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Review

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Zoonosis and Vaccination for Fish Health Managment

Avnish Kumar , Sushil Kumar Middha , Soumya V Menon , BISWARANJAN PAITAL * , Shyam Gokarn , N. Meghana , Rakshith BR , Mani Chandra Harish , Susithra Priyadarshni Mugunthan , Sanwar Mal Kantwa , Talambedu Usha , Akshaya Kumar Hati , Divyadharshini Venkatesan , Abira R , Tapas Ranjan Behera , V. Swarupa , Dipak Kumar Sahoo

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Review

Zoonosis and Vaccination for Fish Health Management

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Abstract: Vaccination is an important method of immunological preventive care required for health management of all animal including fish. More particularly, immunization is important in in-land fisheries for the management of diseases in fish brood stocks and healthy seed production. According to the latest statistics in 2020, 90.3 million tonnes of captured fish production was achieved from the aquaculture sector. Out of the above, 78.8 million tonnes from marine and 11.5 million tonnes from inland waters aquaculture sectors. About 4% decline in fish production was achieved in 2020 than 2018 from inland fisheries sectors. On the other hand, the digestive protein content, healthy fats and nutritional values of fish products are comparitively more affordable as compared to other meat sources. In 2014, about 10% aquatic cultured animals were lost (costing > 10 billion $ global annual loss) due to infectious diseases. Therefore, vaccination in fish especially in brood stocks is one of the most important approaches to stop such losses in the fisheries sector. Fish vaccines consist of either whole killed pathogens, subunit of a protein, a recombinant protein, DNA vaccines or live attenuated vaccines. Challenges existing are adaption of vaccination in fisheries sector, route of administration, use of effective adjuvants and most importantly lack of effective results. Use of autogenous vaccines, vaccination via intramuscular, intraperitoneal or oral routes, and most importantly adding vaccines in feed using top dressing methods or as a constituent in fish feed are now in emerging. These method shall lower the risk of using antibiotics in cultured water which in turn will reduce the environmental contamination.

Keywords: fish vaccine; aquaculture; antibiotic; fish infectious diseases; environmental safety; global market

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1. Introduction

The rate of infectious diseases is at a higher level in animals, which is very dangerous as it may affect humans also based on zoonotic infections. There are more than 200 zoonoses in the world [1] and some of the zoonotic diseases such as avian influenza, severe acute respiratory syndrome, coronavirus disease have become highly contagious [2–4]. Zoonoses can directly affect the production and trade of animals for food, industrial and other applications. Hence it is essential to identify, manage and prevent infectious diseases in animals. Infectious diseases in animals, including fish are caused mainly by microorganisms such as bacteria, viruses, fungi, parasites etc. Some of the infectious agents and their causative diseases are explained in Table 1. In countries such as India with dominant species of cattle, buffalo, sheep, goat etc., the prevalence of infectious diseases are prominent, that 5-6% of cattle buffaloes are affected by contagious diseases [5,6]. Another infectious agent is bovine herpes virus that infects more than 68% of bovine species [7]. In such cases, vaccines have significant role for the management of live stocks (Figures 1 and 2).

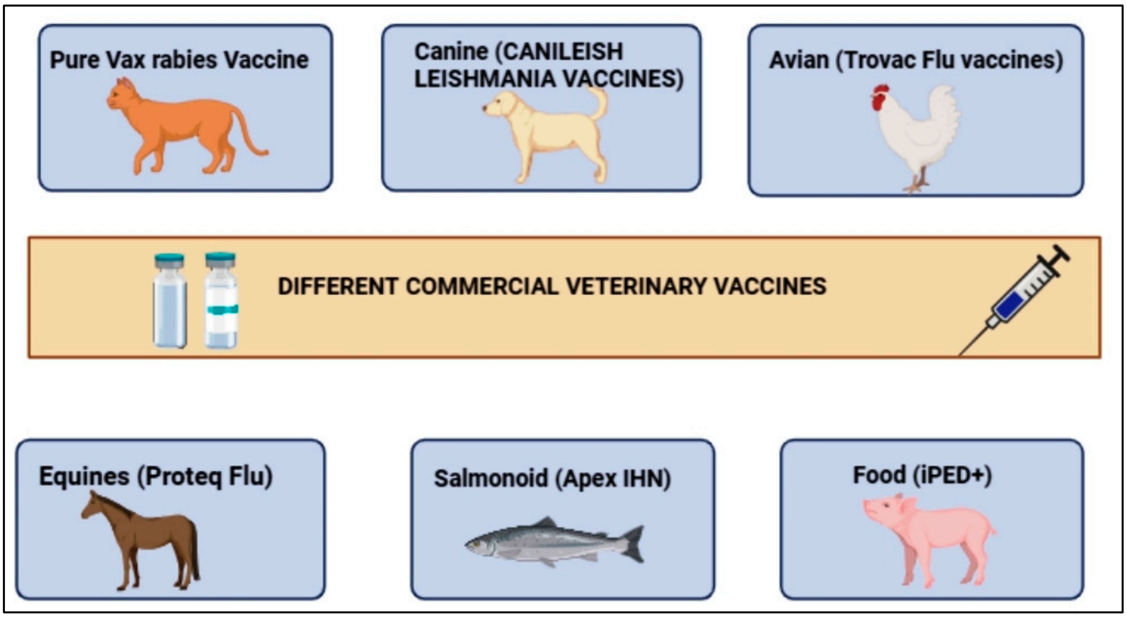

Figure 1. Need of vaccines for live stock management.

