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Review **Derleme**

The Risk of Antibiotic Resistance in Aquaculture: The Future Outlook

Su Ürünleri Yetiştiriciliğinde Antibiyotik Direnci Riski: Geleceğe Bakış

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Abstract: The production of aquatic products is a critical global industry that provides employment and livelihoods to millions of people, aiming to compensate for the increasing population and insufficient terrestrial resources. To bridge the demand–supply gap in seafood production, the use of production technologies in the industry has intensified, but has raised concerns about potential public health threats. For instance, increased stocking densities in aquaculture settings have increased fish stress, creating an environment conducive to pathogen proliferation. Antibiotics are widely used to treat and prevent infections in fish and other animals. The emergence of antibiotic-resistant bacteria in fish and other aquatic animals, as well as in the aquatic environment, has created reservoirs of resistant bacteria and resistance genes. To some extent, antibiotic resistance in aquaculture has contributed to resistance to antimicrobial agents in human pathogens thereby severely limiting therapeutic options during human infections. Therefore, responsible and monitored use of antibiotics in aquaculture is paramount. This review consolidates the knowledge on commonly used antibiotic types in aquaculture, antibiotic administration, antibiotic susceptibility test techniques, and antibiotic resistance in water, fish, and sediments. The challenges, strategies, and constraints in counteracting antibiotic resistance and prospects for antibiotic use in aquaculture are discussed.

Keywords

- Fish
- Water
- Bacteria
- Environment
- Seafood

Özet: Su ürünleri üretimi, artan nüfüs, karasal kaynakların yeterli olmamasına bağlı olarak açığı karşılamak adına milyonlarca insana istihdam ve geçim sağlayan kritik bir küresel endüstridir. Sektördeki üretim teknolojilerinin yoğunlaşması, deniz ürünleri üretimindeki arz-talep açığını kapatmak için ortaya çıkmıştır, ancak potansiyel halk sağlığı tehditlerine ilişkin endişeler gündeme gelmiştir. Örneğin, su ürünleri yetiştiriciliği ortamlarında artan stok yoğunlukları balıklarda stresin artmasına yol açarak patojen çoğalmasına elverişli bir ortam yaratmıştır. Antibiyotikler balıklarda ve diğer hayvanlarda bakteriyel enfeksiyonların tedavisinde ve önlenmesinde yaygın olarak kullanılmaktadır. Balıklarda ve diğer su canlılarında, ayrıca sucul ekosistemlerde antibiyotiklere dirençli bakterilerin ortaya çıkması, dirençli bakterilerin ve direnç genlerinin rezervuarlarını oluşturmuştur. İnsan patojenlerindeki antimikrobiyal maddelere karşı direnç, insan enfeksiyonları sırasında tedavi seçeneklerini ciddi şekilde sınırlamaktadır. Bu derleme, su ürünleri yetiştiriciliğinde yaygın olarak kullanılan antibiyotik türleri, antibiyotik uygulaması, antibiyotik duyarlılık test teknikleri ve su, balık ve sedimentteki antibiyotik direnci hakkındaki bilgileri bir araya getirmektedir. Antibiyotik direnciyle mücadelede karşılaşılan zorluklar, stratejiler ve kısıtlamaların yanı sıra su ürünleri

Anahtar kelimeler

- Balık
- Su
- Bakteri
- Çevre
- Deniz ürünleri

yetiştiriciliğinde antibiyotik kullanımına yönelik beklentiler de tartışılmaktadır.

1. INTRODUCTION

Seafood farming has long been a vital source of nutrition and income for people worldwide (Charlton et al., 2016; Nyboer et al., 2022; Popoola, 2022). Aquaculture has intensified to meet the growing global demand for seafood. Intensification increases production efficiency, yields, and enables more sustainable use of aquatic resources. It addresses the challenges of overfishing and provides a controlled environment for optimizing fish growth. Additionally, intensified aquaculture contributes to economic development by creating employment opportunities and supporting the livelihoods of millions of people worldwide (Kumar et al., 2020; Morshdy et al., 2022; Opiyo et al., 2018). That notwithstanding, intensive aquaculture has consequently increased the frequency of fish stressors, including the proliferation of diverse disease-causing microorganisms, particularly pathogenic bacteria (Chang et al., 2020; Lulijwa et al., 2020; Oviedo-Bolaños et al., 2021; Romero et al., 2012; Zhang et al., 2023). Largely antibiotics have being widely used to prevent and treat bacterial diseases in fish culturevia fish feed, baths or immersion, and injections, amongst others (Gupta et al., 2019; Hurdle et al., 2011; Imran et al., 2022; Shan et al., 2018; Terzi et al., 2020). There have been widespread reports of indiscriminate use of antibiotics in fish farming, leading to antibiotic resistance in the pathogen population (Capkin et al., 2015). Upon exposure to antibiotics, vulnerable bacteria perish allowing surviving ones to transmit resistance traits to future generations through biological mutations, DNA exchange, and rapid replication. (Begum et al., 2018; Frieri et al., 2017; MacGowan and Macnaughton, 2017; Ray et al., 2017). Antibiotic resistance in fish poses a global threat to public health. Resistant bacteria in fish can be transmitted to humans through the consumption of contaminated fish or environmental pathways (Fletcher, 2015; Skandalis et al., 2021). If not curtailed, the continued development of antibiotic resistance in fish may impede Sustainable Development Goal 3, which aims to promote good health and well-being (MacGowan & Macnaughton, 2017).

