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Antibiotics Usage in Aquaculture-An Overview

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Abstract
Antibiotics are used in aquaculture to maintain the health and welfare of stocks; however, the emergence and selection of antibiotic resistance in bacteria poses threats to humans, animals, and the environment. Mitigation of antibiotic resistance relies on understanding the flow of antibiotics, residues, resistant bacteria, and resistance genes through interconnecting systems, so that potential solutions can be identified and issues around their implementation evaluated. Antibiotics are introduced into the aquaculture system via direct application for example in medicated feed, but residues may also be introduced into the system through agricultural drainage water, which is the primary source of water for most fish cultured farms. The approach taken in the present study provides a means to identify points in the system where the effectiveness of interventions can be evaluated and thus it may be applied to other food production systems to combat the problem of antibiotic resistance. Oxytetracycline (OTC) is a tetracycline broad-spectrum antibiotic being widely used in aquaculture as a therapeutic and prophylactic agent ever since it was first approved by USFDA for use in finfish aquaculture. The indiscriminate use of oxytetracycline has led to a lot of problems such as the emergence of antibiotic-resistant bacteria in aquaculture environments which in turn transfer these resistance factors to bacteria of terrestrial animals and human pathogens. Moreover, it can also create problems for industrial health as antibiotic residues can get accumulated in fish meat and fish products. Residues of antibiotics also result in lowering the marketing and export value of aquaculture products. This review article highlights the present scenario of increasing antimicrobial-resistance in pathogenic bacteria and the clinical importance of unconventional or non-antibiotic therapies to thwart the infectious pathogenic microorganisms.

Keywords
Aquaculture, Antibiotic-resistance, antibiotics, oxytetracycline, bacterial diseases

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INTRODUCTION

Aquaculture has become a fast-growing industry due to the increasing demand for fish and seafood products throughout the world. It is estimated that around 156 million tons of fin fish and shellfish are consumed every year, with aquaculture production accounting for approximately 46% [1]. To sustain the rapid and steady growth of the aquaculture industry, antibiotics are widely applied, especially in low- and middle-income countries, to reduce infectious diseases and increase fish culture production [2,3]. Consequently, aquaculture is considered a hot spot for environmental dissemination of antibiotic resistance, and it gets transmitted to humans via the food chain [4,5,6]. Fish pathogens and other aquatic bacteria have been reported to be more resistant to multiple antibiotics due to the increased use of antibiotics [4,7,8]. Most of the global aquaculture production takes place in Asian countries, including Bangladesh, where aquaculture has significantly expanded over the last decade [9.10,11]. Fish aquaculture is one of the most rapidly growing strategic sectors worldwide and its productive industrial activity that will play a crucial role in providing solutions to the millennium challenges [12]. Fish and seafood consumption will be increased by 27%, according to expectations of aquaculture for 2030, in which a doubling of fish production is expected. This has led to a concomitant increase in aquaculture intensity methods, which increases the susceptibility to disease outbreaks and the necessary use of a medical diet especially antibiotics. The development of resistance of bacterial pathogens to the usage of antibiotics has greatly complicated the treatment of life-threatening bacterial infections especially in fish culture farms [13]. Antibiotics are one of the most frequent groups being used as feed additives in the form of growth promoters. Several antibiotics have been in use as growth promoters in fish farms ever since. Aqua farm owners are using various preventive measures to boost up production. Antibiotics are mixed with feed and feed ingredients with a sub-therapeutic dose to maintain good water quality and appropriate dietary management. Some of the antibiotics are widely used in the preparation of human and animal medicine and in animal food production [14,15]. Additionally, antimicrobial-resistant bacteria are commensal or pathogenic for humans (ARB) and are thought to be exchanged between humans and animals through direct or indirect transmission via the food chain or the environment. The linkage between animals, humans, and the importance of the environment in facilitating this linkage, has been coined in the One Health Framework [16]. It is generally recognized that, to be successful, different types of strategies are applied to mitigate the development and the transmission to humans of ARB will require concerted action across the One Health continuum, i.e., from human, animal sectors and the environment [13, 14]. The key objective involved in both human medicine and agricultural production is clearly to reduce the use of antibiotics to the minimum necessary, to reduce selection pressure and prevent AMR development in animals as well as humans [15,16,17]. On the other hand, considering the role of the environment in the development and transmission of AMR is recent, and actions in the environmental sector are currently the least implemented in the framework of public policies [18,19]. In high-income countries such as France, the main sources of environmental contamination take place with ARB and antibiotic residues are from human and animal faecal waste inputs. Consequently, potential hotspots are treated with wastewater effluents, fertilizers of human or animal faecal origin, and fish farm effluents [20,21].