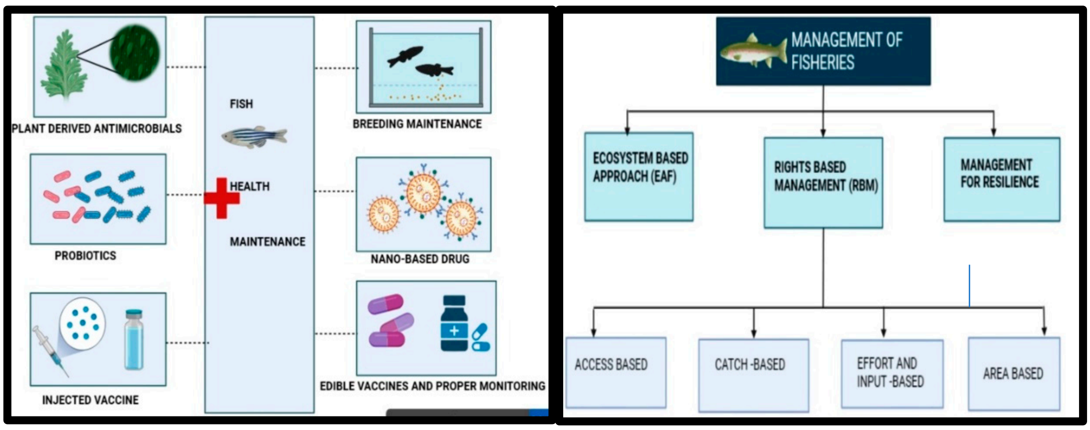

Figure 2. Management of fish health (left pannel) and fisheries resources (right pannel)with multiple approaches.

Overview of management of fisheries, modified after Holsman et al., (2020) (Holsman et al., 2020). Left panel of the figure indicates the ecosystem level management including the environmental

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and disease management while the right panel represents fish immunity management with multi-source approaches for their better production. (Figures are produced form Biorende.com).

In order to develop immunity in animals and reduce the susceptibility of animals to infectious diseases, vaccination is crucial. The prominent examples of reducing infectious diseases in animal, including in fish, is the application of vaccines. Application of vaccines as preventive measures was used to reduce the chance of diseases such as rabies and rinderpest, which can be endemic in nature [8,9]. Even though vaccines are available for animals based on the type of disease, prioritizing them is very necessary. Due to variations in temperature and other animal husbandry conditions, frequent pathogenic infections occur in animals. Numerous vaccines are developed such as live vaccines, and recombinant vaccines in prevention of these infectious diseases, but still the recovery rate from contracting the diseases is very low. For example, bovine viral fever affects cattle and buffaloes and for that, vaccines such as modified live virus (MLV) and killed virus (KV) vaccines are preferred to reduce the infections. Unfortunately, MLV vaccines are not stable whenever there is a temperature variation and get denatured and inactivated when other compounds interfere. KV vaccines are stable as opposite to MLV and KV vaccines cannot activate cytotoxic T-cells, and are moreover costly too [10,11]. However, wide range of commercial vaccines available according to the infectious disease types and rate of infection in animals (as given in Table 1) but availaibility of such vaccines in fish may able to check the contagious diseases which affect their production and redporduction value (Figure 3).

Table 1. Different infectious agents and diseases that are caused in animals.

S. No.	**Infectious agent/Etiological agent**	**Diseases**	**Animals infected**	**Vaccines used to prevent the disease (either used in humans or animals)**
1.	*Avian Influenzae* virus	Avian Influenza	Poultry: Chickens, ducks, turkeys, geese	Afluria Quadrivalent, Fluarix Quadrivalent, FluLaval Quadrivalent, and Fluzone Quadrivalent.
2.	*Herpes* virus, Gallid alphaherpesvirus 2	Marek's disease (fowl paralysis)	Poultry-chickens	HSV vaccine candidate (mRNA-1608), herpes zoster
3.	*Salmonella* sp.	Salmenollosis	Aquatic animals: fishes, tortoises, birds, animals—cattle, pigs, horses	Ty21a, Vivotif (Typhoid Vaccine Live Oral Ty21a), Typbar TCV®, Typhim Vi, Vivotif
4.	*Rabies lyssavirus*	Rabies	Dogs	HDCV or PCEC, human rabies immune globulin (HRIG)
5.	*Bacillus anthracis*	Anthrax	Cattle, sheep, goat, camels	Anthrax Vaccine Adsorbed (AVA) or BioThraxTM
6.	*Brucella* bacteria	Brucellosis	Cattle, sheep, goat, swine, equines	Live attenuated Brucella abortus strain

