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REVIEW PAPER

Antimicrobial Resistance (AMR) and Alternative Strategies for Combating AMR in Aquaculture

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Abstract

Antimicrobial resistance (AMR) in food production systems is regarded as a major threat to public health and nutrition security. Due to the potential for horizontal gene transfer, AMR in aquaculture might eventually spread to clinically important strains found in the environment, thereby affecting human health and the whole ecosystem. It is essential to comprehend the mechanisms driving AMR in aquaculture, including plasmids, integrons, and gene cassettes, to develop AMR risk management strategies. This review article presents an in-depth analysis of AMR in aquaculture and potential risks it presents to public health and the environment. The review provides a comprehensive understanding of the complexities of AMR by delving into the molecular and genetic factors that contribute to its spread. It also highlights the antibiotic usage pattern in different countries. The article also elaborates on alternative strategies that can be adopted to prevent and control fish diseases without negatively impacting the environment. This understanding may aid in the development of plans aimed at halting the spread of AMR and safeguarding public health. The various alternative approaches discussed in the review can offer potential solutions for controlling fish diseases in a manner that is both effective and environmentally safe for ecosystems and public health.

1. Antimicrobial Resistance in Aquaculture

Aquaculture is the fastest-growing food industry and becoming increasingly important at the global level (Garlock et al., 2020). It plays a vibrant role in providing food and means of subsistence for the growing population of the world (Boyd & McNevin, 2015; Golden et al., 2021; Pradeepkiran, 2019). Aquaculture intensification has caused the emergence of new infections and increased dependency on antibiotics and other supplements (Santos & Ramos, 2016; Watts et al., 2017). The disease significantly reduces aquaculture production, which has severe socioeconomic repercussions on individuals and communities. They cause significant damage to the commercial aquaculture industry, resulting in annual financial losses of over 6 billion USD (Shinn et al., 2015; Walker & Winton, 2010). According to estimates, diseases account for 10–50% of the cost of production (Sahoo et al., 2017). Gram-negative bacteria, including *Aeromonas salmonicida, A. hydrophila, Yersinia ruckeri Vibrio harveyi, Pseudomonas fluorescens, Flavobacterium psychrophilum, Citrobacter freundii, and Edwardsiella tarda* are common causes of bacterial diseases in aquaculture that significantly impact production systems. Diseases in aquaculture are also caused by

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gram positive ones such as *Streptococcus spp.*, *Lactococcus spp.*, *Renibiacterium salmoninarum* (Klesius & Pridgeon, 2011) and also, by acid-fast *Mycobacterium* sp. (Lewbart, 2001; Sørum, 2005).

Antibiotics are often used in aquaculture as a preventative or metaphylactic measure to control disease transmission and enhance fish health. They are most commonly administered to the aquatic environment or top coated on fish feed (Cabello, 2006; Okocha et al., 2018; Pham et al., 2015). Managing bacterial diseases in aquaculture can lead to the development of AMR, which can threaten public health as these resistant strains and their genes can spread to humans and cause antibiotic resistant infections (Ferri et al., 2022). In many nations, the indiscriminate use of antibiotics in aquaculture has raised concerns owing to the emergence of antibiotic-resistant bacteria, threats to food safety, and environmental challenges (Okocha et al., 2018; WHO, 2006). Research suggests that 70-80% of antibiotics administered to fish end up in the surrounding water (Burridge et al., 2010a; Cabello et al., 2013). Thus, aquaculture production systems are recognized as "genetic reactors" or "hotspots for AMR genes" where there is a high rate of genetic exchange and recombination, which results in emergence of new resistance profiles (Figure 1) (Baquero et al., 2008; Muziasari et al., 2016). The overreliance on antibiotics in aquaculture has birthed a monster of antibiotic resistance, a problem that looms large. As the possible health hazards linked with the use of antibiotics in animal production become more apparent, it is clear that a more measured approach is needed, one where antibiotics are used sparingly and with the utmost care (Defoirdt et al., 2011). The global use of antimicrobials, primarily antibiotics, in food animals was 131,109 tons in 2013, and is projected to reach 200,235 tons by 2030 (Van Boeckel et al., 2017). Sublethal concentrations of antibiotics introduce selection pressure, allowing resistant bacteria to survive and transfer plasmids through conjugation (Gao et al., 2012; Ferri et al., 2022; Swaminathan et al., 2020).

Antibiotic usage has decreased in certain countries, such as Norway (Evensen, 2016), where vaccination programs and improved husbandry practices have been implemented. However, antibiotics remain the main approach for treating bacterial diseases in aquaculture. Contrary, the major fish-producing Countries still employ antibiotics for curative and preventive measures. This highlights the need for further research and development of alternative methods for fish health management (Burridge et al., 2010b; Chuah et al., 2016). Moreover, the open nature of aquaculture production systems promotes diffusion of antibiotic residues into the surrounding environment, polluting water, fish, plankton, and sediments (Meeting et al., 2004). Multiple studies conducted in specific geographic regions have shown the levels of antimicrobial use in various production systems (Lillehaug et al., 2018; Rico et al., 2013). According to the literature review conducted by Caputo et al. (2022), the People's Republic of China has published the most AMR-aquaculture-related studies, followed by the USA and India. Several studies have found that most antibiotic-resistant bacteria have resistance to beta-lactamases, tetracyclines, sulfonamides, macrolides, and fluoroquinolones, and that *Vibrio* spp. and *Aeromonas* spp. are among the most prevalent antibiotic-resistant microorganisms (Ferri et al., 2022).

This review article summarizes the existing knowledge on antibiotic usage patterns and regulations in major fish-producing countries, as well as the molecular mechanisms of antibiotic resistance gene transfer. By doing so, it provides insights into the extent and impact of antibiotic resistance in the aquaculture industry, as well as potential strategies for addressing the issue. This information can be useful for researchers,

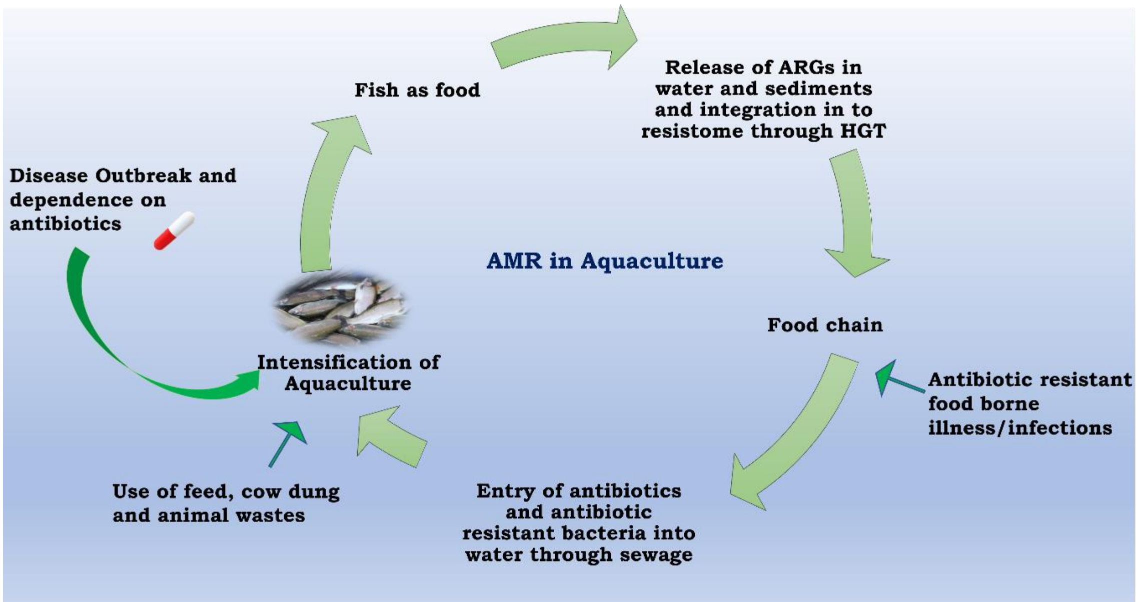

Figure 1. Typical flow of antimicrobial resistance (AMR) in aquaculture. Here ARG depicts Antibiotic resistant genes, HGT: horizontal gene transfer

policymakers, and practitioners working in the field of aquaculture, as well as those working on broader public health issues related to antibiotic resistance.

2. Antibiotic Usage Patterns in Different Countries

Regardless of the fact that antibiotics are often used in aquaculture, there is currently very limited information available on the impact of antibiotic usage in environment. Most reports include information on antibiotic usage and residues in aquaculture products (Hossain et al., 2017). As per the literature survey, the antibiotic usage pattern of commonly used antibiotics in some fish producing countries is presented in Table 1. On the other hand, the bulk of fish and shellfish are produced in Asian countries, where regulatory methods and guidelines for aquaculture are scarce to nonexistent (Chuah et al., 2016). Rico et al. (2013) analyzed the top seven fish-producing countries in Asia (Philippines, India, China, Vietnam, Indonesia, Bangladesh and Thailand) and revealed that a total of 36 different antibiotics had been used in aquaculture in these countries. This highlights the widespread use of antibiotics in the region and the need for further research on the impact of this usage on bacterial resistance and the environment. According to the study, the most commonly utilized antibiotic classes were sulfonamides, trimethoprim, tetracycline, and quinolones (Rico et al., 2013). All seven of the above-mentioned nations have used oxytetracycline and chloramphenicol in aquaculture; however, most Asian nations recently outlawed the use of chloramphenicol in fish farming. The most recent review article on antibiotic usage in aquaculture, which analyzed data from the top fifteen fish-producing nations worldwide, outlined several key characteristics of antibiotic usage in these countries (Lulijwa et al., 2020). According to their findings, 73% of these nations used either fenicol, sulfadiazine, or oxytetracycline. Although some of these countries also administrated antibiotics such as amoxicillin, erythromycin, enoxacin and sulfadimethoxine in aquaculture. The report additionally claimed that 67 different kinds of antibiotics were used in 11 of the 15 nations between 2008 and 2018. The top three countries in terms of antibiotic use were Vietnam (39 antibiotics), China (33 antibiotics) and Bangladesh (21 antibiotics). In addition, the usage of antibiotics for preventive purposes without proper consideration was documented in both China and Vietnam, leading to instances of maximum residue limits (MRLs) being exceeded among Asian producers (Lulijwa et al., 2020).

