



A review on aquaculture adaptation for fish treatment from antibiotic to vaccine prophylaxis

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Abstract

Aquaculture is considered one of the fastest-growing food production sectors, which provides about 41% of the world's fish food. Different types of pathogens, including bacteria, viruses, amoebas, oomycetes, fungi, and ectoparasites, have emerged to cause serious fish diseases. Medicines such as antibiotics and chemicals as well as vaccines have been widely used to combat fish diseases. However, their undesirable use to treat fish in aquaculture develops drug resistance in the surrounding microbes, especially antibiotic resistance in fish-associated bacterial strains in the column water and sediment, is mostly the consequence of applying antibiotics in aquaculture. The rise of antibiotic resistance in aquaculture and multidrug-resistant pathogens in the food chain threatens public health, hampering infection treatment and compromising food safety. Addressing this challenge is vital to protect both public well-being and the aquaculture industry's future. Basic control measures for sustainable, disease-free aquaculture, including alteration of antibiotic resistance genes into other animal pathogens, have been driven by the potential development of antibiotics with respect to environmental impact and consumer safety. Anyhow, vaccination is an effective control measure that overcomes drug resistance conditions in aquaculture; even some therapeutic and prophylactic methods are being simultaneously applied for the treatment of fish diseases. Mostly, antibiotics and probiotics do not show strong effects after the development of new mutant strains and drug-resistant pathogens. Therefore, various types of vaccines have been developed to treat aquatic pathogens effectively by using advanced molecular techniques. Previous studies on fish vaccines have typically lacked comprehensive assessments of vaccine efficacy across varying environments and species, often focusing on single pathogens while neglecting the potential influence of pathogen interactions within complex aquatic ecosystems. This review focuses on advancements in technology and prospects of vaccines used in the aquaculture industries for reducing antibiotics usage. It also discussed the vaccination from traditional to modern new-generation ones including DNA, monovalent, and polyvalent vaccines. The objective is to provide an overview of aquaculture's major bacterial pathogens and how vaccines can substitute antibiotics to protect aquatic animals from various infectious diseases.

Keywords Aquaculture · Bacteria · Disease · Fish · Resistance · Vaccine

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Introduction

As the world's population is growing, the need for food has been enhanced while the major development of traditional land-food production systems became constrained by limited land availability that created food shortages for human beings. Therefore, seafood is viewed as a better source of food to participate in the feeding of the fast-rising human population (Khan et al. 2011). Aquaculture is one of the fastest-growing sectors in food-producing industries as its production has surpassed that of wild catch fisheries (FAO 2017). In the last two decades between 2002 and 2022, world fisheries and aquaculture production increased by 41%, generating 184.6 million metric tons in 2022, which was higher than the reported record of 178.1 million tons in 2021. This marks a 52 million tons increase comparatively with 2002. Finfish including freshwater, diadromous, and marine fish accounted for 76% of the total catch in 2022, however, which was slightly decreased as reported 79% in 2000. Recently in 2022, marine fish produced included 39% of all species followed by freshwater fish (33%), mollusks (13%), and crustaceans (9%) (World Food and Agriculture – Statistical Yearbook 2021).

In aquaculture, production losses are crucial due to disease outbreaks, consequently influencing food insecurity and farmers' livelihoods harmfully. According to the report of FAO (2022), the consequences of diseases affect poor nations severely, causing about half of all productivity losses, which accounts for 90% of all types of aquaculture. Disease-related income losses might reach \$6 billion each year. For instance, the cost of infectious salmon anemia alone in Chile is \$2 billion, which resulted in the layoff of 20,000 people (Lozano et al. 2018). Diseases have cost China, one of the world's largest aquaculture producers, 15% of total fish production loss (Leung and Bates 2012). Various bacteria, viruses, parasites, and fungi constitute the prevalent pathogen disease agents in aquaculture (Dhar et al. 2014). The lack of effective treatment modules for bacterial infections created an urgent need for discovering and implementing effective ways of disease prevention and control (Wilhelm et al. 2006).

Commercial variables influence aquaculture, and stocking densities and rearing conditions are changed to maximize returns within reasonable risk bounds. It is essential to eradicate highly specific pathogens from the stock and to minimize the bacterial burden in the event of opportunistic diseases such as vibrios or motile aeromonads. Antibiotic usage in aquaculture has been a concern for decades. The House of Lords in the UK published "Swann Report" in 1969, which described the unnecessary use of antibiotics in aquaculture and highlighted its possible risks to the health of both animals and consumers. In addition, the resulting data collected from research in Europe and North America recommends that the use of antibiotics should be limited and regulated to certain therapeutic conditions (Aminov 2010).

Antibiotic resistance is a global public health problem. Because of antibiotic resistance and residual difficulties, the use of antibiotics is strictly controlled and regulated. Whenever an antibiotic is administered, regardless of the situation, then the development of resistant bacterial strains may develop. Therefore, it is critical to use antibiotics with high-level caution (Hoelzer et al. 2017).

Generally, disease resistance can be strengthened by employing antibacterial drugs extensively to stimulate the innate immune defense, or using particular vaccinations when specific vaccines are available. Vaccines are employed prophylactically in a high-risk or diseased situation, while they are used therapeutically when there is a disease outbreak in the system (Reinertsen and Haaland 1995). It is recommended to use specific vaccines

according to the “vaccination strategy” for particular diseases to vaccinate, as well as vaccination technique, vaccine type, vaccination schedule, and usage of revaccination. Vaccination is even a cost-effective technique; however, it is getting a higher significant aspect of the treatment management of several hazardous disease conditions in aquaculture productions. Vaccination is an advantageous procedure against various diseases, but still, it has many negative impacts. Anyhow, infectious diseases required the strategic development of vaccine design due to the uncontrolled use of antibiotics in aquaculture, which can lead to an increase in problems like bacterial resistance, environmental challenges, and food safety hazards (Cabello et al. 2016). As a result, fish vaccination has become one of the most significant, simple, and successful methods of preventing and controlling bacterial diseases in fish (Sudheesh and Cain 2017). Several notable advancements have been achieved in the development of viable fish vaccines. However, just a few vaccinations against infectious bacterial illnesses for fish are currently commercially available (Dadar et al. 2017).

For commercial development and use of vaccines, it must consider applications of technique and protocols carefully that can be incorporated into the regular species-specific productions, which are relevant to the ecology and epidemiology of the particular disease, i.e., the geographic range of the disease, seasonal occurrence, and host are an essential consideration for vaccine development and commercialization (Toranzo et al. 2009). The production and development of vaccines have played an essential role in the management of infectious diseases in aquaculture to decrease antibiotic usage in fish. Vaccines are usually more acceptable to treat animals than antibiotics because of their high anticipation against drug resistance, and the protective impact of herd immunity extends to some proportion of unvaccinated animals (Assefa and Abunna 2018). In addition to implementing various techniques in aquaculture, illness surveillance and having sensitive and precise diagnostic tests are essential for ensuring fish health. Even a single strategy for aquaculture health prevention and control is ineffective. How vaccination imparts long-lasting positive effects on fish as compared to antibiotics can be a revelation for understanding the use of bacterial vaccines in fisheries. Therefore, it is important to establish a platform for information exchange on a national or regional level between farmers and responsible parties. This review will go through the disadvantages of antibiotics and will address many forms and applications of bacterial vaccines, which are widely used as a treatment in fish farming. We will discuss the use of conventional aquaculture vaccinations and their applications and will overview the most active molecular methods of novel vaccine development for aquaculture productions.

