Aquaculture International (2022) 30:1971–2000
https://doi.org/10.1007/s10499-022-00884-w

A review on the recent advances and application of vaccines against fish pathogens in aquaculture

Haimanti Mondal[1] · **John Thomas**[1]

Received: 10 March 2022 / Accepted: 21 April 2022 / Published online: 2 May 2022

Abstract
Globally, aquaculture has faced serious economic problems due to bacterial, viral, and various other infectious diseases of different origins. Even though such diseases are being detected and simultaneously treated with several therapeutic and prophylactic methods, the broad-spectrum activity of vaccines plays a vital role as a preventive measure in aquaculture. However, treatments like use of antibiotics and probiotics seem to be less effective when new mutant strains develop and disease causing pathogens become resistant to commonly used antibiotics. Therefore, vaccines developed by using recent advanced molecular techniques can be considered as an effective way of treating disease causing pathogens in aquatic organisms. The present review emphasizes on the current advances in technology and future outlook with reference to different types of vaccines used in the aquaculture industries. Beginning with traditional killed/inactivated and live attenuated vaccines, this work culminates in the review of modern new generation ones including recombinant, synthetic peptides, mucosal and DNA, subunit, nanoparticle-based and plant-based edible vaccines, reverse vaccinology, and monovalent and polyvalent vaccines.

Keywords Bacteria · Aquaculture · Vaccination · Reverse vaccinology · Virus

Introduction

A vaccine is defined as a biologically based preparation that is developed to improve the immunity towards a specific disease or a group of diseases. Vaccines are considered as biological agents that elicit an immune response to a particular antigen obtained from a disease-causing infectious pathogen (Czochor and Turchick 2014). Although aquaculture has led to progress in production, it has also resulted in disease outbreaks which includes several viral and bacterial pathogens. A disease causing is a major limitation in aquaculture which, however, can be controlled by introducing specific-pathogen-free (SPF) brood stock, feed optimization, improvement of husbandry techniques, and good sanitation

Handling editor: Brian Austin

✉ John Thomas
john.thomas@vit.ac.in; th_john28@yahoo.co.in

[1] Centre for Nanobiotechnology, Vellore Institute of Technology (VIT), Vellore, Tamil Nadu, India

(Grisez and Tan 2007). In aquaculture, vaccination is an important aspect. Vaccination has been regarded as an efficient treatment method for the prevention of a wide variety of bacterial as well as viral diseases (Ma et al. 2019). Taking Norwegian salmon farming as an example, the use of antibiotics has fallen to virtually zero as a result of which production has increased enormously (Bostock 2002; Markestad and Grave 1996; Mohamed and Soliman 2013; Rodger 2016). Many bacterial and viral vaccines, either monovalent or multivalent, have been developed successfully and commercialized (Bostock 2002; Mohamed and Soliman 2013; Evelyn 2002). Ma et al. (2019) and Horzinek et al. (1997) reported that vaccination has become one of the most cost-effective as well as sustainable methods of controlling several infectious fish diseases.

The first report on protective immunity was by Snieszko et al. (1938) who used vaccines to prevent disease in carp by immunizing them with the bacterium, *Aeromonas punctata.* The first report in English was in the year 1942 by Duff (1942) who reported protection against *Aeromonas salmonicida* in the rainbow trout, *Oncorhynchus mykiss*, by oral administration and parenteral inoculation. Since the 1940s when the first fish vaccine was used for preventing diseases (Snieszko and Friddle 1949), many vaccines which have a huge impact on reducing the bacterial and viral pathogenic diseases in fishes have been developed (Gudding and Goodrich 2014).

The first fish vaccine was used against enteric-redmouth in fish, for treating yersiniosis in the year 1976 and was licensed by the United States (US) Department of Agriculture, followed by a vaccine for vibriosis (Gudding and Muiswinkel 2013; Bridle and Nowak 2014; Kumar et al. 2015). The vaccines for bacterial infections, yersiniosis, and vibriosis are even now the most highly effective commercial vaccines available in the market.

Vaccination in farmed fish was first done in the year 1970 against infectious bacterial diseases. Vaccination especially vaccination with DNA vaccines is based on the administration of a plasmid which encodes the vaccine against the antigen, rather than the antigen itself. Attenuated bacterial capsule polysaccharides or bacteria, viruses, and toxins and monoantigen vaccines are based mainly on recombinant viral proteins. Perrie et al. (2008) reported that the expression of the plasmid in the somatic cells of the host activates both its humoral and cellular immune responses.

Researchers have carried out extensive studies for preparing various kinds of vaccines in controlling fish diseases caused by bacteria or viruses. Clarke et al. (2013) and Assefa and Abunna (2018) reported the development of vaccines for rainbow trout (*Oncorhynchus mykiss*), Atlantic salmon (*Salmo salar*), tilapia (*Oreochromis niloticus/mossambicus*), seabream (*Sparus aurata*), sea bass (*Dicentrarchus labrax*), yellowtail (*Seriola quinqueradiata*), amberjack (*Seriola dumerili*), catfish (*Ictalurus punctatus*) and Vietnamese catfish (*Pangasianodon hypophthalmus*) (Su et al. 2021).

Aquaculture is an age-old occupation practiced for growing aquatic organisms like fish and shellfish and later harvesting the production of these organisms for human benefit. These aquatic organisms which include both plants and animals are grown in both freshwater as well as marine environments. Aquaculture activities in the world are becoming an integral part of fisheries and aquatic resource management. Among animals, various organisms such as carp, shrimps, oysters, trout, finfish and tuna, are grown in fresh and marine waters. Among plants, seaweeds are grown in tanks, ponds, or nets in the marine, brackish, and freshwaters.

Immunity to a particular disease is usually improved by using a vaccine which generally contains an agent resembling a disease-causing microorganism. Vaccines are usually prepared from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. Additionally, a fish vaccine typically either produces or contains a specific component that later serves as an antigen. This substance can either stimulate an adaptive or innate immune response against a particular pathogen within the fish (Ma et al. 2019). The

role of the agent is to stimulate the body's immune system and to identify the foreign antigen, destroy it, and "remember" it, so that the immune system can easily recognize and destroy any microorganism that it may encounter later.

There are different varieties of vaccines like DNA vaccine and recombinant vaccine which have been reported. Many of them have obtained approval from the US Department of Agriculture (USDA) for use on a wide variety of aquaculture species. In addition, most of them use the conventional methods to successfully protect fishes against several fatal pathogenic fish diseases (Adams 2019; Van Oirschot 1997). Whole cell vaccine is a bacterial suspension of whole bacterial cells that have been killed and is cheaper to produce. There are two types of whole cell vaccines, namely, killed vaccine and attenuated vaccine. Attenuated vaccine provides both cellular as well as humoral immunity, but the disadvantage is that there is always a chance of infection in immunocompromised individuals and also a possibility of reversion to pathogenic forms. Whole-cell killed vaccine is preferable since it is able to provide potent immunization. In addition, it is cheaper when compared to other vaccines and is also very effective. Even though different treatment modalities are currently adopted in aquaculture, vaccination plays a significant role in preventing many of the re-emerging diseases in water based production systems. The advantage of using a vaccine is that it is very cost-effective and can be adopted easily (Belakova et al. 2007).

Till now, over twenty-six fish vaccines are reported to be licensed for use in a wide variety of fishes and are commercially available around the globe (Ma et al. 2019). Among them, DNA vaccines are licensed in Canada; inactivated vaccines in Norway, Chile, Ireland, Finland, Canada, Czech Republic, Singapore, Europe, Japan, Australia, Vietnam, the UK, Taiwan, Spain, Indonesia, Brazil, and Iceland; subunit vaccines in Canada, the USA, Chile, Belgium, and Norway; and attenuated vaccines in Israel and the USA (Ma et al. 2019). In this review, we describe an overview of vaccines from traditional conventional vaccines to modern vaccines used in aquaculture. It also provides a deeper insight into the current and recent molecular advances in fish vaccine development for use in aquaculture.

Vaccine — an overview

From many decades, vaccination has been practiced against infectious diseases. It has now proven to be one of the most cost-effective means of decreasing economic loss due to viral and bacterial infections. A study by Ma et al. (2019) reported that vaccines contain or produce a substance(s) called an antigen(s) that triggers an innate or adaptive immune response in an aquatic organism against a particular pathogenic organism. The immune response protects against disease and resists future infections.

Fishes are the most nascent and diverse group of vertebrates (Sahoo et al. 2021), possessing both innate as well as adaptive defensive immune systems (Secombes and Wang 2012). A developed immune system like an adaptive immune response produces an increase of a population of antibody producing cells (APCs) which are called B-lymphocytes. Later, these B-lymphocyte cells produce antibodies which are specific to a protein that self-configures to bind exactly to a site(s) on the similar antigen. Secombes and Wang (2012) reported that the immune response stimulates the immune functions, hematopoietic lymphoid, and myeloid tissues for pathogen exclusion, neutralization, and homeostasis. It also maintains a memory of the infection and restores functions that were found to be lost during infection.

In the case of inactivated vaccines, inactivating agents, such as formaldehyde, ethylamine, and β-propiolactone, are used to reticulate pathogenic proteins which interact with cellular receptors and block replication of nucleic acids. Pasquale et al. (2015) reported that the killed vaccines are disadvantageous because they not only have the potential for immunosuppressive passenger antigens but also are responsible for initiating toxic reactions caused by immune enhancing adjuvants and reduced immunogenicity due to denaturation of proteins and systemic reactions in response to a particular adjuvant.

For preparation of modified live vaccines, bacteria or one or more viruses that exhibit either attenuated or less natural pathogenic effect for the target species are used. The pathogens are attenuated by using culture kept under abnormal conditions, serial passage in cell culture, chemical or physical factors, or genetic manipulation (Desmettre and Martinod 1997).

Vaccines in aquaculture

The process of vaccinating fishes is carried out by either exposing the immune system of fish to the entire pathogen or part of a pathogen. Immunity develops after a certain period of time. Fish vaccines are classified into modified live vaccines and killed fish vaccines.

Killed fish vaccines consist of heat killed or formalin killed vaccines. The first report on the use of a vaccine in fish was that of a killed vaccine against *Aeromonas salmonicida* as reported by Duff in the year 1942. They investigated oral vaccination in *Oncorhynchus clarkia* (Ma et al. 2019).

Modified live vaccines are generally composed of live microorganisms that tend to possess more immunogenicity due to their ability to proliferate, ease of host entry, and cellular response stimulation in greater numbers in association with both innate and adaptive immunities compared to killed preparations (Levine and Sztein 2004). At present, around three live vaccines which are modified are reported to be licensed in the USA. The vaccines are *Edwardsiella ictaluri* vaccine for use in catfish against enteric septicemia infection, *Arthrobacter* vaccine for salmonids against bacterial kidney disease (BKD), and *Flavobacterium columnare* vaccine for catfish against columnaris infection (Klesius and Pridgeon 2014). Live attenuated vaccines work by stimulating both cell-mediated and humoral immune responses. However, concerns regarding safety to the environment have been raised against live vaccines.

Routes of vaccine administration/vaccine delivery methods

Generally, vaccines are administered to fishes by different routes that include oral, injection (intraperitoneal or intramuscular), and immersion (Adams et al. 2008). The route of administration which is likely to be effective is decided by taking into account factors involving the pathogen, their infection route, immunological memory status, vaccine production techniques, the underlying principles, labor costs, host/fish life phase, and so on (Yanong and Erlacher-Reid 2012). The delivery methods opted may determine the induced immunological response as well as protection level against the pathogen of interest (Palm Jr et al. 1998).

Oral vaccination

The oral vaccination method is considered as one of the methods for vaccinating fish in which the vaccine is first incorporated into the feed and then fed to fish. Like the immersion

method, oral vaccination method is also not cost-effective especially in the case of larger fishes. When compared to the immersion and injection methods, an oral vaccine gives lesser efficacy. Brudeseth et al. (2013) reported a lower level and moderately shorter time period of defense due to the destruction, degradation, and absorption of antigens by the gastrointestinal tract and low antigen transfer rate from intestinal lumen of the fish to the immune reactive cells.

The oral vaccine is administered by incorporating it with the feed or by coating on top of the feed (Mohamed and Soliman; Quentel and Vigneulle 1997). The vaccine is either sprayed over the feed, mixed with the feed, or bio-encapsulated (Dadar et al. 2016). Antigens, which are to be incorporated in the feed, need special attention. To prevent leaching of the antigen from the pellet, vaccines are to be top-dressed on the feed. Plant and LaPatra (2011) reported that antigen delivery in fish feed offers some benefits like cost efficiency, simplicity, and safe administration in all stages to different sizes of fish and imposing low stress. For antigens which are sensitive, various micro-encapsulation methods are evaluated and tested. Rotifers, *Artemia nauplii*, or copepods are incubated in a vaccine suspension and then fed to the fry. They are live organisms which are non-selective filter feeders, and will gather the antigen in their digestive tract as such, and then transform themselves into live microcapsules (Campbell et al. 1993). Oral vaccines can also be administered as a booster vaccine for primary vaccination to increase the protection against certain chronic endemic diseases (Brudeseth et al. 2013) in which this protection is mostly linked to humoral immune responses rather than cellular and innate immune responses (Newaj-Fyzul and Austin 2015).

Vaccination by oral method has the added advantage of easy administration and hence can cause no stress to the fish.