Table 1. Amount (tons) of commonly used antibiotics in aquaculture in different countries

Antibiotic	Country	Use (in Tons)	References
Tetracycline	Scotland	28	Gravningen et al. (2019)
	Italy	7	
	Turkey	39	Hossain et al. (2022)
	Norway	30	Gravningen et al. (2019)
	India	706	Schar et al. (2020)
	Vietnam	370	Shao et al. (2021)
	China	3065	
	Egypt	86	
	Indonesia	645	
	South Africa	107	
Quinolones	Turkey	8	Hossain et al. (2022)
	Norway	5	Gravningen et al. (2019)
	India	186	Shao et al. (2021)
	Vietnam	62	
	China	1393	
	Egypt	11	
Beta Lactam	Scotland	4	Gravningen et al. (2019)
	Italy	4	
	Turkey	16	Hossain et al. (2022)
	India	195	Schar et al. (2020)
	Vietnam	49	Shao et al. (2021)
	China	836	
	Egypt	13	
	Indonesia	182	
Sulfonamides	Italy	2	Gravningen et al. (2019)
	Turkey	7	Hossain et al. (2022)
	Norway	10	Gravningen et al. (2019)
	China (along with phenicol)	278	Shao et al. (2021)
	South Africa	19	

In terms of environmental and health problems, there are a lot of concerns about antibiotic resistance including, changes in biodiversity, food safety issues, and health risks in the feed industry and for farm workers. In Chile, the amount of antibiotics used in salmon farming went up by about 56% between 2005 and 2015 (Lozano et al., 2018). Twenty-three antibiotics from eight distinct classes were identified in Malaysian aquaculture. Thiang et al. (2021) discovered 23 antibiotics with a total concentration of 1.1×10^6 ng/L of which tetracyclines (83%), sulfonamides (72%), and quinolones (69%) had the greatest detection frequency, showing a broad dispersion of antibiotics in Malaysian aquaculture facilities (Thiang et al., 2021). The most prevalent antibiotics were enrofloxacin, sulfamerazine, oxytetracycline, sulfathiazole, tetracycline, ofloxacin, nalidixic acid and minocycline. The study further reported the minocycline presence in aquaculture farms for the first time. Although in comparison to Asian aquaculture farms, the residues found here were at low to moderate levels, with the exception of quinolones, which were found in high concentrations (Thiang et al., 2021). Patil et al. (2022) carried out a study using questionnaires, which included 2936 Indian aquaculture farms producing rainbow trout, pangasius, tilapia and carps, in freshwater, as well as shrimp in brackish water. The findings of the study showed that there are six distinct antibiotic classes that are used to treat infectious diseases. It was shown that farmers who cultured Indian major carps (IMCs) as well as pangasius, used a larger amount of antibiotics notably 4 mg PCU^{-1} (milligram active substance per population correction unit). According to their report, tetracyclines were the most frequently used antibiotics, accounting for 7.12% followed by enrofloxacin (3.41%), sulfamethoxazole+ trimethoprim (0.95% each) and doxycycline (0.95%). The Pangasius farmers were found to be the most frequent users of antibiotics, at 33.33%, followed by IMC (23.28%). It is worth highlighting that the use of antibiotics in shrimp culture is not reported in India (Patil et al., 2022). This is an important factor to consider as it reflects India's commitment to sustainable and responsible aquaculture practices. As per observation of Patil et al. (2022), antibiotics are administered as a top dressing in feed for five to seven days during disease outbreaks, but not for preventative or growth-promoting reasons. Moreover, on average they assessed India's antibiotic usage at 2 mg PCU^{-1} based on primary data from key aquaculture locations. Similarly, Rico et al. (2013) also performed a survey-based investigation on antibiotic usage in shrimp/prawn farms in Bangladesh (14.70 g t^{-1}), pangasius and shrimp farms in Vietnam (47.1 g t^{-1}), tilapia and shrimp farms Thailand (5.92 g t^{-1}) and in China (1.54 g t^{-1}).

In Bangladesh, a wide range of antibiotics are used in aquaculture as well as for larval rearing in captivity and in nurseries (Rico et al., 2012). Ali et al. (2016) demonstrated that seven antibiotics are routinely administered in fish and shellfish farms in Bangladesh to treat infectious diseases. Seventy-seven percent of antibiotics are used in fish feed, while 23% are directly sprayed over the water surface in culture ponds. The predominant antibiotics in Bangladeshi aquaculture were tetracyclines, namely oxytetracycline and chlortetracycline followed by cotrimoxazole, sulfadiazine, amoxicillin, doxycycline, trimethoprim and sulfamethoxazole (Hossain et al., 2017). All of these reports suggest that antibiotics are commonly used to treat microbial infections in aquaculture. Antibiotic overuse in aquaculture can be a double-edged sword. While they are helpful in treating bacterial infections, their overuse can endanger both the environment and public health. As a result, it is critical to look for feasible alternatives that can lessen reliance on these drugs. Norway has provided a shining example of lowering antibiotic consumption in the salmon farming industry by using a vaccination-based method to treat bacterial infections. As a result of this change, the average antibiotic usage in Norwegian salmon farming has dropped to 0.14-0.36 g t^{-1}. It is obvious that a more balanced approach to antibiotic use can help to ensure aquaculture sustainability and safety. In light of these concerns, it is crucial to conduct detailed studies in major food-producing countries to evaluate the level of antibiotic resistance in aquaculture and its potential dangers to public health. These studies will pave the way to develop sustainable and environmentally friendly solutions to replace the use of antibiotics in aquaculture.

3. Underlying Molecular Mechanisms and Genetic Factors that Lead to AMR

The molecular mechanisms driving AMR include the efflux of the antimicrobial agent from the cell and the alteration or deactivation of the target site of the antimicrobial agent, which prevents it from binding to the intended target (Reygaert, 2018; Tenover, 2006) (Figure 2). The ability of microbes to rapidly mutate and adapt to new environments, as well as the acquisition of resistance genes via horizontal gene transfer, are both genetic variables that significantly contribute to AMR (Reygaert, 2018). Thus, effective measures to counteract the spread of resistant microbes require an understanding of the underlying molecular mechanisms and genetic factors that lead to antimicrobial resistance (Table 2).

3.1. Plasmid Mediated Resistance

Plasmids are extrachromosomal mobile genetic elements known to provide resistance to a variety of drugs and hazardous heavy metals (Partridge et al., 2009). Plasmids render bacteria resistant to dangerous heavy metals such as mercury, cadmium, and silver (Ture et al. 2021). The resistant genes code for enzymes that help bacteria to get more nutrients, virulence factors and make it easier for them to fix DNA damage (Stanisich, 1988). In fish, well-known bacterial pathogens like *A. salmonicida, A. hydrophila, P. fluorescens, Vibrio anguillarum, E. tarda* and *Y. ruckeri* have adopted plasmid-mediated AMR (Alderman & Hastings, 1998; Sudarshan et al., 2022). Antibiotic resistance conferred by plasmids affects the therapeutic potential of the vast majority of commonly used antibiotic classes, such as cephalosporins, fluoroquinolones, and aminoglycosides (Bennett, 2008). One of the first instances of plasmid-mediated antibiotic resistance in a fish pathogen was described in 1971 from a strain of *A. salmonicida* isolated in the United States in 1959 (Aoki et al., 1971). As per the same report, these resistant traits could be transmitted to *E. coli*. They discovered 15 years later that pAr-32, a conjugative plasmid, was responsible for the reported resistance (Aoki et al., 1986). This plasmid-mediated method has provided resistance to bacteria against almost all therapeutically significant antibiotic classes, including β-lactams, aminoglycosides, macrolides, tetracyclines, amphenicols, sulfamides, and trimethoprim (Capkin et al., 2015; Capkin et al., 2017). Yu et al. (2012) determined that pCK41 virulence plasmid as utmost important in the pathogenesis of *E. tarda* in fish. The pCK41 plasmid is made up of various genetic elements, including genes that may be associated with virulence, transposases, genes responsible for plasmid maintenance, antibiotic-resistance genes (such as those for kanamycin, tetracycline, and streptomycin), and other genes of unknown function. According to Capkin et al. (2017), 35% of bacteria isolated from fish and water had one or more plasmids. Thus, plasmids play a crucial role in the transmission of antimicrobial resistance genes across bacteria.