Antimicrobial Resistant Bacteria in Aquaculture

Aquaculture has been considered as a “genetic hotspot” for resistance gene transfer. Multiple antibiotic-resistant strains are now being frequently detected both in fin fish and shellfish aquaculture environments, which greatly exhibits threat the medical treatment options as well as increase the unwanted death of fishes cultured in the ponds [22]. Antibiotic resistance is one of the global grand challenges facing humanity in the 21st century [23]. ABR in aquaculture poses a threat to human health and leads to the contamination of the environment with antibiotic residues along with resistant organisms. Many of the classes of antibiotics applied in aquaculture are identical to those used to treat terrestrial farm animals and human patients [24,25,26]. Antimicrobial resistance (AMR) is the term used to describe microbial organisms that can resist to the effects of drugs and chemicals designed to kill them. It is now widely regarded as one of the greatest risks to human and animal health. Antibiotic resistance (ABR) is one of the greatest challenges we face in the 21st century and it is a classical One Health problem with human, animals, and environmental components [23]. The global aquaculture sector is a major user of antibiotics, where the agents are applied to maintain the good health and welfare of stocks, though usage and practices vary widely across the world [9,26]. Accordingly, the problems posed by ABR vary, though much of the burden of the issues encountered falls on low- and middle-income countries (LMICs), and the antibiotics may not be used strongly enforced in wealthier counterparts [23, 9]. In addition to these, probiotics can also be used to modify the microbial composition of fishpond water to improve its water quality. Efforts must be done ensure probiotics works more appropriately and confirmed to be effective under fish farm conditions [27,28]. Anti-microbial resistant (AMR) bacteria are one of the severe threats faced by the world. Antibiotic-resistant bacteria and antibiotic-resistance genes (ARG) transfer between these components, which complicates the tracking of their flow and adds complexity in developing the solutions [23]. China has been one of the largest producers of aquatic products, and the coastal area mainly stands as the main aquaculture base [29]. Poor resistance and susceptibility to disease of various aquatic animals, antibiotics are widely used in aquaculture to prevent and treat bacterial infections in fish culture ponds [30]. As a result, the residual antibiotics in aquatic products pose a great potential risk to food safety, and antibiotics excreted from aquatic animals are dispersed in the water and sediments, thus leading to the emergence of drug-resistant bacteria and antimicrobial resistance (AMR) genes in aquaculture farms and the surrounding environment [31]. Under the pressure of excessive use of antibiotics, the drug-resistant bacteria even appear to demonstrate as multi-drug resistance, which causes serious negative impacts on public health also [32]. The AMR (Antimicrobial resistant) genes are considered as one of the novel environmental pollutants. The existence of drug resistance genes is the key to the development of drug resistance in bacteria. The AMR genes not only spread vertically but also spread from one bacterium to another bacterium horizontally through genetic elements, increasing the number of drug-resistant strains and finally causing difficulties in the treatment of clinical diseases as well as infection in both humans and aquatic animals [33]. *Escherichia coli* also induce diseases in various aquatic animals, thereby causing serious economic losses to the aquaculture industry. In this context, the excessive use of antibacterial drugs in aquaculture has become inevitable, and aquaculture has become one of the most important sources of antibiotic-resistant strains and AMR genes in *E. coli* [30]. Bacteria have different resistance mechanisms to different antimicrobial drugs. For instance, tetracycline-resistant bacteria usually produce a protein that interacts only with the ribosome; thereby, protein synthesis is not affected by the antimicrobial drugs, which is called as ribosome protection. *Escherichia coli* can produce macrolide phosphotransferase, which destroys the lactone ring of macrolide. Moreover, the detection rate of mcr1 was not high (45.56%), and the mcr2 gene was not detected among the 90 *E. coli* isolates from aquaculture farms. The possible reasons are as follows: (1) mcr1 is a relatively universal AMR gene in animals, but the mcr2 gene was carried by a rare plasmid (IncX4 type), and (2) the colistin drugs are one of the "last resorts" for the treatment of multi-drug resistant gram-negative bacterial infections; therefore, the aquaculture farms prefer this type of drugs. There are many reasons for the development of drug resistance in bacteria, which are related to the characteristics of the bacteria, the spread of AMR genes, and the use of drugs [30,31]. The AMR genes are detected in some bacteria, but the drug resistance phenotypes may not be shown because the AMR genes are not expressed, or they may express in very low abundance [34]. Exploring the intrinsic relationship between AMR genes and drug resistance and reducing the spread of AMR genes from the inner roots to curb the trend of drug resistance and still it requires further in-depth research. Recently, the SELECT method (Selection End points in Communities of bacteria) has been implemented to determine PNECs of antibiotics in complex microbial community [35].