Globally, there has been an increase in multidrug resistance, which is a hazard to public health. Recent studies have revealed the rise of bacterial infections that are multidrug-resistant and come from various sources, increasing the need for effective antibiotic usage. Due to rapid use of antibiotics, antimicrobial susceptibility testing identified and screened newly emerging MDR strains (Raharjo et al. 2023; Algammal et al. 2023; Algammal et al. (2022a, b)). Crucial public health consequences result from the rise of antibiotic-resistant bacterial infections in fish. It has an impact on food safety, the spread of antibiotic resistance, aquaculture, the possibility for zoonotic disease, ecosystems, treatment options, and international trade, underscoring the need for a comprehensive One Health strategy to address this problem. To reduce the hazards associated with MDR bacterial infections in fish and protect public health, developing new, powerful, and secure antimicrobial drugs is essential (Irshath et al. 2023; Pepi and Focardi 2021; Heuer et al. 2009). Anyhow, vaccines prevent and control diseases, reduce symptoms and productivity losses from infections, and occasionally assist in disease control (Roeder 2011). Vaccines can potentially decrease antimicrobial resistance by preventing infections and reducing the need for antibiotics.

They also enable the use of targeted antibiotics and reduce disease burdens in communities through herd immunity (Lipsitch and Siber 2016). The distinct spectrum of antibiotics versus vaccines complicates efforts to reduce antibiotic use. Antibiotics are often used broadly in animal production based on clinical signs, while vaccines target specific infections or pathogen strains with a limited spectrum (Hoelzer et al. 2018).

Antibiotic use and limitations

To combat disease outbreaks in aquaculture, the best course of action is prevention. It is common practice to offer antibiotic-medicated food to diseased fish to reduce bacterial infections (Cabello 2006). However, this is generally pricey and useless because unwell fish may continue to be off-feed. Furthermore, excessive chemical use against microbes has led to drug resistance, posing significant challenges to public health and national security. It has also been reported that antibiotic resistance enables bacteria to withstand high antibiotic concentrations, giving a selective advantage to resistant community members. Resistant strains outcompete susceptible ones. A concerning issue is that antibiotics in aquaculture overlap with those used in human medicine, promoting resistance to these drugs (Pepi and Focardi 2021). However, due to the various impacts of antibiotics including short-period protection, repeated treatments during outbreaks of diseases, challenges of resistant strains, and the rise of harmful residues in carcasses, it is recommended not to depend on antibiotics as preventative and treatment measures in fish (Miranda and Zemelman 2002). The introduction and extensive regular use of an anti-*Aeromonas salmonicida* vaccination resulted in a significant reduction in antibiotic use in the farmed salmon culture (Morrison and Saksida 2013). Therefore, several studies have reported and suggested that using different bacterial and viral vaccinations in animal populations could result in a significant reduction in antibiotic usage (Murphy et al. 2017). Anyhow, due to the lack of significant research work, clearly recommending the use of vaccines in place of antibiotics has not been properly reported.

Antibiotic resistance in aquaculture

Evaluating the impact of environmental changes on aquaculture sustainability is essential. The multi-antibiotic resistance index (MAR) metrics of aquaculture resemble human clinical bacteria MAR indices. As temperature rises in aquaculture, the prevalence of emerging infectious diseases (EIDs) is expected to rise (Reverter et al. 2020). Hence, antibiotics are often used in fish farming to prevent infectious diseases that threaten aquaculture outputs (Marcos-López et al. 2010). The current extensive use of medications against microorganism in aquaculture and terrestrial contamination of streams promotes the diversity, evolution, and propagation of antibiotic-resistant bacteria of public health significance (Schar et al. 2018).

Anyhow, it is important to know that the calculated MAR indices derived from aquaculture may be limited due to inconsistent reporting of antimicrobial resistance across nations. However, the MAR index of aquaculture was calculated from the data of 40 different countries, which represented 93% of aquaculture production worldwide. Twenty-eight of the forty nations had investigated MAR indices greater than 0.2, which experts believed to have direct high-risk antibiotic contamination (Krumperman 1983). The worldwide MAR

index of aquaculture-related bacteria was 0.25 (standard deviation = 0.01). Zambia (0.56), Mexico (0.55), and Tunisia (0.53) had the highest MAR values, while Canada (0.02), France (0.03), and the USA (0.08) had the least (Fig. 1) (Reverter et al. 2020).

The presence of antibiotic residues in aquatic habitats can promote the growth of resistant bacteria, promoting the spread of antibiotic resistance. This effect occurs even at lower concentrations than the MIC for routinely detected bacterial strains (Bengtsson-Palme and Larsson 2016). Antibiotic-resistant bacterial strains have been found in high concentrations around aquaculture sites where extensive antibiotics were used. This finding highlights the possibility of modified antibiotics exerting significant selective influence in aquaculture settings, enhancing antibiotic resistance among surrounding environmental bacteria (Zhu et al. 2017). Approximately 90% of aquatic bacteria found in natural environments are resistant to at least one antibiotic, with almost 20% resistant to multiple medicines. Multi-resistant bacteria can emerge when several antibiotics are used in aquaculture at the same time. Bacteria with genes encoding new antibiotic resistance pathways were also found (Lin et al. 2015). Resistance to antibiotics permits microorganisms to withstand high antibiotic concentrations, giving members of resistant colonies a selection advantage. Resistant bacterial strains outnumber those that are vulnerable. Some antibiotics used in aquaculture overlap with those used in human medical treatments, resulting in the development of antibiotic resistance (Romero et al. 2012). Overall, these data highlight the importance of immediate responsible measures at national and worldwide levels to reduce antibiotic usage and the global spread of MAR (Interagency Coordination Group on Antimicrobial Resistance (IACG) 2019).