3.2. Quinolone Resistance

Quinolones are a class of broad-spectrum antimicrobial drugs that are frequently used in human and veterinary medicine and are among the most commonly used antibiotics in aquaculture (Smith, 2008). The rapid emergence of bacterial resistance to quinolones/fluoroquinolones has been linked to chromosomally mediated processes that modify the quinolone targets (i.e. DNA gyrase and topoisomerase IV) and/or over express efflux pumps (Li, 2005). Mutation and the acquisition of resistance-conferring genes are two forms of resistance mechanisms. Quinolone resistance is mostly caused by the high number of mutations in DNA gyrase and DNA topoisomerase (Sudarshan et al., 2022). Resistance mutations in the enzymes DNA gyrase and DNA topoisomerase IV often occur in specific regions of the GyrA and ParE subunits, which are the areas targeted by drugs. This makes it harder for the drug to bind to the enzyme-DNA complex (Hooper, 2003). When these enzymes bind to DNA, they momentarily break the closed circular DNA molecule, let another strand of DNA pass through the break, and then seal the DNA again. This process causes topological modifications to DNA, which play a crucial role in DNA replication, transcription, recombination, and repair.

On the other hand, quinolones bind to specific enzymes, which then results in the stabilization of a complex made up of the drug and enzyme, leading to the accumulation of potentially fatal double-stranded DNA breaks that are unable to be repaired (Froelich-Ammon & Osheroff, 1995). Quinolone-resistance

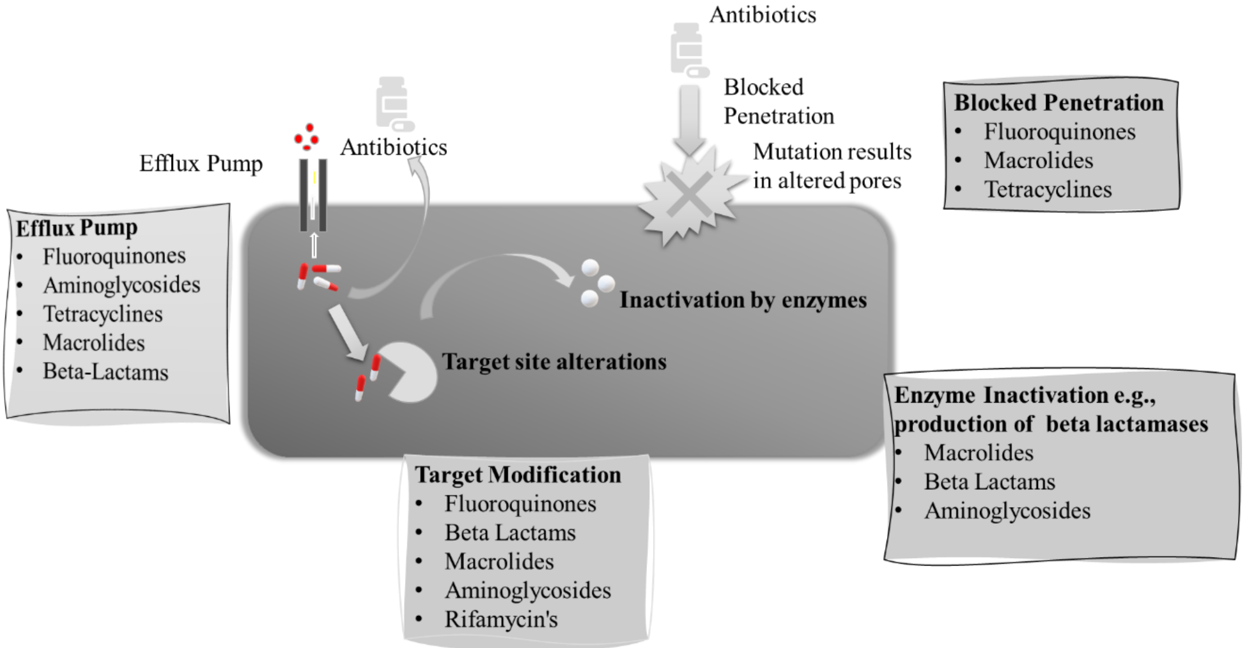

Figure 2. Mechanism of antimicrobial resistances adopted by bacteria

Table 2. Reports of antibiotic-resistant bacteria and their associated genes and carriers documented in various countries worldwide

Resistance Class	Antibiotic	Bacteria	Antibiotic resistant gene (ARG)/pattern	Source	Region	Reference
Plasmid Mediated Resistance	Piperacillin, Amoxicillin, Ampicillin, Streptomycin	*Escherichia coli*	Higher prevalence of multiple ARGs in *E.coli* isolated from rivers than aquaculture farms	Water sample	Aquaculture farms & rivers in Sarawak region, Malaysia	Lihan et al. (2021)
	Tetracyclines, β lactams	Over 10 years, 43 species with several isolates	tetracyclines effulux pumps (*tet*A-D) and β lactams (*amp*C, *bla*$_{\text{pse}}$)	Rainbow Trout	30 trout farms, Turkey	Capkin et al. (2017)
Tetracycline Resistance	Oxytetracycline	*Pseudomonas* and *Stenotrophomonas*	tetA	Water and Zebra Fish	Portugal	Almeida et al. (2021)
		Aeromonas spp, Pseudomonas spp. and *Vibrio spp.*	tet(A), tet(D), tet(E), tet(G), tet(M), and tet(S). tet(A) was the most prevalent	Fish	Gyeonggi-do, South Korea	Cho et al. (2021)
		Epilithonimonas spp	tet(X)	Rainbow trout	Chile	Concha et al. (2021)
		P. damselae	*tet*(B), *tet*(M), and *tet*(W)	Red Seabream and culture water		Obayashi et al. (2020)
	Tetracycline, Doxycycline	*Streptococcus agalactiae*	*tetM*	Diseased Tilapia and Schizothoracines	China	Deng et al. (2019)
Quinolone resistance	Oxolinic, Nalidixic acid	*F. columnare*	*gyr*A, *gyr*B	Asian sea bass	Thailand	Chokmangmeepisarn et al. (2021)
	Enrofloxacin, Norfloxacin, Ofloxacin	*S. agalactiae*	*gyrA, parC*	Diseased Tilapia and Schizothoracines	China	Deng et al. (2019)
	Oxolinic acid	*E. coli*	*qnrA, qnrB* and *qnrS*	Water and sediments of an aquaculture site	Chile	Tomova et al. (2018)
Beta Lactam Resistance	Cephalosporins, Carbapenems	*Enterobacteriaceae*	*bla*$_{\text{KPC}}$, *bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{SHV}}$, *bla*$_{\text{TEM}}$, and *bla*$_{\text{PER-1}}$	Fishes from four integrated agriculture-aquaculture farms	Giza, Egypt	Hamza et al. (2020)
	Sulfonamides, Colistin	Extended-spectrum-ß-lactamase (ESLB) producing *E. coli*	*bla*$_{\text{CTX-M}}$, *bla*$_{\text{TEM}}$, *mcr-1* gene	Red tilapia, Striped catfish & wild fish	Vietnam	Hoa et al. (2020)
	Cefotaxime, Ceftazidime	ESBL-producing *Salmonella enterica*	*bla*$_{\text{CTX-M-3}}$, *bla*$_{\text{CTX-M-14}}$, *bla*$_{\text{CTX-M-15}}$, *bla*$_{\text{SHV-1}}$, *bla*$_{\text{SHV-2}}$ *bla*$_{\text{SHV-12}}$, *bla*$_{\text{CMY-2}}$, *bla*$_{\text{TEM-1}}$ and *bla*$_{\text{OXA-1}}$	Tilapia and mullet from fish retail markets and villages	Egypt	Gawish et al. (2021)
	Ceftriaxone Ceftazidime Penicillin	*Klebsiella pneumonia*e	*bla* CTX-M	Tilapia	Thailand	Thongkao and Sudjaroen (2019)
Macrolide Resistance	Erythromycin	*S. agalactiae*	*ermB*	Diseased Tilapia and Schizothoracines	China	Deng et al. (2019)
	Erythromycin, Clarithromycin, Azithromycin	*Photobacterium damselae*	*mef*(C) and *mph*(G)	Coastal aquaculture site	Japan	Nonaka et al. (2015)
Integrons and gene cassettes associated resistance	β lactams	*K. pneumonia*e	*Int 1*	Tilapia	Thailand	Thongkao and Sudjaroen (2019)
	Tetracyclines, Sulphonamides, β lactams	133 bacterial strains	51% of the fish bacteria containing class 1 integron gene such as sulphonamides (*sul*1, *sul*3)	Rainbow trout	Turkey	Capkin et al. (2017)
Sulfonamides resistance	Sulfonamides	*Vibrio and Mycobacterium*	*sul1* and *sul2*	Water and sediment of grouper mariculture cages	China	He et al. (2017)
Polymyxins	Colistin	ESLB producing *E. coli*	*mcr-1*	Fish gut	Vietnam	Hoa et al. (2020)

determining regions (QRDR) are found on the DNA-binding surface of the enzyme 8 and may be altered by amino acid changes to reduce quinolone binding for each of the target enzymes. Enterobacteriaceae need numerous mutations in their genetic structure before showing any clinically significant resistance. When these organisms are resistant to quinolones, it is always the result of one or more mutations in the QRDR genes. Another well-known mechanism of resistance involves increasing the activity of efflux pumps, which decreases the accumulation of drugs inside the cell, either alone or in combination with reduced expression of outer membrane porins (Poole, 2005; Ruiz, 2003).