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				19 (S19 vaccine), Brucella abortus S19
7.	*Listeria monocytogenes*	Listeriosis	birds, crustaceans	Under clinical trials
8.	SARS-Cov	Severe acute respiratory syndrome	Bats, birds, cattle	COMIRNATY®, COMIRNATY®Original/Omicron BA.1, COMIRNATY®Original/Omicron BA.4-5, VAXZEVRIA, COVISHIELD™, COVID-19 Vaccine, SPIKEVAX, Inactivated COVID-19 Vaccine (Vero Cell), CoronaVac, COVAXIN®, COVOVAX™, NUVAXOVID™, CONVIDECIA,
9.	Nipah virus (NiV)	Nipah	Bats, pigs, horses, goats, sheep	The Nipah Virus Vaccine (PHV02)
10.	Monkey pox virus	Monkey pox	Rope squirrels, dormice, non-human primates etc.	ACAM2000®, JYNNEOS™ (Imvamune or Imvanex or MVA-BN)
11.	*Clostridium botulinum*	Botulism	Fishes mainly trout	Fabrizio Anniballi, Alfonsina Fiore, Charlotta Löfström, Viveca Båverud.
12.	*Mycobacterium sp.*	Mycobacterial infections	All fishes,	Bacille Calmette-Guérin (BCG)
13.	*E. coli*	Avian bacterial infections (AVEC)	All avian sp.	Poulvac *E. coli*,

The list of different causatives, infectious or etiological agents is given in the table. The susceptible animals indicate that the adaptation of vaccination is recomended in animals. Data adapted from The World Health Organization [1].

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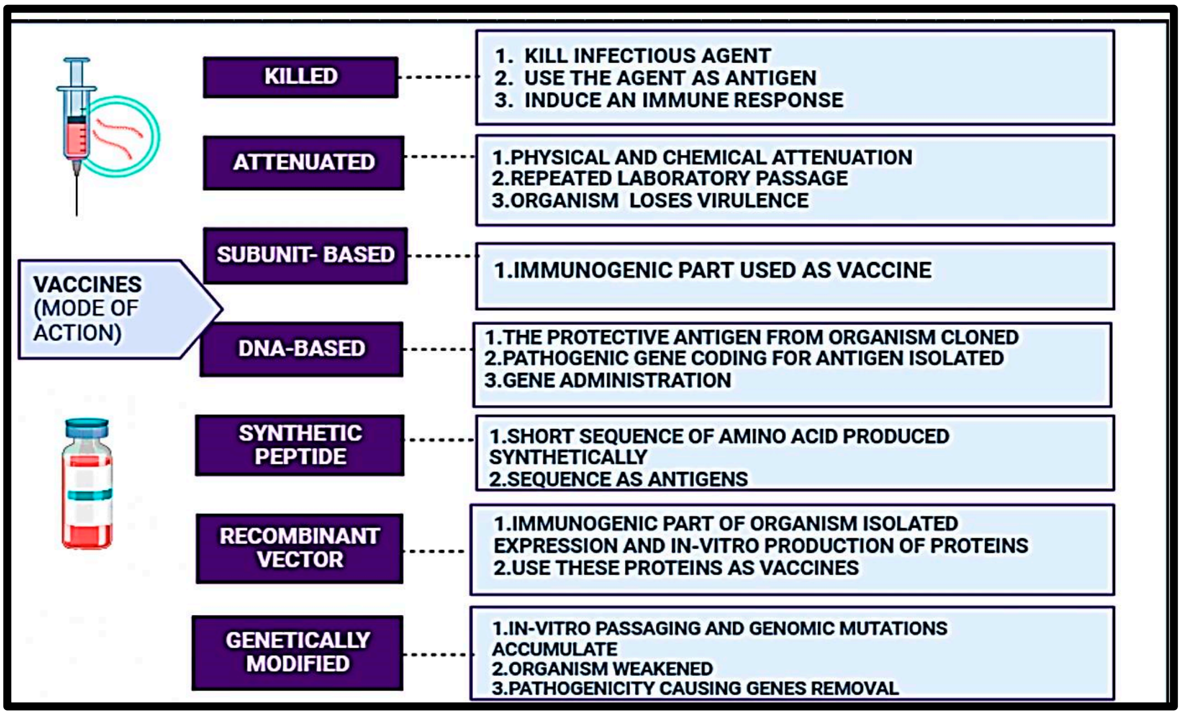

Figure 3. Vaccines classification based on their mode of action and their sources. The figure is modified after Assefa and Abunna [7].