In this review, we discuss commonly used chemicals in fish health, routes of antibiotic administration, commonly used antimicrobial susceptibility testing techniques, and antibiotic resistance in water, fish, and sediment. The challenges, strategies, and constraints in counteracting antibiotic resistance, and prospects for antibiotic use in aquaculture are discussed as well. We hope that the knowledge shared in this review will enhance our understanding of antibiotic usage and pragmatic ways to help curb the growing menace associated with its use in aquaculture.

1.1. Antibiotic Groups Used in Aquaculture

Commonly used antibiotics in aquaculture include various substances. According to Schar et al. (2020), antibiotics such as quinolones, tetracyclines, amphenicols, and sulfonamides, which are classified as critically important for human medicine by the World Health Organization (WHO), account for 27%, 20%, 18%, and 14% use in aquaculture operations respectively. Other classes of antibiotics such as cephalosporins, lincosamides, and macrolides are less used in aquaculture. Enrofloxacin (Dawoodet al., 2018), chloramphenicol and amoxicillin (Apenteng et al., 2022; Abarike et al., 2023) are emerging antibiotics currently used in aquaculture settings (Corum et al., 2022; Uney et al., 2021). The choice of antibiotics in aquaculture is influenced by susceptibility of the fish species to various bacterial diseases, availability and accessibility of different antibiotics, ability to accurately diagnose diseases, presence of antibiotic-resistant bacteria, and regulations in the target markets for fish products, especially those related to food safety and certifications.

1.2. Antibiotic Administration in Aquaculture

In aquaculture, various fish species are commonly treated with antibiotics to manage bacterial infections and ensure their health. In Table 1, fish species, commonly used and routes/mode of antibiotic administration methods in aquaculture are shown.

Table 1. Examples of culture fish, antibiotic types, and route of administration**.**

Fish Species	**Antibiotic (s) Used**	**Mode of Administering**	**References**
Catfish (*Clarias gariepinus*)	Oxytetracycline and furasol	Oral	(Lawal, et al., 2012)
European sea bass larvae (*Dicentrarchus labrax L.*,)	Oxolinic acid	Bath	(Touraki et al., 2012)
Nile tilapia (*Oreochromis niloticus*)	Florfenicol	Oral	(Gaikowski, et al., 2013)
Fairy shrimp (*Branchinella thailandensis*)	Sodium hypochlorite, oxytetracycline dehydrate and chloramphenicol	Bath	(Saejung et al., 2014)
Pangasius catfish	Enrofloxacin and ciprofloxacin	Oral	(Andrieu et al., 2015)
Nile tilapia (*O. niloticus*)	Chlortetracycline, doxycycline, florfenicol flumequine, nalidixic acid sulfadiazine sulfathiazole	Oral and injection	(Mostafa et al., 2017)
Nile tilapia (*Oreochromis niloticus)*	Oxytetracycline (OTC)	Oral and bath	(Julinta et al., 2017)
Crucian carp (*Carassius auratus gibelio*)	Enrofloxacin	Oral, intramuscular and bath	(Shan et al., 2018)
Nile tilapia (*Oreochromis niloticus*)	Oxytetracycline	Oral	(Limbu, et al., 2019)
Nile tilapia (*Oreochromis niloticus)*	Emamectin benzoate	Oral	(Julinta et al., 2020)
Rainbow trout (*Oncorhynchus mykiss*)	Danofloxacin	Oral and injection (intravenous, intramuscular)	(Terzi et al., 2020)
Rainbow trout (*Oncorhynchus mykiss*)	Enrofloxacin	Implantation	(Hjelmstedt et al., 2020)
Yellow catfish (*Pelteobagrus fulvidraco*)	Doxycycline	Oral	(Xu, et al., 2021)
Olive flounders (*Paralichthys olivaceus*)	Lincomycin	Injection	(Lee et al., 2022)
Rainbow trout (*Oncorhynchus mykiss)*	Doxycycline	Injection (IV), (IM) and oral gavage	Altan et al., 2024
Rainbow trout (*Oncorhynchus mykiss)*	Doxycycline	Injection (oral gavage)	Corum et al., 2023
Rainbow trout (*Oncorhynchus mykiss)*	Oxytetracycline	Injection (oral gavage)	Corum et al., 2023
Nile tilapia (*Oreochromis niloticus*)	Enrofloxacin	Injection (IV), (IP) and oral gavage	Corum et al., 2022
Rainbow trout (*Oncorhynchus mykiss)*	Cefquinome	Injection (IV), (IP) and oral gavage	Durna Corum et al., 2022