The emergence of fluoroquinolone resistance in gram-negative pathogens is becoming a global problem. The ability of these pathogens to develop resistance to quinolones is a notable example of the adaptability and evolution of bacteria (Robicsek et al., 2006). Gram-negative bacteria develop high-level resistance to quinolones primarily through mutations in the genes encoding the gyrase subunits, gyrA and gyrB (primarily gyrA). Mutations in the genes encoding the subunits of topoisomerase IV, parC and parE, are less common and considered secondary mechanisms of resistance. This is because topoisomerase IV in gram-negative bacteria is less sensitive to quinolones than gyrase and, therefore, less likely to be targeted by this class of antibiotics (Drlica & Zhao, 1997). It is a well-established fact that plasmid-encoded quinolone-resistance (qnr) genes have their origins in the chromosomes of aquatic bacteria (Hernández et al., 2011). As such, the use of quinolones in aquaculture may pose a risk for the emergence of resistance (Hernández et al., 2011). Han et al. (2012) did their experiment on the AMR patterns in 33 motile *Aeromonas* species against nalidixic acid and ciprofloxacin, as these are widely used for treatment of *Aeromonas*-related infections. In these isolated Aeromonad species, researchers found that 17 of the species had mutations in the regions of their chromosomes that determine resistance to quinolones (QRDRs) in the gyrA gene. Eleven of the strains had mutations in QRDRs in the parC gene. Additionally, one strain had a gene for resistance to quinolones (qnrS1-like) on a plasmid, and four strains had a different gene for resistance to quinolones (qnrS2) also on a plasmid. These findings suggest that resistant strains may act as sources of quinolone resistance.

In another experiment done by Majumdar et al. (2011) it was revealed that *A. hydrophila* strain AO1, isolated from a diseased fish, shows resistance to a number of quinolone antibiotics. The findings imply that *Aeromonas* sp. that contain plasmids with quinolone resistance genes may act as a source of AMR determinants in the environment. Furthermore, a study done by Oppegaard and Sørum (1994) found that the quinolone-resistant *A. salmonicida* isolates were resistant to a higher level of enrofloxacin when compared to the other isolates. This was determined by the minimum inhibitory concentration (MIC) test, which showed that the MIC values for these resistant isolates were 2-4 times higher than the other isolates. The researchers also observed that these resistant isolates had a genetic change, a specific substitution of alanine 67 to glycine, that might have played a role in their increased resistance.

3.3. Integrons and Gene Cassettes Associated with Resistance

Integrons are genetic structures that contain an integrase gene, which is used to integrate gene cassettes into a specific location in the genome known as the ATT site (Ploy et al., 2000). The integrase moves the gene cassettes in and out of the integron and are incapable of independent movement (Rowe-Magnus & Mazel, 2002). Resistant integrons and super integrons are the two types of integrons that have been identified (Fluit & Schmitz, 2004). The vast majority of resistance integron gene cassettes are responsible for encoding antibiotic or disinfectant resistance (Fluit & Schmitz, 2004). Su et al. (2011) isolated bacteria belonging to Enterobacteriaceae from four integrated fish farms in Zhongshan, South China and reported the presence of tetracycline resistance genes, sulfonamide resistance genes, and class 1 integrons. Along with other ARGs, both classic and non-classic class 1 integrons were found. The findings suggested that fish farms might be a repository of very diverse and prolific antibiotic resistant genes and gene cassettes.

Integrons may also play a significant role in the development of numerous antibiotic resistances, which could provide serious health problems to both the general population and aquaculture. The fish pathogen *A. salmonicida* was studied all over the globe for its class 1 integron-mediated antibiotic resistance, and class 1 integrons were shown to have an essential role in mediating antibiotic resistance not only in freshwater but also in marine environments (L'Abée-Lund & Sørum, 2001; Capkin et al., 2017). Capkin et al. (2017) revealed the presence of integrons in different bacterial species found in diseased freshwater fish and water samples. They reported the presence of class I integron-resistant isolates. However, no class II integrons were found in any of the resistant samples (Capkin et al., 2017).

3.4. Tetracycline Resistance

Tetracyclines (TCs) are frequently used in human and animal medicine because they are both affordable and efficient at treating infections caused by Gram-negative and Gram-positive bacteria. These antibiotics prohibit aminoacyl RNA from attaching to the ribosomal acceptor (A) site, thereby inhibiting protein synthesis (Chopra & Roberts, 2001). Bacteria that have developed resistance to tetracyclines often possess unique genetic traits that enable the active pumping out of tetracyclines or the generation of a protein that shields bacterial ribosomes from the effects of tetracyclines

(Tenover, 2006). Most of these genes are linked with transposons or mobile plasmids and can be differentiated through molecular techniques such as DNA-DNA hybridization via oligonucleotide probes and DNA sequencing (Ian & Marilyn, 2001). So far, 61 tetracycline (tet) resistance determinants have been identified and categorized into three types of resistance mechanisms: active efflux pump that pumps tetracycline out of the cell (34), ribosomal protection (13), and enzyme inactivation (13) as well as one gene with an unidentified resistance mechanism (Roberts, 2019).

In an experiment conducted by Akinbowale et al. (2007), four Gram-positive bacteria and 100 Gram-negative bacteria were obtained from diagnostic fish laboratories all over Australia for the purpose of determining tetracycline resistance genes. They reported that bacteria from aquaculture sources in Australia contain a wide range of tetracycline resistance genes, which could potentially be transferred to other types of bacteria. In a subsequent study by Chai and Bong (2022), the presence of 14 different tetracycline gene types and five tetracycline class antibiotics (tetracycline, doxycycline, minocycline, oxytetracycline and chlorotetracycline) in the waters of five marine aquaculture farms in Peninsular Malaysia was examined. The tetracycline was found to be the most prevalent among the five classes analyzed. The research also found a small number of common carriers of tet genes, such as *Enterobacter*, *Vibrio*, *Photobacterium*, and *Pseudoalteromonas*, which have not been previously reported (Chai & Bong, 2022).

3.5. Beta Lactam Resistance

Beta-lactam antibiotics are utilized to treat a wide range of Gram-negative and Gram-positive infections (Bartlett, 2005). The production of β-lactamases, which are hydrolytic enzymes that break down the amide bond of the unique four-membered b-lactam ring, makes the antibiotic ineffective and is a key mechanism adopted by Gram-negative bacteria to become resistant to β -lactams (Helfand & Bonomo, 2003; Majiduddin et al., 2002). Saavedra et al. (2004) isolated *A. hydrophila* from rainbow trout and tested its resistance to β-lactam antibiotics. The results showed that the bacteria had high resistance rates to ticarcillin, carbenicillin and amoxicillin. Unexpected resistance to the clinically used antibiotic imipenem was also reported, suggesting that resistance may have been passed from the environment to the *Aeromonas* population (Saavedra et al., 2004).

In another epidemiological investigation at integrated fish farms by Hamza et al. (2020), it was reported that the majority of Enterobacteriaceae isolates were observed to be resistant to carbapenems and cephalosporins. *Escherichia coli* was also reported to harbour Β-lactam resistant genes and other ARGs when isolated from commercial fish and shellfish, suggesting that this food source may serve as a reservoir for multi-resistant bacteria and aid in the spread of resistance genes (Ryu et al., 2012). Moreover, the extended-spectrum beta-lactamase (ESBL) producing bacteria belonging to Enterobacteriaceae were found in wild fish for the first time in the Mediterranean Sea in Algeria (Brahmi et al., 2018). The ESBL producing Enterobacteriaceae are known for their resistance to several types of antibiotics, making them difficult to treat. The reports of ESBL from the Mediterranean Sea in Algeria suggest that antibiotic resistance is not confined to healthcare settings and can occur in the environment. In aquaculture, pathogenic and environmental bacteria can carry the *ampC* $bla_{\text{TEM-OT12}}$, bla_{PSE}, $bla_{\text{CTX-M1}}$, and $bla_{\text{TEM-OT3-4}}$ genes. Thus, transposition or integron gene cassettes allow the spread of β lactam-mediated antimicrobial genes across bacteria (Boran et al., 2013; Capkin et al., 2017).

3.6. Macrolide Resistance

Macrolides are a type of antibiotic that are known for their intricate macrocyclic structure, which is made up of a lactone ring with 14, 15 or 16 members and is decorated with neutral or amino sugar groups (Dax & Dax, 1997). They are distinct from other antibiotics due to this unique structural feature. These antibiotics are well-known for their ability to limit bacterial protein synthesis by binding to the large 50S ribosomal subunit and interfering with protein elongation, resulting in the dissociation of the peptidyl-tRNA (Schroeder & Stephens, 2016). Two major resistance mechanisms for gram-positive bacteria have been found (Nakajima & Chemotherapy, 1999). The presence of erm (erythromycin-resistant methylase) genes results in structural alterations to rRNA that impede macrolide binding and allow the continuation of bacterial protein synthesis. Other resistance mechanisms that entail enzymatic degradation activation do not appear to be clinically significant (Pechère, 2001).

Gram-negative bacteria are naturally resistant to macrolides due to their impermeable outer membrane and the hydrophobic nature of macrolide antibiotics like erythromycin (Retsema et al., 1987). *Streptococcus dysgalactiae* isolates from Taiwan and Japan were examined and found to be resistant to erythromycin and tetracycline due to the presence of many tetracycline and macrolide resistant genes (Nguyen et al., 2017). Maki et al. (2008) conducted an additional study on *L. garvieae* isolates and determined that the pathogen has developed antibiotic-resistant strains and possesses ermB genes, confirming its resistance to macrolides.