Injection vaccination

Only a small amount of antigen can be injected into the fishes directly by intraperitoneal (IP) or intramuscular (IM) delivery methods when injectable vaccines are given (Plant and LaPatra 2011). In this approach, the time period of protection is more prolonged when compared to immersion method (Vinitantharat et al. 1999). Additionally, vaccines administered by injection have the ability to concentrate as well as to be delivered with compounds like bacterial antigens, bacterial cells, adjuvants, and carriers, which are not possible by other vaccine delivery methods (Dhar and Allnutt 2011).

Intraperitoneal injection is the most productive and efficient way of immunizing fish, and so, most of the recent vaccines have been predominantly delivered via this route. In IP injection, adjuvants, especially oil adjuvants, are used since they give better protection than the immersion method. Fishes are anesthetized and injected intraperitoneally with the vaccine. Commercially, injection guns both manually and automatically operated are used for vaccinating fish by IP injection. This allows each operator to inject 1000–2000 fish in 1 h. The amount of injection depends on the size of the fish.

Heppell and Davis (2000) and Evensen and Leong (2013) reported that IM delivery method is the preferred method for DNA vaccination of fishes and is manually performed via injection needle or by alternatively using devices like compressed air (Dhar et al. 2014). Vaccination by intramuscular injection is preferred by fish farmers. One of the disadvantages of this method is that the stress caused as a result of the vaccination leads to mortality. Intramuscular method of vaccination provides longer duration of protection. The volumes injected per fish are generally 0.1 or 0.2 ml, which gives protection throughout the production cycle (Komar et al. 2006).

Other disadvantages of vaccination by injection are temporary reduced feeding, adhesion formation, inadvertent puncture of intestine, laboratory intensive, and wounds that could possibly occur at the injection site which can provide an entry portal for secondary infections. Moreover, in fish weighing less than 5 g, this method is not practical (Vinitantharat et al. 1999). The main drawback of injectable vaccines is that they cannot be administered economically several times in the fish production cycle. Moreover, because their immune system is under-developed, they cannot be administered in the early life stages of fish (Dhar and Allnutt 2011).

Immersion vaccination

This type of vaccination is a simple and efficacious method of immunizing fish for protection against infection (Sudheesh and Cain 2017; Bøgwald and Dalmo 2019). Dadar et al. (2016) reported that vaccines for immersion type vaccination are live suspensions of attenuated bacteria or vector vaccines or live bacterial vaccines. Formalin inactivated bacteria and live bacterial vaccines are the immersion type of vaccines commercially available (Brudeseth et al. 2013). Fishes are immersed in a dilute vaccine solution for a short period of time and released into the culture unit, typically ponds, or net pens.

Immersion vaccination can be done by both dip and bath vaccination methods. In the dip vaccination method, fishes are immersed usually for about 30 s, in a high concentration of vaccine solution. On the other hand, in bath vaccination, fishes are exposed for a longer period of time, usually one to several hours, in a lower vaccine concentration (Mohamed and Soliman 2013). Vaccination by dip immersion method is preferred since a greater number of fishes can be vaccinated rapidly (Komar et al. 2006). For fry weighing between 0.5 and 5 g, immersion vaccination is widely used and recommended particularly for smaller fishes since it is effective, rapid, convenient, less stressful, and economical. It also gives protection for a significant time period and involves minimal handling stress (Dadar et al. 2016). Several facilitators like ultrasound-mediated uptake (Frenkel et al. 1999), hyperosmotic dip (Huising et al. 2003; Thune and Plumb 1984), and multiple puncture instrument (Nakanishi et al. 2002) have been developed for antigen uptake in immersion vaccination.

The disadvantage of the immersion method is that the duration of immunity is shorter and hence not enough for culturing of several fish species (Mohamed and Soliman 2013). Newaj-Fyzul and Austin (2015) reported that the time taken for development of immunity ranges from 3 to 12 months. This is not ideal for the culture of some fish species. Hence, it requires a booster dose. Moreover, this method cannot be applied in the case of larger fishes due to several factors like longer time duration, cost factor, stress, and also difficulty in using several immune stimulating agents and adjuvants (Mohamed and Soliman 2013; Komar et al. 2004).

Types of vaccines for fish pathogens in aquaculture and their advantages

Inactivated vaccines

Pathogens which are inactivated and have been traditionally used for fish vaccination are produced by either replication or multiplication of pathogenic bacteria. These pathogenic bacteria can be inactivated by using formalin which kills the pathogenic microorganism without harming the protective immunity (Dadar et al. 2016). Toranzo et al. (2009) reported

that bacterial vaccines used in aquaculture are inactivated vaccines acquired from a broth culture of the specific microorganism. These are then exposed to formalin inactivation. Inactivated vaccines are administered via inoculation for conferring protective immunity, although for a few viral diseases, it is considered as an impractical approach since the onset of diseases takes place in the early stages of life (Dadar et al. 2016; Leong et al. 1988).

Nuñez-Ortiz et al. (2016) conducted a study on the effect of formalin against retinopathy (VER) disease and viral encephalopathy in European sea bass (*Dicentrarchus labrax*) and its immunological and protective effects. A greater potency was seen with formalin killed vaccine when injected interperitoneally. Similarly, another study based on a potential inactivated vaccine was described on genotype RGNNV, strain It/411/96. This was inactivated by UV treatment at 254 nm (Valero et al. 2018). Another study by Pascoli et al. (2019) was conducted to investigate the efficiency of formalin-inactivated vaccines to offer in vivo cross-protection against RGNNV which was prepared from two distinct serotypes of betanoda viruses namely, RGNNV strain 283.2009 and striped jack Nervous Necrosis virus (SJNNV) strain 484.2.2009. They reported that the two serotypes are not cross-protective in vivo. Based on the results of their findings, they reported that the production of multivalent formulation, or different types of vaccines based on both fish and virus species requirement, should be suggested for effective protection. Some studies reported that ALV405 antigen of SAV based inactivated viral vaccines can protect the salmonid fishes effectively against pancreas disease (PD) infection by using either single or polyvalent vaccine as a candidate (Jang et al. 2014; Karlsen et al. 2012).

Attenuated vaccines

They are live vaccines that are weakened genetically or chemically and can induce immune responses for a shorter duration in the host (Adams et al. 2008; Dadar et al. 2016). They are composed of live microorganisms like bacteria and viruses that no longer possess the properties to cause the particular infection (Roy 2011; Muktar et al. 2016). These vaccines are reported to have great potential. Its evaluation as well as application in aquaculture was reported in the 1900s (Thornton et al. 1994; Lawrence et al. 1997; Shoemaker et al. 2009; Sun et al. 2010). Presently, four modified live attenuated vaccines are licensed for administration against three bacterial diseases in the USA: enteric septicemia of catfish disease, bacterial kidney disease, columnaris disease (Shoemaker et al. 2009), and one viral carp disease koi herpesvirus (KHV) in Israel (Adams et al. 2008). Dhar et al. (2014) reported that the attenuated viral vaccine for KHV which is under the trade name KV-3/Cavoy is administered via injection or immersion route. Similarly, a live viral vaccine against spring viremia of carp disease is administered through immersion route.

Recently, Zeng et al. (2021) reported the result of a study on a live attenuated gene-deleted vaccine candidate, ΔORF022L, in mandarin fish fry-1 (MFF-1) cells against infectious spleen and kidney necrosis virus (ISKNV). One hundred percent survival of the ΔORF022L-infected fish challenged with ISKNV infection was reported. Moreover, the vaccine induced the response of anti-ISKNV-specific antibody which can be beneficial for controlling the fish diseases.

Recombinant vaccines

In these vaccines, only the pathogen's immunogenic regions can be expressed in the heterologous host and used as vaccines (Adams et al. 2008). Irie et al. (2005) reported that it is possible to examine the stimulated protection by related antigen by vaccinating fish with

the antigen and then infecting fish experimentally with the live pathogen, which could give information regarding the survival level in vaccinated fish. Some researchers, nowadays, are using the recombinant DNA technology for improving the vaccines that are vital and have great potential effects in the aquaculture industry (Sun et al. 2009).

A Belgian company named Pharos developed an IP injectable subunit vaccine by incorporating the recombinant G protein in baculovirus against spring viremia of carp virus. Several researchers have used the recombinant technology to induce protective immune responses against pathogens like *Aeromonas hydrophila* (Poobalane et al. 2010), grass carp virus (He et al. 2011; Lu et al. 2011), and GNNV (Liu et al. 2006; Tanaka et al. 2001).

A study was conducted on an oral recombinant vaccine by Caruffo et al. (2016) against the pathogen, infectious salmon anemia virus (ISAV). They reported that recombinant DNA technology via oral vaccination route can protect the salmon from ISA infection.

Synthetic peptide vaccines

Synthetic peptide vaccines can be used to serve like a subunit vaccine or as a suitable antigenic site (Tam 1988; Coeurdacier et al. 2003). A few studies have been carried out by some researchers to demonstrate whether these peptides can be used for stimulating antibody production for pathogens like nodavirus, rhabdovirus, birnavirus, IHNV, infectious pancreatic necrosis virus (IPNV), and VHS (Emmenegger et al. 1994; Coeurdacier et al. 2003; Estepa et al. 1999; Fridholm et al. 2007). These reports suggested that fish vaccination by using peptides is possible although there is still a lack of the fundamental knowledge of fish immune mechanisms against various antigens (Dadar et al. 2016).

A study was conducted by Cárdenas et al. (2020) on synthetic peptides as a potent antiviral agent and also as an alternative for controlling the viral infections in Atlantic salmons. The peptides from both RNA viruses, infectious salmon anemia virus (ISAV), and IPNV were designed based on in silico analysis and were later tested in vitro in the fish cell lines. Moreover, in vivo tests were also carried out on *Salmo salar* fish with the synthetic peptide GIM 182 of IPNV. The results proved that the use of peptides as antiviral agents in disease control might be a suitable alternative to be explored in aquaculture.

DNA vaccines

Using DNA vaccines in combination with plasmids carrying a specific antigen of pathogens has been gaining wide attention for promoting protective immunity against various fish pathogenic diseases (Robertsen et al. 2016; Donnelly et al. 1996; Ogas Castells et al. 2015). Although these vaccines can first produce both non-specific and early immune responses, and later on specific immunity, the exact protective pathways by which this takes place in fishes remain unclear (LaPatra et al. 2001; Kurath 2008).

Viral genes encoding the surface glycoproteins via IM injection have evoked higher levels of protection against VHSV and IHNV infections in aquaculture (Anderson et al. 1996; Lorenzen et al. 1998; Purcell et al. 2006; Hølvold et al. 2014). The use of VHSV glycoprotein has led to an effective immune response followed by DNA vaccination in rainbow trout (Utke et al. 2007, 2008). *Vibrio anguillarum* which is pathogenic to fishes has extracellular zinc metalloprotease, a known virulence factor for *V. anguillarum*. This toxic substance has been shown to be a strong candidate antigen for developing a DNA vaccine (Norqvist et al. 1990; Milton et al. 1992; Shao 2001; Chen et al. 2002; Denkin and Nelson 2004). They

reported that M99 conditioned Luria-Bertani broth (LB20) supernatant stimulated protease activity in *V. anguillarum* strain NB10 while allowing *V. anguillarum* strain M93Sm to produce protease in LB10 (Denkin and Nelson 2004). An encapsulated DNA vaccine with chitosan was developed by Valero et al. (2016) to protect the European sea bass against nodavirus (NNV) infection. They reported that it has a partially protective effect in European sea bass juveniles and that it up-regulates the transcription of genes related to cell-mediated cytotoxicity (CMC) — cd8a and tcrb — and interferon (IFN) — mx, ifn, and ifng. A study conducted by Nusbaum et al. (2002) reported that DNA vaccination induced a strong protective immunity against certain viral fish infections, specifically in rainbow trout and Atlantic salmon infected with Rhabdoviruses and herpes viruses infecting the channel catfish. They reported that immunity established shortly after vaccination was cross-protective between the two viral pathogens. No increased survival was found upon challenge with bacterial pathogens. Within 2 months after vaccination, the cross-protection disappeared while the specific immunity to homologous virus remained high.

A study conducted by Reyes et al. (2017) on a DNA vaccine against IPNV demonstrated that at times oral immunization using feed can give better results compared to IP injection in Atlantic salmons. They showed that the delivery method for DNA vaccination via feed was immunogenic and safer to use in fishes since they exhibit great potential against IPNV as well as other pathogenic infections that currently have threatened the whole aquaculture industry.

Mucosal vaccines

Mucosal vaccines are now gaining wide attention in aquaculture due to the longer period of immunity in the vaccinated fishes (Dadar et al. 2016). The development of mucosal vaccines against pathogenic infections in aquaculture is currently the focus of research since they have the potential to elicit the protective responses at the mucosal surfaces by blocking the pathogens at the initial site of replication (Muñoz-Atienza et al. 2021). A study was performed on the mucosal and systemic responses of the B and T cells upon immunizing with mucosal vaccines against pathogens in teleost fishes via different routes of administration which included oral, immersion, and nasal vaccination (Muñoz-Atienza et al. 2021).

Munang'andu et al. (2012) reported that one of the problems in designing protective mucosal vaccines for finfish is determining the dose of the protective antigen required for conferring immunity. Comparatively, since injectable vaccines are presumed to be more protective in nature, the conditions and the doses required to develop effective mucosal vaccines need to be designed with due care (Dadar et al. 2016).

Plant-based edible vaccines

Since the use of conventional vaccines like live attenuated and inactivated vaccines is expensive and also since injecting vaccines is impractical for the protection of a huge population of fishes (Shahaid and Daniell 2016), plants could provide an economical platform to develop efficient vaccines (Dhama et al. 2013). Since plant vaccines are cost-efficient, free of live attenuated pathogens, they are potent edible vaccines that are capable of getting rid of various pathogenic fish diseases for sustainable aquaculture (Shahaid and Daniell 2016; Clarke et al. 2013; Kolotilin et al. 2014). Plant-based vaccines can help in reducing the intake of multiple boosters of live attenuated viral or bacterial vaccines (Dadar et al. 2016).

