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

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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.
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 monoaotigen 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 salmon. 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. para-haemolyticus*, 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).
| 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 *Vibrio-* | 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 *Yersinio-*| 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 davidieli | -                          | 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)                           |
| 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 \textit{Ei}\textsubscript{ΔevpB} against enteric septicemia of catfish (ESC) disease in fry and fingerlings of channel catfish, \textit{Ictalurus puntatus}, via immersion route. It displayed the avirulent nature of the \textit{Ei}\textsubscript{ΔevpB} strain and gave better protection to the channel catfish fingerlings and fry against the pathogen \textit{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, \textit{Pangasius hypophthalmus} against ESC (Triet et al. 2019).

\textbf{Bacterial cold-water disease}

\textit{Flavobacterium psychrophilum} (syn., \textit{Flexibacter psychrophilus} and \textit{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).

\textbf{Mycobacteriosis (fish tuberculosis)}

Mycobacteriosis is considered as a chronic disease which is caused by a bacterium, \textit{Mycobacterium marinum} (Bosner 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 (\textit{Odontesthes bonariensis}), turbot, snakehead fish (\textit{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.

\textbf{Bacterial kidney disease}

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

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.

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