Epigenetic modifications

The collection of molecular alterations known as the epigenome coordinates with the genome and controls how genes are expressed. Epigenetic alterations last longer and manifest symptoms earlier in contrast to DNA mutations. Aside from the programmed

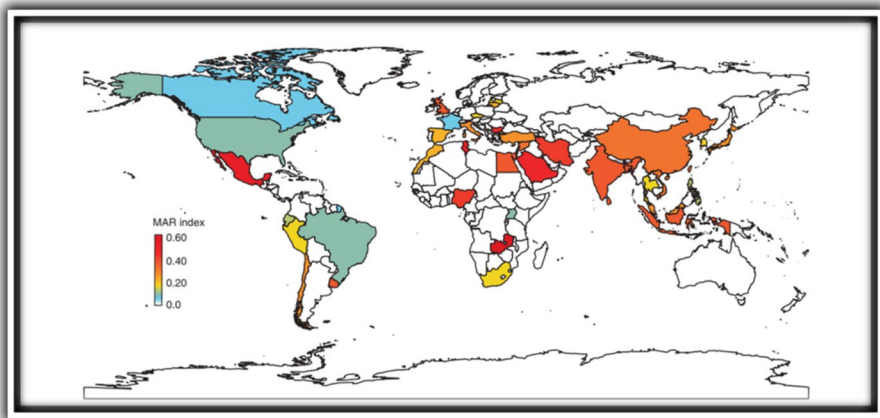


Fig. 1 The worldwide multi-antibiotic resistance (MAR) index is calculated using aquaculture microorganisms. Countries with insufficient data and no established MAR index are represented in white (Reverter et al. 2020)

epigenetic regulation that supports cellular proliferation, epigenetic regulation may be altered by the environment, highlighting the need of studying epigenetic processes in detail (Sarropoulou et al. 2018). Epigenetics participates in the development of drug resistance in microorganisms especially influencing antibiotic resistance in bacteria (Ghosh et al. 2020). Antibiotic resistance driven by epigenetic inheritance in bacteria may be a process that drives evolution (Adam et al. 2008). In response to challenging environmental conditions, reversible epigenetic modifications can provide gene expression with a flexible and adaptable phenotype (Herrel et al. 2020), as well as boost the capacity for organisms to adapt to environmental change (O’Dea et al. 2016).

DNA methylation is an epigenetic remodeling where methyl groups became detached from S-adenosyl methionine and makes a covalent bond to cytosine, and to guanosine, inside a dinucleotide CpG site (Moore et al. 2013). It has been demonstrated that epigenetic pathways are crucial for bacterial and archaeal resistance to heat stress (Blum and Payne 2019), having significant implications for microbial activity in the world dealing with climate change (McCaw et al. 2020). Recent research suggests that epigenetics play a crucial role in the development of drug resistance in bacteria. In the bacterial genome, the methylation of adenines and cytosines can alter mutation rates, regulating antibiotic sensitivity. Epigenetic processes reveal new roles in antibiotic resistance (Quandt et al. 2013). Some researchers are beginning to point to an epigenetic involvement with major implications for microbial activities in a warmer climate.

Epigenetic modifications in fish have the potential to impact antibiotic resistance by affecting different aspects of the fish’s microbiome and bacterial physiology. The relationship between epigenetic alterations in fish and antibiotic resistance constitutes an evolving area of investigation that provides insights into the intricate mechanisms responsible for the development of antibiotic resistance in fish populations. A comprehensive understanding of these mechanisms is vital for developing effective strategies to manage and mitigate antibiotic resistance in both aquaculture and wild fish populations (Consuegra et al. 2023; Pepi and Focardi 2021; Algammal et al. 2022a, b). Anyway, how epigenetic modifications can contribute to antibiotic resistance in fish is discussed below:

Genetic regulation Epigenetic modifications possess the capacity to influence the expression of genes associated with antibiotic resistance. For instance, they can facilitate the overexpression of genes responsible for drug efflux pumps, which actively remove antibiotics from within the cells, thereby reducing the fish’s susceptibility to these drugs. Additionally, epigenetic changes can inhibit the expression of genes responsible for drug targets, ultimately diminishing the efficacy of antibiotics (Pepi and Focardi 2021; Wikumpriya et al. 2023).

Inheritance Epigenetic modifications can be inherited from one generation to the next in fish. Consequently, if fish encounter antibiotics and undergo epigenetic changes that confer antibiotic resistance in their DNA, these changes can be passed down to their offspring. Over time, this can result in a fish population with a heightened prevalence of epigenetic modifications linked to antibiotic resistance (Liu et al. 2022).

Adaptive responses Fish can exhibit epigenetic alterations as an adaptive response to antibiotic exposure. When exposed to antibiotics, fish with specific epigenetic changes that enhance their resistance to these drugs may gain a survival advantage. This can lead to the

selection of fish carrying these advantageous epigenetic modifications within the population (Pepi and Focardi 2021).

Epigenetic flexibility Fish possess the ability to display epigenetic plasticity, enabling them to adapt their epigenetic modifications in response to changing environmental conditions. If fish encounter antibiotics on a recurring basis, they may develop epigenetic modifications that confer antibiotic resistance as a protective mechanism (Moghadam et al. 2015).

Transgenerational impacts Epigenetic modifications in fish can extend their effects across generations. Even if the initial exposure to antibiotics occurs in one generation, the resulting epigenetic changes can persist and affect subsequent generations. This cumulative effect can lead to an increasing prevalence of antibiotic resistance within fish populations over time (Li et al. 2022).

Biofilm formation Epigenetic modifications may also influence the ability of bacteria to form biofilms. Biofilms are protective structures that bacteria can create on various surfaces, including fish tissues. These biofilms provide a physical barrier that shields bacteria from the impact of antibiotics. Epigenetic changes affecting bacterial genes involved in biofilm formation could promote antibiotic resistance by enhancing biofilm formation (Herrera et al. 2006; Shikongo-Nambabi et al. 2010).

Immune system function Epigenetic changes in the fish's immune system genes could impact the fish's ability to mount an effective immune response against antibiotic-resistant bacteria. If epigenetic modifications reduce the fish's immune defenses, it may become less effective at clearing bacterial infections, including those caused by antibiotic-resistant strains (Consuegra et al. 2023; Mukiibi et al. 2022; Bojarski et al. 2020).

Vaccination strategies

Bacterial infections are perhaps the major disease types in aquaculture that are the most concerning due to so many distinct primary and opportunistic pathogens implicated in disease outbreaks. Cultured fish are sensitive to a wide spectrum of bacterial infections at all stages of their development. Pathogens like *Staphylococcus*, *Edwardsiella*, *Pseudomonas*, *Flavobacterium*, *Aeromonas*, and other pathogens are mostly responsible for significant mortality and morbidity in several cultured freshwater fish species in various semi-intensive or intensive pond culture methods (Saikia et al. 2017). Bacterial infection continues to be a serious issue in rainbow trout, carp, tilapia, and catfish aquaculture (Rodger 2016). Infectious ailments continue to be the leading cause of death and morbidity in all cultured species, even though chemotherapeutic and preventive drugs have a negative impact like drug resistance and accumulation in the human body. To avoid substantial economic losses, illness outbreaks must be avoided, which necessitates the development of vaccines against key pathogens. With more strict antibiotic usage regulations and rising antibiotic resistance challenges (Mohamad et al. 2021), immunization is the most effective disease control technique. Since the first commercially approved fish vaccines were available (against enteric red mouth in 1976, followed by a vibriosis vaccine in 1977), much research has been conducted to develop vaccinations against many other major fish diseases. Recently, several potentially efficient vaccines that target various infectious agents have surfaced, providing

hopeful immunization options for disease management in the aquaculture industry. Despite this, there are numerous essential infections for which no therapy or vaccination is present (Nayak 2020).