1.3. Oral Route

Oral administration is done by adding antibiotics to the water in which fish live or by mixing it with the feed administered (Shan et al., 2018; Terzi et al., 2020). The majority of practitioners use this method though there are concerns. For instance, oral administration of antibiotics leaves large amounts of antibiotic residues in the environment. In addition, fish do not effectively metabolize antibiotics and will pass approximately 75% of unused antibiotics back into the environment through feces (Okocha et al., 2018). Thus, this method has several disadvantages. Oral methods invariably contribute to the development of drug-resistant bacteria. Resistant bacteria can survive and multiply in the presence of those antibiotics, whereas susceptible bacteria can be eliminated. This can lead to the proliferation of resistant strains, thereby increasing the overall level of antibiotic resistance in aquaculture environments (Watts et al., 2017). The oral administration of antibiotics in aquaculture can facilitate the transfer of resistance genes from antibiotic-exposed bacteria to others present in aquatic environments, thus increasing bacterial resistance (Sáenz et al., 2019). Other theoretical perspectives indicate that orally administered antibiotics could remain in the water and can contribute to the contamination of aquatic ecosystems when discharged through effluents from aquaculture facilities, promoting the development and persistence of antibiotic resistance in environmental bacteria (Okon et al., 2022). Oral antibiotics used in aquaculture can also affect non-target organisms, including bacteria that are beneficial or part of the natural microbial community. Disruption of the normal microbiota in aquatic environments can create ecological imbalances, allowing opportunistic or resistant bacteria to thrive.

1.4. Injection

Antibiotics could be injected intramuscularly, intraperitoneally, or intravenously into individual fish in response to a diseases situation. This enables precise dosage delivery and quicker action than other administration methods (Lee et al., 2022; Mostafa et al., 2017). Similarly, injecting antibiotics into fish can also contribute to the development of increased antibiotic resistance in aquaculture through various means, as described previously for oral administration. Moreso the injection method may not reach all infected fish in the population. This is because infections in aquaculture settings can spread rapidly, and treating individual fish can be logistically challenging. Thus, pathogenic bacteria may still persist and can potentially develop resistance to the antibiotics used. Unsuccessful eradication creates opportunities for bacterial transmission to other fish, further spreading antibiotic-resistant strains (Skandalis et al., 2021). In addition, administering an appropriate dosage of antibiotics through injection can be challenging. Sometimes, underdosing occurs when the antibiotic concentration is insufficient to eliminate bacteria, which can again lead to the development of resistant strains (Pereira et al., 2022; Rossiter et al., 2017). Conversely, overdosing a times occurs leading to the selection and survival of more resistant bacteria that can withstand higher antibiotic concentrations (Manyi-Loh et al., 2018; Raju et al., 2022).

1.5. Bath Administration

This method of administration works well for skin and gill infections but may contaminate the environment and lead to the growth of antibiotic-resistant bacteria (Saejung et al., 2014; Touraki et al., 2012). Also, bath treatments may result in variable doses and exposure levels in individual fish within a population (Jansen et al., 2016; Limbu et al., 2018). Factors such as fish size, behavior, and water flow can affect the amount of antibiotics absorbed by fish (Yukgehnaish et al., 2020). This can lead to inconsistent treatment outcomes and inconsistent effectiveness in controlling infections. Bath treatments expose the target pathogens and the normal microbiota and non-target organisms of fish in the aquatic environment to antibiotics. This exposure can disrupt the natural microbial balance, potentially leading to the development of antibiotic resistance in non-target bacteria and impacting the overall ecological health of the system. The exposure of bacteria to sub-lethal concentrations of antibiotics during bath treatments can promote the selection and survival of antibiotic-resistant strains. Resistant bacteria can emerge and spread within a treated population or be released into the environment, thereby contributing to the overall problem of antibiotic resistance (Bengtsson-Palme et al., 2018; Serwecińska, 2020; Ye et al., 2021).

Aquaculture operators and researchers need to carefully consider the specific requirements of the aquaculture system and adhere to the regulations and best practices for responsible antibiotic use to address the challenges associated with the oral, injection, and bath methods of administering antibiotics to cultured fish. In addition, antibiotic resistance can be minimized by using antibiotics only when necessary, adhering to proper dosage guidelines, following withdrawal periods, and considering alternative disease management strategies, such as using probiotics and prebiotics, which minimize the use of antibiotics.

Implementing good aquaculture management practices, such as improving water quality, optimizing nutrition, and enhancing biosecurity measures, can also help reduce the reliance on antibiotics and promote a healthier and more sustainable aquaculture industry (Treves-Brown, 2013).