Nanovaccines/nanoparticle-based vaccines (nanodelivery of vaccines)

Nanoparticles are currently attracting a lot of attention among researchers in the area of developing vaccines for aquaculture even though the deployment of nanomaterials is at an infant stage (Dadar et al. 2016). These vaccines contain several dispersed nanosized materials which include alginate, chitosan, and poly(lactic-co-glycolic acid) (PLGA) with several specific physical characteristics which are incorporated with antigens and immunostimulants for improving their delivery and also for enhancing the intensity of immune responses (Ji et al. 2015).

A study which was conducted on an oral DNA vaccine using chitosan/triploy and chitosan phosphate nanoparticles against *Vibrio anguillarum* in Asian sea bass, *Lates calcarifer*, showed that it induced immune responses (Vimal et al. 2012). In another study reported by Shaalan et al. (2016), a nanoparticle-based vaccine against pathogen ISAV was administered which proved to be very promising in fishes. Moreover, they displayed a protection rate of 77% against ISAV in Atlantic salmons (Rivas-Aravena et al. 2015).

A recent study reported the use of various organic materials like PLGA, nanopoliplexes, chitosan, and virus-like particles (VLPs) for developing nanovaccines to control pathogenic fish diseases. They showed that oral nanovaccines can be used in fish aquaculture (Angulo et al. 2020). Another recent study reported that selenium nanoparticles have proven to be a novel tool for controlling various bacterial as well as viral fish diseases (Nasr-Eldahan et al. 2021).

Monovalent and polyvalent vaccines

A polyvalent vaccine is the ideal formulation of a vaccine that can simultaneously protect against a majority of infectious diseases to which a specific fish species is susceptible (Busch 1997; Ma et al. 2010). Polyvalent vaccines gave either superior or similar protection compared to respective monovalent vaccines in turbot and salmonids (Muktar et al. 2016). In recent years, most of the commercial vaccines that have been developed for fishes include two, three, four, and five vaccines (Busch 1997; Brudeseth et al. 2013).

A study was conducted on the efficacy of a polyvalent vaccine, ME-VAC Aqua Strept, via injection and immersion methods against streptococcal bacterial infections in Nile tilapia fish, *Oreochromis niloticus.* This inactivated polyvalent vaccine displayed a combined protection against several bacterial infections like streptococcosis, enterococcosis, and lactococcosis in tilapia fish (Abu-Elala et al. 2019).

Current status of fish vaccines and its applications-

Bacterial vaccines

Vaccination plays a key role in commercial fish farming on a large scale. Vaccines are available for fishes including salmon, trout, channel catfish, Japanese amberjack and yellowtail, European seabream and sea bass, Atlantic cod, and tilapia (Muktar et al. 2016). Generally, based on the inactivated bacterial pathogens, empirically developed vaccines have been confirmed to be very efficacious in fishes (Sommerset et al. 2005). Some of the bacterial fish vaccines and experimental vaccination trials conducted are shown in Table 1.

Vibriosis

Vibriosis has been reported as a major bacterial disease occurring in marine fishes with a global distribution. The vibrios which cause some of the crucial infections in marine animals include *Vibrio anguillarum*, *Aliivibrio salmonicida*, *V. ordalii*, *V. harveyi*, *V. parahaemolyticus*, and *V. vulnificus* biotype 2 (Woo et al. 2002). Severity of the disease caused by these pathogens depends on its source, the strain of *Vibrio*, age of the marine animal, developmental stage, and also ambient environment (Jayasree et al. 2006).

The pathogen, *V. anguillarum*, causing vibriosis, consists of around 23 O serotypes, among which serotypes O1 and O2 only are well known while O3 serotype known to a lesser extent is correlated with mortalities (Jayasree et al. 2006; Bowser 1999). Although many commercial vaccines for *V. anguillarum* have been developed for use via injection or bath methods (Toranzo et al. 2009; Newman 1993), a majority of them include either O1 only or mixtures of O1 and O2a serotypes in their formulations. In addition, a polyvalent oil-adjuvanted vaccine that includes the combination of *V. anguillarum* with various other pathogens like *Aliivibrio salmonicida*, *V. ordalii*, *Aeromonas salmonicida*, IPNV, and *Moritella viscosa* has been made available in the market for use in salmonids via IP route (Jayasree et al. 2006). Generally, the injectable vaccines are reported to provide an excellent protection against vibriosis (Magnadottir 2010).

Recently, a novel feed-based and whole-cell oral polyvalent vaccine was developed against vibriosis in the Asian sea bass, *Lates calcarifer*, which can be used as a promising candidate for the large-scale immunization of fishes in aquaculture (Mohamad et al. 2021). The results demonstrated the efficacy of the vaccine in eliciting innate as well as adaptive immune responses against vibriosis in Asian sea bass.

Yersiniosis

This is a freshwater enteric red mouth (ERM) disease caused by a bacterium, *Yersinia ruckeri* (EC 2003), in rainbow trouts. It can also affect other fishes like Atlantic salmon in freshwater and in the marine environment also occasionally (Moeller 2005). At present, a recently developed formalin inactivated whole-cell vaccine has been made available for *Y. ruckeri*, biotype 1 with serovar I (Hagerman strain) (Toranzo et al. 2009).

A recent study reported the effect of ERM immersion vaccines against the pathogen *Yersinia ruckeri* in the rainbow trout, *Oncorhynchus*, *mykiss* based on both biotypes 1 and 2 with serotype O1 (Yang et al. 2021). They showed that both vaccine biotypes 1 and 2 can protect the fish against the infection.

Enteric septicemia of catfish

The causative organism that is responsible for causing enteric septicemia of catfish is *Edwardsiella ictaluri.* The channel catfish is considered to be the most susceptible one among these ictalurids (Toranzo et al. 2009; Moeller 2005). The very first commercial bacterins were licensed for use via oral or immersion methods (Toranzo et al. 2009; Muktar et al. 2016). An attenuated *E. ictaluri* strain with deficient O-antigen was developed that provided an acquired immunity for at least 4 months in channel catfish followed by a bath immersion without the booster vaccination (Klesius and Shoemaker 1998).

Table 1 Licensed bacterial fish vaccines and experimental vaccination trials conducted

Disease	Pathogen	Fish host	Type of vaccine	Delivery methods	Target antigens	Vaccine available/ status	References
Vibriosis	*Vibrio anguillarum*, *Vibrio salmonicida*, *Vibrio ordalii*	Salmonids, grouper, sea bass, sea bream, cod, yellowtail, ayu, halibut	Inactivated/killed	Immersion, IP	Inactivated *Vibriosis*	Commercial (AquaVac Vibrio Oral), ALPHA MARINE™ Vibrio	Angelidis et al. (2006); Mikkelsen et al. (2011); Galindo-Villegas et al. (2013)
Yersiniosis	*Yersinia ruckeri*	Atlantic salmon, rainbow trout	Inactivated Lipopolysaccharide	Immersion	Inactivated *Yersiniosis*	Experimental	Siwicki et al. (1998); Raida et al. (2011); Skov et al. (2012); Bridle et al. (2012); Deshmukh et al. (2012); Ispir and Dorucu (2014); Chettri et al. (2015); Ghosh et al. (2016); Jaafar et al. (2018)
Enteric septicemia of catfish (ESC)	*Edwardsiella ictaluri*	Catfish	Inactivated Outer membrane proteins	IP	Inactivated *Edwardsiella ictaluri*	AQUAVAC-ESCO	Thinh et al. (2009); Glenney and Petrie-Hanson 2006
Bacterial kidney disease (BKD)	*Renibacterium salmoninarum*	Salmonids	Avirulent live culture	IP	*Arthrobacter davidanieli*	-	Salonius et al. (2005)
Mycobacteriosis	*Mycobacterium marinum*	Pejerrey, turbot, Pacific and Atlantic salmon, snakehead fish, European sea bass and red drum, tilapia	Avirulent heat-killed	IP	-	Experimental	Ravid-Peretz et al. (2019); Ziklo et al. (2018)

Table 1 (continued)

Disease	Pathogen	Fish host	Type of vaccine	Delivery methods	Target antigens	Vaccine available/ status	References
Rainbow trout fry syndrome (RTFS) or bacterial cold-water disease (BCWD)	*Flavobacterium psychrophilum* (syn., *Flexibacter psychrophilus* and *Cytophaga psychrophila*)	Salmonids	Live attenuated	Immersion	-	B.17-ILM	Bøgwald and Dalmo (2019)
Furunculosis	*Aeromonas salmonicida* subsp. *salmonicida*	Salmonids	Inactivated	Immersion, IP	Inactivated *Aeromonas salmonicida* spp.	-	Thornton et al. (1991)
Columnaris disease	*Flavobacterium columnaris*	Freshwater finfish species, Nile tilapia, bass, bream, salmon, turbot	Attenuated	Immersion	Attenuated *Flavobacterium columnare*	Experimental	Shoemaker et al. (2011); Mohammed et al. (2013)
Enteric redmouth disease (ERM)	*Yersinia ruckeri*	Salmonids rainbow trout	Inactivated	Immersion oral	Inactivated *Yersinia ruckeri*	Experimental	Costa et al. (2011); Villumsen et al. (2014); Nguyen et al. (2018)

Ma et al. (2019); Bøgwald and Dalmo (2019); Miccoli et al. (2021)

A study was conducted on a novel live attenuated vaccine called *Ei*Δ*evp*B against enteric septicemia of catfish (ESC) disease in fry and fingerlings of channel catfish, *Ictalurus punctatus*, via immersion route. It displayed the avirulent nature of the *Ei*Δ*evp*B strain and gave better protection to the channel catfish fingerlings and fry against the pathogen *E. ictaluri* when compared to AQUAVAC-ESC (Abdelhamed et al. 2018). Similarly, another study on a live attenuated vaccine, mutant WzM-L3, was reported to have the potential to protect the Vietnamese catfish, *Pangasius hypophthalmus* against ESC (Triet et al. 2019).

Bacterial cold-water disease

Flavobacterium psychrophilum (syn., *Flexibacter psychrophilus* and *Cytophaga psychrophila*) have been causing BCWD or peduncle disease since 1948, in salmonids. In addition, in the rainbow trout, the same pathogen has been involved in causing the rainbow trout fry syndrome since 1980s (Toranzo et al. 2009; Muktar et al. 2016).

Since no commercial vaccines are available against this disease, a few countries have started using the autogenous vaccines from single isolates (Toranzo et al. 2009). Oil-adjuvanted IP vaccines provided significant protection against this disease in rainbow trouts (La Frentz et al. 2002). In a recent study, it was reported that no effective vaccines are available against this bacterial cold-water disease (Takeuchi et al. 2021).

Mycobacteriosis (fish tuberculosis)

Mycobacteriosis is considered as a chronic disease which is caused by a bacterium, *Mycobacterium marinum* (Bowser 1999) that has been reported to affect around 200 saltwater as well as freshwater species (Toranzo et al. 2009). This disease has been documented in several cultured fishes including Pejerrey (*Odontesthes bonariensis*), turbot, snakehead fish (*Channa striatus*), Pacific and Atlantic salmon, European sea bass, tilapia, and red drum. In addition, mycobacteriosis is a significant threat particularly to sea bass cultured on the Red Sea coasts and in the Mediterranean since the 1990s (Colorni 1992; Colorni et al. 1993, 1996; Diamant et al. 2000). Currently, no vaccine has been developed for preventing this disease in fishes.

Bacterial kidney disease

BKD is caused by a bacterium, *Renibacterium salmoninarum*, representing the diplobacillus group (Muktar et al. 2016). This is a chronic systemic disease that has been stated to occur in salmonids and causes mortalities in fishes in marine as well as freshwater environments (Sanders and Fryer 1980; Evelyn 1993; Evenden et al. 1993; Fryer and Lannan 1993; Toranzo and Barja 1993; Kaattari and Piganelli 1997; Wiens and Kaattari 1999).

Even though a lot of vaccination trials have been reported using classical bacterins, live attenuated or recombinant vaccines, there are some evidences to show that this bacterium can stimulate an immune response (Wood and Kaattari 1996). However, since pathogens are being transmitted vertically and also due to the intracellular nature and the immunosuppressive role of p57 protein, the ability of the vaccine to protect is doubtful (Toranzo et al. 2009; Muktar et al. 2016; Newman 1993). A commercial live

vaccine has been reported to be licensed under the trade name "Renogen" by Novartis in South Africa (S.A) for BKD prevention (Toranzo et al. 2009). However, recently, a study reported that bacterin-killed vaccines have proven to possess doubtful efficacy to control this disease since not much is known regarding the potential of neither the vaccine nor its virulence mechanisms (Delghandi et al. 2020).

Viral vaccines

As of today, very few viral vaccines have been licensed but most viral fish vaccines available for sale in aquaculture are either based upon inactivated virus or recombinant subunit proteins (Sommerset et al. 2005). Killed/inactivated viral vaccines are not effective unless administered via injection and require high doses, and although cost-effective, they are difficult to develop and do not give adequate protection (Muktar et al. 2016). Biering et al. (2005) reported that live viral vaccines have been tested in fish and that it gave protection against the disease. They are easy to administer and is also cost-effective. Some of the viral fish vaccines and vaccine trials used in aquaculture are mentioned in Table 2.