3.7. Phenicol Resistance

The chloramphenicol acetyltransferase enzyme acetylates Chloramphenicol at the 3-hydroxyl group using acetyl-S-CoA, thereby inactivating the antibiotic causes Chloramphenicol resistance (Schwarz & White, 2005). Chryseobacterium isolates from fish and aquatic habitats were assessed for resistance to chloramphenicol and florfenicol by Michel et al. (2005). The results revealed that most of the isolates displayed significant multi-resistance to the majority of antimicrobial drug classes, with the majority being resistant to phenicol. A study on *Piaractus mesopotamicus, a* small-scaled Pacu, revealed that florfenicol increased the diversity and relative abundance of ARGs and mobile genetic elements (MGEs) in their gut microbiome (Sáenz et al., 2019). Gordon et al. (2007) conducted an AMR assessment in a river receiving effluents from freshwater fish farms and reported that AMR *Aeromonas* sp. could be useful indicators of florfenicol, oxolinic acid and oxytetracycline resistance in the freshwater ecosystem. In another study, optrA gene, which confers resistance to oxazolidinones and phenicols was also identified in well-known aquaculture pathogen, *L. garvieae* (Cai et al., 2021). Gordon et al. (2008) described a multi-resistant strain of *A. bestiarum* and demonstrated that Plasmid pAB5S9 conferred resistances against phenicols, sulphonamides, streptomycin, and tetracycline antibiotics.

3.8. Transposon Mediated Resistance

Transposons are also known as "jumping genes" due to their ability to relocate themselves throughout the genome (Babakhani & Oloomi, 2018). Retrotransposons (Class 1) and DNA transposons (Class 2) are the two main categories of transposons (Class 2). It has been reported that Class 2 transposons can be found in both prokaryotes and eukaryotes, but Class 1 transposons are primarily found in eukaryotes (Babakhani & Oloomi, 2018). L'Abée-Lund and Sørum (2001) reported that *A. salmonicida* carries the transposon Tn5393 on a conjugative R plasmid with streptomycin, sulphonamide, and tetracycline resistance genes. Kim et al. (1993) previously observed a fish pathogen, *Pasteurella piscicida*, that carried a transposon with tetracycline and kanamycin resistance determinants. Chenia and Vietze (2012) reported transposons Tn1721 and Tn5706 present in Acinetobacter and Moraxella strains are crucial in facilitating the spread of tetA and tetH genes that confer resistance to tetracycline in salmon fish farms. The presence of transposons carrying antibiotic resistance genes in various fish pathogens, such as *A. salmonicida* and *P. piscicida*, highlights the potential of these genes to spread among bacteria. This emphasizes the need for continued monitoring and appropriate use of antibiotics in fish farming to reduce the risk of antibiotic resistance development and spread.

4. Overview of AMR in Ornamental Fish

A growing number of bacteria isolated from ornamental fish have developed resistance to multiple antibiotics and some of these bacteria are zoonotic pathogens that pose a risk of infection to fish handlers (Weir et al., 2012). Investigations revealed that guppy also harbours MDR infections caused by organisms like *Aeromonas*, *Pseudomonas* and *Acinetobacter* (Preena et al., 2019). Moreover, the studies have uncovered the presence of MDR infections caused by various organisms, including *Lactococcus, Edwardsiella, Comamonas, Pseudomonas* and *Aeromonas* in both goldfish and koi carp (Preena, Arathi, et al., 2020). The *Serratia marcescens,* resistant to many antibiotics, was initially identified in guppy by Dharmaratnam et al. (2017). Proper sanitation and hygiene are just as important as limiting antibiotic usage when it comes to maintaining the health of ornamental fish. Overfeeding can lead to waste, water quality issues and disease development; therefore, it's important to clean tanks and equipment regularly.

5. Problems Associated with Antibiotic Resistance in Public Health

AMR in bacteria is a global threat linked to high rates of morbidity and mortality (Akova, 2016). Resistance of key bacterial pathogens to conventional antimicrobial treatments and the advent of MDR bacteria are rising at an alarming rate (Frieri et al., 2017). The emergence of antibiotic resistance was initially documented in animal models as early as the 1940s (FRISCH et al., 1943) and subjectively reported among patients in the 1970s (Cates, 1978). According to a study, methicillin-resistant *S. aureus* (MRSA) kills more people each year than emphysema, HIV/AIDS, Parkinson's disease, and homicide, put together in America (America, 2011). It is estimated that strains resistant to isoniazid and rifampicin are responsible for 3.7% of newly reported cases and 20% tuberculosis cases that have already been treated globally (Organization, 2014).

Drug resistant strains of *Mycobacterium tuberculosis* are threatening and are one of the world's most widespread infectious diseases (Bari et al., 2008). Infections caused by resistant microbes don't respond to treatment, which leads to longer illness and a higher risk of death, longer hospital stays, and more people moving around with infections (Bisht et al., 2009). If the antimicrobial resistance crisis is not fixed, it is thought that the global economy could lose about $ 100 trillion by the year 2050 (World Bank, 2016). Antibiotic resistance has been identified as a global health issue and is regarded by leading health organizations as the most significant health problem of the twenty-first century.

The erroneous therapeutic and non-therapeutic use of antimicrobials in animals, mainly fish, is unquestionably regarded as one of the primary causes of resistance in humans (Ferri et al., 2017). In recognition of the importance of understanding the risk of AMR in the aquaculture industry, the Indian Council of Agricultural Research (ICAR) in New Delhi launched a "Network Programme on Antimicrobial Resistance (AMR) in Aquaculture and Fisheries" in 2018. Promoting responsible antibiotic use in aquaculture and implementing efficient surveillance and control mechanisms to monitor the development of antibiotic-resistant bacteria are necessary to address the danger of spread of AMR from aquaculture to humans. Enhanced waste management procedures and increased attention to cleanliness and biosecurity in aquaculture operations are recommended to further lessen the likelihood of environmental contamination and the transmission of antibiotic-resistant bacteria. Implementing a One Health strategy to reduce the danger of AMR necessitates cooperation and coordination amongst numerous fields, including environmental, animal, and human health.

6. Regulations of Antibiotic Usage in Aquaculture

Antibiotic usage in aquaculture is strictly regulated in developed nations. Determining maximum residual levels (MRLs) for antibiotics in food, for instance, has largely been influenced by regulatory bodies such as the Food and Drug Administration (FDA), the European Medicines Agency (EMA), the European Union (EU) in developed countries and the Codex Alimentarius Commission of the FAO. In the European Union, the use of veterinary drugs is regulated through EU Council Regulations No 37/2010 and No 470/2009 (EC, 2009), which outline procedures for setting MRLs for veterinary medicinal products in food products of animal origin. In most European countries, the antibiotics that are allowed for use in aquaculture include erythromycin, florfenicol, oxytetracycline, sulfamides and sarafloxacin (Kümmerer, 2009). In the United States, the use of oxytetracycline, florfenicol, and sulfadimethoxine/ ormetoprim are allowed for use in aquaculture (Table 3) (Romero et al., 2012). The FDA has banned the indiscriminate use of antibiotics in animals used for food production and also keeps records of the quantity of antimicrobial active ingredients in medications that are marketed or distributed for use in animal production (Grossman & Review, 2014).

In other nations, the policies regarding the use of antibiotics in aquaculture vary greatly depending on the country and its government (Table 4). To meet export requirements, the majority of these nations have, however, harmonised their MRLs and antibiotics legislation with those of the EC and the FDA (Bondad-Reantaso et al., 2012; Lozano et al., 2018; Somga et al., 2012; Van Tai & production, 2012). Evidence suggests that the FDA and EC have influenced national MRLs for restricted antibiotics in aquaculture products of major fish-producing countries. These nations have implemented EC MRLs in order to comply with export regulations in Japan, the United States, and European Union member states.

Table 3. Approved FDA drugs in aquaculture

S.No	Drug	Proprietary Name	Clinical effectiveness field study/Usage	Dosage
Immersion				
1.	Chloramine – T	Halamid aqua	Prevent bacterial gill disease induced mortality in Salmonids	12 mg/L for 60 min. on 3 alternate days
			Prevent and control columnaris in *Sander vitreus*	10 mg/L and 20 mg/L for 60 min. on 3 alternate days
			Control mortality of *Sander vitreus*, *Micropterus salmoides* and *Lepomis macrochirus* caused by *F. columnare*	20 mg/L for 60 min. on 3 alternate days
2.	Formalin	Formalin-F and Formacide-B	Effective for ectoparasites and fungal infections	1) 250μL/L up to 1 h for cemented tanks & raceways and 12-25μL/L in earthen Ponds for prolonged period 2) 1000 to 2000 μL/L for 15 min. b) Up to 1500 μL/L for 15 min.
		Formacide-B	Parasiticide for penaeid shrimp	50 - 100 μL/L in cemented tanks for upto 4 h and 25 μL/L in earthen ponds for prolonged period
3.	Oxytetracycline hydrochloride (administration through water)	OxyMarine, Terramycin-343 soluble powder and Pennox 343	Antimicrobial	200 to 700 mg/L OTC through water for 2 to 6 h
Medicated Feeds				
4.	Florfenicol	Aquaflor	Prevention of catfish mortality from enteric septicemia caused by *E. ictalurid*, *F. psychrophilum*, and *A. salmonicida* infections in freshwater-reared salmonids	10 mg/kg of body weight 10 consecutive days
5.	Oxytetracycline dihydrate	Terramycin 200	Salmonids and catfish	56 to 85 mg/kg body weight for 10 days
6.	Sulfadimethoxine/ormetoprim	Romet ® -30	Treatment for bacterial infections in catfish caused by *E. ictaluri*	50 mg/kg body weight for 5 days