Vaccines for a wide variety of fish species are readily accessible, including Atlantic salmon, rainbow trout, sea bass (*Dicentrarchus labrax*) and sea bream (*Sparus aurata*), tilapia (*Oreochromis niloticus/mossambicus*), amberjack (*Seriola dumerili*) and yellowtail (*Seriola quinqueradiata*) in Japan, catfish (*Ictalurus punctatus*), and Vietnamese (*Pangasianodon hypophthalmus*). Although live attenuated immunizations have been approved for use in catfish in the USA, most of these vaccines are based on whole-cell formulations that have been destroyed in formalin (Klesius and Pridgeon 2014). Canada has approved the use of a DNA vaccine to prevent infectious hematopoietic necrosis (IHN) in Atlantic salmon (Alonso and Leong 2013); similarly, a subunit vaccine (peptide; VP2) is used in Norway (against infectious pancreatic necrosis virus, IPNV); and a recombinant vaccine against infectious salmon anemia virus, ISAV, is used in Chile. Numerous multivalent vaccines designed specifically for Atlantic salmon are available, and micro-dose administration methods are being employed more frequently (i.e., 50 µl versus 100 µl). There are still few possibilities for vaccines that especially target carp and tilapia despite being well established as farmed species. The number of marketed vaccines for trout has also decreased after the monovalent furunculosis vaccine was taken off the market.

Fish species, immune system status, production cycle, life history, when disease occurs, farming technology (handling, mechanization, etc.), environment (e.g., temperature, salinity), stress factors, nutrition, and cost benefits are all significant considerations for the use of commercial vaccines in fish. The responsible use of medicines in agriculture alliance provides guidelines for the use of fish vaccinations. The bulk of commercial vaccinations contain adjuvants and are delivered intravenously (Adams and Subasinghe 2019).

Types of fish bacterial vaccines

There are many different kinds of vaccines available today, including subunit, DNA, synthetic peptide, recombinant vector, killed, attenuated, and DNA vaccines. Whole organism vaccines performed better than other forms of immunizations. However, the majority of immunizations do not entirely prevent infections (Dadar et al. 2016). Most traditional vaccinations include antigens that are so weak that they do not produce protection in the recipient. Furthermore, it may be difficult for developers to prevent emerging pathogens, the presence of antigenic shift and antigenic drift during host immune evasion by pathogenic organisms, besides microbes that cannot be grown *in vitro*, and the development of these vaccines is a slow and time-consuming process, which often poses difficulties in timely countering of starting to emerge and reemerging pathogens. As a result, enhanced vaccine design methodologies are being created to uncover additional forms of successful vaccinations (Gudding 2014).

Conventional fish vaccines

Traditionally, fish vaccines were made up of inactivated entire organisms (e.g., bacteria or viruses) with or without adjuvant (Tafalla et al. 2014), although there are now a variety of live attenuated or subunit protein vaccines available, frequently made with adjuvants. Recently, the majority of licensed vaccinations used in aquaculture were created using conventional methods and ideas that were comparable to those that Jenner and Pasteur first put

out more than a century ago (Ulmer et al. 2012). In the 1990s, some modified live vaccinations were developed and commercialized for use in aquaculture. These vaccinations were effective, and their usage led to increasing commercial aquaculture output, while reducing the need for chemical therapies and feed-delivered antibiotics (Gudding and Muiswinkel 2013).

Components in preparation are shown on the left, production processes are shown in the middle, and administration channels are shown on the right. Injection-based immunization is shown by the fish receiving injections, while oral administration is represented by the fish-eating feed pellets. The arrangement of the fish in the aquarium serves as an example of immersion immunization (Fig. 2).

Inactivated/killed vaccine

The inactivated or killed vaccines are mostly made from virulent disease-causing bacterium by modifying to loss its characteristics of causing infection or reproduce. These modifications can be brought by using chemical, radiation, or physical methods in such a way that the microbial agents do not lose their antigenicity (Tlaxca et al. 2015). So far, the majority of bacterial vaccines used in aquaculture are inactivated vaccines generated from a broth culture of a particular strain(s) and then formalin-inactivated. Bacterins that contain both bacterial cells and extracellular products produce better outcomes. Some bacterial

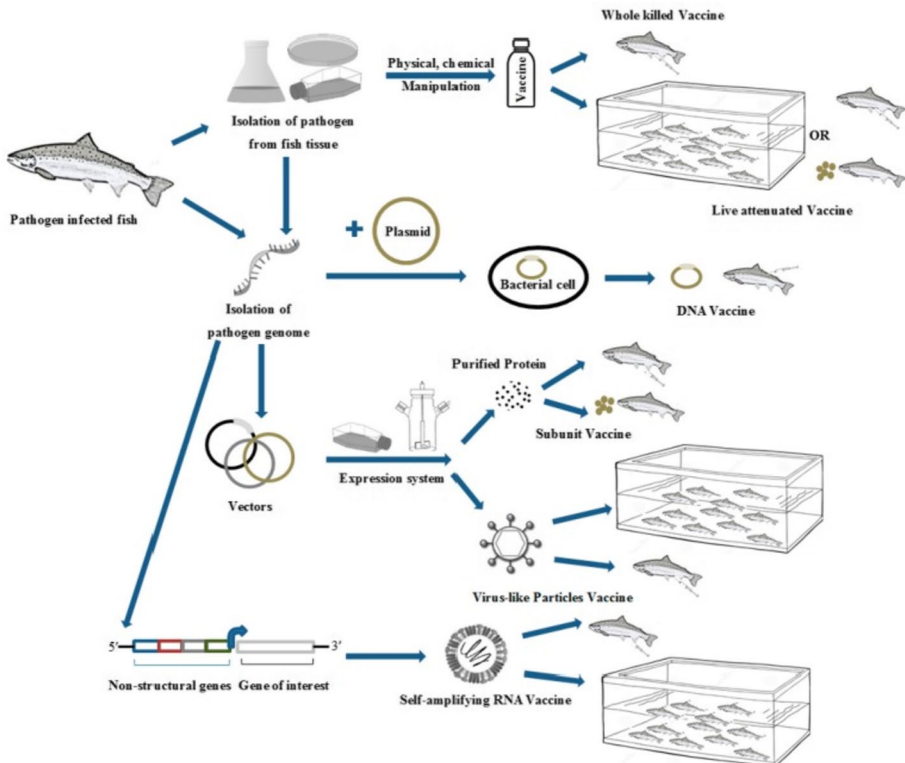


Fig. 2 Various methods for developing fish vaccines (Ma et al. 2019a)

vaccines exhibit these characteristics as well, albeit not all immunizations reach appropriate protection levels when given as aqueous formulations by injection or immersion, such as those designed for salmonids against the *Aeromonas salmonicida* subspecies of *salmonicida*. Only an injectable vaccination with bacteria that has been given an oil adjuvant may achieve these levels (Toranzo et al. 2009).