Infectious pancreatic necrosis virus

IPNV is a viral disease which caused by a pathogen called aquatic birnavirus. This virus is related to infectious bursal disease (IBD) of poultry and in some studies these two viruses were reported to be morphologically different (Woo et al. 2002). This virus has been reported to cause problems in rearing fish in both seawater as well as freshwater.

A vaccine for Atlantic salmons has been made available in the UK under provisional marketing authorization (PMA) (Sommerset et al. 2005). A novel bivalent DNA vaccine developed against IPNV that resulted in inducing significant immune responses in rainbow trout has been reported (Xu et al. 2017). A recently conducted study on oral vaccines against IPNV reported that genetically engineered recombinant *Lactobacillus casei* provided promising protection in salmonids (Hua et al. 2021).

Spring viremia of carp

The causative organism that is responsible for this disease is spring viremia of carp virus (SVCV) that can be lethal, highly contagious, and lead to a viral infection associated with various hemorrhagic symptoms in cyprinids, particularly the common carp, *Cyprinus carpio*, resulting in a great economic loss for the fish culture industry worldwide (Baudouy et al. 1980; Fijan 1984, 1999; Ahne et al. 2002; Ashraf et al. 2016).

A study performed by Muiswinkel et al. (2018) reported that new DNA vaccines containing glycoprotein of SVC virus, including formulations administered via injection or oral route, have been developed that are proven to be very promising in preventing this infectious disease and protecting the young fishes as well as the carp production.

Recently, a single-walled carbon nanotube (SWCNT)–based subunit vaccine with mannose-modified glycoprotein was reported to be effective against SVCV in common carp. It displayed improved immune efficiency by immersion vaccination (Gong et al. 2021). Another promising bacterial ghost–based DNA vaccine was reported to be effective in common carp against SVCV based on *Escherichia coli* DH5α. It also improved the immune efficiency of the vaccine on a large scale (Zheng et al. 2021).

Table 2 Licensed viral fish vaccines and vaccine trials used in aquaculture

Disease	Pathogen	Fish host	Type of vaccine	Delivery methods	Target antigens	Vaccine status	References
Infectious pancreatic necrosis	IPNV *Birnavirus*	Salmonids, turbot, sea bass, sea bream, Pacific cod	1. Inactivated 2. Subunit 3. Subunit	1. IP 2. IP 3. Oral	1. Inactivated IPNV 2. VP2 Protein 3. VP2 and VP3 capsid proteins	Experimental	Reyes et al. (2017)
Infectious hematopoietic necrosis	IHNV *Rhabdovirus*	Salmonids	DNA	IM	G glycoprotein	-	Vendramin et al. (2018)
Pancreatic disease	SAV *alphavirus*	Salmonids	Inactivated	IP	Inactivated SAV	1. Experimental and Commercial (Norvax® Compact PD)	Chang et al. (2017); Lund et al. (2016)
Infectious salmon anemia	ISAV *Orthomyxovirus*	Atlantic salmon	Inactivated	IP	Inactivated ISAV	Experimental	Caruffo et al. (2016); Robertsen et al. (2016)
Infectious spleen and kidney necrosis	ISKNV *Iridovirus*	Mandarin fish, Asian sea bass, Japanese yellowtail, grouper	1. Subunit 2. Inactivated	IP	Inactivated ISKNV	-	Zhao et al. (2019)
Spring viremia of carp	SVCV *Rhabdovirus*	Carp	1. Inactivated 2. subunit	1. IP 2. IP	1. Inactivated SVCV 2.G glycoprotein	-	Dhar et al. (2014); Dixon and Stone (2017)
Koi herpes virus disease	KHV *Herpesvirus*	Carp	Attenuated DNA	Immersion, IP	Attenuated KHV	-	Dhar et al. (2014); Aonullah et al. (2017)

Ma et al. (2019); Bøgwald and Dalmo (2019); Miccoli et al. (2021)

Pancreas disease

This disease is caused by salmonid alphavirus (SAV) (Røsaeg et al. 2021) named salmon pancreas disease virus (PDV) that is closely related to sleeping disease causing virus of rainbow trout (Muktar et al. 2016).

There is a vaccine available for this disease under a pre-market approval (PMA: Provisional marketing authorization) (Sommerset et al. 2005). Clynav, a recombinant DNA vaccine that contains puK-SPDV-poly2#1 plasmid which is responsible for coding of several proteins from salmonid alphavirus subtype 3, has been approved in Norway and EU against this disease (Jansen et al. 2016; Dalmo 2018; Aida et al. 2021). Recently, a study conducted by Røsaeg et al. (2021) reported the efficacy of vaccines against PD in Atlantic salmons. When fish was vaccinated with two different PD vaccines, they showed variations in the efficacy of PD vaccines.

Reverse vaccinology

In recent years with increase in advances in biotechnology, a latest technology, reverse vaccinology has been brought into focus. This latest technology is helpful for developing a vaccine against various pathogenic organisms. Rappuoli (2000) reported that it takes several years to develop a successful and a potent vaccine. This concept of vaccinology has reduced the vaccine production time from 5–10 to 1–2 years. It predicts the immunogenic sequences by utilizing the bioinformatics approach and also the regions being predicted by this software, expressing as recombinant proteins (Dadar et al. 2016).

Recently, this technology has been applied to marine species like *Photobacterium damselae* subsp. *piscicida*. Many studies on reverse vaccinology have reported that there are significant complications (Andreoni et al. 2016). Vaccine designing by using software has been achieved in two major intracellular infectious fish pathogens, *Flavobacterium columnare* and *Edwardsiella tarda*, causing columnaris and edwardsiellosis, respectively (Mahendran et al. 2016).

The report of a study conducted by Ellul et al. (2021) highlighted the potential of reverse vaccinology of the lumpfish, *Cyclopterus lumpus*, against *Pasteurella atlantica* to prevent pasteurellosis in aquaculture. They performed an in silico study and functional analysis which revealed that the strongest gene target candidates are prioritized in the vaccine development for preventing these disease outbreaks.

Recent molecular advances for development of vaccines for fish and its effective vaccination strategies

Immunoprophylactic approaches that are responsible for stimulating sensors for nucleic acids of viruses, toll-like receptors (TLRs), high mobility group box proteins (HMGBs), retinoic acid inducible gene-I (RIG-I)–like receptors (RLRs), and pattern recognition receptors (PRRs) in fishes like grass carp have been reported. Recent molecular studies suggest that they play a significant role in activating the fish immune system against viral diseases and can also be manipulated to achieve the desired protection levels (Rao and Su 2015). In addition, toll-like receptors specifically identify the pathogen associated molecular patterns (PAMPs) in microbes, activating their immune signaling of cascades and thereby enhancing innate immunity. It is also reported that they play an important role in adaptive immunity. Thus, the

addition of TLRs as an adjuvant and TLR activators in vaccine formulation for use in fish and aquatic animals may provide an effective vaccine (Rauta et al. 2014).

Another recent development in molecular biology is the advancement in designing as well as developing the vaccines including marker vaccines, structural vaccinology (SV), immunomics-based vaccines, designer cell lines, and dendritic cells (Delany et al. 2014; Finco and Rappuoli 2014; Effio and Hubbuch 2015; Singh et al. 2015). In the case of vaccines which do not induce strong immune responses, adjunction with improved adjuvants could play a key role in vaccine development by improving the level of protection towards the desired level (Pérez et al. 2013).

Safety of fish vaccines

The concern regarding safety of fish vaccines involves the poor immunogenic ability of vaccines that may later result in severe diseases and also decreased production in the vaccinated fishes (Dadar et al. 2016). Moreover, the vaccines need to pass certain safety guidelines which include an experiment that uses 10 times the immunizing dose (Shoemaker et al. 2009). Due to the use of killed or inactivated pathogenic agents, inactivated or killed vaccines are reported to be safe for application in marine animals. The only concern is the application of the modified live vaccines.

DNA vaccines are considered to be safe and advantageous since they require only an immunogenic part of the pathogen. Moreover, they have advantages like the potential of co-administration of multivalent vaccines, low-cost production processes, stability in storage due to elevation of chemical stability of the plasmid DNA, and modification of DNA sequences rapidly to target the mutants of a novel pathogen. In addition, they have advantages like safety regarding disease transmission, confrontation with live attenuated vaccine, and proper conformation of protein folding belonging to the antigen of pathogens that are not invariably produced with recombinant proteins. It does not require adjuvant administration to improve immune responses and their efficacy to promote both cell-mediated and humoral immunity (Restifo et al. 2000; Adams and Thompson 2006; Utke et al. 2007, 2008). In addition, they do not require the oil adjuvants that may result in certain side effects as reported in the case of polyvalent oil-adjuvant vaccines (Dadar et al. 2016).

In the year 2005, Apex-IHN®, a DNA vaccine, was authorized for use against IHN by the Veterinary Biologics and Biotechnology Division of the Canadian Food Inspection Agency for marketing. It has also been approved in the USA, and there is a possibility of using these vaccines to induce protection against other viral fish infections like VHS in trout (Lorenzen and LaPatra 2005). In addition to providing protection against VHS in rainbow trouts, Pacific and Atlantic salmons, this vaccine also induces both adaptive as well as innate immune responses in other fishes (Purcell et al. 2006; Hølvold et al. 2014; Aida et al. 2021; Corbeil et al. 1999, 2000; Traxler et al. 1999; Lorenzen et al. 2002; Garver et al. 2005). Similarly, Clynav, another DNA-recombinant vaccine, has been developed by Elanco Animal Health and approved in both EU and Norway against pancreas disease in salmonids (Jansen et al. 2016; Aida et al. 2021).

Conclusion and future outlook

At present, the advancements in biotechnology have had a great impact on the development of new vaccines against several infectious pathogens by reducing the risk of disease outbreaks and the resulting losses in the aquaculture industry. On the other hand, there are

various health-related problems in fishes that need to be addressed for improvement of fish health and also to maintain sustainable fish production in aquaculture.

Development of fish vaccines is quite time-consuming and expensive and hence non-profitable for developing vaccines against all known pathogens that are being identified. The focus of fish vaccination in aquaculture has therefore been on a cost-effective technology to monitor pathogens that cause mass mortalities. Significant progress has been made in the development and manufacture of safe, inexpensive, and cost-efficient vaccines that can recognize protective antigens. However, most of the efforts to develop aquatic animal vaccines are at an infant stage. In addition, problems that come in the way of developing multivalent, affordable vaccination strategies are yet to be figured out.

The cost of fish production is generally lower when compared to other aquatic animals. Hence, low-cost vaccines are preferred for use against fish pathogens. Moreover, accessory antigens are required against viral pathogens like, IHSV, VHSV, PDV, and ISAV along with multivalent vaccines for salmonids. There is also a need to improve the new generation system producing protein glycosylation as well as reassembling the tertiary structure. Since majority of the antigens are protein-based and some are polysaccharide-based, a few of the protective immune responses require inclusion polysaccharides for induction that may create a big impact on the future of vaccine development.

In killed/inactivated vaccines, unless the adjuvants are added to enhance the potency of the vaccine formulation, long-lasting and adequate protection cannot be achieved. Currently available injection vaccines are able to induce significant protection against bacterial infections like vibriosis, winter ulcers, and furunculosis. In addition, for high value fish species like salmonids, modern multivalent fish vaccines comprising antigens from various pathogens are preferred. Although a high dosage of antigens is helpful to induce protective immunity against the viral infections, it can later turn into a major challenge to develop such efficacious antiviral vaccines. Therefore, to meet certain essential requirements regarding improvement of antiviral responses to vaccination, rather than replacing them fully, future fish vaccines are anticipated to involve the existing vaccines without-adjuvant platform.

Generally, live attenuated microorganisms are reported to be unstable and can revert to virulence and, hence, the use of modified live vaccines has safety concerns. To overcome this, newly developed molecular methods like genetically modified organisms (GMOs) can be used since they have an advantage over random mutagenesis. Foreign genes can be introduced into live vaccines to expand their protection level against other infections.

Aquaculture is one of the rare food-producing sectors where DNA vaccines have entered. Genetic adjuvants and also the adjuvants that are non-encoded as plasmid but included as a part of vaccine may be a better approach towards better functioning to develop future DNA vaccines.

At present, commercial vaccines may or may not have the desired protective effect. Scientists and researchers need to have a better understanding of the safety concerns so that they can raise an awareness among the consumers regarding the positive impact of safer and cost-effective vaccines. Moreover, in order to improve protection, increasing the production and availability of vaccines and development of several autogenous vaccines can bring about a real change in the future of vaccines.

Due to several infectious diseases, factors, like the introduction of novel species, intensive aquacultural practices, interaction between fish farmed and wild fish, growing trade in ornamental fishes, breaking out of the emerging, and re-emerging diseases, have enhanced the production losses. In addition, problems associated with biosecurity along with lack of knowledge in fish immunology have also enhanced the losses. Vaccination has made

it possible to induce active immunity to diseases. In addition, due to the intensive culture systems, several industries have resorted to use vaccines routinely since they confer a high degree of protection if used correctly. Efficacy of the fish vaccines has been improved using immunostimulants, adjuvants, and vaccine carriers.

Many researchers revealed that injection vaccines confer protection from 6 months to 1 year which is considered much longer when compared to other methods. Since modified live vaccines have the ability to induce immune responses, they can survive and replicate within the host. They later confer protection for longer duration stimulating strong immune responses.