Antibiotics Being Used in Aquaculture

Antibiotics are substances given in a controlled amount, meant to kill or reduce the growth of microorganisms, particularly in case of bacterial infections. These are usually naturally occurring substances and are mostly produced by microorganisms containing genes encoding resistance to different antibiotics they produce. Prophylactic use of antibiotics in aquaculture increases the risk of selection of antibiotic resistance. As a "genetic hotspot" for gene exchange, aquaculture can supply antibiotic resistance determinants to natural environments such as rivers which are in turn considered as reservoirs and acts as a dissemination route for reintroduction of antibiotic resistance into humans [36,37]. Studies from Bangladesh, India, Indonesia, and Thailand have reported that they have observed some antibiotic residues in aquaculture products and aquaculture water [38,39]. Chloramphenicol was recorded in fish from Bangladesh (~5ng/L) [39)]and in shrimps from India (~32ng/L) [39] and Indonesia (~45ng/L) [38]. In Thailand, erythromycin and tetracyclines were detected in aquaculture water up to 180 ng/L [40], whereas fluoroquinolones were detected in higher concentration (avg. 5130 ng/L, max 46100 ng/L) than aquaculture wastewater in Vietnam (avg. 235, max 1130 ng/L) [41]. Recently, it was reported that, the concentrations of 14 antibiotics were detected in both fin fish and shellfishes and that exceeded the country specific MRL guidelines. Antibiotics that are commonly used in aquaculture is to prevent or cure infectious diseases caused by the bacteria in Asia, Canada, Europe, the USA, and many other countries worldwide [26, 42]. Antibiotics are routinely applied in two ways: (i) prophylactic use by bath treatments to the diseased fishes or mixed with feed and (ii) therapeutic use for the treatment of bacterial infections [43]. In addition to these, antibiotics such as oxytetracycline and forfenicol are also used as growth promoter for the aquaculture cultured species [44]. The use of excessive antibiotics in aquaculture might speed up the resistance development in aquaculture environment and fish farming systems. Furthermore, consumption of fish treated with antibiotics may cause deleterious effects on human health [45]. The use of antibiotics in aquaculture may contaminate the whole culture environments as well as farmed organisms through different ways where feed is considered as one of the most important sources [46]. In-feed mixed antibiotics are combined with metals, which can select for ARGs and mobile genetic elements (MGEs) in the animal gut micro biomes [47]. In Bangladesh, the aqua farmers reported that, the antibiotics like renamycin when combined with (oxytetracycline) had significantly controlled the bacterial infection when used at a proper dose rate of 50 mg/Kg body wt./day for 3-5 days with 80-90% efficacy. Besides these, some other antibiotics like Acimox (vet) Powder, Bactitab, Chlorsteclin, Cotrim-Vet, Fish cure, Orgacycline-15%, Otetra vet power 50, Oxin WS, Oxysentin 20%, Ranamox, Renamycin and Sulfatrim were used in Bangladesh aquaculture [48]. [49] reported that, in order to get rid of bacterial infections, farmers in Bangladesh were in habit of using various antibiotics and antimicrobials in aquaculture like Renamycin, Bactitab, Chlorsteclin, Cotrim-Vet, Orgacycline-15%, Oxysentin 20% and Sulfatrim. Oxysentin 20% and Orgacycline-15% were effective against EUS, while Chlorsteclin was effective against the diseases like dropsy, tail and fin rot, gill rot of fish etc .About 80% of antimicrobials of both antibiotics and metals are used in aquaculture and sometimes end up with uneaten medicated feeds; unabsorbed antibiotics and secretions of culture organisms enter aquatic environments closely related to aquaculture facilities, therefore provides a favourable environment for the development and enrichment of persistent aquatic ARGs [9,50]. Antibiotics are specific types of antimicrobial substances that either kill or inhibit the growth of bacteria. Both the antibacterial agents, antibiotics are widely used in the treatment and prevention of bacterial infections. The discovery of penicillin in 1928 and the introduction to the medical industry in the 1940s marked the beginning of the antibiotic era. Most antibiotics are naturally occurring substances initially developed for treating infections in humans, but the use was quickly extended to disease treatment and prevention in food animals as well [51]. Apart from therapeutic use of antibiotics, the animal feed has commonly been supplemented with low concentrations of antibiotics as growth promoters in many countries to improve the feed efficiency, weight gain and animal health in fish farms [52]. High doses of metals particularly copper (Cu) and zinc (Zn), were also found to enhance the growth of the fishes [53]. Antibiotics are extensively used to prevent and control bacterial infections in medical care, livestock husbandry, and aquaculture practices. Information on the regulation and application of antimicrobials in aquaculture varies according to the country. The increase in production and density of fishes in cultured farms causes diseases to emerge [54]. Just like in other types of animal production (cattle, pigs, and poultry), the aquaculture industry also uses antibiotics to control various bacterial infections [25]. Different types of antibiotics, includes β-lactams, tetracyclines, Quinolone, Macrolide, Phenicol, sulphonamides and plasmid mediated resistance are now widely used for disease treatment and growth promotion [43,55,56]. The antibiotics are administered by farmers, either by hand mixing the antibiotics with the feed or by direct application into the water surface during disease outbreaks. Most of the farmers related to aquaculture production, generally lack the proper knowledge on how to use antibiotics [43]. As a result of this, overuse, or misuse of antibiotics in aquaculture leads to mass mortality. In addition, several studies have shown that antibiotics administered by feed will enter the aquatic environment through excretions or leaching from uneaten medicated feed, and up to 80% of the antibiotics will remain in sediments or the water after application [57]. Increasing global awareness and stricter regulations have led to a reduced application of antibiotics in many economically important production systems, especially those intended for the international market [58,43]. To evaluate the effects of regulations and aquaculture practices on antibiotic resistance, national surveillance of ARGs should be conducted, which have already been implemented in some countries [59,60]. Antibiotics are biologically active molecules that can exert toxic effects in the aquatic environment. These pharmaceuticals are considered contaminants of increasing concern, based on their common presence in different environmental contexts, and the lack of specific regulations for monitoring. The antibiotics fluoroquinolone, ciprofloxacin, amoxicillin, azithromycin, clarithromycin, and erythromycin are used in aquaculture. Antibiotics are usually administered to aquaculture in the addition to feed or by immersion through closed containers [61]. In China, the ecological risk for the antibiotics like ciprofloxacin, erythromycin, enrofloxacin, ofloxacin, and tetracycline was determined, and they exhibited medium to very high risks especially to algae and bacteria in aquatic ecosystem [62].

Antibiotic Resistant Bacteria in Aquaculture

Bacteria are ubiquitous in nature; thriving in soil, water and air and interconnected with ecosystems, featuring human, animals and environment collectively indicates the burden of AMR and that is multifaceted into the nature [63]. Antibiotic selection pressure is one of the fundamentals in the development of resistance in bacteria. In addition to this, the phenomenon of horizontal gene transfer (HGT), transformation, transduction or conjugation carry genetic elements and elevate antimicrobial resistance and virulence in microorganisms.