The practice of wild harvest began in the 1600s when English fishermen made their first voyages to the Gulf of Maine [13]. Since then, several advances in technology have given rise to new fishing methods such as handline, and longline. The 20th century marked the beginning of exponential growth for the industry, where global fish harvest has quadrupled over the last 50 years [14]. As per statistics provided by The Food and Agriculture Organization (FAO), capture fish production is expected to hit 95 million tons (Mt) but will stand second when compared to the aquaculture production which is anticipated to reach 105 Mt [15]. The total fish weight is estimated to double in India, Mexico and Brazil by 2050 as stated by FAO food balance sheets and the total fish demand for the top 10 countries for human consumption is listed in Table 1 [16,17]. The controlled production of aquatic organsims such as fish, algae, molluscs, and other aquatic plants is known as aquaculture or aquafarming. In contrast to commercial fishing, which includes wild fish capturing, aquaculture involves raising populations of freshwater, brackish water, and saltwater species in controlled or semi-natural environments. However, their production is hamprered severely by several (infectious) diseases.

Artisanal fisheries ecosystems can naturally home for many diseases, and many of these have negative economic effects on aquaculture or fisheries. Diseases are also can be contagious in oceanic ecosystems. In hosts, different levels/percentage of infections occur, for example, 49% in fish, 21% crustaceans, 28% in molluscs and 1% in echinoderms are susceptible to various diseases [16,17]. Exotic fishes may become more susceptible to diseases in the new enviromental conditions compared to the local wild varieties. Opportunistic infections may impair the aquaculture sector due to reasons such as high stocking densities of monoculture, leading to greater host contact with pathogenic organisms, which in turn cause increased stress for the fish and degrade the water quality [16,17]. The main objective is to prevent the occurrence of diseases in aquaculture which can be met by maintaining good water quality, moderating stocking density, production of disease resistant genetically modified stocks, use of immuno-stimulants and therapeutics against fish pathogens, and utilization of vaccines against bacteria, viruses and other pathogens in fish [16,17].

Therapeutics can be used to controll any diseases in aquatic system but a preventive approach to the management of diseases is by the administration of vaccines (Figure 1). A vaccine can be a suspension of weakened or killed microorganisms, toxins or any other biological preparation. It usually consists of a protein or a polysaccharide antigen which produces an immunological response in an organism to provide protection from the infecting pathogen [18]. There are different types and generations of vaccines, that are classified based on their mode of action in the below mentioned Figure 1and Table 1. Currently, there are three major modes of administration of vaccines to fish such as oral vaccines that are incorporated into the feed. This is an easy to apply method, causing less stress in the fish. Immersion vaccines are applied by dipping the fish for a short time in concentrated solution of vaccine, and injection vaccines as the name suggests, are injected into the fish. The current review is an attempt to update information on fish vaccines and their efficacy and future prospect using a systematic literature survey [16–18]. It is to be noted that different commercial veterinary vaccines available in the current scenario such as Canine (Canileish Leishmania vaccines), Avian (Trovac Flu vaccines), Equines (Proteq Flu), Salmonoid (Apex IHN), Food (iPED+) and (PureVax rabies vaccine) are available currently [12].

2. Materials and Methods

A systematic literature survey was performed to review this topic of fish vaccines [19]. We used search terms such as "vaccines", "*fish vaccines*", "fish" etc., in PubMed, AGRICOLA databases and Google scholar. The inclusion criteria was only to include peer-reviewed or not peer-reviweed but authentic articles, books and published online sources, and the search was made using traditional methods in the available electronic databases. The articles written in the English language were included in the study [19].

2.1. Data Sources and Search Strategy

The database PubMed/MEDLINE is considered as a large database in biomedical sciences, and the Google search engine, specifically Google Scholar, is usually considered as the online storehouse of the entire published, peer-reviewed, and non-peer-reviewed articles. Similarly, AGRICOLA stores about 6 million articles or records related to agriculture and allied biological sciences [19,20]. It is to be noted that the topic of fish and fisheries or the current topic on fish vaccines is exclusively done in artisanal fisheries, open sea, or open river culture systems. Hence all the collected literature is included in the AGRICOLA database.

Scopus, Science Direct, and Web of Science were also searched to find relevant articles. Out of all the literature available in the above electronic databases on fish vaccines, only peer-reviewed or authentic literature (such as in FAO, https://www.fao.org/home/en, and WHO, https://www.who.int/) published in English were screened alone, with the term "fish vaccines" or with additional associated search terms. Search terms such as "fish", "physiological responses", "disease", "infectious disease", "immunity", "fish production", "economic loss", "mortality", "contagious diseases", "immunology", "immune system", "vaccines", "landing value", "growth" and "reproduction", "metabolism", "fish" or "fish vaccine", were searched in Hence the above three databases electronically similarly mentioned in recent reviews [19–21].