Antibody titers are reported to have positive predictive values for vaccine protection. After oral immunization, the bivalent killed whole-cell *Vibrio cholerae* O1 and O139 vaccine has produced higher antibody titers as well as a strong O-antigen-specific B memory response. Additionally, rainbow trout immunized with a non-microencapsulated rifampicin live attenuated oral vaccine against *Flavobacterium psychrophilum* has shown higher antibody titers compared to those obtained in vaccinated fish with microencapsulated vaccine. However, overall, all determinants of particular antibody titers have focused on the identification of specific IgM antibodies and no studies to date have been reported on the presence of IgD or IgT antibodies in fishes.

Fish vaccines produced in future against several infectious pathogens, including bacteria, viruses, and so on should be environmentally friendly and cost-effective. They should be suitable for production on large scale, should be easily available, suitable, and affordable even for small fish farmers. Plant biotechnological strategies and its applications in development of fish vaccines are possible solutions that may satisfy the requirements for the production of fish vaccines. More research needs to be carried out for this.

Acknowledgements The authors are thankful to VIT Vellore for providing the required facilities to carry out this work.

Author contribution Not applicable

Data availability Not applicable

Code availability Not applicable

Declarations

Ethics approval Not applicable

Conflict of interest The authors declare no competing interests.

References

Abdelhamed H, Lawrence ML, Karsi A (2018) Development and characterization of a novel live attenuated vaccine against enteric septicemia of catfish. Front Microbiol 9:1819. https://doi.org/10.3389/fmicb.2018.01819

Abu-Elala NM, Samir A, Wasfy M, Elsayed M (2019) Efficacy of injectable and immersion polyvalent vaccine against streptococcal infections in broodstock and offspring of Nile tilapia (*Oreochromis niloticus*). Fish Shellfish Immunol 88:293–300. https://doi.org/10.1016/j.fsi.2019.02.042

Adams A (2019) Progress, challenges and opportunities in fish vaccine development. Fish Shellfish Immunol 90:210–214. https://doi.org/10.1016/j.fsi.2019.04.066

Adams A, Thompson KD (2006) Biotechnology offers revolution to fish health management. Trends Biotechnol 24(5):201–205. https://doi.org/10.1016/j.tibtech.2006.03.004
Adams A, Aoki T, Berthe C, Grisez L, Karunasagar I (2008) Recent technological advancements on aquatic animal health and their contributions toward reducing disease risks-a review. In: Diseases in Asian Aquaculture, 6th edn. Fish Health Section, Asian Fisheries Society, Colombo, pp 71–88
Ahne W, Bjorklund HV, Essbauer S, Fijan N, Kurath G, Winton JR (2002) Spring viremia of carp (SVC). Dis Aquat Org 52(3):261–272. https://doi.org/10.3354/dao052261
Aida V, Pliasas VC, Neasham PJ, North JF, McWhorter KL, Glover SR et al (2021) Novel vaccine technologies in veterinary medicine: a herald to human medicine vaccines. Front Vet Sci 8:654289. https://doi.org/10.3389/fvets.2021.654289
Anderson E, Mourich D, Fahrenkrug S, LaPatra S, Shepherd J, Leong J (1996) Genetic immunization of rainbow trout (*Oncorhynchus mykiss*) against infectious hematopoietic necrosis virus. Mol Mar Biol Biotechnol 5(2):114–122
Andreoni F, Amagliani G, Magnani M (2016) Selection of vaccine candidates for fish pasteurellosis using reverse vaccinology and an in vitro screening approach. Methods Mol Biol 1404:181–192. https://doi.org/10.1007/978-1-4939-3389-1_12
Angelidis P, Karagiannis D, Crump EM (2006) Efficacy of a *Listonella anguillarum* (syn. *Vibrio anguillarum*) vaccine for juvenile sea bass *Dicentrarchus labrax*. Dis Aquat Org 71(1):19–24. https://doi.org/10.3354/dao071019
Angulo C, Tello-Olea M, Reyes-Becerril M, Monreal-Escalante E, Hernández-Adame L, Angulo M et al (2020) Developing oral nanovaccines for fish: a modern trend to fight infectious diseases. Rev Aquac 13(3):1172–1192. https://doi.org/10.1111/raq.12518
Aonullah AA, Nuryati S, Alimuddin MS (2017) Efficacy of koi herpesvirus DNA vaccine administration by immersion method on *Cyprinus carpio* field scale culture. Aquac Res 48(6):2655–2662. https://doi.org/10.1111/are.13097
Ashraf U, Lu Y, Lin L, Yuan J, Wang M, Liu X (2016) The spring viremia of carp virus: recent advances. J Gen Virol 97(5):1037–1051. https://doi.org/10.1099/jgv.0.000436
Assefa A, Abunna F (2018) Maintenance of fish health in aquaculture: review of epidemiological approaches for prevention and control of infectious disease of fish. Vet Med Int 2018:5432497. https://doi.org/10.1155/2018/5432497
Baudouy AM, Danton M, Merle G (1980) SVCV infection of carp (author's transl). Ann Rech Vet 11(3):245–249
Belakova J, Horynova M, Krupka M, Weigl E, Raska M (2007) DNA vaccines: are they still just a powerful tool for the future? Arch Immunol Ther Exp 55(6):387–398. https://doi.org/10.1007/s00005-007-0044-4
Biering E, Villoing S, Sommerset I, Christie KE (2005) Update on viral vaccines for fish. Dev Biol (Basel) 121:97–113
Bøgwald J, Dalmo RA (2019) Review on immersion vaccines for fish: an update 2019. Microorganisms 7(12):627. https://doi.org/10.3390/microorganisms7120627
Bostock J (2002) Animal Pharm Report. In: Campbell R, Adams A, Tatner (eds) Aquaculture: a global market study. PJB Publications Ltd., Richmond, p 106
Bowser PR (1999) Diseases of fish. Cornell University, Ithaca, pp 18–25
Bridle A, Nowak BF (2014) Vaccination against yersiniosis. In: Gudding RA, Evensen Ø (eds) Fish Vaccination, 1st edn. John Wiley & Sons, Ltd, pp 226–235
Bridle AR, Koop BF, Nowak BF (2012) Identification of surrogates of protection against yersiniosis in immersion vaccinated Atlantic salmon. PLoS One 7(7):e40841. https://doi.org/10.1371/journal.pone.0040841
Brudeseth BE, Wiulsrød R, Fredriksen BN, Lindmo K, Løkling K-E, Bordevik M et al (2013) Status and future perspectives of vaccines for industrialised fin-fish farming. Fish Shellfish Immunol 35(6):1759–1768. https://doi.org/10.1016/j.fsi.2013.05.029
Busch RA (1997) Polyvalent vaccines in fish: the interactive effects of multiple antigens. Dev Biol Stand Aquat Animal Health Div, Alpharma, Inc., Bellevue 90:245–256
Campbell R, Adams A, Tatner MF, Chair M, Sorgeloos P (1993) Uptake of *Vibrio anguillarum* vaccine by *Artemia salina* as a potential oral delivery system to fish fry. Fish Shellfish Immunol 3(6):451–459. https://doi.org/10.1006/fsim.1993.1044
Cárdenas C, Guzmán F, Carmona M, Muñoz C, Nilo L, Labra A et al (2020) Synthetic peptides as a promising alternative to control viral infections in Atlantic salmon. Pathogens 9(8):600. https://doi.org/10.3390/pathogens9080600
Caruffo M, Maturana C, Kambalapally S, Larenas J, Tobar JA (2016) Protective oral vaccination against infectious salmon anaemia virus in *Salmo salar*. Fish Shellfish Immunol 54:54–59. https://doi.org/10.1016/j.fsi.2016.03.009

Chang CJ, Gu J, Robertsen B (2017) Protective effect and antibody response of DNA vaccine against salmonid alphavirus 3 (SAV3) in Atlantic salmon. J Fish Dis 40(12):1775–1781. https://doi.org/10.1111/jfd.12644

Chen J, Liu S, Li Y, Wang X, Du Z, Yu D et al (2002) Purification of an extracellular protease from *Vibrio anguillarum* and its physicochemical properties. J Fish Sci China 9:318–322

Chettri JK, Jaafar RM, Skov J, Kania PW, Dalsgaard I, Buchmann K (2015) Booster immersion vaccination using diluted *Yersinia ruckeri* bacterin confers protection against ERM in rainbow trout. Aquaculture 440:1–5. https://doi.org/10.1016/j.aquaculture.2015.01.027

Clarke JL, Waheed MT, Lössl AG (2013) How can plant genetic engineering contribute to cost-effective fish vaccine development for promoting sustainable aquaculture? Plant Mol Biol 83:33–40. https://doi.org/10.1007/s11103-013-0081-9

Coeurdacier J-L, Laporte F, Pepin J-F (2003) Preliminary approach to find synthetic peptides from nodavirus capsid potentially protective against sea bass viral encephalopathy and retinopathy. Fish Shellfish Immunol 14(5):435–447. https://doi.org/10.1006/fsim.2002.0449

Colorni A (1992) A systemic mycobacteriosis in the European seabass *Dicentrarchus labrax* cultured in Eilat (Red Sea). Isr J Aquacult Bamidgeh 44:75–81

Colorni A, Ankaoua M, Diamant A, Knibb W (1993) Detection of mycobacteriosis in fish using the polymerase chain reaction technique. Bull Eur Assoc Fish Pathol 13:195–198

Colorni A, Ucko M, Knibb W (1996) Epizootiology of *Mycobacterium* spp. in seabass, seabream and other commercial fish. In: In: Seabass and seabream culture: problems and prospects. Eur. Aquacult. Soc. Spec. Publ, Verona, pp 259–261

Corbeil S, Lapatra SE, Anderson ED, Jones J, Vincent B, Hsu YL et al (1999) Evaluation of the protective immunogenicity of the N, P, M, NV and G proteins of infectious hematopoietic necrosis virus in rainbow trout *Oncorhynchus mykiss* using DNA vaccines. Dis Aquat Org 39(1):29–36. https://doi.org/10.3354/dao039029

Corbeil S, LaPatra SE, Anderson ED, Kurath G (2000) Nanogram quantities of a DNA vaccine protect rainbow trout fry against heterologous strains of infectious hematopoietic necrosis virus. Vaccine 18(25):2817–2824. https://doi.org/10.1016/s0264-410x(00)00078-5

Costa AA, Leef MJ, Bridle AR, Carson J, Nowak BF (2011) Effect of vaccination against yersiniosis on the relative percent survival, bactericidal and lysozyme response of Atlantic salmon, *Salmo salar*. *Aquaculture* 315(3-4):201–206. https://doi.org/10.1016/j.aquaculture.2011.02.031

Czochor J, Turchick A (2014) Introduction. Yale J Biol Med 87(4):401–402

Dadar M, Dhama K, Vakharia VN, Hoseinifar SH, Karthik K, Tiwari R, Khandia R, Munjal A, Salgado-Miranda C, Joshi SK (2016) Advances in aquaculture vaccines against fish pathogens: global status and current trends. Rev Fish Sci Aquac 25(3):184–217. https://doi.org/10.1080/23308249.2016.1261277

Dalmo RA (2018) DNA vaccines for fish: review and perspectives on correlates of protection. J Fish Dis 41(1):1–9. https://doi.org/10.1111/jfd.12727

Delany I, Rappuoli R, De Gregorio E (2014) Vaccines for the 21st century. EMBO Mol Med 6(6):708–720. https://doi.org/10.1002/emmm.201403876

Delghandi MR, El-Matbouli M, Ledouble MS (2020) Renibacterium salmoninarum – the causative agent of bacterial kidney disease in salmonid fish. Pathogens 9(10):845. https://doi.org/10.3390/pathogens9100845

Denkin SM, Nelson DR (2004) Regulation of *Vibrio anguillarum* empA metalloprotease expression and its role in virulence. Appl Environ Microbiol 70(7):4193–4204. https://doi.org/10.1128/FAEM.70.7.4193-4204.2004

Deshmukh S, Raida MK, Dalsgaard I, Chettri JK, Kania PW, Buchmann K (2012) Comparative protection of two different commercial vaccines against *Yersinia ruckeri* serotype O1 and biotype 2 in rainbow trout (*Oncorhynchus mykiss*). Vet Immunol Immunopathol 145(1-2):379–385. https://doi.org/10.1016/j.vetimm.2011.12.014

Desmettre P, Martinod S (1997) Research and development. In: Pastoret PP, Blancou J, Vannier P, Verschueren C (eds) Veterinary Vaccinology. Elsevier Press, Amsterdam, The Netherlands, pp 175–194

Dhama K, Wani MY, Deb R, Karthik K, Tiwari R, Barathidasan R, Kumar A, Mahima, Verma AK, Singh SD (2013) Plant based oral vaccines for human and animal pathogens–a new era of prophylaxis: current and future perspectives. J Exp Biol Agric Sci 1(1):1–12

Dhar A, Allnutt F (2011) Challenges and opportunities in developing oral vaccines against viral diseases of fish. J. Mar. Sci. Res Dev 2:1–6. https://doi.org/10.4172/2155-9910.S1-003

Dhar AK, Manna SK, Allnutt FCT (2014) Viral vaccines for farmed finfish. Virus Dis 25(1):1–17. https://doi.org/10.1007/s13337-013-0186-4

Diamant A, Banet A, Ucko M, Colorni A, Knibb W, Kvitt H (2000) Mycobacteriosis in wild rabbitfish *Siganus rivulatus* associated with cage farming in the Gulf of Eilat. Red Sea Dis Aquat Org 39(3):211–219. https://doi.org/10.3354/dao039211

Dixon P, Stone DA (2017) Spring viraemia of carp. Fish Virus Bacteria Pathobiol Protect 26:79–90