The FAO (2020) reports that about 28% and 20% of aquaculture imports are rejected by the EU and US, respectively, due to the presence of antibiotic residues. Vietnam, China, Bangladesh, and Thailand's aquaculture products are rejected quite frequently because they contain antimicrobial residues that exceed the permissible limit (FAO, 2020). In a recent instance in May 2017, the USA kept certain Chinese products on alert because they were suspected of containing nitrofurans, fluoroquinolones, and chemicals such as gentian violet and malachite green that could not be detected without physical testing (FDA 2017). The FDA rejected 27 shipments of shrimp from India in 2017 and 2018 (US 2019). This was closely followed in January 2019, when 26 lines were rejected as a result of the presence of two prohibited antibiotics, nitrofurans and chloramphenicol. Thus, it is imperative to harmonize lists of antibiotics that can be used for treating finfish diseases because of the environmental ramifications, which put the health of humans and other animals at risk. As a result, global health agencies should collaborate to reduce antibiotic usage in aquaculture by sharing information and implementing cutting-edge pharmacosurveillance systems. Aquaculture operations are expected to see the implementation of more sophisticated tracing systems that can be integrated with management systems in the near future. This integration is likely to result in greater transparency with regards to data sharing.

7. Antibiotic Alternatives

7.1. Sustainable Aquaculture Practices

To improve the hygienic conditions and productivity of fish, fish farmers in the USA developed a novel technology known as "spilt-pond" (Chuah et al., 2016). This novel method utilises conventional ponds but partitions them into an algae growing basin and a fish keeping section. In this approach, the high animal density during the production period permits increased production, and the continuous water filtration results in improved water quality and a decrease reliance on antimicrobials. In addition, the use of antimicrobials in aquaculture could be minimized with the help of control methods such as appropriate husbandry, adequate feed composition, and biological control (Rodgers & Furones, 2009). Moreover, RAS can help prevent AMR in aquaculture by reducing the use of antibiotics, improving water quality management and biosecurity through closed-loop systems.

7.2. Other Antibiotic Alternatives

Both antibiotic residue in aquaculture products and the spread of resistance among human pathogens pose significant risks to public health. As a result, new infection control methods are desperately needed to ensure the long-term viability of the aquaculture sector (Defoirdt et al., 2007). Thus, several alternatives have drawn a lot of attention as a possible substitute for antibiotics (Soltani et al., 2021) for instance, (i) antimicrobial peptides (Bhat et al., 2022) (i) phytotherapy and immunostimulants (Vaseeharan & Thaya, 2014), (ii) probiotics (Irianto & Austin, 2002) (iii) bacteriophages (Ninawe et al., 2020) (iv) organic acids (Ng & Koh, 2017)

7.2.1. Antimicrobial Peptides (AMPs)

AMPs are germline-encoded, amphipathic and cationic with a molecular weight less than 13 kDa (Bhat et al., 2022; Chaturvedi et al., 2020). These crucial elements act as the first line of defense against a variety of microbes, despite the fact that they do not possess a high level of specificity or memory (Ravichandran et al., 2010). They are reported in a diverse range of organisms, including insects, fish, animals, and humans, and are well-known to defend their hosts from microbial invasion (Hancock & Scott, 2000). While tremendously

Table 4. Regulatory agencies for antibiotic usage in different countries

Country	Regulating Agency
Vietnam	Ministry of Agriculture and Rural Development (MARD) and Ministry of Fisheries (MOFI)
Chile	Ministry of Economy, Development and Tourism in Chile SERNAPESCA
China	Ministry of Agriculture of the People's Republic of China (MAPRC)
India	Marine Product Export Development Authority of India (MPEDA) Coastal Aquaculture authority
Philippines	Food and Drug Administration-Department of Health (FDA-DOH) in conjunction with Bureau of Animal Industry (BAI) and the Bureau of Fisheries and Aquatic Resources (BFAR)
Thailand	the Ministry of Agriculture and Cooperatives and the Department of Fisheries, FDA-Ministry of Public Health in
Indonesia	Ministry of Oceanic and Fisheries
South Korea	Ministry of Food and Drug Safety (MFDS)
Brazil	Brazilian Ministry of Agriculture, Livestock, and Food Supply (MAPA)
Philippines	Food and Drug Administration-Department of Health (FDA-DOH), Bureau of Animal Industry (BAI) and the Bureau of Fisheries and Aquatic Resources (BFAR)

varied in sequence and structure, all endogenous peptides exhibit common features like cationiticity, hydrophobicity, and amphipathic structure (Chaturvedi et al., 2020; Hancock & Rozek, 2002). The peptides have a high proportion of basic amino acid residues, specifically lysine and arginine, and demonstrate a significant prevalence of hydrophobic amino acid residues, comprising approximately 50% of the total composition (Hancock, 2001). The three-dimensional conformation of these amphiphilic peptides is maintained through the formation of disulfide bonds, which serve to segregate the hydrophilic and positively charged regions from the hydrophobic regions, thereby stabilizing the overall structure (Hancock, 2001).

Defensins and cathelicidins are among the thoroughly characterised AMPs (Cederlund et al., 2011). Gramicidin, an antimicrobial compound isolated from *Bacillus brevis*, was the first antimicrobial peptide to be reported from prokaryotic cells in 1939 (Dubos, 1939). Later in 1944, Gause and Brazhnikova (1944) reported that gramicidin can cure infected lesions on guinea pig skin. Thus, gramicidin was the first AMP to be produced on a large scale to be used as an antibiotic (Van Epps, 2006). AMPs from eukaryotes were identified for the first time in 1896 from a component in wheat flour that inhibited bread yeast (Jago & Jago, 1926). In 1942, this chemical was identified and isolated as a peptide from wheat endosperm. In 1943, with the discovery of penicillin and streptomycin, the 'Golden Age of Antibiotics' began (Bentley, 2009; Zaffiri et al., 2012). However, as antibiotics became more widely used, research interest in looking for peptides as therapeutic agents rapidly diminished (Bentley, 2009; Zaffiri et al., 2012). As antibiotic-resistance among bacteria became a growing concern in the 1960s, the importance of natural, host-derived peptides as a potential source of antimicrobial compounds re-emerged, and research on AMPs began to gain renewed interest and momentum (Davies, 2006; Katz et al., 2006). In the 1950s and 1960s, researchers discovered that a positively charged peptide from human neutrophils possessed the capacity to eliminate bacteria, marking the beginning of the study of AMPs (Hirsch, 1956; Nakatsuji & Gallo, 2012; Zeya & Spitznagel, 1966).

There are currently 153 human host defense peptides, 363 annotated mammalian peptides, 1120 active amphibian peptides, and 1117 peptides from frogs alone in Antimicrobial Peptide Database (APD3). Moreover, 49 peptides from reptiles, 45 from birds, and 633 from arthropods, of which 367 are from insects, 75 are crustaceans, and 8 are myriapods are reported (Wang et al., 2016). In addition, there were also 175 from chelicerates, of which 88 scorpions and 44 from spiders. Additionally, 6 AMPs from protozoa and 52 AMPs from molluscs have been reported (Wang et al., 2016). Currently, 144 fish peptides are documented in the database. Besides possessing antimicrobial activity, AMPs are recognized to participate in biological processes such as immunomodulatory functions, wound healing, and regulation of cell growth and differentiation (Chaturvedi et al., 2020; Mayer et al., 2010; Shabir et al., 2018; Steinstraesser et al., 2011). Moreover, in comparison to antibiotics, AMPs possess the ability to act on bacterial cells in multiple ways, and one of their defining features is that they selectively target microbial cells without causing harm to mammalian cells. (Bhat et al., 2022; Bhat et al., 2020; Lee et al., 2013; Matsuzaki, 2009).

One of the key benefits of AMPs is that they quickly target bacterial structures, particularly membranes in a non-specific manner (Chaturvedi et al., 2020). The capability of AMPs to swiftly disrupt bacterial cell membranes and other critical components within the cell limits the opportunity for bacteria to undergo changes in the membrane (Mookherjee & Hancock, 2007; Navon-Venezia et al., 2002). As a result, the likelihood of bacteria developing high levels of resistance is reduced, as multiple mutations would be needed to become resistant to AMPs. Multiple investigations have adopted strategies to enhance the bacterial killing capacity and host stability of AMPs in biological systems (Bhat et al., 2020; Bhat et al., 2022; Cárdenas et al., 2020; Chiou et al., 2002). These studies will pave the way for the development and design of AMPs that have strong antimicrobial activity and are highly stable in the host.

7.2.2. Phytotherapy and Immunostimulants

The application of phytotherapy in the aquaculture industry is a very recent and still-emerging area of study (Bhat et al., 2021; Raman, 2017). As an alternative to synthetic drugs for the treatment of many fish diseases, phytotherapy is gradually becoming accepted (Eirna-Liza et al., 2018). The phytotherapy may be used for boosting the immune system of cultured organisms against a variety of aquatic diseases because of its cost-effectiveness and benign nature (Chong et al., 2020; Jeyavani et al., 2022). To effectively manage fish health, the herbal remedies are applied as decoctions (each one separately), concoctions (each one together), or in combination with other medications (Harikrishnan, 2003).

