish, snakeheads, tilapia, goby, gourami, etc.
	Ichthyophoniasis/ ichthyosporidiasis	*Ichthyophonus* spp.	Trouts, groupers, flounders, herrings, and cods
	Aspergillomycosis (red disease)	*Aspergillus flavus*, *Aspergillus* spp.	*Penaeus monodon* and other *Penaeus* spp., tilapia, etc.
	Black gill disease (fusarium disease)	*Fusarium solani*	All *Penaeus* species
Parasitic diseases	Ichthyophthiriasis (Ich/white spot)	*Ichthyophthirius multifiliis*	All fish species
	Trichodiniasis	*Trichodina* spp.	Mainly freshwater fish (tilapia, etc.)
	Dactylogyrosis	*Dactylogyrus* spp.	Freshwater and salt water fish
	Gyrodactylosis	*Gyrodactylus* spp.	Most freshwater species
	Black spot disease	*Diplostomum* spp.	Salmonids, freshwater and marine fish
	Argulosis	*Argulus* spp.	Mainly freshwater species of tropical waters
	Lernaesis	*Lernaea* spp.	Freshwater fish (carp, catfish, rare in tilapia)

increase in the animal production as a consequence of increasing population and the demand for meat. Antibiotics in low doses in feed enhance the general health and feed efficiency of animals resulting in improved growth and meat production (Angulo et al., 2005; Lekshmi et al., 2017). Currently, antibiotics in livestock and poultry are intended for growth promotion, disease prophylaxis, and disease control as well (Landers et al., 2012). Antibiotics such as tetracycline, sulfasuxidine, streptothricin, and streptomycin as feed additives showed growth-promoting effects in chicken and pig prompting their quick adoption as antibiotic growth promoters (Moore et al., 1946; Jukes & Williams, 1953). Following this, several antibiotics were employed in poultry and animal husbandry in the western countries. The inappropriate use of antibiotics exposes bacteria to sublethal concentration promoting the development of antibiotic resistance. The use of antibiotics for growth promotion has been banned in the European Union since January 2006 (Castanon, 2007).

The continuous use of antibiotics in agricultural settings leads to the development of resistance. The problem is more confounding when antibiotics are used in sublethal concentrations that allow a clonal population of resistant bacteria to proliferate, which eventually overgrow the susceptible population under selection pressure. Populations of resistant bacteria can persist in the environments where antibiotics are used. The genetic factors responsible for resistance usually reside on transmissible elements such as the plasmids and transposons. Exchange of genetic materials among bacteria living in the same ecosystem usually involves mechanisms such as transformation and conjugation. Phage-mediated transfer of antibiotic resistance via transduction can also occur among closely related bacteria (Kirchhelle, 2018).

8 Antibiotic Use in Aquaculture

The developing economies of Asia and South America have witnessed a phenomenal growth of aquaculture industry in the last two decades. Farming of shrimp and fish is considered a viable and remunerative economic activity due to the intense demand for food fish, both in domestic and international markets. Although the increasing global population and decreasing wild capture from the oceans are considered as important drivers of this demand, increase in per capita consumption and preference for food fish over animal meat owing to its health benefits are also important reasons. The modern aquaculture has transformed into a highly intensive, profit-oriented activity with high inputs of seed, feed, chemical, and biological agents for health and water quality management. Disease outbreaks in such systems can have detrimental effects on the economic prospects of the producer. This eventually compels the industry to use chemotherapeutic agents such as antibiotics to prevent or treat disease outbreaks in fish farms. Antibiotic use in aquaculture is of similar proportion to that of livestock with most antibiotics classified as critically important for human health and being employed for uncertain purposes. The extensive use of antibiotics in aquaculture and agriculture involves 51 antibiotics, 39 (76%) of which are important in human medicine (Done et al., 2015). Studies have found associations between antibiotic resistance and antimicrobial use in aquaculture (Sapkota et al., 2008; Ryu et al., 2012; Shah et al., 2014).