2.2. Study Selection

The entire published, peer-reviewed articles in English language books, journals, periodicals, and various authentic reputed webpages on "fish vaccines" or "vaccines" in relation to the search terms in search engines were screened in this review article. Articles not containing any of the above terms were strictly not included in the review. Articles matching within the subject area of the Pila sp. were included in the review, whereas any auxiliary articles in which the above term(s) was merely used were excluded from the review. A total of 10,000 articles on "fish", 1,553 articles on "vaccine" and 26 articles on "fish vaccines" in AGRICOLA were screened for this study. Similarly, 4,018 hits in PubMed and about 4,89,000 hits (because all hits were not articles) in Google Scholar were screened on "fish vaccines" in PubMed and Google Scholar, respectively. Higher results, such as 4,89,000 hits in Google Scholar, were reduced with additional search terms. All the articles were filtered based on inclusion criteria and articles merely mentioning the words but not on the subject area were excluded.

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Articles were picked unbiased irrespective of the region of publication, geographical study area, and authors, but only peer-reviewed or authentic resources were screened for the review as done in other recent review articles [19–21].

2.3. Data Extraction

The entire review process was streamlined securely and reliably with consistency on fish vaccines. To achieve this, we have covered the origin of vaccines, their development in animals, then their development in fish, their efficacy and success rate, commercialization, commercially available fish vaccines, immunity in fish, disease and their contagiousness in fish, loss of economic value in fish, hampering growth, production, and reproduction of fish. Finally, we divided the topics into various subsections based on their relatedness. We have covered the status of fish and fisheries, the current status of various fish diseases and their contagiousness, the need for fish vaccines, and the future prospects of these vaccines, as done in several other articles [19–21].

2.4. Synthesis and Analyses

After confirming the relatedness of an article based on their content and peer-review or reliability of the electronic source, about 187 articles from all three electronic sources such as PubMed, AGRICOLA, Google Scholar, and reliable webpages such as fao.org and who.int/. Some of the repeating articles among all databases were carefully screened. The subject area of every article was extracted and categorized as mentioned in each section of this review article, associated with fish or fish vaccines.

3. Status of Available Vaccines

Infections caused by bacteria are among the most common illnesses that affect fish. Environmental factors that cause stress in fish also multiply susceptibility to such infections in fish. However, a dearth of anti-viral medicines, efficient viral vaccinations, and illness resistance makes viral infections harder to treat. Viral illnesses in animals or in fish have less avaiable effective treatment system unlike bacterial infections. It is difficult to control a wide array of bacterial illnesses that affect fish which utilise antimicrobials as the only treatment method (Table 1, Fig 1). Therefore, the vaccination of fish, particularly broodstocks, is one of the most important ways that may be utilised in the fisheries business in order to reduce losses. It is because the broodstocks of an aquatic animals are used to produce and supply seeds of that species for mosty artisanal fishreies. So, healthy and immunised seeds can be produced form such immunised brrodstocks. Vaccination practices have been increasing in aquaculture business. Due to various legal guidelines several farms have been routinely vaccinating their fish, which, when administered in the appropriate manner, provide a high level of protection. With regards to Enteric Red Mouth and Vibriosis, the concept of immunizing fish on a commercial scale has finally been realized (Table 1, Figures 1–3).

3.1. Early Works on Fish Vaccination

Fish were immunized for the first time successfully via an oral vaccine in carp and trout against *Aeromonas punctata* in 1938 and *Aeromonas salmonicida* in 1942, respectively [30]. The vaccinations against enteric red mouth disease (ERM), also known as yersiniosis and vibriosis were the first bacterial vaccines to be made available for commercial purchase in the United States in the late 1970s. Both of these diseases are usually known as yersiniosis. Bioveta, a Czechoslovak business, created the first viral immunization for fish in the year 1982 [30]. This immunization was designed to prevent diseases caused by limited numbers of viruses. A vaccine was developed in order to give protection against Carp rhabdovirus, which is the virus responsible for spring viremia in grass carp (SVC). The vaccine was created by fusion of two deactivated SVC virus strains in oil followed by injection. The vaccination included no live virus. The only carp vaccine that is currently in the market for commercial sale in Asia is an inactivated injection that protects against grass carp bleeding disease,

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which is caused by the reovirus. The manufacturer of a vaccine for koi herpesvirus for sale in Israel, makes use of an attenuated strain of the CyHV-3 [30].