Moreover, the antimicrobial resistance is transmissible from the microorganisms; therefore, bacterial strains acquire more than one antibiotic resistance gene (ARG). The perpetual exchange and acquisition lead to the generation of a pool of ARGs in the environment, which is responsible to turn non-pathogenic bacteria into a multidrug-resistant strain and thereby exist outburst of infectious diseases in fish culture systems [64]. There exists a potential bridging between aquatic and human pathogen resistomes that leads to emergence of new AMR bacteria and the dissemination of their AMR genes into animal and human populations [65]. Some of the bacteria like *Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa* have been found to confer higher resistance to the antibiotic fluoroquinolones and third generation to cephalosporin and colistin. Ineffectiveness of last resort antibiotic pose a serious concern to safeguard the public health [66]. Moreover, the emergence of gram-positive bacteria such as methicillin is very resistant to the bacteria *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae* and shows additional challenges. Whereas *Salmonella Typhi* also shows resistance to the antibiotics like ampicillin and trimethoprim-sulfamethoxazole and found to decrease by ~ 2.4 and ~ fourfold, respectively [63]. The sediments and watercourses also demonstrate a high percentage of antibiotic-resistant bacteria and can serve as sources of antibiotic-resistant bacterial genes for fish pathogens. Furthermore, it has been found that resistant bacteria from aquaculture may be transferred to terrestrial animals and as well as in the human environment and can transfer their resistance genes to opportunistic animals or human pathogens [67]. The application of antimicrobials in aquaculture ponds has a consequence in the formation of drug-resistant bacteria repositories in aquatic species and their ecosystem [68,69,70]. Antibiotics used inappropriately or irrationally can lead to the development of antibiotic-resistant bacteria in many of the fish culture ponds [71]. The longer an antibiotic is exposed to the aquatic environment, the higher the chance of resistance developing, and administering these medications into aquatic environments allows them to survive for lengthy periods. [72] reported that aquaculture of low- and middle-income countries contributed higher levels of antibiotic-resistant bacteria. Several previous studies and reviews confirmed that the higher intensities of antibiotic-resistant bacteria and resistance genes are isolated from aquaculture environments worldwide [73]. Gram-negative bacteria have more global importance because of their higher burden of infection, evolution, and antimicrobial resistance when compared to Gram-positive bacteria [74]. Antibiotic-resistant bacteria and resistance gene can be transmitted from one to other bacteria through horizontal or vertical gene transfer mechanism. Consequently, the whole population might be contaminated by antibiotic-resistant genes or bacteria in the aquaculture environment [75,76]. Some resistant bacteria and resistance genes are commonly detected in aquaculture, which are pathogenic to fin fish or shellfish and for the human health [77,78]. These studies revealed a higher occurrence of resistance to quinolones, florfenicol, and oxytetracyclines in Chilean salmon aquaculture. Most of the salmon aquaculture farmers applied oxytetracycline and florfenicol in their aquafarms to control or prevent *Piscirickettsia salmonis* [79]. Antibiotic resistance is one of the severe threats faced by the world. Antibiotic-resistant bacteria and resistance genes are widely detected in almost all the major aquaculture-producing countries worldwide. Prophylactic or therapeutic applications of antibiotics in aquaculture may exert the selection pressure to the natural bacterial population and enhance the ability to produce antibiotic-resistant bacteria or resistance genes to the aquaculture environment. Bacterial resistance to antibiotics is presently considered one of the most critical threats for human health and affecting the ability to treat a wide range of bacterial infections worldwide [80,81]. Antibiotic resistance has already reached in upsetting levels in many countries globally, and some of the countries are currently using their last resort antibiotics for the treatment of bacterial infection. Furthermore, international scientists need to take alternative initiatives to limit the development and spread of bacterial infections and bacterial resistances in aquaculture farms. One of the important approaches that should be ensured such as good husbandry conditions and use of nutritious fish feed specifically in developing countries. In addition, to these, application of phage therapy against the various bacterial infections in aquaculture might be helpful to reduce the burden of antibiotics and antibiotic resistances [82]. Infections caused by multi-drug resistant pathogens, such as bacteriophages, mutants are bioengineered with lytic phage's and lytic endolysins alone or in combination with antibiotics that is needed to be considered [83]. Recent systematic review on the abundance of antimicrobial-resistant bacteria in aquaculture environments calculated that, they exhibit multi-antimicrobial resistance (MAR) index as the ratio, and it takes place between the number of resistant bacterial isolates and the total number of combinations tested [72]. The application of antimicrobials in fishes may lead to the imbalance in the composition of the gut micro biota, reflected by shifts in diversity, as well as in the taxa proportion [84,85,86]. This phenomenon may lead to the colonization or overgrowth of opportunistic pathogenic bacteria and finally leads to mass mortality in fish culture [87, 88, 84, 89]. Antimicrobials present in the aquatic environment can also affect other animals in proximity to aquaculture sites, including fin fish or shellfishes. Indeed, bivalves also have been used for monitoring antibacterial-resistant bacteria in the environment due to their capacity to filter and concentrate microorganisms from the surrounding media [90,91,92].

Genes Conferring Antibiotic Resistance

Consequently, aquaculture is considered a hot spot for environmental dissemination of antibiotic resistance and its transmission from humans through the food chain [22, 5,72]. Fish pathogens and other aquatic bacteria have been reported that, it is high resistant to multiple antibiotics due to the increased use of antibiotics [22, 7, 8]. Furthermore, the presence of mobile genetic elements (MGEs) such as plasmids harbouring antibiotic resistance genes (ARGs) plays an essential role and allow them for the horizontal gene transfer of ARGs between aquatic bacteria, fish pathogens, and even human-associated pathogens also [93,94]. Plasmids carrying ARGs in aquatic fish pathogens are not uncommon and have been frequently detected [76, 95]. For instance, incompatible IncA/C host range plasmids containing different genes like qacE2, tetA, tetD, tetE and floR along with various aminoglycoside resistance genes have been isolated from ornamental fishes [96]. The occurrence of ARGs on MGEs poses high risk for humans consuming these fishes, because these ARGs may get transferred through the food chain 95, 3]. Antibiotic resistance genes (ARGs) are the culprit and now they have been widely recognized as emerging environmental pollutants [97]. Antibiotics in surface waters also influence the risk of developing antimicrobial resistance genes, which may pose adverse effects on humans and other organisms and also in the aquatic environments [98,95]. The existence of residual antibiotics in the aquatic environment might facilitate the development of antibiotic resistance, thus enhancing the risks of antibiotic resistance in fish culture farms [62]. Similar to most antibiotics, ARGs are ancient and naturally occurring substances. However, they are currently accumulating in human-impacted environments [99,100,101]. According to a recent modelling study, antibiotic resistance would continue to grow across the countries in the coming years [102]. A wide range of ARGs have been identified in aquaculture such as, ARGs encoding tetracycline resistance (tetA, tetB, tetC, tetD, tetE and tetG), quinolone resistance (qnrA, qnrB, qnrS1 and aac(60)-Ib-cr), macrolide resistance (mphA and erm), aminoglycoside resistance (aph, aad and aac(60)-Ib), chloramphenicol resistance (catA2, cml and floR), b-lactams resistance (blaCTX-M and blaTEM), sulfonamide resistance (sul1, sul2 and sul3) and etc [103,104]. High prevalence (81%) of resistant strains were found in Chilean salmon farms, and many strains were exhibited positive to genes resistant to tetracycline (e.g., tetA and tetG) [105]. It should be noted that metals also contribute as co-selective agents driving the enrichment of genetic elements harbouring both the metal resistance genes and ARGs in the micro biomes of animals and agroecosystems [106,107]. Hence, more public attention was paid to the antibiotic usage in animals and its potential risks are required to respond to antibiotic resistance issue less than One Health framework [108,109]. ARGs (Anti-microbial resistant genes) from farmed animals receive antibiotics or metals can also be transmitted directly to humans via farm animals by human contact or indirectly by the animal-environment-human pathways [110]. Various anthropogenic activities play key roles for the environmental transmission of ARGs including the manure application, farm wastewater discharge, etc. These above-mentioned factors make our livestock systems not only a rich reservoir but also one of a significant ARG hotspot constituting risks to both environmental and public health worldwide [111]. The knowledge of antimicrobial (antibiotic and metal) usage for food animals, ARG pollution in livestock systems, its intricate environmental transmission and potential mitigation approaches have been dramatically expanded with the recent development of rapid molecular tools such as high-throughput qPCR chips and metagenomic sequencing. Previous publications have reviewed the global antibiotic use in animals [112, 26], reported the antibiotic resistance in the animal industry at various scales [113]. Antibiotic resistance genes (ARGs) are the culprit and now widely recognized as emerging environmental pollutants. Most of the antibiotics, ARGs are ancient and naturally occurring substances. However, they are currently accumulating in human-impacted environments [99,100101], which could be largely attributed to the intensive anthropogenic usage of antibiotics in the last few decades. According to a recent modelling study, antibiotic resistance would continue to grow across globe in the coming years [102]. Meanwhile, it should be noted that metals are also contributing as co-selective agents driving the enrichment of genetic elements harbouring both metal resistance genes and ARGs in the micro biomes of animals as well as in agroecosystems [107].