The information on the use of antibiotics in aquaculture is critically lacking. The main reason is that most of the world aquaculture is concentrated in developing economies of Asia and the South America where strict monitoring of antibiotic usage is still lacking. According to a study, antibiotic use ranges from 1 g per metric ton of fish produced in Norway to 700 g per metric ton in Vietnam (Defoirdt et al., 2011; Watts et al., 2017). At least 12 different classes of antibiotics are applied in aquaculture globally, a majority of which belong to the group of "highly" or "critically important" antibiotics to human medicine as classified by the World Health Organization (WHO) (Heuer et al., 2009; Defoirdt et al., 2011). Antibiotics are commonly used in intensive farming systems owing to disease risks, poor farm management practices, and a lack of access to vaccines and other preventive therapeutics (Lulijwa et al., 2020). A study in 2012 reported the application of diverse antibiotics in shrimp (*Penaeus monodon*), Nile tilapia (*Oreochromis niloticus*), and catfish (*Pangasianodon hypophthalmus*) farms in Asia, with Vietnam and China in forefront of antibiotic use, predominantly tetracycline, quinolone, and sulfonamides (Rico et al., 2012).

A recent survey of published literature on antibiotics usage in aquaculture between 2008 and 2018 revealed that 67 antibiotics were used in 11 countries out of 15 surveyed, with oxytetracycline, sulfadiazine, and florfenicol being the most commonly used antibiotics (Lulijwa et al., 2020). Vietnam, China, and Bangladesh were the leading users of antibiotics in aquaculture. Antibiotics such as oxytetracycline, sulfadiazine, and florfenicol were employed by more than two-thirds of the surveyed countries; more than half of them used amoxicillin, erythromycin, sulfadimethoxine, and enrofloxacin. Antibiotics are used in all *Pangasius* farms in Vietnam. While 17 antibiotics are used commonly in farms, 24 antibiotics are applied in hatcheries for bacterial control (Phu et al., 2016). Limited studies are available on the use of antibiotics in African aquaculture farms (Limbu, 2020). Oxytetracycline, chloramphenicol, and gentamicin are some of the most common antibiotics used in African catfish (*Clarias gariepinus*) farms in Nigeria, with nearly 85% of the fish tested carrying detectable levels of antibiotic residues (Okocha et al., 2021). Studies have found residues of antibiotics such as erythromycin in farmed shrimp in India (Swapna et al., 2012), chloramphenicol in Bangladesh (Hassan et al., 2013), and tetracyclines, sulfonamides, fluoroquinolones, and florfenicol in Iran (Mahmoudi et al., 2014; Barani & Fallah, 2015).

Some of the antibiotics such as fluoroquinolones and tetracyclines can remain in water for a considerable period of time, and if adequate withdrawal period is not allowed after the application of antibiotics in fish farms, antibiotic residues could be found in farmed fish after harvest (Pham et al., 2015). These antibiotic residues can have serious ill effects on human health such as allergy, carcinogenicity, mutagenicity, aplastic anemia, and changes in the gut microbiota apart from promoting antibiotic resistance development in human-associated bacteria (Hu & Cheng, 2014).

The direct effect of antibiotic use is the development of antibiotic resistance in the farm environment, while the presence of sublethal levels of antibiotic residues in farmed fish and shellfish can promote resistance development in human microbiome. Long-term exposure to antibiotic residues and their metabolites in food can induce several chronic disorders (Fig. 1).

The bactericidal compounds used in aquaculture definitely pose a food safety risk in terms of antimicrobial-resistant bacteria and adverse drug reactions (Liu et al., 2017) and need to be discouraged (Boyd & Massaut, 1999). In a study conducted in Vietnam among different livestock producers, only 7% of the aquaculture farmers were aware of antibiotics in specific commercial feeds compared to 43% of poultry producers and 32% of piggery producers (Pham-Duc et al., 2019). However, most aquaculture farmers (57.5%) knew about the prohibition of certain antibiotics compared to 27.5% piggery producers and 16.5% poultry producers. It was observed in the study that poultry farmers and aquaculture farmers use antibiotics as a means to prevent infection rather than to treat the infection as in the case of piggery farmers (Pham-Duc et al., 2019).