The main idea behind the application of phytotherapy in fish farming is (i) it can help reduce the need for chemotherapeutic parasiticides with lower environmental threats, as well as treat fish infections to prevent mortality and, consequently, economic losses (ii) use of phytotherapeutics makes fish less likely to develop disease resistance (Kulkarni et al., 2013) as a result of their mode of action affecting multiple targets simultaneously (Bakkali et al., 2008). To endure their environment, unfavourable weather, and pathogenic diseases, plants produce a broad variety of bioactive chemicals, which are commonly referred to as secondary metabolites (SMs). These include alkaloids, essential oils, phenolics, saponins, terpenes, and carbohydrates (Varijakzhan et al., 2020). Secondary metabolites have the ability to influence the recognition, binding, catalytic activity, and turnover of protein-protein interactions (Hoseinifar et al., 2020). Numerous phytochemicals are reported to elicit immune molecules in shellfish and finfish (Sharma et al., 2010). Herbal immunostimulants such as Bemisiatabaci (Srinivasan et al., 2001), Neem Azal-T/S (El-Shazly & El-Sharnoubi, 2000), 1-cysteine, nemicidine, nemol, vimicidine and curcumin (Gangopadhyay, 1994; Tandel et al., 2021) are reported to act as immunostimulants.

Artemia nauplii supplemented with herbal products such as stressol-I and stressol-II significantly promoted growth and productivity and decreased osmotic stress in *Penaeus indicus* (Chitra, 1995). Herbal extracts of thyme, rosemary and fenugreek were observed to boost growth performance in European sea bass (Yilmaz et al., 2006). The growth performance of *Labeo rohita* was improved by supplementing its diet with *Achyranthes aspera* extract, suggesting that the herbal supplement acts as an immunostimulant and growth promoter in addition to being a natural antibiotic (Hasan-Uj-Jaman et al., 2017). Studies were also carried out to examine the efficacy of fluid propolis (Miljanović et al., 2022), Himalayan thyme leaf extract (Tandel et al., 2021) and five compounds (Curcumin, Eugenol, Cinnamaldehyde, Stigmasterol and Morin) (Tandel et al., 2021) as anti-oomycete agents. Currently, several studies are being conducted on the application of phytochemicals and herbal extracts against fish pathogens and parasites (Bhat et al., 2021; Miljanović et al., 2022; Tandel et al., 2021). While the research is still in its infancy stages, it is believed that in the future, it may eventually offer an effective strategy to address the issue of AMR in aquaculture.

7.2.3. Probiotics

Probiotics describe substances that are beneficial to human health (Lilly & Stillwell, 1965). The need for sustainable aquaculture has prompted more study of probiotics for fish and other aquatic animals (Gatesoupe, 1999). It has been demonstrated that probiotics are useful in stimulating the development, survival, and overall health of aquatic animals (Hai, 2015). In aquaculture, probiotics are administered to combat both Gram-positive and Gram-negative bacteria (Capkin & Altinok, 2009). The use of Gram-positive bacteria as probiotics is prevalent all over the world. Members of the endospore-forming bacillus genus have widespread use, with *Bacillus subtilis* having extensive application in aquaculture (Hai, 2015; Hong et al., 2005). Reports have suggested that *Bacillus* sp. promote healthy gut microbiota, improve digestion and feed utilization in fishes (Akanmu, 2018; Balcázar & Rojas-Luna, 2007). Overall, *Bacillus subtilis* serves multiple functions, contributing to the health and productivity of aquaculture systems.

Furthermore, probiotics are shown to enhance the health, vitality, and growth of aquatic organisms (Hai, 2015). For instance, the immunological response and disease resistance of *Miichthys miiuy* were improved by the oral administration of live or heat-killed *Clostridium butyricum* CB2 (Pan et al., 2008).

Probiotics are a great water quality enhancer since they reduce harmful substances like ammonia, pH, and nitrite (Nimrat et al., 2012). Research into the probiotic potential of the bacteria has led to a variety of potential uses, such as improving water quality by shifting the make-up of waterborne microbial populations and decreasing the prevalence of diseases in farmed species (Wang et al., 1999). As a result, it is believed that the Bacilli can neutralize any possible infections that may exist in the rearing water (Irianto & Austin, 2002). Probiotic administration may have some advantages, including (i) preventing the growth of harmful bacteria due to competition (Balcazar, 2003; Balcazar et al., 2004; Moriarty, 1997) (ii) the supply of digestive aiding enzymes and nutrients (Prieur et al., 1990) (iii) the absorption of dissolved organic matter by direct bacterial mediation (Garriques, 1995; Moriarty, 1997) (iv) improved performance in terms of larval survival, pathogen reduction, immune system fortification, growth rate, and resistance to stress (Balcázar et al., 2006; Dimitroglou et al., 2011; Gatesoupe, 1999).

Probiotic strains have also been demonstrated to alter host innate immune responses, allowing for the prospective infection to be eliminated (Pérez-Sánchez et al., 2014). They are predicted to have benefits for the environment in addition to operational and economic ones (Iribarren et al., 2012). A study found that oral treatment of rainbow trout with *Clostridium butyricum* improved their resistance to vibriosis by enhancing the ability of leucocytes to engulf and destroy pathogens (Sakai et al., 1995). *Bacillus* has been the subject of extensive research in aquaculture due to its potential to improve the health of cultured fish in a variety of ways, including growth, feed conversion efficiency, immunity, and protection from diseases and infections (Kuebutornye et al., 2019). Juvenile shrimp, *Litopenaeus vannamei,* exposed to the probiotic *B. subtilis* UTM 126, had a higher rate of survival after being infected with vibriosis (Balcázar & Rojas-Luna, 2007). Soltani et al. (2019) reported the presence of *Bacillus* sp. in the digestive tracts of fish and shellfish and their capability to generate enzymes and antibacterial compounds, which may be effective and beneficial in aquaculture (Soltani et al., 2019). Similarly, Kim et al. (2022) reported that bacterial species, *Acidithiobacillus thiooxidans* and *Exiguobacterium aestuarii*, recovered from the Saemangeum reservoir might enhance the quality of culture water, with *E. aestuarii* potentially being effective as a probiotic for *L. vannamei*. The scientific literature on the use of probiotics in aquaculture is expanding, and numerous studies have shown how beneficial probiotics are for aquatic species. In depth study is required to fully appreciate their potential maximise their application in various aquaculture systems.

7.2.4. Bacteriophages

Bacteriophages are bacteria's natural enemy and are effective against bacteria. In aquaculture, phage treatment is increasingly recognized as a potential alternative to antibiotics for treating bacterial pathogens (Rao & Lalitha, 2015). The first phage was discovered in an ocean environment (Spencer, 1955) and are thought to be the most abundant viruses in the ocean (Breitbart, 2012). *Myoviridae, Siphoviridae*, and *Podoviridae* are the three families of bacteriophages that are most prevalent in the aquatic ecosystem (Paul & Sullivan, 2005). Bacteriophages have a distinct advantage over antibiotics as they keep replicating at the site of infection as long as the host bacteria is present (Gon Choudhury et al., 2017; Jamal et al., 2015). They are a good alternative for treating bacterial infections in aquaculture because of their ability to target zoonotic pathogens, fast replication, non-toxicity, high specificity to the host bacteria and no negative effect on other beneficial microorganisms in the environment (Hudson et al., 2013; Jamal et al., 2015; Rong et al., 2014).