Infectious illnesses are having a negative effect on aquaculture practises all around the world. Major financial and survival issues are caused by the pathogenic illnesses for aquaculture in India. Antibiotic resistance patterns, residual effects, and environmental impact have all increased the need for establishing appropriate alternate preventive methods [31–39]. Vaccinations have been shown to be an effective technique of disease control, in this scenario allowing for increased fish productivity. *Aeromonas hydrophila* is a widely spread pathogen in all farmed fish species in India. Most vaccine research has focused on bacterial illnesses including *Aeromoniasis* and *Edwardsiellosis*. Despite major effort and potential pilot programs for developing vaccines against several parasitic and fungal infections, India's aquaculture sector has no universally applicable immunizations. Indian researchers are attempting to develop a vaccine to protect the fish business, listing the problems associated in manufacturing and exploring the opportunities of earning money from such vaccines. Scientists in India are working on a vaccine to prevent the spread of a disease that threatens the country's fish industry [31].

3.2. Properties of Fish Vaccines and Vaccination Process

Vaccinations are intended to prevent disease in fish. An ideal viral vaccine is safe for the host, immunizer, and receiver. Simpler, less expensive immunization is required. It should be ethically safe before being injected into a fish. Such viral vaccine is known to be harmless, latent, or attenuated. Vaccination should be 100% effective in various hosts against all viral pathogen serotypes and strains. Vaccination should protect against mucosal, humoral, and cell-mediated infections. It may activate an animal's immune system, causing a memory response to be triggered. In reaction to natural illnesses, animals' immune systems rapidly manufacture specialized antibodies. These antibodies destroy the virus within the host if the animal has a strong immune system [30,31]. The immunizations should be non-toxic to fish and their habitat, cheap to mass-produce, easy to administer, generate a strong immune response even in the most vulnerable fish, and have few, if any, adverse effects. The molecular research discovered that immunoprophylactic approaches for grass carp activate viral nucleic acid sensors, TLRs, HMGBs, RLRs, and pattern recognition receptors (PRRs). They increase the resistance of fish against viruses. Most importantly, they may be adjusted to provide optimal protection [30,31]. Microbes' toll-like receptors recognize pathogen-associated molecular patterns (PAMPs), initiating immunological signaling cascades that increase innate immunity. They also have an impact on immune system adaptability. TLR adjuvants and activators may thereby increase immunization of fish and aquatic animals [30].

3.3. Types of Fish Vaccines

Fish vaccines can be of protein, live attenuated vaccines, Virus-like particles, bacterines and DNA vaccines. Challenges remain in the fishing industry when it comes to the adaptation of vaccination, including the method of administration, use of effective adjuvants, and most importantly the lack of data from more focused research on the mucosal immunity mechanism. The use of autogenous vaccinations which include intramuscular, intraperitoneal, oral vaccinations and most significantly the incoproration of vaccines in feed via top dressing methods in feed or as a constituent in fish feed, are all examples of emerging practices [30,31].

3.3.1. Whole Cell Vaccines

Whole cell vaccines that have been killed or inactivated can be characterized as a suspension of pathogens that have been destroyed (either by heat or chemical treatment) but still provide protection when administered to the host. These vaccines are cheap to make. The first vaccine against *Aeromonas salmonicida* to protect cutthroat trout (*S. almo clarki*), was developed by using chloroform-inactivated cells. Pathogens such as *Vibrio anguillarum*, *Vibrio salmonicida*, *Vibrio ordalli*, *Yersinia ruckeri* and *Aeromonas salmonicida* are combated by applying these vaccines to fish (Table 2). These killed

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vaccinations are commercially available as formalin-inactivated whole cell vaccines, which can be given with or without adjuvants. Even though the specific protective antigens from these bacterial vaccines are yet to be explored, they are working effectively. Vaccines against deadly fish viruses including infectious pancreatic necrosis virus (IPNV), infectious hematopoietic necrosis virus (IHNV), viral hemorrhagic septicemia virus (VHSV), and spring viremia of carp virus have been produced (SVCV). When inactivated IPNV is injected into rainbow trout fry, the fish are well-protected, but when given to brook trout with Freund's complete adjuvant, the fish have a significant humoral response but little protection. Formaldehyde is used to sterilize fish. Although inoculation with inactivated vaccines is effective in preventing the spread of diseases, this method is deemed unsuitable for some viruses because of the age at which symptoms first appear. The humoral immune response is induced by killed vaccines and to maintain the protection, booster dosages are required. The high cost of cell culture manufacture, difficulty of purification, and limited administration options are the primary drawbacks of heat-killed vaccine (Table 2).

Table 2. List of vaccines proved to be preventing infections in fish.