Donnelly JJ, Ulmer JB, Liu MA (1996) DNA vaccines. Life Sci 60(3):163–172. https://doi.org/10.1016/s0024-3205(96)00502-4

Duff DCB (1942) The oral immunization of trout against Bacterium salmonicida. J Immunol 44:87e94

EC (European Commission) (2003) The use of fish by-products in aquaculture, Report of scientific committee on animal health and animal welfare, scientific co-operations and networks, Ireland, pp 25–29

Effio CL, Hubbuch J (2015) Next generation vaccines and vectors: designing downstream processes for recombinant protein-based virus-like particles. Biotechnol J 10(5):715–727. https://doi.org/10.1002/biot.201400392

Ellul RM, Kalatzis PG, Frantzen C, Haugland GT, Gulla S, Colquhoun DC, Middelboe M, Wergeland HI, Rønneseth A (2021) Genomic analysis of *Pasteurella atlantica* provides insight on its virulence factors and phylogeny and highlights the potential of reverse vaccinology in aquaculture. Microorganisms 9(6):1215. https://doi.org/10.3390/microorganisms9061215

Emmenegger E, Huang C, Landolt M, LaPatra S, Winton J (1994) Immune response to synthetic peptides representing antigenic sites on the glycoprotein of infectious hematopoietic necrosis virus. Vet Res 26(5-6):374–378

Estepa A, Fernandez-Alonso M, Coll J (1999) Structure, binding and neutralization of VHSV with synthetic peptides. Virus Res 63(1-2):27–34. https://doi.org/10.1016/s0168-1702(99)00055-6

Evelyn TPT (1993) Bacterial kidney diseases-BKD. In: Inglis V, Roberts RJ, Bromage NR (eds) Bacterial diseases of fish. Blackwell Scientific Publications, Oxford, pp 177–195

Evelyn TPT (2002) Finfish immunology and its use in preventing infectious diseases in cultured finfish. In: Lavilla-Pitogo CR, Cruz-Lacierda ER (eds) Diseases in Asian Aquaculture IV. Fish Health Section, Asian Fisheries Society, Cebu, pp 303–324

Evenden AJ, Grayson TH, Gilpin ML, Munn CB (1993) Renibacterium salmoninarum and bacterial kidney disease – the unfinished jigsaw. Annu Rev Fish Dis 3:87–104. https://doi.org/10.1016/0959-8030(93)90030-F

Evensen Ø, Leong JAC (2013) DNA vaccines against viral diseases of farmed fish. Fish Shellfish Immunol 35(6):1751–1758. https://doi.org/10.1016/j.fsi.2013.10.021

Fijan N (1984) Vaccination of fish in European pond culture: prospects and constraints. Symp Biol Hung 23:233–241

Fijan N (1999) Spring viremia of carp and other viral diseases of warm-water fish. In: Woo PTK, Bruno DW (eds) Fish Diseases and Disorders. CAB International, Oxon, pp 177–244

Finco O, Rappuoli R (2014) Designing vaccines for the twenty-first century society. Front Immunol 5:12–17. https://doi.org/10.3389/fimmu.2014.00012

Frenkel V, Kimmel E, Iger Y (1999) Ultrasound-induced cavitation damage to external epithelia of fish skin. Ultrasound Med Biol 25(8):1295–1303. https://doi.org/10.1016/s0301-5629(99)00069-1

Fridholm H, Eliasson L, Everitt E (2007) Immunogenicity properties of authentic and heterologously synthesized structural protein VP2 of infectious pancreatic necrosis virus. Viral Immunol 20(4):635–648. https://doi.org/10.1089/vim.2007.0043

Fryer JL, Lannan CN (1993) The history and current status of *Renibacterium salmoninarum*, the causative agent of bacterial kidney disease in Pacific salmon. Fish Res 17(1-2):15–33. https://doi.org/10.1016/0165-7836(93)90004-Q

Galindo-Villegas J, Mulero I, García-Alcazar A, Muñoz I, Peñalver-Mellado M, Streitenberger S et al (2013) Recombinant TNFα as oral vaccine adjuvant protects European sea bass against vibriosis: insights into the role of the CCL25/CCR9 axis. *Fish Shellfish Immunol* 35(4):1260–1271. https://doi.org/10.1016/j.fsi.2013.07.046

Garver KA, LaPatra SE, Kurath G (2005) Efficacy of an infectious hematopoietic necrosis (IHN) virus DNA vaccine in Chinook *Oncorhynchus tshawytscha* and sockeye *O. nerka* salmon. Dis Aquat Org 64(1):13–22. https://doi.org/10.3354/dao064013

Ghosh B, Nguyen TD, Crosbie PBB, Nowak BF, Bridle AR (2016) Oral vaccination of first-feeding Atlantic salmon, *Salmo salar* L., confers greater protection against yersiniosis than immersion vaccination. Vaccine 34(5):599–608. https://doi.org/10.1016/j.vaccine.2015.12.044

Glenney GW, Petrie-Hanson L (2006) Fate of fluorescent microspheres in developing *Ictalurus punctatus* following prolonged immersion. Fish Shellfish Immunol 21(1):32–41. https://doi.org/10.1016/j.fsi.2005.10.003

Gong YM, Zhang C, Li Y, Chen G, Wang GX, Zhu B (2021) Optimization of immunization procedure for SWCNTs-based subunit vaccine with mannose modification against spring viraemia of carp virus in common carp. J Fish Dis 44(12):1925–1936. https://doi.org/10.1111/jfd.13506

Grisez L, Tan Z (2007). Vaccine development for Asian aquaculture. The Fish Site, Intervet Norbio Singapore Pte Ltd.
Gudding R, Goodrich T (2014) The history of fish vaccination. In: Gudding R, Lillehaug A, Evensen Ø (eds) Fish vaccination, 1st edn. John Wiley & Sons, Inc., New York, pp 1–11
Gudding R, Muiswinkel WBV (2013) A history of fish vaccination science-based disease prevention in aquaculture. Fish Shellfish Immunol 35(6):1683–1688. https://doi.org/10.1016/j.fsi.2013.09.031
He Y, Yang Q, Xu H, Wu H, Wu F, Lu L (2011) Prokaryotic expression and purification of grass carp reovirus capsid protein VP7 and its vaccine potential. Afr J Microbiol Res 5(13):1643–1648. https://doi.org/10.5897/AJMR11.221
Heppell J, Davis HL (2000) Application of DNA vaccine technology to aquaculture. Adv Drug Deliv Rev 43(1):29–43. https://doi.org/10.1016/s0169-409x(00)00075-2
Hølvold LB, Myhr AI, Dalmo RA (2014) Strategies and hurdles using DNA vaccines to fish. Vet Res 45:21. https://doi.org/10.1186/1297-9716-45-21
Horzinek MC, Schijns VECJ, Denis M, Desmettre P, Babiuk LA (1997) General description of vaccines. In: Pastoret PP, Blancou J, Vannier P, Verschueren C (eds) Veterinary vaccinology. Elsevier Press, Amsterdam The Netherlands, pp 132–152
Hua X, Zhou Y, Feng Y, Duan K, Ren X, Sun J, Gao S, Wang N, Li J, Yang J, Xia D, Li C, Guan X, Shi W, Liu M (2021) Oral vaccine against IPNV based on antibiotic-free resistance recombinant *Lactobacillus casei* expressing CK6-VP2 fusion protein. Aquaculture 535:736425
Huising MO, Guichelaar T, Hoek C, Kemenade BMLV, Flik G, Savelkoul HFJ, Rombout JHWM (2003) Increased efficacy of immersion vaccination in fish with hyperosmotic pre-treatment. Vaccine 21(27-30):4178–4193. https://doi.org/10.1016/s0264-410x(03)00497-3
Irie T, Watarai S, Iwasaki T, Kodama H (2005) Protection against experimental *Aeromonas salmonicida* infection in carp by oral immunisation with bacterial antigen entrapped liposomes. Fish Shellfish Immunol 18(3):235–242. https://doi.org/10.1016/j.fsi.2004.07.006
Ispir U, Dorucu M (2014) Efficacy of lipopolysaccharide antigen of *Yersinia ruckeri* in rainbow trout by intraperitoneal and bath immersion administration. Res Vet Sci 97(2):271–273. https://doi.org/10.1016/j.rvsc.2014.07.020
Jaafar RM, Al-Jubury A, Chettri JK, Dalsgaard I, Kania PW, Buchmann K (2018) Secondary immune response of rainbow trout following repeated immersion vaccination. J Fish Dis 41(1):117–123. https://doi.org/10.1111/jfd.12682
Jang YH, Subramanian D, Heo M-S (2014) Efficacy of formalin-killed *Pseudomonas anguilliseptica* vaccine on immune gene expression and protection in farmed olive flounder, *Paralichthys olivaceus*. Vaccine 32(16):1808–1813. https://doi.org/10.1016/j.vaccine.2014.01.088
Jansen MD, Jensen BB, McLoughlin MF, Rodger HD, Taksdal T, Sindre H, Graham DA, Lillehaug A (2016) The epidemiology of pancreas disease in salmonid aquaculture: a summary of the current state of knowledge. J Fish Dis 40(1):141–155. https://doi.org/10.1111/jfd.12478
Jayasree L, Janakiram P, Madhavi R (2006) Characterization of *Vibrio* spp. associated with diseased shrimp from culture ponds of Andhra Pradesh (India). J World Aquacult Soc 37(4):523–532. https://doi.org/10.1111/j.1749-7345.2006.00066.x
Ji J, Torrealba D, Ruyra A, Roher N (2015) Nanodelivery systems as new tools for immunostimulant or vaccine administration: targeting the fish immune system. *Biology (Basel)* 4(4):664–696. https://doi.org/10.3390/biology4040664
Kaattari SL, Piganelli JD (1997) Immunization with bacterial antigens: bacterial kidney disease. In: Gudding R, Lillehaug A, Midtlyng PJ, Brown F (eds) Fish vaccinology. Karger, Basel, pp 145–152
Karlsen M, Tingbo T, Solbakk IT, Evensen O, Furevik A, Aas-Eng A (2012) Efficacy and safety of an inactivated vaccine against Salmonid alphavirus (family Togaviridae). Vaccine 30(38):5688–5694. https://doi.org/10.1016/j.vaccine.2012.05.069
Klesius PH, Pridgeon JW (2014) Vaccination against enteric septicemia of catfish. In: Fish vaccination. John Wiley & Sons, Chichester, pp 211–225
Klesius PH, Shoemaker CA (1998) Development and use of modified live *Edwardsiella ictaluri* vaccine against enteric septicemia of catfish. Adv Vet Med 41:523–537. https://doi.org/10.1016/s0065-3519(99)80039-1
Kolotilin I, Topp E, Cox E, Devriendt B, Conrad U, Joensuu J, Stöger E, Warzecha H, McAllister T, Potter A, McLean MD, Hall JC, Menassa R (2014) Plant-based solutions for veterinary immunotherapeutics and prophylactics. Vet Res 45(1):375. https://doi.org/10.1186/s13567-014-0117-4
Komar C, Enright WJ, Grisez L, Tan Z (2004). Understanding fish vaccination. Reprinted from AQUA Culture AsiaPacific Magazine, November/December
Komar C, Enright WJ, Grisez L, Tan Z (2006). Understanding fish vaccination. The Fish Site, Intervet.

Kumar G, Ledouble SM, Saleh M, El-Matbouli M (2015) Yersinia ruckeri, the causative agent of enteric redmouth disease in fish. Vet Res 46:103. https://doi.org/10.1186/s13567-015-0238-4

Kurath G (2008) Biotechnology and DNA vaccines for aquatic animals. Rev Sci Tech 27(1):175–196. https://doi.org/10.20506/RST.27.1.1793

La Frentz BR, La Patra SE, Jones GR, Congleton JL, Sun B (2002) Characterization of serum and mucosal antibody responses and relative percent survival in rainbow trout (*Oncorhynchus mykiss*) (Walbaum), following immunization and challenges with *Flavobacterium psychrophilum*. J Fish Dis 25(12):703–713. https://doi.org/10.1046/j.1365-2761.2002.00424.x

LaPatra SE, Corbeil S, Jones GR, Shewmaker WD, Lorenzen N, Anderson ED et al (2001) Protection of rainbow trout against infectious hematopoietic necrosis virus four days after specific or semi-specific DNA vaccination. Vaccine 19(28-29):4011–4019. https://doi.org/10.1016/S0264-410X(01)00113-X

Lawrence ML, Cooper RK, Thune RL (1997) Attenuation, persistence, and vaccine potential of an *Edwardsiella ictaluri* pur. A mutant. Infect Immun 65(11):4642–4651. https://doi.org/10.1128/iai.65.11.4642-4651.1997

Leong J, Fryer J, Winton J (1988) Vaccination against infectious hematopoietic necrosis virus. Fish Vaccin 1:193–203

Levine MM, Sztein MB (2004) Vaccine development strategies for improving immunization: the role of modern immunology. Nat Immunol 5(5):460–464. https://doi.org/10.1038/ni0504-460

Liu W, Hsu C-H, Chang C-Y, Chen H-H, Lin C-S (2006) Immune response against grouper nervous necrosis virus by vaccination of virus-like particles. Vaccine 24:6282–6287. https://doi.org/10.1016/j.vaccine.2006.05.073

Lorenzen N, LaPatra S (2005) DNA vaccines for aquacultured fish. Rev Sci 24(1):201–213

Lorenzen N, Lorenzen E, Einer-Jensen K, Heppell J, Wu T, Davis H (1998) Protective immunity to VHS in rainbow trout (*Oncorhynchus mykiss*, Walbaum) following DNA vaccination. Fish Shellfish Immunol 8:261–270

Lorenzen N, Lorenzen E, Einer-Jensen K, LaPatra SE (2002) Immunity induced shortly after DNA vaccination of rainbow trout against rhabdoviruses protects against heterologous virus but not against bacterial pathogens. Dev Comp Immunol 26(2):173–179. https://doi.org/10.1016/s0145-305x(01)00059-3

Lu L, Xu H, He Y, Li J (2011) Protection of grass carp, *Ctenopharyngon idellus* (Valenciennes), through oral administration of a subunit vaccine against reovirus. J Fish Dis 34(12):939–942. https://doi.org/10.1111/j.1365-2761.2011.01310.x

Lund M, Røsæg MV, Krasnov A, Timmerhaus G, Nyman IB, Aspehaug V et al (2016) Experimental Piscine orthoreovirus infection mediates protection against pancreas disease in Atlantic salmon (*Salmo salar*). Vet Res 47(1):107. https://doi.org/10.1186/s13567-016-0389-y

Ma Y, Zhang Y, Zhao D (2010). Polyvalent attenuated live vaccine for preventing and curing vibriosis of cultivated fish. Google Patents.