Initially, killed vaccines were administered in vaccination of aquaculture productions by various experiments. It has been reported that the first commercially approved vaccine for fish was made by modifying *Yersinia ruckeri*, which were administered against enteric red mouth disease (Gudding and Muiswinkel 2013). Similarly, formalin-killed immersion vaccines were developed for the treatment of salmon and trout vibriosis (caused by *Vibrio* spp.) The first immersion-delivered salmonid vaccines were developed using a method that also created latent bacterial infections in Atlantic salmon (*Salmo salar*) (Shoemaker et al. 2009). These early immersion vaccines against *A. salmonicida* were ineffectual, as Bricknell et al. (1997) reported on the first injection-based bacterial immunization in Atlantic salmon. Currently, large-scale aquaculture vaccines, as Bricknell et al. (1997) reported the inactive form of immersion vaccines against *A. salmonicids*, which were administered for vaccination of Atlantic salmon.

Recently, enterprises of large-scale commercial aquaculture, who are experts in high-value species such as Atlantic salmon, are dominating the market, and depend mostly on lethal polyvalent injectable vaccinations including adjuvants and several antigens to protect aquaculture against many diseases (Evensen 2016). In Japan and Europe, they also use killed vaccinations in rainbow trout (*Oncorhynchus mykiss*), amberjack (*Seriola dumerili*), and yellowtail (*Seriola quinqueradiata*) against infections of *Lactococcus* spp. or/and *Streptococcus* spp. (Sommerset et al. 2005). A killed vibriosis vaccine, coupled with *Photobacterium damsela* (subsp. *piscicida*), is also accessible and utilized in the culture of European sea bream and sea bass. Furthermore, only a bacterin (ERM vaccine) as an oral vaccination is available commercially. A modified isolated pathogen of interest to autogenous vaccines has the characteristic of site-specific response, which can regulate aquaculture production for greater versatility. These vaccines are used in collective interaction with veterinary-client-patient (Yanong 2009). Besides, the frequently dead bacterial strains modified to inactivated autogenous homologous vaccines may afford manufacturers a profitable substitute for vaccinations as commercially. These vaccines may tailor against specific diseases as well as may provide a responsive treatment for emerging diseases when commercial vaccinations may ineffective and harmful to a given operation (Adams 2019).

The development of vaccines also has been problematic against some intracellular bacterium as for *Piscirickettsia salmonis* (salmonid rickettsial septicemia). This bacterium causes *salmonid rickettsial septicemia* (SRS, *piscirickettsiosis*) which has been reported as the most devastating aquaculture disease in Chile. However, the inactivated form *P. salmonis* bacterins are accessible due to their limited effectiveness, and research into novel vaccine development based on recombinant proteins is continuing (Kuzyk et al. 2001). While the long-term efficacy of the vaccines has yet to be established, these novel techniques may offer a remedy where even inactivated bacterins are ineffective (Table 1).

Live attenuated vaccines

Aquaculture might benefit greatly from live attenuated vaccinations (Table 2). However, live vaccine causes infection during vaccination. When vaccinated fish adopt resistant strain, the antigen might spread gradually and widely across the population over time

Table 1 Some popular inactivated bacterial fish vaccines

Disease	Pathogen	Fish host	Type of vaccine	References
Vibriosis	<i>Vibrio anguillarum</i> , <i>Vibrio ordalii</i> , <i>Vibrio salmonicida</i>	Salmonids, grouper, sea bream, sea bass, cod, yellowtail, halibut, ayu	Inactivated/killed	Angelidis and Karagiannis (2006), Mikkelsen et al. (2011), Galindo-Villegas et al. (2013)
Yersiniosis	<i>Yersinia ruckeri</i>	Rainbow trout, Atlantic salmon	Inactivated	Siwicki et al. (1998), Ghosh et al. (2016), Jaafar et al. (2018)
Enteric septicemia of catfish (ESC)	<i>Edwardsiella ictaluri</i>	Catfish	Inactivated	Thinh et al. (2009), Glenney and Petrie-Hanson (2006)

Table 2 Popular live attenuated fish vaccines

Disease	Pathogen	Fish host	Type of vaccine	References
Rainbow trout fry syndrome (RTFS) or bacterial coldwater disease (BCWD)	<i>Flavobacterium psychrophilum</i> (syn., <i>Flexibacter psychrophilus</i> and <i>Cytophaga psychrophila</i>)	Salmonids	Live attenuated	Bøggwald and Dalmo (2019)
Columnaris disease	<i>Flavobacterium columnaris</i>	Freshwater finfish species, Nile tilapia, bass, bream, salmon, turbot	Live attenuated	Shoemaker et al. (2011), Mohamed and Soliman (2013)
Streptococcosis	<i>Streptococcus agalactiae</i>	Freshwater tilapia, Asian sea bass, salmonids	Live attenuated	Zhang et al. (2019)
Fish septicemia and ulcers	<i>Aeromonas veronii</i>	Catfish, loaches	Live attenuated	Zhang et al. (2020)
Bacterial kidney disease (BKD)	<i>Renibacterium salmoninarum</i> and <i>Piscirickettsia salmonis</i>	Salmonids	Live attenuated	Salonius et al. (2005), Delghandi et al. (2020)
Dropsy, carp erythrodermatitis	<i>Aeromonas hydrophila</i>	Indian major carps	Live attenuated	Jiang et al. (2016)
Streptococcus	<i>Streptococcus iniae</i>	Tilapia, Japanese flounder	Live attenuated	Liu et al. (2019)
Salmonid rickettsial septicemia	<i>Piscirickettsia salmonis</i>	Salmon	Live attenuated	Vargas et al. (2021)

(Desbois and Monaghan 2023). Live vaccinations also have the ability to boost the immune system of cellular components. The subspecies of *Pfiesteria piscicida*, including *Aeromonas salmonicida* (*A. salmonicida*), *Edwardsiella ictaluri* (*E. ictaluri*), *Photobacterium damsela* (*P. damsela*), and *Edwardsiella tarda* (*E. tarda*), have been studied for research purposes in laboratories. However, for practical applications, some issues like safety, longevity in fish and the environment, a potential return to virulence, and the potential for transmission to non-target species, such as wild fish, must be considered before deploying these live attenuated strains. The only vaccine currently authorized in the USA for the prevention of ESC (enteric septicemia of catfish) is specific to the bacterium *E. ictaluri*, which is recommended for 9-day-old catfish (Klesius and Shoemaker 1999). These are traditional vaccinations that are used to prevent illness in food-producing animals and humans (Shoemaker and Klesius 2014). They are prepared for virulence loss without killing the organisms by numerous laboratory passages and physical and chemical attenuation. Live vaccinations have been demonstrated in laboratory trials to be efficacious in fish. They stimulate mucosal, cellular, and humoral immune responses. The weakened pathogen multiplies in the intended host without causing any clinical symptoms (Shoemaker et al. 2009).