1.6. Common Antibiotic Susceptibility Tests used in Aquaculture

Antibiotic susceptibility testing is essential for controlling bacterial infections in fish (Syal et al., 2017; Terzi et al., 2020). This test helps to monitor the emergence of antibiotic-resistant bacteria and determine which antibiotics should be used to treat bacterial infections (Baltekin et al., 2017; Syal et al., 2017). This examination has shown promise in aquaculture environments and is crucial for controlling bacterial infections in fish populations. Finding the best antibiotics to treat bacterial infections in fish is paramount for breeding healthy fish for consumption. To date, disk diffusion and microdilution are the two predominant techniques used to analyze antibiotic susceptibility tests (Goel et al., 2009; Jayachandran et al., 2018). Generally, antibiotic susceptibility test (AST) methods have major limitations. This includes the constantly evolving bacteria antibiotic resistance mechanisms of bacteria that enable them to adapt and develop new mechanisms to evade antibiotics. As traditional AST methods rely on established resistance patterns, continually evolving can evade these methods as they become outdated and fail to detect emerging resistance. Therefore, traditional susceptibility test methods may not accurately detect certain types of resistance, such as low-level resistance, inducible resistance, or specific mechanisms, such as efflux pumps or enzymatic inactivation of antibiotics. This can lead to the misinterpretation of susceptibility results and inappropriate antibiotic selection. Testing the susceptibility of certain bacteria is inherently challenging because of their slow growth and fastidious nature. Examples include certain species of Mycobacterium and anaerobic bacteria (Van Belkum et al., 2020). These organisms may require specialized test methods or prolonged incubation periods, further adding to the time and complexity of susceptibility testing. Bacteria with biofilm features can exhibit increased antibiotic resistance compared with their planktonic counterparts. Therefore, standard susceptibility test methods may not adequately capture the antibiotic resistance displayed by biofilm-associated bacteria. Antibiotic susceptibility testing is typically performed under laboratory conditions, which may not completely represent the complex environment encountered in fish bodies during infection. Factors such as the host immune response, bacterial interactions, and tissue penetration of antibiotics cannot be fully simulated in vitro. As a result, susceptibility test results may not always accurately predict the clinical response to antibiotics (Ahmed et al., 2018; Berlanga et al., 2017; Sønderholm et al., 2017).

1.7. Disc Diffusion Method

The disk diffusion method, a longstanding approach in AST, remains widely used due to its versatility and applicability for testing most bacterial pathogens (Matuschek et al., 2014). To interpret AST results, critical values called breakpoints are employed. These breakpoints define the boundary between susceptibility and resistance for each antimicrobial agent International organizations, such as the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST), establish these breakpoints (Satlin et al., 2020). While various European national antimicrobial breakpoint committees (e.g., BSAC, CA-SFM, DIN, and SRGA) have developed their own disk diffusion methods, there was no standardized method calibrated to European breakpoints. Consequently, EUCAST initiated the development of a harmonized disk diffusion method calibrated to the minimum inhibitory concentration (MIC) for accurate interpretation of results (Matuschek et al., 2014).

In the disc diffusion method, a petri dish containing isolated fish-derived bacterial colonies is positioned on sterile paper discs with a specific antibiotic concentration (Jonasson et al., 2020). As the antibiotics diffused out of the disc and into the agar medium, the zone of inhibition surrounding the disc is measured. The susceptibility of bacteria to antibiotics can be determined by the size of the zone of inhibition (Bakht et al., 2011; Jonasson et al., 2020). Several aquaculture studies have used the disk diffusion assay as a model to study antibiotic susceptibility potency against isolates from fish species. Recently, Wanja et al. (2020) used the disk diffusion assay to study the susceptibility rate of some selected antibiotics (including ampicillin, tetracycline, co-trimoxazole, streptomycin, kanamycin, gentamicin, and chloramphenicol) on some 48 isolates belonging to *Aeromonas*, *Proteus*, *Klebsiella*, *Citrobacter*, *Salmonella*, *Streptococcus*, *Pseudomonas*, *Escherichia*, *Serratia*, and *Micrococcus*. They reported that the overall susceptibility rates for each antibiotic for all the bacterial isolates were the highest for gentamicin (100%, n = 48) and kanamycin (92%, n = 44). In addition, Wamala et al. (2018) used a disk diffusion assay to evaluate the susceptibility of 14 antibiotics against isolates (*Aeromonas hydrophila*, *Aeromonas sobria*, *Edwardsiella tarda*, *Flavobacterium* spp, and *Streptococcu*s spp.) from *Oreochromis niloticus* (Nile tilapia) and *Clarias gariepinus* (African catfish). This study revealed that all isolates tested were susceptible to at least ten of the 14 antibiotics evaluated. Through a disc diffusion assay, they further revealed that all isolates expressed high levels of resistance to penicillin, oxacillin, and ampicillin. Moreover, using a disc diffusion assay, Pauzi et al. (2020) reported the antibiotic resistance of *A. hydrophila* to amikacin, ampicillin, cefotaxime, amoxicillin, trimethoprim-sulfamethoxazole, erythromycin, and streptomycin, with a multiple antibiotic resistance index of 0.5. This indicates that these drugs are not sufficiently potent to kill the aforementioned isolates, making it imperative to look for alternative antibiotics when the disease persists. We are optimistic that studies of this nature will provide baseline information for future reference and fish disease management.

1.8. Broth Microdilution Method

The broth microdilution method involves evaluating the resistance of bacteria to various antibiotic concentrations in a liquid medium. Following incubation, the bacteria are cultured in wells containing antibiotics at different concentrations and bacterial growth evaluated. The concentration at which bacterial growth is inhibited is known as the minimum inhibitory concentration (MIC) of that antibiotic (Indira, 2014; Pfaller & Diekema, 2012). It is important to note that the appropriate antibiotic susceptibility test depends on the type of bacteria being examined. Microdilution assays provide valuable information regarding the sensitivity of pathogens to antimicrobial substances and aid in determining appropriate treatment regimens in aquaculture. For example, Assane et al. (2021) used a broth microdilution method to evaluate the susceptibility of *A. jandaei* isolates from tilapia to enrofloxacin, florfenicol, oxytetracycline and thiamphenicol. They reported that strains isolated from tilapia in an earthen pond were resistant to oxytetracycline, whereas strains isolated from fiberglass tanks were sensitive to all antimicrobials. Monitoring changes in inhibition concentration values over time can help detect emerging resistance trends, allowing for the early implementation of appropriate management strategies and the development of alternative treatment options.