Phage therapy would prove particularly helpful in the early stages of fish like eyed-eggs and fry, which lack a fully developed immune system and, therefore cannot benefit from vaccines. Phages appear to be one of the most promising alternatives to antibiotics for aquaculture, which explains the growing interest in both private and public research. Vibriophages are some of the most studied bacteriophages in aquaculture, having the potential to combat the vibriosis infection, which causes significant financial losses in shrimp farms (Chatterjee & Haldar, 2012). The *Flavobacterium*, specifically *F. psychrophilum*, and *F. columnare*, which infect tilapia, salmonids, eels, and catfishes remains the second most targeted group for bacteriophage studies (Declercq et al., 2013; Long et al., 2014). Other bacterial species have also been investigated as potential targets for bacteriophage therapy, including *Aeromonas* spp., known to infect salmonids, *Pseudomonas* spp., which is frequently associated with infections in the ayu, and *Lactococcus* spp., which has been identified as a prevalent pathogen in trout, tilapia, and yellowtail populations (Austin & Austin, 2016; Fernández-Álvarez et al., 2016; Nishimori et al., 2000). China, the US, and Korea are considered the leading countries in industrial research on phage for breeding industries due to their high patent proportions (Gon Choudhury et al., 2017). Several private enterprises have expressed interest in utilizing phage-based solutions for improving aquaculture, but currently, there are only a limited number of commercially available products. These include a bacteriophage cocktail developed by Intralytix, which targets *V. tubiashii* and *V. coralliitycis* infections in oysters (Intralytix, 2016), and a therapy created by Phage Biotech Ltd. for *V. harveyi* infections in shellfish hatcheries (Phage Biotech, 2017). Additionally, Proteon Pharmaceuticals has developed BAFADOR® for controlling *Pseudomonas* spp. and *Aeromonas* spp. in aquaculture (Grzelak, 2017), while ACD Pharma is testing a product that targets Y. ruckeri responsible for yersiniosis in salmonids (Pharma, 2021). Further, Fixed Phage Ltd. (Mattey, 202$^{0)}$ is exploring the use of bacteriophages in aquaculture feed pellets, creating a targeted and convenient delivery system. These innovative solutions offer a ray of hope for aquaculture producers seeking to promote sustainable and responsible practices while ensuring a safe and healthy food supply for all. Several research groups around the world have been trying to isolate and identify phages that target *Vibrio* species for possible use in biocontrol (Alagappan et al., 2010; Bhowmick et al., 2008; Chrisolite et al., 2008; Dubey et al., 2021; Liu et al., 2022; Shivu et al., 2007; Stalin & Srinivasan, 2017; Surekhamol et al., 2014). In order to prevent vibriosis infection in the Indian shrimp farms, several researchers were successful in isolating and characterizing bacteriophages from marine waters (Alagappan et al., 2010; Shivu et al., 2007; Stalin & Srinivasan, 2017). The LUMI-NIL MBL product, developed by Mangalore Biotech Laboratory, is intended for biocontrol of luminous bacterial diseases in shrimp hatcheries (Mangalore Biotech Laboratory, 2019). Recently, the Indian Council of Agricultural Research and M/S Salem Microbes signed a memorandum of understanding (MOU) for the technology transfer of "phage therapy" for the management of bacterial disease in shrimp hatchery rearing systems (Bhat et al., 2022). Insights obtained from these reports may hasten the development of phage therapy in major fish producing countries (Khairnar et al., 2013). Bacteriophages have demonstrated great potential as a treatment for fish bacterial diseases; however, additional research is needed to fully understand the efficacy and safety of these products before they can be widely adopted in the aquaculture industry. With continued research and development, bacteriophage-based therapies could revolutionize the aquaculture industry, offering a pathway towards a more sustainable and resilient future.

7.2.5. Vaccines

Immunoprophylaxis or vaccine measures have become a significant element in achieving sustainability in aquaculture (Dadar et al., 2017; Gudding & Van Muiswinkel, 2013). Vaccines stimulate fish immune system, and act as defense mechanism against infections and protect the host from infection (Shah & Mraz, 2020). Vaccines are produced by extracting antigens from agents that have been made non-pathogenic in different ways (Strugnell et al., 2011). On the basis of their method of preparation, fish vaccines are often categorized into three groups: inactivated or killed vaccines, live or attenuated vaccines and genetically engineered vaccines (Su et al., 2021). Inactivated vaccines are pathogenic microorganisms that have been inactivated yet retain immunogenicity and the capacity to produce particular resistance in aquatic animals after inoculation (Su et al., 2021). As inactivated vaccines don't persist in the environment or in fish that have been vaccinated, they are usually found safe (Baxter, 2007).

Attenuated vaccines are not inactivated, but genetically or chemically weakened such that they are alive and produce an immune response in the host for a brief time without causing disease or death (Adams et al., 2008). As the residual virulence in targeted species might spread to non-target species, it may not be desirable to provide attenuated or avirulent forms of the virus (Salgado-Miranda et al., 2013; Shao, 2001). Subunit vaccines were developed to address the shortcomings of attenuated live vaccines, as they only contain the antigenic component of a pathogen (Hansson et al., 2000). These are produced by removing or creating specific protein structures from bacteria, known as epitopes, which are included in the vaccine (Liljeqvist & Ståhl, 1999).

By mixing many immunogenic antigens, i.e., producing multivalent subunit vaccines, the protective efficacy of subunit vaccinations against bacteria is enhanced (Xing et al., 2018). Subunit vaccines have a number of disadvantages, the most significant of which is that they generate a lower immune response than killed or live attenuated vaccines and often have shorter half lives in vivo due to reduced number of immunogenic components (Xiang et al., 2006). Oral administration or injection are the most efficient and successful methods of vaccination in fisheries (Shah & Mraz, 2020).

The study by Polish scientists Snieszko et al. (1938) on protective immunity in carp infected with *A. punctata* is possibly the earliest report of disease prevention using vaccination. Later, English researcher Duff presented the first paper confirming *A. salmonicida* protection in trout vaccinated by parenteral injection and oral administration (Duff, 1942). In 1976, the United States authorized the first aquaculture vaccination for the prevention of yersiniosis in salmonids (Tebbit et al., 1980). Vaccination procedures and vaccines themselves have evolved throughout time. Bacterial vaccines, including those for yersiniosis and vibriosis, are the most successful ones now available in the market (Mondal & Thomas, 2022).

Other vaccines, which are experimentally designed and used now are recombinant and DNA vaccines. In addition to traditional subunit or inactivated vaccines, which are derived from the pathogenic organism, alternative vaccination strategies have been developed utilizing messenger RNA (mRNA) as the active ingredient. These mRNA vaccines have demonstrated superior safety and efficacy profiles in comparison to traditional DNA or viral vector-based vaccines (Ulmer et al., 2015). The future of mRNA vaccines is extremely bright since they have tremendous potential and are much superior to those vaccines (Pardi et al., 2018). Also, the ease of manufacturing and easy design contribute to its future success (X. Cai et al., 2021). Innate immune sensing of mRNA has aided in active vaccination and passive immunization against a variety of infectious diseases and cancers (Pardi et al., 2018). In addition, the mRNA vaccine will gain popularity due to its efficiency in different delivery strategies, safety, and efficacy, as well as its scalable production (Wang et al., 2021). mRNA vaccine is known to bring about more effective immune responses than conventional fish vaccines and has shown prospective for the future of vaccines in aquaculture, providing a substantial deal of economic potential for farmers (Ma et al., 2019). Since mRNA has acted as a boon in the Covid-19 vaccination process, it has great potential in other fields. There is an immense potential for mRNA vaccines in aquaculture. Certain advancements in mRNA vaccines, like application mode, can be a milestone in controlling disease outbreaks in aquaculture.

7.2.6. Organic Acids

The use of dietary organic acids in aquaculture has recently attracted a lot of scientific and economic attention (Ng & Koh, 2017; Sidiq et al., 2023). Short-chain organic acids (C1-C7) and their salts or combinations, often known as "acidifiers", have received greater attention from aquaculture researchers as viable substitutes for antibiotic growth promoters (Lückstädt, 2008; Ng & Koh, 2011). According to research, certain organic acids are highly effective at killing serious foodborne pathogens, including *E. coli* and *Salmonella* spp. (Skřivanová et al., 2006; Van Immerseel et al., 2003). Furthermore, it is widely known that organic acids are able to exert their antimicrobial effect on microorganisms while inhibiting or preventing the development and spread of acid-sensitive bacteria by directly decreasing the pH of the environment through the release of hydrogen ions (Stratford & Eklund, 2003). The antibacterial effectiveness of organic acids is primarily due to their ability to permeate through the bacterial membrane and dissociate in neutral cytoplasmic pH (both bacteriostatic and bactericidal) (Cherrington et al., 1991). As in olive flounder (Park et al., 2011) and Pacific white shrimp (da Silva et al., 2016), organic acids are reported to benefit gut microbiota. Thus, fish feeds containing organic acids and their salts are known to positively impact the bacterial communities in the digestive tract of fish, resulting in improved gut health without relying as much on antibiotics (Sidiq et al., 2023).

8. Conclusion

This review suggests that the unregulated use of antibiotics in aquaculture in any nation has the potential to impact human and animal health on a global scale. Antibiotic resistance is currently occurring at an accelerated rate due to factors such as the misuse and overuse of antibiotics in aquaculture, inadequate monitoring and regulation of antibiotic use and urgent action is required to counteract its negative impacts. Considering that resistance has developed to almost all existing antibiotics and is expected to develop to any future antibiotics used in disease management in aquaculture practice, it is essential to explore what might be done to mitigate the effects of these trends. Most likely, major aquaculture-producing nations are consuming an excessive amount of antibiotics. Moreover, several of them lack or do not strictly enforce strict legislative and regulatory frameworks. Thus, the issue should be addressed by combining local and global prevention efforts. Further, establishing a global database on AMR and implementing better monitoring methods to track and restrict the use of antibiotics in aquaculture are both essential steps in gaining a deeper understanding of this problem. Collaboration and cooperation on a global scale are essential for establishing standardized guidelines and regulations for the appropriate use of antibiotics. More so, bringing together researchers, policymakers, producers, and consumers in networks can facilitate the sharing of information and ideas that will lead to more sustainable and accountable aquaculture.

Along with the previously listed roadways, there are other crucial acts that can assist in addressing this situation. Improving biosecurity measures and disease prevention practices in aquaculture by promoting sustainable and responsible aquaculture practices, such as integrated multi-trophic aquaculture (IMTA) and recirculating aquaculture systems (RAS). Improving the skills and knowledge of aquaculture farmers, extension workers, and regulators about responsible antibiotic use and alternatives can improve the effectiveness and adoption of sustainable disease management strategies. Investing in research and development to provide new and effective antibiotic alternatives, as well as better diagnostic tools and monitoring systems, can help enhance disease management and minimise antibiotic use in aquaculture. When it comes to overcoming the difficulties of AMR in aquaculture, the scientific community will continue to play a crucial role in the future. Finally, by gaining deeper insights into the dynamics of aquatic ecosystems and their interactions with the environment and microbial communities, we can devise effective strategies that promote responsible and sustainable aquaculture practices while ensuring public health protection.

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