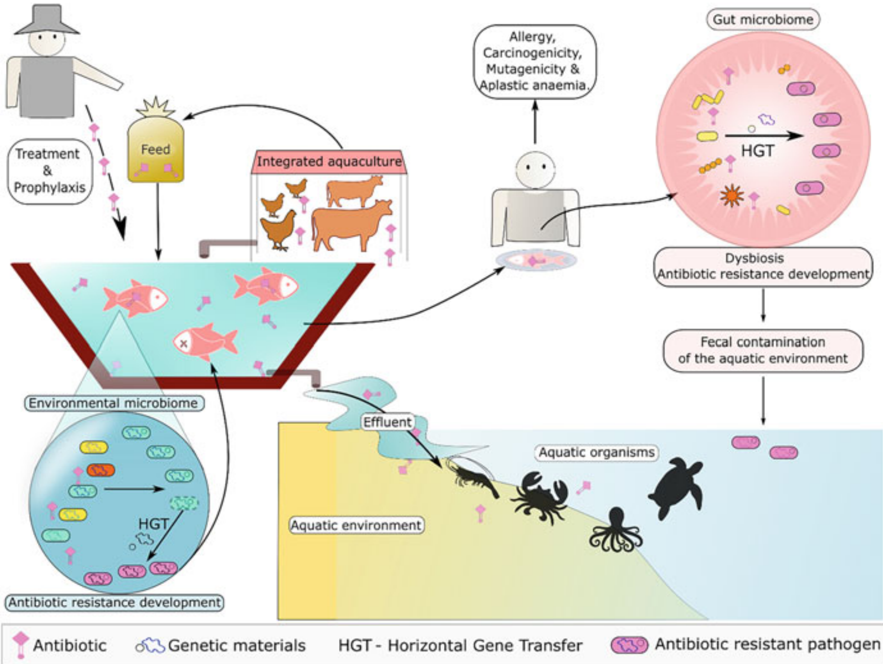

Fig. 1 Antibiotic use in aquaculture, resistance development, and dissemination of resistance genes through horizontal transfer

9 Antimicrobial Use and Resistance Development

The problem of indiscriminate application of antibiotics in fish and shrimp farms is confounded by poor quality of drugs employed in aquaculture, which actually contain lower concentrations of active ingredients. This results in the application of sublethal concentration of antibiotics leading to the development of resistance in bacteria (Lulijwa et al., 2020). Bacteria exposed to concentrations lower than the cidal concentrations gradually evolve to resist the antibiotic. The general mechanisms by which bacteria resist antimicrobial compounds include the production of enzymes that hydrolyze or modify the antibiotic making them ineffective, alterations in antibiotic targets thorough mutations in genes encoding them, and active efflux of antibiotic molecules (Kumar & Varela, 2013; Kumar et al., 2017). Farmers use antibiotics arbitrarily without any guidance from veterinarians, and in most cases, antibiotics are incorporated in feed at suboptimal conditions often leading to treatment failures and exposure of general population of bacteria in water and sediment to sub-lethal levels of antibiotics (Phu et al., 2016). The antibiotic residues remain in the sediment or are released to the environment through farm effluents. The farmers are also exposed to the ill effects of antibiotic residues, and there are high chances of farm workers being the carriers of antibiotic-resistant bacteria. The release of antibiotic-resistant bacteria and the residues into the aquatic environment can eventually result in the wider spread of resistant bacterial populations. Resistant bacteria in farm workers can contribute to the dissemination of such bacteria in the community. Thus, the use of antibiotics in aquaculture settings can have far-reaching consequences on the resistance development and spread of resistant bacteria via food, humans, and the environment. The use of antibiotics in fish farms can result in antibiotic residues and antibiotic-resistant bacteria being found in products derived from nonedible portions of fish as well. A study revealed the presence of antimicrobial resistance genes (ARGs) in mariculture sediments, and these were derived from the fish meal used in mariculture (Han et al., 2017). Fish pond water and sediment could act as reservoirs of ARGs, which can be transmitted to related and unrelated bacteria in the environment leading to the development of clonal populations of resistant bacteria that eventually replace the antibiotic-sensitive populations due to the continued application of antibiotics. This horizontal spread of antibiotic resistance genes is of particular concern, as the antimicrobial resistance developed in farm environments could soon be found in human pathogenic bacteria, since many bacteria found in aquaculture environments are opportunistic human pathogens of zoonotic potentials (Ma et al., 2021). Since the antibiotics used in aquaculture in many cases are similar to those employed for treatment of infectious diseases, the development of resistance in aquaculture environments may soon translate into a clinical problem. Bacteria such as the livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA), extended-spectrum β-lactamase-producing *E. coli* and *Klebsiella* spp. and carbapenem-resistant *Enterobacteriaceae* (CRE) represent some of the highly resistant groups of bacteria that are difficult to treat when associated with human infections.