1.9. Multidrug Resistance Bacteria in Aquaculture

The rise of multidrug-resistant (MDR) strains poses a significant global challenge in both veterinary medicine and human health. An isolate is classified as MDR if it exhibits resistance to three or more classes of antimicrobials (Leal et al 2023). Bacteria exposed to antibiotics or other antimicrobials may develop resistance through a variety of mechanisms, such as mutations and bacterial acquisition of resistance genes (Algammal et al., 2022; Sivaraman et al., 2020). Antibiotics are commonly detected in aquaculture water with geographical variations due to different farming practices and species composition (Yuan et al 2023). The prevalence and distribution of MDRisolates in water sources represent a critical global issue with significant implications for public health. Numerous surveillance studies have highlighted the alarming presence of MDR bacteria in various water bodies, including rivers, lakes, and municipal water supplies. For example, bacterial strains including *Salmonella, Escherichia coli, Pseudomonas* spp., *Aeromonas* spp., and *Vibrio* spp. have been identified as the most prevalent MDR found in water (Legario et al., 2020; Patil et al., 2016; Yang et al., 2017). Antibiotic presence in water could be affected by solubility, frequency of use, and growth stages of cultured organisms. Environmental conditions such as dry seasons and extreme temperatures, also influence antibiotic concentrations (Yuan et al 2023). Factors such as antibiotic pollution, contamination from human and animal waste, and the potential for horizontal gene transfer contribute to the emergence and persistence of MDR isolates in the aquatic environment. Martínez (2015) and Chen et al. (2019) demonstrated that antibiotic residues in water can create selective pressures, driving the evolution of antibiotic resistance in aquatic environments. A report by Ikhrami et al. (2024) showed that antibiotic resistance genes have recently emerged as environmental contaminants. Water from irrigation canals, which receives contamination from river pollutants, can become a hotspot for antimicrobial resistant genes such as sulfonamide (sul1), tetracycline (tetA), beta-lactam (blaGES), and multidrug resistance.

In addition to the immediate health risks posed by MDR isolates in water, there are broader concerns regarding their impacts on ecosystems and the environment. The presence of antibiotic-resistant bacteria in aquatic ecosystems can disrupt the ecological balance and biodiversity, potentially leading to long-term environmental consequences. Studies conducted by D'Costa et al. (2011) and Wright (2016) highlighted the role of aquatic environments in facilitating the transfer of resistance genes between bacteria and accelerating the spread of antibiotic resistance. Furthermore, the spread of antibiotic resistance through water sources has implications beyond human health and affects agriculture and animal husbandry. Aquaculture serves as a hotspot for the transfer of resistance genes. In a review by Hossain et al (2022), MDR strains are increasingly detected in fish and the aquaculture environment, posing a significant threat to medical treatment options and contributing to unwanted deaths. Also, effluents from wastewater treatment plants on farm ways can increase the prevalence of antibiotic resistance bacteria in waterbodies. It has been found that MDR bacteria isolates persist in aquatic environments and these bacteria isolates possess genes associated with resistance. In some studies, for instance, *Aeromonas* spp. strains from urban wastewater treatment and *Clostridium perfringens* from water samples have been reported. Sustainable solutions should prioritize the protection of public health, the preservation of ecosystems, and the promotion of responsible antibiotic usage across various sectors, as emphasized by Larsson (2014) and Collignon et al. (2018). Considering all of the above, a conclusion can be made that the interconnectedness of aquaculture, terrestrial environments, and human populations facilitates bacterial transmission. The One Health concept, recognizing links between human, animal, and environmental health, offers a holistic approach to tackle antimicrobial resistance. By embracing this approach, we can safeguard the future of aquaculture while ensuring health, food safety, and environmental protection (Milijasevic et al., 2024). Understanding these factors and their geographical and seasonal variations is essential for devising effective mitigation strategies. Such strategies include improving water treatment processes, promoting antibiotic stewardship, and adopting a One Health approach that integrates efforts across human and veterinary medicine, agriculture, and environmental sciences. By collectively addressing this issue, as proposed by Wang et al. (2021), we can work towards safeguarding water quality and minimizing the risks associated with MDR bacteria in water sources, ensuring access to safe and clean water. Some other fish-related bacteria with antibiotic resistance genes have also been isolated from fish. For example, *Listeria innocua* isolated from catfish fillets and *Enterococcus faecium* strain isolated from ready-to-eat raw fish have been reported in rainbow trout. The dissemination of antibiotic resistance genes in the environment poses a significant concern (Chen et al., 2010). Table 2 shows bacteria isolates with antimicrobial resistance from commonly cultured fish.

Table 2. Bacterial isolates with antimicrobial resistance from commonly cultured fish.