Ma J, Bruce TJ, Jones EM, Cain KD (2019) A review of fish vaccine development strategies: conventional methods and modern biotechnological approaches. Microorganisms 7(11):569. https://doi.org/10.3390/microorganisms7110569

Magnadottir B (2010) Immunological control of fish diseases. Mar Biotechnol (NY) 12(4):361–379. https://doi.org/10.1007/s10126-010-9279-x

Mahendran R, Jeyabaskar S, Sitharaman G, Michael RD, Paul AV (2016) Computer-aided vaccine designing approach against fish pathogens *Edwardsiella tarda* and *Flavobacterium columnare* using bioinformatics softwares. Drug Des Devel Ther 10:1703–1714. https://doi.org/10.2147/DDDT.S95691

Markestad A, Grave K (1996) Reduction in antibacterial drug use in Norwegian fish farming due to vaccination. In: In Programme and book of abstracts. Symposium on Fish Vaccinology, Oslo, p 46

Miccoli A, Manni M, Picchietti S, Scapigliati (2021) State-of-the-art vaccine research for aquaculture use: the case of three economically relevant fish species. Vaccines 9:140. https://doi.org/10.3390/vaccines9020140

Mikkelsen H, Lund V, Larsen R, Seppola M (2011) Vibriosis vaccines based on various sero-subgroups of *Vibrio anguillarum* O2 induce specific protection in Atlantic cod (*Gadus morhua* L.) juveniles. Fish Shellfish Immunol 30(1):330–339. https://doi.org/10.1016/j.fsi.2010.11.007

Milton DL, Norqvist A, Wolf-Watz H (1992) Cloning of a metalloprotease gene involved in the virulence mechanism of *Vibrio anguillarum*. J Bacteriol 174(22):7235–7244. https://doi.org/10.1128/jb.174.22.7235-7244.1992

Moeller RB (2005) Bacterial diseases of fish. Cichlid-forum California, pp:4–15

Mohamad A, Zamri-Saad M, Amal MNA, Al-saari N, Monir MS, Chin YK, Yasin I-S (2021) Vaccine efficacy of a newly developed feed-based whole-cell polyvalent vaccine against vibriosis, streptococcosis and motile aeromonad septicemia in Asian seabass, *Lates calcarifer*. Vaccines 9(4):368. https://doi.org/10.3390/vaccines9040368

Mohamed LA, Soliman WS (2013) Development and efficacy of fish vaccine used against some bacterial diseases in farmed Tilapa. Nat Sci 11(6):120–128

Mohammed H, Olivares-Fuster O, La Frentz S, Arias CR (2013) New attenuated vaccine against columnaris disease in fish: choosing the right parental strain is critical for vaccine efficacy. Vaccine 31(45):5276–5280. https://doi.org/10.1016/j.vaccine.2013.08.052

Muiswinkel WBV, Pilarczyk A, Řehulka J (2018) Vaccination against spring viremia of carp (SVC) – from the past till the future. Bull Eur Assoc Fish Pathol 38(6):254–260

Muktar Y, Tesfaye S, Tesfaye B (2016) Present status and future prospects of fish vaccination: a review. J Vet Sci Technol 7(2):1000299. https://doi.org/10.4172/2157-7579.1000299

Munang'andu HM, Fredriksen BN, Mutoloki S, Brudeseth B, Kuo TY, Marjara IS, Dalmo RA, Evensen Ø (2012) Comparison of vaccine efficacy for different antigen delivery systems for infectious pancreatic necrosis virus vaccines in Atlantic salmon (*Salmo salar L.*) in a cohabitation challenge model. Vaccine 30(27):4007–4016. https://doi.org/10.1016/j.vaccine.2012.04.039

Muñoz-Atienza E, Diaz-Rosales P, Tafalla C (2021) Systemic and mucosal B and T cell responses upon mucosal vaccination of teleost fish. Front Immunol 11:622377. https://doi.org/10.3389/fimmu.2020.622377

Nakanishi T, Kiryu I, Ototake M (2002) Development of a new vaccine delivery method for fish: percutaneous administration by immersion with application of a multiple puncture instrument. Vaccine 20(31-32):3764–3769. https://doi.org/10.1016/s0264-410x(02)00291-8

Nasr-Eldahan S, Nabil-Adam A, Shreadah MA, Maher AM, Ali T (2021) A review article on nanotechnology in aquaculture sustainability as a novel tool in fish disease control. Aquac Int 29:1459–1480. https://doi.org/10.1007/s10499-021-00677-7

Newaj-Fyzul A, Austin B (2015) Probiotics, immunostimulants, plant products and oral vaccines, and their role as feed supplements in the control of bacterial fish diseases. J Fish Dis 38(11):937–955. https://doi.org/10.1111/jfd.12313

Newman S (1993) Bacterial vaccines of fish. Annu Rev Fish Dis 3(6):145–185. https://doi.org/10.1016/0959-8030(93)90033-8

Nguyen TD, Crosbie PBB, Nowak BF, Bridle AR (2018) The effects of inactivation methods of *Yersinia ruckeri* on the efficacy of single dip vaccination in Atlantic salmon (*Salmo salar*). J Fish Dis 41(7):1173–1176. https://doi.org/10.1111/jfd.12803

Norqvist A, Norrman B, Wolf-Watz H (1990) Identification and characterization of a zinc metalloprotease associated with invasion by the fish pathogen *Vibrio anguillarum*. Infect Immun 58(11):3731–3736. https://doi.org/10.1128/iai.58.11.3731-3736.1990

Nuñez-Ortiz N, Pascoli F, Picchietti S, Buonocore F, Bernini C, Toson M, Scapigliati G, Toffan A (2016) A formalin-inactivated immunogen against viral encephalopathy and retinopathy (VER) disease in European sea bass (*Dicentrarchus labrax*): immunological and protection effects. Vet Res 47(1):1–11. https://doi.org/10.1186/s13567-016-0376-3

Nusbaum KE, Smith BF, DeInnocentes P, Bird RC (2002) Protective immunity induced by DNA vaccination of channel catfish with early and late transcripts of the channel catfish herpes virus (IHV-1). Vet Immunol Immunopathol 84(3-4):151–168. https://doi.org/10.1016/s0165-2427(01)00399-3

Ogas Castells ML, La Torre JL, Grigera PR, Poggio TV (2015) A single dose of a suicidal DNA vaccine induces a specific immune response in salmonids. J Fish Dis 38(6):581–587

Palm RC Jr, Landolt ML, Busch RA (1998) Route of vaccine administration: effects on the specific humoral response in rainbow trout *Oncorhynchus mykiss*. Dis Aquat Org 33:157–166

Pascoli F, Guazzo A, Buratin A, Toson M, Buonocore F, Scapigliati G, Toffan A (2019) Lack of in vivo cross-protection of two different betanodavirus species RGNNV and SJNNV in European sea bass *Dicentrachus labrax*. Fish Shellfish Immunol 85:85–89. https://doi.org/10.1016/j.fsi.2017.10.033

Pasquale AD, Preiss S, Silva FT, Garcon N (2015) Vaccine adjuvants: from 1920 to 2015 and beyond. Vaccines 3(2):320–343. https://doi.org/10.3390/Fvaccines3020320

Pérez O, Romeu B, Cabrera O, González E, Batista-Duharte A, Labrada A, Pérez R, Reyes LM, Ramírez W, Sifontes S, Fernández N, Lastre M (2013) Adjuvants are key factors for the development of future vaccines: lessons from the Finlay adjuvant platform. Front Immunol 4:1–12. https://doi.org/10.3389/fimmu.2013.00407

Perrie Y, Mohammed AR, Kirby DJ, McNeil SE, Bramwell VW (2008) Vaccine adjuvant systems: enhancing the efficacy of sub-unit protein antigens. Int J Pharm 364(2):272–280. https://doi.org/10.1016/j.ijpharm.2008.04.036

Plant KP, LaPatra SE (2011) Advances in fish vaccine delivery. Dev Comp Immunol 35(12):1256–1262. https://doi.org/10.1016/j.dci.2011.03.007

Poobalane S, Thompson KD, Ardo L, Verjan N, Han H-J, Jeney G, Hirono I, Aoki T, Adams A (2010) Production and efficacy of an *Aeromonas hydrophila* recombinant S-layer protein vaccine for fish. Vaccine 28(20):3540–3547. https://doi.org/10.1016/j.vaccine.2010.03.011

Purcell MK, Nichols KM, Winton JR, Kurath G, Thorgaard GH, Wheeler P, Hansen JD, Herwig RP, Park LK (2006) Comprehensive gene expression profiling following DNA vaccination of rainbow trout against infectious hematopoietic necrosis virus. Mol Immunol 43(13):2089–2106. https://doi.org/10.1016/j.molimm.2005.12.005

Quentel C, Vigneulle M (1997) Antigen uptake and immune responses after oral vaccination. In: Gudding R, Lillehaug A, Midtlyng PJ, Brown F (eds) Fish vaccinology, vol 90. Development of Biological Standards, Karger, Basel, pp 69–78

Raida MK, Nylen J, Holten-Andersen L, Buchmann K (2011) Association between plasma antibody response and protection in rainbow trout *Oncorhynchus mykiss* immersion vaccinated against *Yersinia ruckeri*. PLoS One 6(6):e18832. https://doi.org/10.1371/journal.pone.0018832

Rao Y, Su J (2015) Insights into the antiviral immunity against grass carp (*Ctenopharyngodon idella*) reovirus (GCRV) in grass carp. J Immunol Res 2015:670437. https://doi.org/10.1155/2015/670437

Rappuoli R (2000) Reverse vaccinology. Curr Opin Microbiol 3(5):445–450. https://doi.org/10.1016/s1369-5274(00)00119-3

Rauta PR, Samanta M, Dash HR, Nayak B, Das S (2014) Toll-like receptors (TLRs) in aquatic animals: signaling pathways, expressions and immune responses. Immunol Lett 158(1-2):14–24. https://doi.org/10.1016/j.imlet.2013.11.013

Ravid-Peretz S, Colorni A, Sharon G, Ucko M (2019) Vaccination of European sea bass *Dicentrarchus labrax* with avirulent *Mycobacterium marinum* (iipA::kan mutant). Fish Shellfish Immunol 90:317–327. https://doi.org/10.1016/j.fsi.2019.04.057

Restifo N, Ying H, Hwang L, Leitner W (2000) The promise of nucleic acid vaccines. Gene Ther 7(2):89–92. https://doi.org/10.1038/sj.gt.3301117

Reyes M, Ramírez C, Nancucheo I, Villegas R, Schaffeld G, Kriman L, Javier G, Patricio O (2017) A novel "in-feed" delivery platform applied for oral DNA vaccination against IPNV enables high protection in Atlantic salmon (*Salmo salar*). Vaccine 35(4):626–632. https://doi.org/10.1016/j.vaccine.2016.12.013

Rivas-Aravena A, Fuentes Y, Cartagena J, Brito T, Poggio V, La Torre J, Mendoza H, Gonzalez-Nilo F, Sandino AM, Spencer E (2015) Development of a nanoparticle-based oral vaccine for Atlantic salmon against ISAV using an alphavirus replicon as adjuvant. Fish Shellfish Immunol 45(1):157–166. https://doi.org/10.1016/j.fsi.2015.03.033

Robertsen B, Chang CJ, Bratland L (2016) IFN-adjuvanted DNA vaccine against infectious salmon anemia virus: antibody kinetics and longevity of IFN expression. Fish Shellfish Immunol 54:328–332. https://doi.org/10.1016/j.fsi.2016.04.027

Rodger HD (2016) Fish disease causing economic impact in global aquaculture. In: Adams A (ed) Fish vaccines, 1st edn. Springer, Basel, pp 1–34

Røsaeg MV, Thorarinsson R, Aunsmo A (2021) Effect of vaccines against pancreas disease in farmed Atlantic salmon. J Fish Dis 44(12):1911–1924. https://doi.org/10.1111/jfd.13505

Roy PE (2011) Use of vaccines in finfish aquaculture. In: School of Forest Resources and Conservation, Florida Cooperative Extension Service, Institute of Food and Agricultural Sciences. University of Florida, Florida

Sahoo S, Banu H, Prakash A, Tripathi G (2021) Immune system of fish: an evolutionary perspective. In: Maria del Mar Ortega-Villaizan MM, Chico V (eds) Antimicrobial immune response. IntechOpen, London. https://doi.org/10.5772/intechopen.99541