Detection of Antibiotic Resistance Bacteria and Genes in Waters

Antibiotic-resistant bacteria and resistance genes are widely detected in almost all the major aquaculture-producing countries worldwide. The frequently isolated antibiotic resistant bacteria are *Vibrio* spp., *Aeromonas* spp., *Bacillus* spp., Pseudomonas spp., *Enterobacteriaceae, Streptococcus* spp., *Exiguobacterium* spp., etc. Other bacteria species like *Flavobacterium* are also detected in the aquaculture environments [114]. Some of the most frequently detected antibiotic resistance genes along with their respective antibiotic classes are tetracycline (tetA, tetB, tetK, tetM), quinolone (qnrA, qnrB, qnrS), sulfonamides (sulI), and others. Some resistant bacteria and resistance genes are commonly detected in aquaculture, which are very pathogenic to fin fish shellfish and human health [98, 95]. **[**115] have recently reported that probiotics used in aquaculture contain antibiotic-resistant pathogenic bacteria particularly *Klebsiella pneumoniae* which may pose serious threat to aquaculture organisms and also human health. Multiple antibiotic-resistant bacteria and resistance genes both were present in the aquatic ecosystem, and significant associations were documented for different antibiotics in natural water bodies [116]**.** The ARGs combining with minerals and humus from the environment may exist for a long time [117,118]. It is well known that the ARGs have unique biological characteristics, and they have the tendency to spread by horizontal gene transfer from various bacteria of different species and self-amplify among the same species [119,120]. Multi-resistant *Aeromonas salmonicida* have been described from many countries in various parts of the world, and transferable resistance plasmids are commonly detected in these strains. Typical transferable resistance determinants are those conferring resistance to the antibiotics like sulphonamide, tetracycline, trimethoprim, and streptomycin. Quinolones are used to control bacterial infections from the 1980s resulted in the development of quinolone resistance in strains of *Aeromonas salmonicida*. This resistance in *Aeromonas* was mainly mediated by mutation in the gyrase A gene, gyrA, and so far, not been shown to be transferable gene [121]. The sediments were regarded as an important plot for accumulation and transmission of ARGs. [95] reported that several ARGs (sul1, tetG, tetW, tetX, and intl1 gene) were detected in water and sediment of aquaculture fish farms especially in Jiangsu Province, China. [122] explored the ARGs in the sediments from bullfrog farms and confirmed that these identified ARGs were able to encode resistance to over 10 categories of antibiotics, such as aminoglycosides, beta-lactams, chloramphenicol, fluoroquinolones, macrolides, polypeptides, sulphonamides, and tetracyclines. It plays a key pathway for bacteria to acquire ARGs, which influenced the removal and transfer of ARGs in the bacterial community. One of the most important mobile genetic materials is the integrons that would capture, rearrange, and express mobile gene cassettes which are in turn responsible for the spread of ARGs and further accelerate the prevalence and transmission of ARGs into the environment [123]. Some of the studies have suggested that the nutrients also promote the ARGs propagation either directly or indirectly [124,125]. Furthermore, the long-time input of nitrogen and phosphorus not only changed the composition of the bacterial community but also drove the propagation of ARGs in fish culture ponds [126]. For all these reasons, the environmental risk assessment (ERA) of antibiotics in the environment and their potential to select for AMR cannot only rely on the testing of isogenic bacterial cultures with gradients of selective agents. Instead, the determination of PNECs must rely on methodological approaches dealing with mixed bacterial communities [127]. Indeed, it is known that several ARGs that have emerged in human bacterial pathogens, such as blaCTX-M and mcr-1 genes, originated either from environmental or commensal bacteria [128]. Considering the selection of new ARB is more likely to be seen in the environment contaminated by one or more antimicrobial compounds, and environment enriched with autochthonous bacteria, allochthonous potential pathogenic bacteria and selective antimicrobial compounds are possible hotspots for the selection of new ARB equipped with new ARGs. The evolution of resistance to antibiotics in bacterial bio film communities would be faster than in planktonic communities since the physical proximity of the bacterial populations within the bio film facilitates the horizontal transfer of genes by the process of conjugation [129,130]. While horizontal gene transfers are major drivers of bacterial evolution, their rates strongly depend on surrounding conditions. Transfers of new ARGs to pathogens and their subsequent maintenance and dissemination are likely rare. Besides these the major human source of water contamination, spreads from OWPs as fertilizers can also ultimately contribute to a more diffuse and incidental contamination of aquatic environments due to continuous runoff, leaching or infiltration [131]. The concentrations of antibiotics seen in the sediment increase with proximity to sewage outflows. The cooler and more reducing conditions in sediments are associated with poor biodegradation rates and the accumulation of persistent antibiotics such as fluoroquinolones, macrolide, and sulphonamides [132]. Indeed, along with the sediment core corresponding to several decades of accumulation, antibiotic concentrations also reflected in the persistence properties of the antibiotics and also in the market authorization [132,133]. Moreover, antimicrobial contamination of migratory birds raises further questions on the capacity of these animals to disseminate ARB and ARGs over very long distances. Globally, almost all of these studies showed that the occurrence of ARB in aquatic or terrestrial wildlife reflects both the diet of the wildlife and have greater impact on human activities [134].