Fish Species	Isolates	Aquaculture Facility	Resistance to Antibiotic (s)	References
Catfish	*Aeromonas hydrophila*	Pond	Tetracycline	(Nawaz et al., 2006)
Nile tilapia	*Aeromonas caviae*	Wet market	Tetracycline, nitrofurantoin and augmentin	(Ashiru, et al., 2011)
Catfish (*Clarias gariepinus*) and Tilapia (*Tilapia mossambica*)	*Salmonella spp.*	Wet market and ponds	Chloramphenicol, clindamycin, rifampicin, spectinomycin, and tetracycline	(Budiati et al., 2013)
Diseased catfish (*Clarias gariepinus*)	*Aeromonas hydrophila*	River	Ampicillin	(Laith & Najiah, 2014)
African catfish *(Clarias gariepinus)*	*Salmonella Spp.*	Fish farm and wet market	Penicillin, clindamycin, tetracycline, and rifampicin	(Sing et al., 2016)
Common carp (*Cyprinus carpio carpio*) fingerlings	*Aeromonas Spp.*	Pond	Sulfadiazine-trimethoprim, oxytetracycline, florfenicol	(Patil et al., 2016)
Channel catfish	*Aeromonas veronii*	River	Ciprofloxacin, levofloxacin, and norfloxacin	(Yang et al., 2017)
Red hybrid tilapia (*Oreochromis* spp.)	*Aeromonas hydrophila* and *Edwardsiella tarda*	River	Novobiocin, ampicillin, spiramycin, and chloramphenicol	(Lee & Wendy, 2017)
Nile tilapia (*Oreochromis niloticus*)	*Streptococcus iniae* and *Streptococcus agalactiae*	Grow-out cages, ponds and hatcheries	Oxolinic acid, sulphamethoxazole-trimethoprim	(Legario et al., 2020)
Pangasius catfish (*Pangasius hypophthalmus*)	*Escherichia coli*	Freezing factories	Colistin, ampicillin, cefotaxime, streptomycin, meropenem, tetracycline, sulfamethoxazole/trimethoprim and nalidixic acid	(Salako et al., 2020)
Nile tilapia	*Aeromonas hydrophila, A. veronii, Pseudomonas fluorescens* and *P. aeruginosa*	Fish farm	Sulphonamide and tetracycline	(Sherif et al., 2021)
Nile tilapia	*Streptococcus Spp.*	Fish farm	Florfenicol and tetracycline	(Oviedo-Bolaños et al., 2021)
Yellow catfish	*Aeromonas vero nii*	Pond	Ampicillin, tetracycline, trimethoprim-sulfamethoxazole	(Li, et al., 2022)

Verner-Jeffreys et al. (2009) observed a high prevalence of MDR bacteria and associated antimicrobial resistance genes in ornamental fish. For example, 47 of 94 *Aeromonas* spp. isolates recovered from tropical ornamental fish were tolerant to 15 or more antibiotics, representing seven or more classes of antimicrobials. The quinolone and fluoroquinolone resistance gene, qnrS2, was detected at a high frequency (37% of tested recent isolates were positive using PCR). In addition, the study found that (17.7%) of the isolates were identified as target microorganisms (high and critical priority pathogens on the WHO list). The same study reported that 80% of 628 strains of tetracycline-resistant (Tetr) and sulphamethoxazole-resistant (Sulr) bacteria associated with fish and shrimp samples were found resistant to more than one antibiotic. These findings suggest that ornamental fish act as reservoirs for both MDR bacteria and their resistance genes. Aeromonas pathogens were found in the gut and skin of treated fish, and biofilms became MDR to streptomycin, sulfamethoxazole, quinolones, fluoroquinolones, oxytetracycline, florfenicol, chloramphenicol, and trimethoprim. This increases the transfer of relevant genes to wider aquatic environments during harvesting (Naviner et al., 2011). These findings suggest that aquaculture fish also act as a reservoir for both MDR bacteria and resistance genes (Arias-Andres et al., 2018). The prevalence and distribution of MDR isolates in fish can be attributed to various factors, including the use of antibiotics in aquaculture. Miranda et al. (2018) highlighted the role of antibiotic use in fish farming as a major driver of antibiotic resistance in aquatic systems. Additionally, the interconnectedness of aquatic ecosystems enables the exchange of resistance genes between bacteria, facilitating the spread of resistance, as demonstrated in a study on fish by Bhullar et al. (2012). There is a correlation between the prevalence and distribution of MDR isolates in fish and their habitats. We hypothesized that lay aquaculture practitioners may have difficulty understanding the aetiology of these isolates and may misapply antibiotics to which the isolates have developed drug resistance. It is clear that efforts to reduce the prevalence of MDR bacteria in fish must take into account both environmental and human health impacts. Generally, antibiotic concentrations and ARG abundance in sediment are much higher than those in water (Yuan et al 2023). Antibiotics present in the water column can adhere to suspended particulate matter and eventually settle into sediment. Sediments tend to accumulate antibiotics due to their gradual hydrolysis in water. Numerous studies have demonstrated that antibiotic concentrations in sediments are higher than in water, primarily because of greater stability. In aquaculture settings, antibiotic residues may progressively accumulate in sediment, potentially contributing to the evolution of antibiotic-resistant pathogens (Yuan et al., 2023).