Several studies have suggested that the antimicrobial resistances found in bacteria associated with aquaculture can be transferred to human pathogenic bacteria (Kruse & Sørum, 1994; Rhodes et al., 2000). Zoonotic pathogens resistant to multiple antibiotics and carrying resistance genes have been isolated from aquaculture farms including water, sediment, shrimp or fish, farm workers, probiotics, feed, etc. (Miranda & Zemelman, 2001; Cabello, 2006; Grema et al., 2015; Chuah et al., 2016; Santos & Ramos, 2018). Similarities in ARGs between fish and human pathogenic bacteria have speculated the human health implications of antibiotic use and resistance development in aquaculture settings (Kim et al., 2004; Obayashi et al., 2020). A study reported high levels of resistance to tetracycline, amoxicillin, and augmentin among *Aeromonas* spp. isolated from tilapia, trout, and koi aquaculture systems, and these bacteria harbored transmissible Class 1 integron-associated antibiotic resistance genes (Jacobs & Chenia, 2007). In Nigerian fish farms where antibiotics such as chloramphenicol, tetracycline, and gentamicin are used, aquaculture-associated bacteria were highly resistant to these antibiotics (Olatoye & Afisu, 2013; Fakorede et al., 2020). The association of ARGs with highly transmissible genetic elements such as the plasmids or integrons has been reported in several zoonotic bacterial pathogens such as *Aeromonas hydrophila*, *Vibrio cholerae*, and *Salmonella enterica* (Cabello, 2006; Ishida et al., 2010; Defoirdt et al., 2011; Zhang et al., 2015). The use of antibiotics in Chilean salmon aquaculture resulted in antibiotic residues and the presence of resistant bacteria harboring ARGs in 8-km-distant marine sediments. A metagenomic study of Chinese mitten crab *Eriocheir sinensis from* farm environment revealed plasmids as the predominant mobile genetic elements carrying the ARGs (Fang et al., 2019). The resistance of *Aeromonas* isolates from the aquaculture environment in Israel correlated with the use of sulfadiazine and trimethoprim and tetracycline antibiotics (Patil et al., 2016). Multidrug resistance and the presence of ARGs were more frequently encountered in *Aeromonas* spp. isolated during the culture period compared to those isolated prior to stocking. The occurrence of antibiotic-resistant bacteria in fish gut correlated with the high use of antibiotics florfenicol and oxytetracycline in Chilean salmon farms (Higuera-Llantén et al., 2018). Similarly, mass mortality of *Penaeus monodon* larvae in a hatchery in India was attributed to antibiotic-resistant *V. harveyi* (Karunasagar et al., 1994). Multiple antibiotic-resistant *Vibrio* spp. resistant to antibiotics such as ampicillin, cefoxitin, streptomycin, aztreonam, and sulfamethoxazole (21%) were detected in aquaculture facilities, a few of which harbored transferable SXT element (García-Aljaro et al., 2014). *Vibrio* spp. such as *Vibrio aestuarianus* and *Vibrio harveyi* isolated from gilthead sea bream reared in Italian mariculture were resistant to ampicillin, amoxicillin, erythromycin, and sulfadiazine (Scarano et al., 2014).

The spread of colistin resistance mediated by plasmid-borne *mcr-1* gene from pigs in China indicates how antimicrobial resistance development in livestock can eventually spread in the community (Liu et al., 2016). This was the first instance of plasmid-mediated resistance mechanism to polymyxins that could be horizontally transmitted. The presence of colistin resistance gene on a transmissible plasmid resulted in its faster dissemination in livestock and, finally, to humans. Subsequently, the use of colistin as a growth promoter was banned in China in 2016. However, the colistin resistance has already been reported from more than 30 countries (Walsh & Wu, 2016). Multidrug-resistant, *mcr-1*-positive *E. coli* was isolated from farmed rainbow trout in Lebanon (Hassan et al., 2020). The *mcr-1* gene was present on IncX4 plasmids, and in addition to colistin, the isolates were resistant to as many as 14 antibiotics (Hassan et al., 2020). The emergence of resistance to last-resort antibiotics such as polymyxins could mean a dead end to antimicrobial efficacy against pathogenic bacteria. The World Health Organization (WHO) has marked colistin as a "reserved" antibiotic and classified it as a highest priority critically important antibiotic (HPCIA), meaning this antibiotic should be used only when all other chemotherapeutic options have failed. On the contrary, colistin is widely used in livestock and poultry for growth promotion and treatment of infections. Although colistin is propagated as a therapeutic agent in poultry, its use is not restricted to treatment. The antibiotic is used for growth promotion and prophylaxis as well (Apostolakos & Piccirillo, 2018).