Salonius K, Siderakis C, MacKinnon AM, Griffiths SG (2005) Use of *Arthrobacter davidanieli* as a live vaccine against *Renibacterium salmoninarum* and *Piscirickettsia salmonis* in salmonids. Dev Biol 121:189–197

Sanders JE, Fryer JL (1980) Renibacterium salmoninarum gen. nov., sp. nov., the causative agent of bacterial kidney disease in salmonid fishes. Int. J. Syst. Bacteriol. 30(2):496–502. https://doi.org/10.1099/00207713-30-2-496

Secombes CJ, Wang T (2012) The innate and adaptive immune system of fish. In: In: Infectious disease in aquaculture: prevention and control. Woodhead Publishing Limited, Sawston, pp 3–68. https://doi.org/10.1533/9780857095732.1.3

Shaalan M, Saleh M, El-Mahdy M, El-Matbouli M (2016) Recent progress in applications of nanoparticles in fish medicine: a review. Nanomed.: Nanotechnol. Biol. Med. 12(3):701–710. https://doi.org/10.1016/j.nano.2015.11.005

Shahaid N, Daniell H (2016) Plant based oral vaccines against zoonotic and non-zoonotic diseases. Plant Biotechnol J. 14(11):2079–2099. https://doi.org/10.1111/pbi.12604

Shao ZJ (2001) Aquaculture pharmaceuticals and biologicals: current perspectives and future possibilities. Adv Drug Deliv Rev 50(3):229–243. https://doi.org/10.1016/s0169-409x(01)00159-4

Shoemaker CA, Klesius PH, Evans JJ, Arias CR (2009) Use of modified live vaccines in aquaculture. J World Aquacult Soc 40(5):573–585. https://doi.org/10.1111/j.1749-7345.2009.00279.x

Shoemaker CA, Klesius PH, Drennan JD, Evans JJ (2011) Efficacy of a modified live *Flavobacterium columnare* vaccine in fish. Fish Shellfish Immunol 30(1):304–308. https://doi.org/10.1016/j.fsi.2010.11.001

Singh RK, Badasara SK, Dhama K, Malik YPS (2015). Progress and prospects in vaccine research, In: Malik YPS, Sagar P, Dhama K, Singh RK (eds) Current trends and future research challenges in vaccines and adjuvants. In: Souvenir, National Workshop Organized at Indian Veterinary Research Institute, Izatnagar 243122, Bareilly, Uttar Pradesh, India during 19–20 November, pp. 1–19.

Siwicki AK, Morand M, Terech-Majewska E, Niemczuk W, Kazun K, Glabski E (1998) Influence of immunostimulants on the effectiveness of vaccines in fish: in vitro and in vivo study. J Appl Ichthyol 14(5):225–227

Skov J, Kania PW, Holten-Andersen L, Fouz B, Buchmann K (2012) Immunomodulatory effects of dietary beta-1,3-glucan from *Euglena gracilis* in rainbow trout (*Oncorhynchus mykiss*) immersion vaccinated against *Yersinia ruckeri*. Fish Shellfish Immunol 33(1):111–120. https://doi.org/10.1016/j.fsi.2012.04.009

Snieszko SF, Friddle SB (1949) Prophylaxis of furunculosis in brook trout (*Salvelinus fontinalis*) by oral immunization and sulfamerazine. Progress Fish-Cult 11:161–168

Snieszko S, Piotrowska W, Kocylowski B, Marek K. (1938) Badania bakteriologiczne i serogiczne nad bakteriami posocznicy karpi. Memoires de l'Institut d'Ichtyobiologie et Pisciculture de la Station de Pisciculture Experimentale a Mydlniki de l'Universite Jagiellonienne a Cracovie Nr 38.

Sommerset I, Krossøy B, Biering E, Frost P (2005) Vaccines for fish in aquaculture. Expert Rev Vaccin 4(1):89–101. https://doi.org/10.1586/14760584.4.1.89

Su H, Yakovlev IA, van Eerde A, Su J, Clarke JL (2021) Plant-produced vaccines: future applications in aquaculture. Front Plant Sci 12:718775. https://doi.org/10.3389/fpls.2021.718775

Sudheesh PS, Cain KD (2017) Prospects and challenges of developing and commercializing immersion vaccines for aquaculture. Int Biol Rev 1(1):1–20. https://doi.org/10.18103/ibr.v1i1.1313

Sun K, Zhang W-W, Hou J-H, Sun L (2009) Immunoprotective analysis of VhhP2, a *Vibrio harveyi* vaccine candidate. Vaccine 27(21):2733–2740. https://doi.org/10.1016/j.vaccine.2009.03.012

Sun Y, Liu C-S, Sun L (2010) Isolation and analysis of the vaccine potential of an attenuated *Edwardsiella tarda* strain. Vaccine 28(38):6344–6350. https://doi.org/10.1016/j.vaccine.2010.06.101

Takeuchi M, Fujiwara-Nagata E, Katayama T, Suetake H (2021) Skin bacteria of rainbow trout antagonistic to the fish pathogen *Flavobacterium psychrophilum*. Sci Rep 11:7518. https://doi.org/10.1038/s41598-021-87167-1

Tam JP (1988) Synthetic peptide vaccine design: synthesis and properties of a high-density multiple antigenic peptide system. Proc Natl Acad Sci 85(15):5409–5413. https://doi.org/10.1073/pnas.85.15.5409

Tanaka S, Mori K, Arimoto M, Iwamoto T, Nakai T (2001) Protective immunity of sevenband grouper, *Epinephelus septemfasciatus* Thunberg, against experimental viral nervous necrosis. J Fish Dis 24(1):15–22. https://doi.org/10.1046/j.1365-2761.2001.00259.x

Thinh NH, Kuo TY, Hung LT, Loc TH, Chen SC, Evensen O, Schuurman HJ (2009) Combined immersion and oral vaccination of Vietnamese catfish (*Pangasianodon hypophthalmus*) confers protection against mortality caused by *Edwardsiella ictaluri*. Fish Shellfish Immunol 27(6):773–776. https://doi.org/10.1016/j.fsi.2009.08.012

Thornton JC, Garduno RA, Newman SG, Kay WW (1991) Surface-disorganized, attenuated mutants of aeromonas-salmonicida as furunculosis live vaccines. Microb Pathog 11(2):85–99. https://doi.org/10.1016/0882-4010(91)90002-r

Thornton J, Garduno R, Kay W (1994) The development of live vaccines for furunculosis lacking the A-layer and O-antigen of *Aeromonas salmonicida*. J Fish Dis 17(3):195–204. https://doi.org/10.1111/j.1365-2761.1994.tb00215.x

Thune R, Plumb J (1984) Evaluation of hyperosmotic infiltration for the administration of antigen to channel catfish (*Ictalurus punctatus*). Aquaculture 36:1–8

Toranzo AE, Barja JL (1993) Virulence factors of bacteria pathogenic for cold water fish. Annu Rev Fish Dis 3:5–36

Toranzo A, Romalde J, Magarinos B, Barja J (2009) Present and future of aquaculture vaccines against fish bacterial diseases. In: Rogers C, Basurco B (eds). The use of veterinary drugs and vaccines in Mediterranean aquaculture. CIHEAM Opt Méditerranéennes 86:155–176

Traxler GS, Anderson E, LaPatra SE, Richard J, Shewmaker B, Kurath G (1999) Naked DNA vaccination of Atlantic salmon *Salmo salar* against IHNDis, V. Aquat. Organ. 38(3):183–190. https://doi.org/10.3354/dao038183

Triet TH, Tinh BTT, Hau LV, Huong TV, Binh NQ (2019) Development and potential use of an *Edwardsiella ictaluri* wzz mutant as a live attenuated vaccine against enteric septicemia in *Pangasius hypophthalmus* (Tra catfish). Fish Shellfish Immunol 87:87–95. https://doi.org/10.1016/j.fsi.2019.01.005

Utke K, Bergmann S, Lorenzen N, Köllner B, Ototake M, Fischer U (2007) Cell-mediated cytotoxicity in rainbow trout, *Oncorhynchus mykiss*, infected with viral haemorrhagic septicaemia virus. Fish Shellfish Immunol 22(3):182–196. https://doi.org/10.1016/j.fsi.2006.04.008

Utke K, Kock H, Schuetze H, Bergmann SM, Lorenzen N, Einer-Jensen K, Köllner B, Dalmo RA, Vesely T, Ototake M, Fischer U (2008) Cell-mediated immune responses in rainbow trout after DNA immunization against the viral hemorrhagic septicemia virus. Dev Comp Immunol 32(3):239–252. https://doi.org/10.1016/j.dci.2007.05.010

Valero Y, Awad E, Buonocore F, Arizcun M, Esteban MA, Meseguer J, Chaves-Pozo E, Cuesta A (2016) An oral chitosan DNA vaccine against nodavirus improves transcription of cell-mediated cytotoxicity and interferon genes in the European sea bass juveniles gut and survival upon infection. Dev Comp Immunol 65:64–72. https://doi.org/10.1016/j.dci.2016.06.021

Valero Y, Mokrani D, Chaves-Pozo E, Arizcun M, Oumouna M, Meseguer J, Esteban MÁ, Cuesta A (2018) Vaccination with UV-inactivated nodavirus partly protects European sea bass against infection, while inducing few changes in immunity. Dev Comp Immunol 86:171–179. https://doi.org/10.1016/j.dci.2018.05.013

Van Oirschot JT (1997) Classical attenuated vaccines. In: Pastoret PP, Blancou J, Vannier P, Verschueren C (eds) Veterinary vaccinology. Elsevier Press, Amsterdam, pp 258–260

Vendramin N, Alencar ALF, Iburg TM, Dahle MK, Wessel Ø, Olsen AB, Rimstad E, Olesen NJ (2018) Piscine orthoreovirus infection in Atlantic salmon (*Salmo salar*) protects against subsequent challenge with infectious hematopoietic necrosis virus (IHNV). Vet Res 49:1–12. https://doi.org/10.1186/s13567-018-0524-z

Villumsen KR, Neumann L, Ohtani M, Strøm HK, Raida MK (2014) Oral and anal vaccination confers full protection against enteric redmouth disease (ERM) in rainbow trout. PLoS One 9(4):e93845. https://doi.org/10.1371/journal.pone.0093845

Vimal S, Taju G, Nambi KSN, Majeed SA, Babu VS, Ravi M, Hameed AS (2012) Synthesis and characterization of CS/TPP nanoparticles for oral delivery of gene in fish. Aquaculture 358:14–22. https://doi.org/10.1016/j.aquaculture.2012.06.012

Vinitantharat S, Gravningen K, Greger E (1999) Fish vaccines. Adv Vet Med 41:539–550. https://doi.org/10.1016/s0065-3519(99)80040-8

Wiens GD, Kaattari SL (1999) Bacterial kidney diseases (*Renibacterium salmoninarum*). In: PTK W, Bruno DW (eds) Fish diseases and disorders, vol 3. CAB Intern. Intern. Publ., London, pp 269–302

Woo, Burno DW, Lim L (2002) Diseases and disorders of fin fish in cage culture. CABI Publishing, Walling ford

Wood PA, Kaattari SL (1996) Enhanced immunogenicity of *Renibacterium salmoninarum* in chinook salmon after removal of the bacterial cell surface associated 57 KDa proteins. Dis Aquat Org 25(1-2):71–79. https://doi.org/10.3354/dao025071

Xu L, Zhao J, Liu M, Ren G, Jian F, Yin J, Feng J, Liu H, Lu T (2017) Bivalent DNA vaccine induces significant immune responses against infectious hematopoietic necrosis virus and infectious pancreatic necrosis virus in rainbow trout. Sci Rep 7:5700. https://doi.org/10.1038/s41598-017-06143-w

Yang H, Zhujin D, Marana MH, Dalsgaard I, Rzgar J, Heidli M et al (2021) Immersion vaccines against *Yersinia ruckeri* infection in rainbow trout: comparative effects of strain differences. J Fish Dis 44(12):1937–1950. https://doi.org/10.1111/jfd.13507

Yanong RP, Erlacher-Reid C (2012) Biosecurity in aquaculture, part 1: an overview. USDA Southern Regional Aquaculture Center, Stoneville, pp 25–59

Zeng R, Pan W, Lin Y, He J, Luo Z, Li Z, Weng S, He J, Guo C (2021) Development of a gene-deleted live attenuated candidate vaccine against fish virus (ISKNV) with low pathogenicity and high protection. iScience 24(7):102750. https://doi.org/10.1016/j.isci.2021.102750

Zhao Z, Zhang C, Jia Y-J, Qiu D-K, Lin Q, Li N-Q, Huang Z-B, Fu X-Z, Wang G-X, Zhu B (2019) Immersion vaccination of fish *Siniperca chuatsi* against infectious spleen and kidney necrosis virus with a SWCNTs-based subunit vaccine. Fish Shellfish Immunol 92:133–140. https://doi.org/10.1016/j.fsi.2019.06.001

Zheng Y-Y, Zhang C, Li Y, Zhang P-Q, Chen G, Wang G-X, Zhu B (2021) Immersion immunization of common carp with bacterial ghost-based DNA vaccine inducing prophylactic protective immunity against spring viraemia of carp virus. J Fish Dis 44(12):2021–2029. https://doi.org/10.1111/jfd.13516

Ziklo N, Colorni A, Gao LY, Du SJ, Ucko M (2018) Humoral and cellular immune response of European seabass *Dicentrarchus labrax* vaccinated with heat-killed *Mycobacterium marinum* (iipA::kan Mutant). J Aquat Anim Health 30(4):312–324. https://doi.org/10.1002/aah.10042