The presence and distribution of MDR bacteria in aquatic sediments represent a critical environmental concern with potential implications for both ecosystems and human health. Factors contributing to the emergence and persistence of MDR bacteria in sediment environments are multifaceted. Sediments can act as sinks for antibiotic residues and resistance genes, providing favorable conditions for the selection and maintenance of antibiotic-resistant bacteria. Munir et al. (2011) demonstrated the accumulation of resistance genes in the sediments of a river receiving effluents from wastewater treatment plants. Additionally, sediment bacteria can exchange resistance genes through horizontal gene transfer, as shown in the research by Ma et al. (2019). Several studies have examined the prevalence of MDR bacteria in sediment samples collected from aquatic environments. For example, Amos et al. (2015) reported a high prevalence of antibiotic-resistant bacteria in sediment samples from rivers, lakes, and coastal areas, highlighting the extensive distribution of MDR bacteria in sediment matrices (Amos et al., 2015). Furthermore, a study conducted by Czekalski et al. (2016) investigated sediment samples from wastewater treatment plants and identified MDR bacteria, suggesting that these treatment systems may serve as reservoirs for antibiotic-resistance genes in sediment environments (Czekalski et al., 2016). Mitigating the prevalence of MDR bacteria in sediments is crucial for protecting aquatic ecosystems and minimizing potential human health risks.

1.10. Challenges Associated with Antibiotic Resistance in Aquaculture

The effects of antibiotic resistance in cultured fish are diverse. This poses a challenge for fish farmers, as it becomes increasingly difficult to treat infections effectively and maintain fish health (Algammal et al., 2022; Lafferty et al., 2015; Minich et al., 2018; Wamala et al., 2018). This can lead to higher mortality rates, slower growth rates, and financial losses for the fish farmers. Antibiotic-resistant bacteria present in aquaculture systems have the potential to spread to surrounding water bodies, potentially affecting other aquatic organisms, such as wild fish, and disrupting the ecological balance, aggravating the issue on a broader scale (Okeke et al., 2022; Preena et al., 2020).

Antibiotic-resistant bacteria in aquaculture pose a risk to human health. If fish-carrying resistant bacteria are not properly processed before consumption, transfer of antibiotic-resistance genes to humans is possible. This can compromise the effectiveness of antibiotics in treating human infections and contribute to the overall burden of antibiotic resistance in humans. The transmission of antibiotic-resistant bacteria from aquaculture to humans raises concerns regarding the risk of treatment failure and the limited availability of effective antibiotics to combat bacterial infections in both medical and agricultural contexts (Bengtsson-Palme et al., 2014; Collignon et al., 2018).

Addressing antibiotic resistance in aquaculture requires a holistic approach emphasizing antibiotic use, disease prevention strategies, and robust surveillance systems. It is important to address the problem of antibiotic resistance in fish culture through open discussions among aquaculture farmers, governments, and researchers. These discussions should aim to develop and promote sustainable aquaculture practices that prioritize fish health and environmental and human well-being. Implementing responsible and careful use of antibiotics, strengthening biosecurity measures, promoting disease prevention through effective management practices, exploring alternative strategies for disease control, such as vaccines and probiotics, and improving the management of water quality in aquaculture systems should be priorities (Barnes et al., 2022; Desbois et al., 2021; Garza et al., 2022). Additionally, there is a need to increase the surveillance and monitoring of antibiotic resistance in aquaculture settings to guide evidence-based interventions and policy decisions (Hoa et al., 2011).

1.11. Strategies to Deal with Antibiotic Resistance in Aquaculture

Addressing antibiotic resistance in aquaculture is a critical challenge for the industry and public health. According to WHO 2014, there is a need to encourage and promote responsible antibiotic use in human and veterinary medicine to minimize unnecessary antibiotic use. Various strategies include:

1. Reduced antibiotic use. This is considered a fundamental strategy and includes limiting the prophylactic and growth-promoting use of antibiotics. In a study by Li et al. (2018), the impact of increasing antibiotic resistance in water was reduced by regularly monitoring water sources for the presence of antibiotics and resistant bacteria to identify contamination and track changes in resistance patterns. This information can be useful for implementing appropriate control measures. Belkina et al. (2017) stressed the need to raise public awareness and conduct educational campaigns on antibiotic resistance and its environmental impact, as this could lead to impactful behavioral changes.

2. Alternative disease management practices. Adopting alternative disease management practices is crucial. Research suggests the potency of probiotics, immune stimulants, and herbal remedies as alternatives to antibiotics (Dangtip et al., 2019). Medicinal plants are gaining recognition as sustainable alternatives to antibiotics in aquaculture. Recent studies underscore the effectiveness of these natural compounds in boosting the immune response of aquatic species, thereby reducing dependence on synthetic antibiotics (Bondad-Reantaso et al., 2023). These plants provide eco-friendly solutions with minimal environmental impact and help address the issue of antibiotic resistance (Rahimi et al., 2022). The presence of phytogenic compounds such as phenolics, essential oils, pigments, alkaloids, terpenoids, tannins, polypeptides, polysaccharides, steroids, and flavonoids has shown promising results as immunostimulants, antibacterials, antioxidants, antiparasitics, and antivirals (Abdallah et al., 2023).

3. Enhanced monitoring and surveillance. There is a need for better data collection and reporting of antibiotic usage to track resistance patterns in aquaculture settings (Cabello,2006).