Types of vaccine	Name of vaccine	Fish	Infection	Remark
Inactivated or heat killed whole cell Vaccine	Apha Ject® 1000, Norway	Salmon	Infectious pancreatic necrosis virus	monovalent
	Inactivated SVCV	Carp	Spring viremia of carp virus	SVCV emulsified in oil
	Formalin-inactivated IHNV	Rainbow Trout	Infectious haematopoietic necrosis virus	
	killed VHSV	Rainbow Trout	Viral haemorrohagic septicaemia virus	--
Attenuated vaccines	Attenuated KHV Israel	Carp	Koi Herpes Virus	
	Attenuated *Flavobacterium columnare*	All fresh water finfish	*Flavobacterium columnare*	--
	Septicemia due to enterococci	Catfish	*Edwardsiella ictaluri*	--
	Kidney infection in Fish due to bacteria	Pacific Salmon and Atlantic salmon	*Renibacterium salmoninarum*	--
Recombinant vaccines	Recombinant G protein	Carp	SVCV	--
	CIBA-Nodavac-R	All types of fishes infected with	Red-spotted grouper NNV	First vaccine indigenously developed in India

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Synthetic peptide vaccines	Subunit vaccine IPNV aquabirnavirus	Nervous necrosis virus (NNV), Rainbow trout and Atlantic salmon	Infectious pancreatic necrosis viruses	Target : VP2, VP3 and Capsid proteins
DNA vaccines	Apex IHN, Canada	Salmon	Viruses having G antigen	Target : G glycoprotein
	DNA	Salmonids	Infectious hematopoietic necrosis Rhabdovirus	
Mucosal vaccines	MicroMatrix™ delivery system (*Piscirickettsia salmonis*, ISAV and IPNV, Centrovet)	Atlantic salmon	*Y. ruckeri V. anguillarum*, *P. salmonis* and IPNV or other similar mucosal infection.	Pathogen killed by heat or inactivated by formalin
Plant-based edible vaccines	Under development in plant *Nicotiana benthamiana*	Salmonids	PMCV and Cardiomyopathy syndrome	--
Nanoparticle-based vaccines	Chitosan-NPs based vaccine formulation NPrgpG, pICrgpG, CSrgpG, NpiV,	Zebrafish	Viral hemorrhagic septicimia virus.	Under experimental trials
	OCMCS-hyaluronic Acid OCMCS/aerA-NPs, OCMCS-HA/aerA-NPs	European carp	*Aeromonas hydrophila*	Under experimental trials
Monovalent and polyvalent vaccines	ME-VAC Aqua Strept	Nile tilapia fish, Nile tilapia	*Streptococcus* infections	Effective against bacterial strains, *Streptococcoci*, *Enterococcoi*, and *Lactococci*

Table shows the 'available' list of fish vaccine. Data are collected from Mondal and Thomas, [30] and Dhar et al. [39].

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3.3.2. Attenuated Vaccines

Attenuated vaccines are genetically or chemically weakened microbes that can produce short-lasting immune responses in the host [32]. They contain live bacteria and viruses that no longer cause the illness.

3.3.3. Recombinant Vaccines

Recombinant Vaccines are those which use only the immunogenic areas of the pathogen to be produced in a heterologous host, and then utilised as vaccines [33]. Additionally, recombinant vaccine can be a genetically modified organism (bacteria or virus) with reduced pathogenicity and thus recombinant and attenuated to produce vaccines.

3.3.4. Synthetic Peptide Vaccines

Synthetic peptide vaccines can act as subunit vaccines, antigenic sites or the peptides that have been tested to induce antibodies against infectious pathogens such as nodavirus, rhabdovirus, birnavirus, IHNV, IPNV and VHS [33].

Among various vaccines for fish, mRNA vaccines are in huge demands compared to conventional vaccines. Live attenuated vaccines (LAV) are successful in reducing diseases, but their safety and efficacy are still doubtful. The mRNA vaccine, on the other hand, is non-infectious, hence is safer

3.3.5. DNA Vaccines

DNA vaccines containing plasmids that carry a pathogen's antigen have garnered attention as a potential way to boost fish defense against illnesses. Aquaculture researchers have boosted VHSV and IHNV resistance by injecting viral genes expressing surface glycoproteins intramuscularly (IM). VHSV glycoprotein and DNA immunization elicited an immune response in rainbow trout [33].

3.3.6. Mucosal Vaccinations

Mucosal vaccinations are used in aquaculture due to their effectiveness. Mucosal vaccines against pathogenic infections are being developed, because they can elicit protective responses at mucosal surfaces by preventing pathogen reproduction. Oral, immersion, and nasal teleost fish mucosal vaccines stimulate B and T cells to induce systemic and mucosal responses. It has been shown that mucosal vaccines work if they imitate the natural route of infection, such as going through mucosal surfaces [34]. For example, rainbow trout (*Oncorhynchus mykiss*), a bony fish renowned for a specialized mucosal immune system, was studied by Magadan et al. [35]. The olfactory organ of this fish has Nasopharynx-associated lymphoid tissue (NALT), which is distinguished by a widespread network of myeloid and lymphoid cells. Myeloid and lymphoid cells that were activated by the nasal immunization showed distinctive dynamics of IgM and IgT repertoires at systemic and mucosal locales, demonstrating an unusual capacity to induce splenic Ig responses.