The colistin resistance gene *mcr-1* has spread from livestock to humans, and this theory has been strengthened by the predominance of *mcr-1* harboring bacteria in livestock and poultry compared to the hospitals (Walsh & Wu, 2016). A study from India reported the occurrence of colistin-resistant bacteria in meat, fish, fruits, and vegetables (Ghafur et al., 2019), suggesting that these diverse foods can disseminate *mcr-1 E. coli* in the community. A study from China found a higher prevalence of *mcr-1 E. coli* in provinces with high aquaculture activities (Shen et al., 2018). Colistin-resistant *Edwardsiella ictaluri* has been reported from Vietnamese *Pangasius* farms (Tu et al., 2008). Aquaculture environments are thus increasingly being viewed as hotspots of antibiotic resistance development and reservoirs of ARGs, although more studies are necessary to establish a direct link between aquaculture and antibiotic resistance in human pathogens.

Although the ill effects of antibiotic use in food animals are evident, a majority in the meat industry presume a steep decline in the production if antibiotics are withdrawn (Manyi-Loh et al., 2018) The USA, the European Union, and Japan strictly regulate the use of antibiotics in fish farms, and a very few antibiotics are allowed for treatment purposes. Countries such as Norway have completely banned the use of antibiotics in agriculture without significantly affecting the livestock production. In Norway, the antibiotic use in aquaculture has decreased by 99% since 1980 with the help of a strong legal framework and farmer education. Further, the long-term beneficial effects of antibiotic withdrawal from the animal production would make the industry more productive, environment-friendly, and sustainable. These examples have shown that good farming practices combined with prophylactic measures involving the use of vaccines can effectively replace antibiotic use without compromising on the economic gains (Watts et al., 2017). The developed countries have either completely banned the use of antibiotics or reduced their application to minimum essential quantities; however, the situation is contrasting in developing countries where most of the aquaculture occurs. A majority of these countries experiencing rapid growth of aquaculture industry, however, lack legislation and antibiotic stewardship to control antibiotic use in fish and shrimp farming. Nevertheless, developing countries such as China, India, Thailand, and Vietnam are taking rapid measures to regulate and minimize the use of antibiotics in aquaculture.

Antibiotic growth promoters have least or no effect on the health as well as the growth of animals, and the same could be achieved without their use. A study investigated the potential impact of withdrawal of antibiotic growth promoters (AGPs) from livestock (Laxminarayan et al., 2015) and found that AGPs have a very low or no effect on growth in well-managed farming systems in developed countries, while the impact was more significant in developing countries with least efficient farming systems. Optimized farming practices are oblivious to the effect of withdrawal of AGPs and can attain the same production output without them. The developed countries are gradually eliminating the antibiotics as growth promoters and restricting them only to treatment purposes. The focus is on the developing economies where the demand for animal food products is expected to double by the next decade. While the animal production in developed countries has remained stagnant or decreased, it continues to grow rapidly in developing economies. The global meat production is estimated to increase by 76%, from 258 million tons in 2005–2007 to 455 million tons in 2050, most of which will occur in developing countries. However, this growth is characterized by factors such as the high-intensity production systems that are profit-oriented, disease-prone environments, public health risks, etc., all of which are expected to promote the use of antibiotics as a routine management practice. This situation calls for a strong legal framework in developing countries that restricts the use of antibiotics in animal production systems. The dependency on antibiotics will be phased out gradually when farmers realize better productivity with scientific management practices without the use of antibiotics.