Usage of Antibiotics in India

India has been referred as 'the Anti-microbial resistance (AMR) and the capital of the world' [135]. In India, average peak water concentrations applied in aquaculture farms are Oxytetracycline (OTC) and Erythromycin were recorded as 49 µg/L and 1.6 µg/L respectively while OTC were frequently detected in sediments with concentrations up to 6908 µg/kg. In 2014, India was the highest consumer of antibiotics, followed by other countries like China and the United States. However, the per capita consumption of antibiotics in India is much lower than in several other high-income countries [136]. India became a greatest hub to multidrug-resistant (MDR) and extensively drug-resistant bacteria (XDR) *Mycobacterium tuberculosis* demand efforts to mitigate the onset of tuberculosis disease. Additionally, the genomic plasticity of these organisms enables them to develop more resistance against the last-resort antibiotics like Carbapenemases and Colistin either by recombination or genetic acquisition and may represent a daunting task, because of the availability of antibiotics which would no longer be effective against these organisms. Studies focusing on the coastal part of India demonstrated various gastrointestinal infections due to *Vibrio* species and members of family *Enterobacteriaceae*. Prevalence of such pathogenic microorganisms is not restricted to the water bodies whilst studies have shown their prevalence in a variety of aquatic biota including fishes, shrimp and shellfish culture [137]. The discovery of bla $_{NDM-1}$ (New Delhi metallo-β-lactamase) and associated controversy necessitated the policymakers to initiate the development of AMR containment-related policies for India in the year 2011[138]. Antimicrobial resistance (AMR) refers to the ability of a microorganism to resist an antimicrobial drug such as an antibiotic, and it is a very serious global public health challenge (AMR). Antibiotic resistance has now become much more extensive during from the last few decades [139,140]. Application of too high dose or extreme low dose, over prescription of drugs, and incorrect duration of prescription usually intensifies the problem in fish farming [141,142]. Lack of awareness further leads to the indiscriminate use of antibiotics for treatment of diseases and as growth promoters. Indiscriminate use of antimicrobial is considered as the primary driving force for AMR in animal husbandry, removing the sensitive population and allowing proliferation of the mutant strains. Even the commensal bacteria like E. coli and *Enterococci* can serve as a reservoir for resistance genes and can transfer them when conditions are favourable and therefore, used internationally as indicators for prospects of Gram-positive and negative bacterial resistance [141]. The use of indigenous traditional knowledge (ITK) is based on the treatment can be applied as an alternate therapy. It requires the development and validation for cost effective, safe and easily available as alternate medicine. It can reduce the presence of resistance genes in existing microbial population as chromosomal genes and they are transferred vertically while genes on plasmids, transposons, integrons, etc and they spread horizontally with more efficiently and receive further favour from resistance selection pressure induced by the intensive use of antimicrobials [141,142]. This is observed in case of Zoonotic *Salmonella Typimurium.* The main mechanism causes AMR include chemical modification of antibiotics, systemic elimination of antibiotics by efflux pump, modification of drug target and alternate defence strategies of pathogenic bacteria like bio film formation [143]. In case of Gram-negative bacteria also the AIs diffuse out very freely and reach the threshold value, and finally generate positive feedback loop to synthesize more effective AIs [144]. Approved antibiotics in India are the antibiotics that are in anthropogenic or veterinary use do not apply to aquaculture. The USFDA (United States Food and Drug Administration) is responsible to approve the antimicrobials that can be used in aquaculture. In India, authorities like MPEDA and CAA can also play a vital role in categorizing and approving the safety of antibiotics for aqua cultural aspects. Finally, the composite and perpetual efforts are made by the Government of India to combat the AMR spread are commendable. As it eventually helps to contain the spread of AMR in India.