However, attenuated live vaccines are typically seen to be safe, and various issues need to be resolved to ensure that they do not revert to their original virulent state, maintain prolonged virulence, or become virulent in people who have already had vaccinations but have compromised immune systems. This situation could affect the efficacy of live vaccines as well as the regulatory process around them, along with the possibility of contamination with harmful bacteria. Currently, there are three live modified vaccines for aquaculture that are available in the US market including *E. ictaluri* vaccine against enteric septicemia of catfish (ESC), *Flavobacterium columnare* vaccine against columnaris also for catfish, and *Arthrobacter* vaccine against bacterial kidney disease (BKD) for salmonids (Klesius and Pridgeon 2014). A type of live *Arthrobacter* vaccine, known as Renogen, is used against BKD that contains non-pathogenic soil bacteria which can also give cross-protection from infectious *Renibacterium salmoninarum* (*R. salmoninarum*) (Shoemaker et al. 2009). The USA has approved two live bacterial vaccines that were developed using a sequential passage strategy and rifampicin at enhancing dose concentrations (Shoemaker et al. 2007). This technique was used to attenuate *Vibrio anguillarum* (*V. anguillarum*) for rainbow trout vaccination. This method has also been used to reduce the strength of *Flavobacterium psychrophilum* (*F. psychrophilum*) to attenuate, proving its security and effectiveness in salmonid species. The *F. psychrophilum* vaccine has been studied and improved under certain conditions after its formation. It has been demonstrated to provide substantial cross-protection against various strains of *F. psychrophilum*. This antibiotic mutagenesis approach was also practiced against other pathogens of fish including *E. tarda* in Japanese flounder and channel catfish, *A. hydrophila* and *Flavobacterium* spp. in Nile tilapia (*Oreochromis niloticus*) or carp species and channel catfish (*Ictalurus punctatus*), and *V. anguillarum* in Japanese flounder. Various compounds, including novobiocin and acriflavine dye, have been applied to attenuate *E. ictaluri*, *Streptococcus iniae* (*S. iniae*), *Streptococcus agalactiae* (*S. agalactiae*), and *Aeromonas hydrophila* (*A. hydrophila*); however, these vaccines have yet to be marketed (Laith et al. 2019). The *Arthrobacter* vaccination for BKD is considered more beneficial because of its individuality from gram-positive *R. salmoninarum* live strain; however, using rather a live *A. davidanieli* bacterium induces immunity to *R. salmoninarum* by cross-protection (Salonius et al. 2005). The application of this antigenic cross-reactivity microbe as an antigen can be successful, and additional ways for attenuating fish pathogens, such as antigenic cross-reactivity bacteria, the use of phylogenetic relations, and serial passages, have been investigated (Itano et al. 2006).

In the case of bacterial strains, molecular modification of pathogens has resulted in the generation of live vaccines against certain fish ailments. Some research on the effects of genetic recombination on the surface polysaccharides of *Edwardsiella* spp. has proved encouraging. The inhibition of polysaccharide production by inhibiting the O-polysaccharide (OPS) gene subsequently induces immunity after exposure to the virulent wild-type bacteria in catfish. Besides, other research has also generated attenuated *Streptococcus* spp. by removing virulence factors such as M-like proteins, phosphoglucomutase, and polysaccharides. Mutant strains of *Vibrio mimicus* (*V. mimicus*), *Francisella asiatica* (*F. asiatica*), and *Vibrio alginolyticus* (*V. alginolyticus*) are more examples of how genetic changes can result in attenuation (Ma et al. 2019a, b). These have protected fish and proved that live vaccination technology for aquaculture needs to be improved more.

DNA vaccines

A DNA vaccine is synthesized through modifications by identification and cloning a pathogen's protective antigen. Some pathogenic fish viruses, such as VHSV and IHNV, have defensive antibodies that target their surface glycoprotein. In eukaryotic cells, the genes for glycoproteins and regulatory sequences make it possible to synthesize DNA vaccines, whereas in bacterial culture, plasmid is produced, purified, and administered through quality assurance testing before being utilized as a vaccine. After receiving the DNA vaccination, host cells absorb the genetic material to produce the glycoprotein. This circumstance causes the antigen to be detected by the fish's immune system. DNA vaccines have the potential to substitute traditional vaccinations in aquaculture by inducing particular immune responses that includes antibodies, cytotoxic cells, and T-helper cells after DNA vaccination. However, only one microbial gene is encoded by a particular DNA sequence; hence, there is no reoccurrence to virulence, which is an important feature in aquaculture environmental safety. Therefore, the safety of host, surrounding environment, and consumer must be resolved before the use of DNA vaccines in aquaculture operations (Toranzo et al. 2009). The effect of DNA vaccines was also investigated against *R. salmoninarum* which causes bacterial kidney disease in salmon and stands out among the majority of DNA vaccines created for aquaculture that have mostly been administered for Bacterial diseases. However, this vaccination was revealed to be ineffective (Dhar et al. 2014). For the *Piscirickettsia salmonis* infection, which fish were immunized against, a more general strategy has been tried with a comprehensive plasmid DNA expression library. The level of protection was later discovered to be quite low, despite a pathogen-specific antibody response (Miquel et al. 2003). It has been reported that hybrid striped bass is shielded against *Mycobacterium marinum* by a DNA vaccine that encodes the naturally produced mycobacterial antigen Ag85A (Pasnik and Smith 2005).