10 Legislation

Vietnam, China, and Bangladesh are among the top countries using antibiotics in food animals (Lulijwa et al., 2020). The data available on the type and quantity of antibiotics used in aquaculture farms across the world is scarce. Nevertheless, surveillance reports and statistical studies indicate direct relationship between antibiotic use in animals like cattle, pigs, and aquaculture sector and antibiotic resistance in bacteria isolated from food-producing animals (Van et al., 2008). With an increase in the global perception towards the devastating effects of antibiotic overuse in aquaculture, more and more regulations are being framed to restrict their use. The local regulations for the use of antibiotics in aquaculture and other animal rearing practices vary widely depending on the countries. Many countries continue to use antibiotics inadvertently as growth promoters in food animals. The first country to ban the use of antibiotics for nontherapeutic purposes is Sweden. This was followed by Denmark, the Netherlands, the UK, and other EU countries which banned the use of antibiotics for prophylactic purposes as well (Agyare et al., 2018). Some countries like Japan, the USA, and European countries have strict regulations, and only few antibiotics are licensed for use in aquaculture. Many antibiotics with profound effect on the development of bacterial antibiotic resistance such as chloramphenicol, which is classified as a suspected carcinogen (Lees et al., 2020), have been banned; however, they are allowed to be used for prophylactic purposes.

Antibiotics are used with twin goals of growth enhancement and prophylaxis. The European Union has banned the application of antibiotics for these two purposes effective from 2006. In certain countries, prescriptions to use antibiotics are mandatory, and the antibiotic use should be reported to the government agencies. From January 2017, the use of antibiotics for growth promotion has been completely banned in the USA. Further, the rule says that all clinically relevant antibiotics must be prescribed by a veterinarian. Following the administration of antibiotics, a withdrawal period must be observed strictly before the animal is prepared for consumption.

Aquaculture produce intended for export from countries with liberal regulations on antibiotic use will have to comply with the stringent regulations of importing countries. This has resulted in many countries coming forward with strict regulations for antibiotic use in aquaculture sector (Defoirdt et al., 2011). In addition, many countries have imposed maximum residue levels (MRLs) for aquaculture produce, which will further control the routine use of antibiotics for growth and prophylactic purposes (Codex Alimentarius, 2018). The European Commission (EC), the Food and Drug Administration (FDA), the Norwegian Food Safety Authority (NFSA), Codex, and government ministries are the important regulatory authorities involved in framing and implementation of regulations with regard to the use of antibiotics in aquaculture farms (Lulijwa et al., 2020). In Europe, EU Council Regulations No 37/2010 of 22 December 2009 and No 470/2009 of 06 May 2009 regulate the use of veterinary drugs by establishing MRLs for veterinary medicinal products in foods of animal origin. The use of chloramphenicol, nitrofurans, and furazolidone in aquaculture is banned, and MRLs are set via Regulation No 37/2010. Norway controls the use of antibiotics in aquaculture by making it mandatory for pharmacies to sell these antibiotics only on prescription by veterinarians or fish pharmacologists. The antibiotic drugs such as chloramphenicol, enrofloxacin, and rifampin are banned for use in aquaculture in the USA. The list of drugs authorized by FDA includes oxytetracycline, sulfadimethoxine-ormetoprim, florfenicol, sarafloxacin, erythromycin, and sulfonamides potentiated with trimethoprim (Chuah et al., 2016). In other countries, namely, India, Thailand, the Philippines, Brazil, Vietnam, and Bangladesh, respective government authorities regulate and control the use of antibiotics and have listed the banned and licensed drugs for use in aquaculture (Lulijwa et al., 2020). These countries, however, make use of the FDA and EC regulations and MRLs as the baseline for setting up regulations taking into consideration the regional requirements and preferences. The use of antibiotics categorized as critically important in human treatment should be treated as noncompliance and such farms/industries be denied certification. The use of vaccines and immune-stimulants should be propagated as health management tools in place of antibiotics.

11 Conclusions and Way Forward

The rising global population has put food production sector under tremendous pressure while also contributing to its rapid growth. Aquaculture is one such sector which has grown phenomenally in the last few decades, from traditionally extensive, sustenance-oriented farming to highly intensive, commercial farming. The use of banned antibiotics for growth promotion, prophylaxis, and treatment of diseases in aqua farms has raised the fear of antimicrobial resistance development and dissemination among human pathogens. The problem is more severe in developing countries which lack strong legal and infrastructural framework to regulate antimicrobial use. In the context of one health concept, it is imperative that the aquaculture sector finds alternate, environment-friendly methods of disease management and avoids the use of antibiotics identified as critical in human medicine.

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