Application of Antibiotics in Andhra Pradesh

Antibiotic usage in aquaculture varies with region, species, and production phase like hatchery, nursery, and grow-out ponds [58,145]. Bangladesh's aquaculture sector is expanding since the state's inland output is marginally lower than China's. Indeed, the aquaculture industry serves as a second source of export revenue for the government of A.P [146,147]. Apart from the massive use of antibiotics, aquaculture also uses a variety of medicines to keep fish healthy and produce more in quantity. Some of the compounds like Sodium chloride, Potassium permanganate, malachite green, formalin, glutaraldehyde, methylene blue, Iodine and hydrogen peroxide are the most frequently utilized compounds [148]. In aquaculture, when compared to other animal production sectors, some of the important strategies like vaccination and antibiotics are used to control infectious bacterial diseases. Antimicrobial use in aquaculture differs from cattle farming due to the greater diversity of species, farming practices, and different application methods. The application of antimicrobials in aquaculture ponds has a consequence in the formation of drug-resistant bacteria repositories in aquatic species and in the ecosystem [149, 69, 150]. Several issues are seen regarding improper use of aquatic medications, such as lack of information about chemical use, sufficient dosage, form of application, and indiscriminate use of antibiotics have been reported by [151]. Some of the antibiotics are administered indiscriminately in the current investigation, although the specific causes of the disease were unknown. Some farmers do not use the prescribed treatment doses. A total of 15 antibiotics were identified and farmers were reported with irresponsible and frequent use of such drugs without approval and without knowing their effects on fish health [152]. Several aqua drugs have been found to be used as oxygen precursors, ammonia reducers, growth promoters, antiparasitic enzymes, and probiotics to aid digestion and keep the aquatic environment healthy. Antibiotics with six categories of the compounds, includes nutritional supplements, disinfectants, saline, ammonia removed probiotics, and pesticides, were administered in different ways by the fish farmers of Mymensingh [152]. Andhra Pradesh stands first in aquaculture production both from brackish water and freshwater resources and occupies fourth place in marine fish production in India. Andhra Pradesh state has been considered as the hub of modern aquaculture and the production trends in the state that reflects directly on the country's production [153]. Tilapia and Pangasius, also offer great opportunities for cage culture. The focus on the production of genetically improved tilapia for market and it is treated as cheap source of proteins which is highly enhancing [154]. To protect cultured fin fishes and shrimp, farmers are focusing to apply a wide range of aqua–medicines, drugs, antibiotics, and other chemicals in aquaculture to control production loss. Besides these, aquaculture drugs and chemicals are also used in pond construction, soil and water management practices, enhancement of natural aquatic productivity, feed formulation, manipulation of reproduction, growth promotion and processing and value addition of the final product [155]. Hence, a serious concern has been raised by different international organizations like FAO and OIE on irresponsible use of drugs and antibiotics, which often leads to the development of Antimicrobial Resistance (AMR) in fish culture. The amount of information on chemical use in aquaculture and its significance for human health assurance, environmental protection, and sustainable development of the sector, has been increasing. It has been reported that various aquaculture drugs have been used widely in health management, construction of the pond, soil and water quality improvement, productivity enhancement, feed formulation, manipulation of reproduction, growth promotion, processing, and value addition of the final product [156]. Most of the aqua-medicine, drugs and chemicals are commercially available in the markets and are categorized in to six types, i) Those chemicals and formulations used for water quality management in fish cultured ponds, ii) Anti-parasitic drugs and chemicals iii) Disinfectants and sanitizers iv) Probiotics and water remediation products v) Feed Supplements and growth promoters vi) Antibiotics [157]. In fish culture farms, parasitic infestations were major cause of concern flowed by alteration through water quality and bacterial infections. Single or multiple parasites were involved along with bacterial infections leading to severe damage to host tissues. During the process, fish parasites interfere with the nutrition of hosts, disrupt metabolism and secretary functions of alimentary canal and finally damage nervous system thereby reducing growth rate and finally leads to mass mortality, which in turn results in substantial economic loss to the fish culture farmers [158]. Fish farmers in Andhra

Pradesh employed using organic products like Neem (*Azadirachta indica*) extracts or Neem oil to control fish parasitic infestations. Some farmers use farm made fermented extract locally called as "Jivamrutam" which contain cow urine, cow dung, molasses, rice bran and sometimes Black gram (Vigna mungo). After 5-6 days of fermentation, the fermented product is applied to the fish culture ponds. As per their view, application of the product was very useful in protecting the fish farms against parasitic infestations and helped to enhance plankton production also. To control diseases problems, varieties of anti-bacterial, anti-fungal agents and disinfectants were used both in fin fish, shrimp ponds and hatcheries. Aquaculture farmers use a variety of chemicals in the treatment of disease as preventive or control measure which included chemical preparations like Aquakleen, BKC, bleaching; EDTA, efinol, formalin, lime, urea, and TSP were the mostly used. Bleaching powder, Timsen, EDTA, Polgard, Virex, Aquakleen, Germnill, Pond safe were widely used as disinfectant and water quality management especially in Bangladesh aquaculture [159]. Antibiotics like Oxymycin, Enrox, Lexin Powder, Hydrodox, Oxytetracycline, Cefintas AQ were commonly used in aquaculture [157]. The active ingredients of such antibiotics were mainly Oxytetracycline, Chloro-tetracyclin, Amoxicillin, Co-trimoxazole, Sulphadiazine and Sulphamethoxazole.. Mostly used antibiotics in Andhra Pradesh are Renamycin, Oxysentin 20% Chlorsteclin Oxy-D Vet, Aquamycin, Orgamycin 15 %, Orgacycline-15% etc. Major active ingredients of the antibiotics are oxytetracycline, chlorotetracycline, amoxicillin, doxycycline [48]. Farmers are now in practice of using various probiotic formulations, aqua drugs and chemicals, various antimicrobials, sanitizers, antiparasitic drugs and even antibiotics in fish culture system, as preventive and control measures to protect various infections against the bacterial pathogens [160].

Table 1. Approved antibiotics that are being used in aquaculture industry.

S.No.	Name of the affected fish species	Name of the approved antibiotics	Action regarding disease aspects	Route/Mode of administration of antibiotics	Dosage of antibiotics mg/kg	References
1	Freshwater-reared salmonids, Walleye, Fresh water reared warm water finfish	Chloramine-T Halamid® Aqua	For the control of mortality in freshwater-reared salmonids due to bacterial gill disease and *columnaris* associated with *Flavobacterium* spp.	Prolonged bath Or Immersion	(20 mg/L for 60 minutes every alternated day as many as 3 times)	[161]
2	Finfish fry and fingerlings Salmonid	Oxytetracycline hydrochloride (Terramycin343; OxymarineTM)	Salmonids: For control of ulcer disease caused by *Haemophilus piscium*, furunculosis caused by *Aeromonas salmonicida,* Bacterial hemorrhagic septicemia caused by *A. liquefaciens*, and pseudomonas disease, for control of mortality due to cold-water disease associated with *Flavobacterium psychrophilum*. Freshwater-reared *Oncorhynchus mykiss:* For control of mortality due to columnaris disease associated with *Flavobacterium columnare* Used in finfish fry and fingerlings of salmonids due to bacterial gill disease (BGD) caused by *Flavobacterium Branchiophila* For the control of gaffkemia caused by *Aerococcus viridians.*	Oral/Injection/ Immersion	(200-700 mg/L water for 2-6 hours) 2.5–3.75 g/100 lb. of fish/day Maximum dose = 8.33 mg/kg/10 days 2.50-3.75 g/100 lb fish	[162]
3	Salmonids, catfish, *Oncorhynchus mykiss* and Lobster	Oxytetracycline dihydrate Terramycin® 200	For the control of mortality in freshwater-reared salmonids due to cold water disease associated with *Flavobacterium psychrophilum* For the control of mortality in freshwater reared *Oncorhynchus*	Oral via Medicated feeds	For feed use. In Salmonids, 21 days; Catfish, 21 days; Lobster, 30 days. Oxytetracycline tolerance in the flesh is 2.0 ppm	[163]