A high vaccine dose may be instantly related to increased disease prevention. To make immunizations more effective, however, there are various techniques besides only increasing the amount of antigen/DNA that can be used. One of these strategies is the combination of a DNA vaccine with additional plasmids that encode regulatory proteins or the insertion of molecular adjuvant-coding genes into the DNA vaccine vector. This concept remains relatively unexplored in the context of fish, although there have been preliminary discoveries. According to a study, interferon regulatory factor-1 (IRF-1) may be employed as a vaccine adjuvant in Japanese flounder. IRF-1 is linked to cytokine signaling and host responses against pathogenic pathogens (Caipang et al. 2005). To demonstrate the complexity of developing effective vaccines, it may be necessary to implement a system of vaccinology

approach in light of transcriptomics, epigenetics, proteomics, and metabolomics platforms along with bioinformatics (Hagan et al. 2015). Numerous institutions have the essential resources, knowledge, and expertise to facilitate such a strategy. After the completion of whole-genome sequencing programs, researchers now have improved insights into the transcriptome and proteome response brought on by vaccination for major aquaculture fish species. The new next-generation sequencing (NGS) technology could be useful in the study and development of fish vaccines. NGS is a recent technical advancement in nucleic acid sequencing that has changed the science of genomics. NGS, which is now accessible in nearly all molecular biology laboratories, gives a massive volume of sequence data at a reasonable cost. The research on fish disease has greatly benefited from this progress. NGS is increasingly being used to track aquatic viruses and bacteria, examine the virulence and development of illnesses, and identify as-yet-unidentified causative agents that result in mortality. In theory, the comprehensive information obtained from NGS could help to accelerate vaccine development and lead to highly effective vaccines. NGS provides the opportunity to evaluate epigenetic changes following vaccination. This can shed light on the different ways that different fish (such as non-responders) and lineages react to vaccines, as well as how vaccines might cause epigenetic changes that improve gene expression. Fish DNA vaccine research is currently in its early stages. However, studies using model antigens produce very encouraging outcomes, inducing both cellular and humoral immune reactions (Avarre 2020).

Monovalent and polyvalent vaccines

Polyvalent vaccines are considered the most effective vaccines due to its active characteristic in a particular condition especially when species-specific fish becomes susceptible simultaneously to many infectious diseases (Busch 1997; Ma et al. 2010). Furthermore, polyvalent vaccines need to cover all significant serotypes of every pathogen present within a specific geographic region. Illustrative instances of the effectiveness of polyvalent vaccines can be observed in the cases of salmonids and turbot. In these examples, polyvalent vaccines have demonstrated equivalent or enhanced protective capabilities to monovalent vaccines. Unfortunately, turbot fish could not be protected against infection by the utilization of a commercially available polyvalent vaccine designed for *M. viscosa* and salmon as one of its five antigens and a mineral oil adjuvant. It was reported that a particular anti-*M. viscosa* response was not affected significantly, but the resultant weight increase in vaccinated turbot was not lowered compared to controls 7 weeks after vaccination. Although both vaccinated and unvaccinated fish had high anti-*M. viscosa* antibody levels 5 weeks after vaccination. Another vaccine component brought a vaccination-induced antibody response against *A. salmonicida*. It is important to cautiously follow the procedure of polyvalent vaccines for vaccinations due to the possibility of antigen competition, particularly when providing these vaccines via injection. While monovalent vaccines stimulated effective protective immunity, polyvalent vaccines prompted stronger protection than monovalent vaccines, possibly due to more powerful and effective systemic immune responses elicited by multivalent vaccines (Björnsdóttir et al. 2004).

It is widely acknowledged that fish have a less broad and effective immune system than mammals (Klesius et al. 2004). On the other hand, monovalent vaccines generally have efficacy as polyvalent vaccines. However, as compared to monovalent furunculosis vaccines that only target furunculosis, vaccine formulations containing antigens from *A. salmonicida*, *V. salmonicida*, and *V. anguillarum* have high efficiency against

furunculosis. It might be the result of immunological interactions between *A. salmonicida* and *V. salmonicida* (Hoel et al. 1997). Additionally, cross-protection between antigens of atypical furunculosis and furunculosis-causing bacteria has been reported. The vaccination against *A. salmonicida* subsp. *salmonicida* provided a cure for atypical furunculosis but did not treat classical furunculosis, indicating that the cross-protection appears to be unidirectional (Björnsdóttir et al. 2005).

Due to the random interactions between adjuvant and antigen, it is impossible to synthesize or develop a vaccine that gives protection against every infectious virus that a certain fish may come in contact with. Administrators of salmon farms must identify which infectious diseases are crucial and vaccinate their livestock accordingly (Table 3). Unfortunately, determining the immunological effect of synchronized vaccination is also difficult. It was proved that simultaneous vaccination of a polyvalent oil-AV and a DV enhances specific antibody formation; however, the particular anti-viral response may be disturbed (Skinner et al. 2010).

The majority of rainbow trout are protected against well-known bacterial infections including *Aeromonas salmonicida* subsp. *salmonicida*, *Yersinia ruckeri*, and *Vibrio anguillarum* by widely used vaccinations, but disease outbreaks still occur. Under experimental conditions, administration of the multicomponent vaccination resulted in protection against three specific bacterial diseases (yersiniosis, vibriosis, and furunculosis). It has been discovered that pentavalent vaccine IP infusion promotes particular antibody responses in trout against different bacterial antigens and controlled gene expression (Marana et al. 2019).

Nanovaccines

Nanovaccines for fish have emerged as a cutting-edge solution in aquaculture, revolutionizing disease prevention and health management strategies for aquatic species. These innovative vaccines utilize nanotechnology to optimize the delivery of antigens and adjuvants, enhancing the immune response in fish (Vinay et al. 2016). By employing nanoparticles like liposomes, polymeric nanoparticles, or virus-like particles (VLPs) as carriers, nanovaccines mimic pathogen structures, ensuring prolonged antigen exposure and promoting robust antibody production and cellular immunity (Celis-Giraldo et al. 2021; Jeong et al. 2020). Importantly, these vaccines reduce the stress associated with conventional vaccination methods, including handling and injection, thus improving the overall welfare of farmed fish. Additionally, nanovaccines can be tailored to target specific pathogens of concern in aquaculture, minimizing non-target effects. This precision is particularly significant in reducing antibiotic use, supporting environmentally sustainable practices, and mitigating antibiotic resistance challenges (Thompson et al. 2023; Mondal and Thomas 2022). Furthermore, as fish farmers increasingly recognize the economic benefits of disease prevention through nanovaccines, ongoing research and development efforts aim to refine formulations and address aquaculture-specific challenges (Du et al. 2022; Nasr-Eldahan et al. 2021; Fajardo et al. 2022). Nanovaccines for fish promise to revolutionize disease control in aquaculture and align with the growing emphasis on sustainable and responsible farming practices, promoting the health and productivity of aquatic populations.

Table 3 Available vaccines for major infectious bacterial diseases of fish

Disease	Pathogen	Fish host	Type of vaccine	References
Vibriosis	<i>Listonella anguillarum</i>	Sea bass, marine and freshwater fishes	Bivalent vaccine	Angelidis and Karagiannis (2006)
Photobacteriosis	<i>Photobacterium damsela</i>	Wild and farmed marine fishes	Oral biofilm vaccine	Su and Chen (2022)
Lactococcosis	<i>Lactococcus garvieae</i>	Rainbow trout, Japanese yellowtail, cobia, and grey mullet	Oral biofilm vaccine	Su and Chen (2021)

Challenges of vaccinations in aquaculture

A vaccination strategy is an essential factor for overall fish health management. It is the most successful safety strategy for preventing the transmission of fish diseases by inducing defense mechanisms against bacterial disease outbreaks. As a result, a detailed understanding of diseases and pathogen profiles, as well as a basic economic background of operational costs, is required to design appropriate vaccination strategies (Mohd-Aris et al. 2019). Immunoprophylaxis is usually beneficial because it reduces disease-related economic losses. The same concept is true for vaccination usage in aquaculture, as it can also be utilized as a vaccine in the domain of aquaculture. However, with antibiotics and other chemical agents to treat disease outbreaks in fish farms, the development of the immune system along with other desirable advantages can also be achieved. Antibiotic use in aquaculture causes the development of antimicrobial resistance in both pathogenic and non-pathogenic microorganisms, potentially providing a threat to the environment, as well as the well-being of humans and animals (Mamun et al. 2019). As a result, long-term antibiotic use in commercial bioproduction, such as fish culture, is not appropriate.