4. Improved farm management. Practices, such as improved water quality control and reduced stocking densities, can help prevent disease outbreaks, reducing the need for antibiotics (Mohanty et al., 2019).

5. Regulatory measures. Regulating the use of certain antibiotics in aquaculture is pertinent and has been proposed by several research studies. For instance, Rico et al. (2014a) discuss the potential benefits of stricter regulations on antibiotic use in fish farming.

6. Design of novel antibiotics to mitigate antibiotic resistance in aquaculture systems. Nanotechnology has emerged as a promising tool for biomedical applications to treat diseases. Shine et al. (2020) explored the antimicrobial potential of Parkia biglobosa-mediated gold nanoparticles, which effectively inhibited the growth of some clinical isolates. Another study by Cai et al. (2016) explored the potential of novel antimicrobial peptides in aquaculture disease management.

7. To effectively combat antibiotic resistance, we must recognize it as both an environmental concern and a challenge related to livestock and wildlife. Integrating the One Health approach into the public health system is crucial for effectively addressing the emergence and spread of antibiotic-resistant bacteria and resistance genes (Ajayi et al., 2024)

By adopting these strategies, aquaculture can move towards a more sustainable and responsible approach to antibiotic use, reducing the risk of antibiotic resistance in fish and promoting healthier aquatic ecosystems.

Constraints to the Adoption of Antibiotic Resistance Strategies

Although multiple strategies have been proposed to combat antibiotic resistance in aquatic environments, implementing these strategies may differ. However, these strategies face several constraints and challenges that hinder their adoption and effectiveness. There may be limited resources, infrastructure, or the political will to enforce regulations and best practices in some regions. This can lead to inconsistent results and a continued increase in antibiotic resistance. Transitioning away from antibiotics may require investment in infrastructure, research, and the development of new techniques, which aquaculture farmers or aquaculturists may not be able to fund. Rico et al. (2014b) addressed the economic considerations related to reducing antibiotic use in aquaculture. Additionally, the limited availability of alternatives has become a challenge. In some cases, viable alternatives to antibiotics are limited or underdeveloped. This underscores the need for research and innovation to identify and develop effective non-antibiotic disease management strategies (Dangtip et al., 2019).

Lack of awareness and education among fish farmers and aquaculture practitioners is a dwindling factor. Practitioners and farmers may lack knowledge of antibiotic-related issues and alternative strategies. To understand the etiology and pathogenesis of disease outbreaks in an aquaculture setting, it is imperative to know the type of antibiotics to administer and the manufacturer’s requirements, such as the effective mode of administration, dosage required, and application time. It is important to recognise that regulatory and political challenges may not adequately address the use of antibiotics in aquaculture in some countries (Cabello,2006). One of the constraints that has gained prominence is the persistence of microbial resistance in aquaculture. Several studies investigated the resistant traits in isolated microbes. Genes responsible for antibiotic resistance may continue to circulate in bacterial populations and the environment, thus posing ongoing challenges (Ma et al., 2019).

Addressing these constraints requires collaborative efforts among governments, industry stakeholders, researchers, and policymakers. Strategies to promote responsible antibiotic use and alternative disease management practices must consider economic, educational, regulatory, and cultural factors influencing adoption.

1.12. Conclusion and Future Outlook

Fish products are of great economic value and provide important nutrients. Against this background, aquaculture farmers have shifted from traditional fish-rearing methods to more intensive methods. However, the increasing incidence of bacterial transmission during intensive fish farming is a concern. Aquaculture is a contributing factor in spreading bacteria, as has been made evident in the majority of the studies analyzed. Although antibiotics are effective in the treatment of bacterial infections, surprisingly, it is evident that the isolates obtained are resistant to the most commonly used antibiotics (colistin, ampicillin, cefotaxime, streptomycin, meropenem, tetracycline, sulfamethoxazole/trimethoprim and nalidixic acid) as reported in most of the literature reviewed.This calls for immediate actions to reduce the growing risk of antibiotic resistance.

Although numerous studies have investigated multidrug resistance in many cultured fish there has not been a promising proposal to curb microbial antibiotic resistance. Against this background, we outline the following recommendations that would be valuable in curbing the issues of microbial resistance to boost modern aquaculture practices:

1. Diversifying intensive farming methods to limit or prevent the spread of bacteria is pertinent and should be an area of research interest.

2. Understanding disease development in aquaculture is crucial. This understanding is essential, as some bacteria may originate from fish feed, enabling accurate administration of the appropriate antibiotic dosage.

3. Model studies to understand the cellular activity of most antibiotic drugs have shown that antibiotic and bacterial membrane interactions observed in vitro do not occur in the same way in physiological environments. Due to the complexities and uncertainties that exist during the transition from in vitro to in vivo with the regularly used mode of antibiotic administration, it would be valuable

to strategically develop a paradigm that can decipher the in vitro efficacy of antibiotics, has the capacity to accurately predict their physiological consequences in vivo, and can kill bacteria without developing any resistance, such as nanotechnology.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS

Supervision: E.D.A.Writing, review & editing: E.D.A., E.O., E.Y. All authors approved the final draft.

ETHICAL STATEMENTS

Local Ethics Committee Approval was not obtained because experimental animals were not used in this study.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable for the present study as no new data was created or analyzed.

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