			mykiss due to columnaris associated with *Flavobacterium columnare.* For the control of mortality in catfish due to *enteric septicemia* of catfish associated with *Edwardsiella ictaluri*. For the control of mortality in freshwater-reared salmonids due to cold water disease associated with *Flavobacterium psychrophilum.* For the control of mortality in freshwater-reared salmonids due to furunculosis associated with *Aeromonas salmonicida.* For the control of mortality due to columnaris disease associated with *Flavobacterium columnare* in freshwater-reared finfish and for the control of mortality due to *streptococcal septicemia* associated with *Streptococcus iniae* in freshwater-reared warm water finfish			
4	Freshwater-reared finfish including warm water finfish, salmonids catfish and Channel catfish Salmonid	Florfenicol Aquaflor® Type A		Oral via Medicated feeds	10 mg/kg fish per day for 10 consecutive days	[163]
			For the control of furunculosis in salmonids (trout and salmon) caused by *Aeromonas salmonicida.*			
5	Rainbow trout, Catfish and Salmonids	Sulfadimethoxine/ ormetoprim combination (Romet-30 ®)	For the control of bacterial infections in catfish caused by *Edwardsiella ictaluri* (*enteric septicemia* of catfish).	Oral via Medicated feeds	(50 mg/kg fish BW for 5 days consecutively)	[163]
			Withdrawal times for Salmonids, 42 days; and for catfish, 3 days			
6	Trout (rainbow, brook, brown)	Sulfamerazine fish grade	Furunculosis caused by *Aeromonas salmonicid.*	NA	It may not be used within 21 days of harvest (21 CFR	[163]

	Turbot		It may not be used within 21 days of harvest		558.582). Note: This product is currently not marketed	
7	Fin fish	Oxy Marine Oxytetracycline HCL soluble powder-343, TETROXY Aquatic	For marking of skeletal tissues in finfish fry and fingerlings as an aid identification	Immersion	200–700 mg oxytetracycline/L of water for 2–6 hours	[162]
8	Fin fish	Chemotherapeutants Sulphonamides (incl. potentiated) Finfish Bacterial diseases Quinolones	Treatment of bacterial fish diseases	Oral –medicated feed; injection; topical; bath	7.5 g for 5-7 days	[164]
9	Fin fish	Parasiticides/ Fungicides Acetic acid	Control of sea lice on salmon; treatment of parasites in ornamental fishponds; control of protozoa and trematodes on fin fishes	Oral –medicated feed; bath; dip; flush	1000 to 2000 ppm dip for 1 to 10 minutes as a parasiticide for fish	[165]
10	Fin fish Ictaluridae (catfish), Salmonidae, Esocidae and Percidae	Tricaine methanesulfonate Tricaine-S MS-222	Anaesthesia	Injection	It may not be used within 21 days of harvesting fish for food. The drug should be limited to hatchery or laboratory use	[166] [167] [163]
11	Finfish and their eggs, Penaeid shrimp Salmon, Trout, Catfish, Largemouth bass Bluegill and crustaceans	Formalin (Formaldehyde solution)	For the control of Protozoa and Monogenetic Tremetodes, and on the eggs of Salmon, Trout and Pike (esocids) for control of Fungi of the family Saprolegniacea	Prolonged chemical bath	38% of Formaldehyde 1–3 ppm	[166] [167] [163]
12	Brood finfish And bloodstock	Chorionic gonadotropin Chorulon®	For improving spawning function in male and female brood finfish and also for the Spawning aid	Intramuscular injection just ventral to the dorsal fin for one to three injections.	At a dose of 50 to 510 I.U./lb. body weight (BW) for males and 67 to 1816 I.U./lb. BW for females	[163]
13	Finfish	Sodium chloride	Treatment of Parasites and osmoregulatory aid	Dip, chemical bath	Used in a 0.5% to 1.0% solution for an indefinite period as an	[166] [167]

					osmoregulatory aid for the relief of stress and prevention of shock; and 3% solution for 10 to 30 minutes as a parasitide	
14	Finfish eggs	Povidone iodine	Treatment of egg surface disinfectant	Chemical bath	Used in a 100 mg l-1 solution for 10 minutes as an egg surface disinfectant during and after water hardening	166] [167]
15	Finfish	Magnesium sulphate	Used to treat external monogenic trematode infestations in fish at all the life stages. Used to treat external crustacean infestations in fish	Prolonged chemical bath	Fish are immersed in a 30,000 mg, MgSO4 l-1 and 7000 mg NaCl l-1 solutions for 5 to 10 min.	[163]

CONCLUSIONS AND PERSPECTIVES

Oxytetracycline (OTC), which is a broad-spectrum antibiotic, has been widely used in aquaculture as a therapeutic and prophylactic agent ever since its approval by USFDA for use as an antimicrobial in aquaculture. It is one of the most used antibiotics in aquaculture, and it is indicated to treat various fish bacterial infections like furunculosis, aeromonosis, pseudomonosis, lactococcosis, and vibriosis, through fish feed, bath treatment, and injection (Leal et al., 2019). Treating the wastewater from the livestock industry can significantly reduce the richness of ARGs/MGEs and efficiently control the dissemination of ARGs/ ARB from fish farming especially the aquaculture practices (An et al., 2018; Gros et al., 2019; He et al., 2020). Furthermore, international scientists need to take alternative initiative to limit the development and spread of bacterial infections and bacterial resistances in aquaculture. Other probable approaches that should be ensured include such practices as good husbandry conditions and use of nutritious fish feed specifically in developing countries. In addition, the use of phage therapy against the bacterial infection in aquaculture might be helpful to reduce the burden of antibiotics and antibiotic resistances (Donati et al. 2021).

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CONFLICT OF INTEREST

No conflict of interest was found.

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