Following the adoption of vaccination as a common technique for managing bacterial infections in farmed fish, antibiotic use has reduced dramatically, from 47 tons to around 1 ton of active substances in Norway (Gudding et al. 1999). During the rearing process, vaccinations are performed in many fish species against different diseases, as rainbow trout and salmon vaccinate against three to five diseases. As a result, production has increased dramatically over the last half-decade, an achievement that would have been impossible without the administration of such efficient vaccinations. Vaccines have proven to be a reliable and low-cost way to treat and prevent infectious fish diseases in aquaculture. Anyhow, vaccination has shown a significant reduction in losses associated with specific diseases, resulting in a decrease in antibiotic use. As demonstrated by the collaboration between immunologists and vaccinologists, it is critical to increase collaboration between basic and applied sciences to advance in the field of fish vaccinology. Understanding the immune systems of various fish species is crucial, with consideration of cellular and mucosal immunity.

Live vaccines have proven highly effective in defeating various diseases, including rainbow trout fry syndrome (RTFS), columnaris disease, *Streptococcus* infections, dropsy, bacterial kidney disease, fish septicemia, and ulcers. It is imperative to promote research aimed at developing secure live vaccines to enhance disease prevention. When it comes to DNA bacterial vaccines, they have yet to be studied further from the standpoint of bacterial disease protection. Compared to vaccines used in higher vertebrates, most fish vaccines require a higher antigen mass. However, the current availability of commercial vaccines remains limited due to the issues such as efficacy challenges and the complexities of producing substantial antigen quantities. These vaccines are essential for inducing a robust immune response, both at the local and systemic levels. Ensuring their protection from degradation until they reach the immune induction site is also crucial (Mutoloki et al. 2015).

Overall, bacterial vaccines designed for the aquaculture sector have exhibited superior accomplishments compared to their viral counterparts, a fact supported by the observable disparity in the quantity of commercially available salmonid vaccines within Norway (PHARMAQ AS. PHARMAQ – Products 2015). The aquaculture sector places considerable emphasis on extracellular bacteria due to the nature of viruses as viruses primarily infect host cells from the insides. However, there are a few exceptions to this such as

Piscirickettsia salmonis, which is activated intracellularly and presents challenges in the development of vaccines (Sommerset et al. 2005). A powerful immune response to extracellular bacterial infections is mostly determined by humoral factors. Therefore, creating vaccines that elicit antibody responses to ensure the protection of aquatic creatures is challenging progress. Conversely, targeting intracellular pathogens needs a synergistic effort of diverse immune responses, which includes humoral, cytotoxic, and cell-mediated reactions. Designing a vaccine capable of eliciting such a comprehensive range of responses presents a challenging task. In contrast, bacterial vaccines possess certain advantages that contribute to their relatively simpler development compared to viral vaccines. Factors such as their larger size and the specific antigens/immunogens they comprise contribute to these differences (Villumsen et al. 2014). It is recommended to employ a strategy based on globally recognized and accepted principles for preventing, managing, and resolving issues in aquaculture while being tailored to local circumstances.

Conclusion

Vaccines have been routinely used as low-cost preventative strategies against contagious diseases in humans. For the production of human vaccines, numerous cutting-edge immunological methods, including genetic engineering and nanotechnology, have been used. However, due to several scientific, financial, and commercialization barriers, these advanced technologies could not be utilized in aquaculture. In aquaculture, commercial approval for vaccines remains limited, especially for precious species including salmonids, yellowtail, sea bream, sea bass, and catfish. Despite the challenges of commercialization, there has been a significant upswing in research dedicated to aquaculture vaccinology in recent years, resulting in the development of numerous effective immunization regimens. However, fish vaccinations may face limitations related to difficulty in administering vaccines to certain species, varying immune responses among different fish species, precise timing and environmental conditions, and achieving long-term protection against certain rapidly mutating pathogens. The innovative technique aided in the development of perfect vaccinations with precise biological and physical properties. The ideal fish vaccine ensures the safety of both the fish and the environment, proves economically viable for extensive production, offers straightforward administration, prompts robust immunity during periods of heightened vulnerability, and results in minimal adverse effects. Implementing vaccination strategies within aquaculture settings reduces the necessity for antibiotics and effectively shields fish populations against contagious illnesses, thereby diminishing the potential for the emergence of drug resistance. To prevent bacterial diseases in fish, various vaccines for freshwater and marine fish species have been formulated using advanced biotechnology techniques like next-generation sequencing, formulation of DNA vaccines, and live attenuated and killed vaccines, which are currently accessible in the commercial market. All of this progress in vaccine research is based on biotechnology-based techniques; however, it is always funding-dependent. Furthermore, government and stakeholder parties must need to resolve major aquaculture issues like infectious diseases by administration of the latest technologies. Therefore, there is a need for funding for sustainable aquaculture initiatives to identify the fundamental disease epidemiology and the immune systems across various farmed species, which can support and allow the development of relevant vaccines for practical applications. To deal with the rising number of infectious illnesses in aquaculture, vaccine research must expand. As a result, biotechnology offers a wide

range of uses in aquaculture disease management. Novel views and methods for research could involve the exploration of bacterial vaccines, particularly those sourced from marine microorganisms, as potential alternatives within aquaculture, diverging from the conventional practice of employing the same antibiotics employed in human treatments. Regarding recommendations, it is crucial to decrease antibiotic utilization in aquaculture, elevate the standard of fish farm maintenance, and elevate facility hygiene standards. Furthermore, the effectiveness of fish vaccines in various settings and species should be evaluated in-depth in future studies, taking into account the intricate relationships between numerous infections. To further improve protection in aquaculture, research into novel vaccine formulations that take into account the multifactorial problems in aquatic habitats is also crucial.

Author contribution N.I. did the conceptualization, investigation, writing—original draft, and editing. Z.A. did the investigation and writing—original draft. K.W. did the writing—review and editing. C.S. did the writing—original draft preparation. C.M. did the project administration and resources. C.W. did the funding acquisition and resources. Q.W. did the supervision, investigation, writing—original drafts, editing, project administration, and funding acquisition.

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Declarations

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