3.3.7. Plant Based Edible Vaccine

Plants might provide an inexpensive foundation for the creation of cost-effective, edible, live attenuated pathogen-free vaccinations that can reduce several pathogenic fish illnesses to maintain sustainable aquaculture. Plant-based vaccines may minimize the frequency of live attenuated virus or bacterial booster doses. Modern plant researchers suggest that plants cells could express mammalian proteins after cloning [36]. Specific plant cell cultures or whole plants can be used as expression hosts. To express mammalian genes in plants, cloned complementary DNA must be spliced with a plant promoter, terminator, or regulatory region. Selectable markers help to identify recombinants [37]. Plant based vaccines would be easy and convenient to consume orally. Follicle-associated epithelium M cells will grab the protein unit to activate mucosal immunity [34,37].

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3.3.8. Nanoparticles Based Vaccine

Nanoparticles provide tailored vaccination delivery, antigen stability, and adjuvant effectiveness. Vaccinating particular body parts with these systems might prevent disease transmission. Nanoparticles can increase weak antigen immunogenicity and release kinetics, stability, and targeted dispersion over traditional adjuvants. Oral immunization is preferred in aquaculture, since each fish in a pond espcially small fishes cannot be injected with vaccines. Maintaining gastrointestinal stability is difficult with oral vaccines. Nanoparticles may solve this problem [38]. Alginate, chitosan, and PLGA have different chemicals mixed with antigens and immunostimulants to enhance delivery and immune responses.

3.4. Advancements in Vaccine Development

New biotechnology developments have enabled the quick production of vaccines against a wide range of pathogens. In bioinformatic approaches, software predicts the gene regions that could be expressed. These genes are used to produce recombinant proteins useful for vaccine [32]. Andreoni et al. [40] used this software-based approach to investigate vaccines against intracellular infections, viz. *Flavobacterium columnare* and *Edwardsiella tarda* in *Photobacterium damselae* subsp. piscicida fishes. It causes most common significant diseases of fish columnaris and edwardsiellosis, respectively [41]. Both an *in-silico* examination and a functional analysis could lead to the conclusion that an effective candidate gene exists, which could be prioritized to develop a vaccine for preventing the further spread of a disease. This would definitely cut down on the amount of time of process in needed in developing a novel vaccine. There are approximately 30 vaccines available that have the potential to protect fish against the most lethal bacterial and viral diseases.

4. Contemporary Need of Vaccines for Fish, a Growing Field of Research

Fisheries production was estimated to be 90.3 million tonnes across the world with a decline of 4% in 2020-21 [16]. Etiological diseases in fish and their treatment methods are always challenging. Immunization of fish is to combat the normal diseases and have a renewable production for its sustainability in aquaculture. Spreading of any infectious diseases in fish may be mutliplied under the environmental stress caused due to the pollutants. One of the species affected due to such stress is the production of shrimps. A total loss of one billion US dollars was reported by Briggs et al. [43]. Infectious agents or parasites are normally present in water such as bacteria, viruses, algae, etc. Some of the major etiological agents and infected species of fish are shown in Table 3 [44].

Table 3. Infectious diseases in fishes and economic losses estimate.

Sr. No.	Causative agent	Diseases	Type of fish infected	Loss in production /economic loss (%)	References
1.	*Aeromonas* bacteria	Aeromonas infections	Carps, fresh water fishes	80-100%	[45]
2.	*Pseudomonas* sp.	Strawberry disease	Carps, rainbow trout, tench	50%	[46]
3.	*Shewanella putrefaciens*	Shewanellosis	Carps, rainbow trout, zebra fish	-	[45,46]
4.	*Mycobacterium* sp.	Mycobacteriosis	All fresh water and marine fishes	50%	[47]
5.	*Flavobacterium flavobacter*	Bacterial gill diseases	All fishes	60-70%	[48]

6.	*Birnavirus*	Necrosis	Freshwater fishes like salmonids	50%	[16]
7.	*Retrovirus*	Anaemia	Walley pike	50%	[49]
8.	Ranavirus	Anaemia	Carp	50%	[50]
9.	Megalocytivirus	Anaemia	Carp and other fresh water fishes	60-70%	[50]

Due to the severity and varied symptoms in fish, the total production of fish and their diversity is hugely affected, especially in India. Disease outbreak is mainly due to the practices in aquaculture. .

Reviews have focused on various vaccines for fishes, among which mRNA vaccines are in huge demand in comparison with conventional vaccines. Live attenuated vaccines (LAV) are successful in reducing diseases, but their safety and efficacy are still doubtful. The mRNA vaccine on the other hand is non-infectious, hence is safer [51,52]. Other types of vaccines used are nanoparticulate vaccines (nanogels, micelles), liposomal vaccines (natural or synthetic lipids) which combat infectious diseases [53,54].

The history, types and mode of administration of vaccines in fish are different for different vaccines. The first ever vaccine was a killed *Aeromonas salmonicida* vaccine for immunization of trouts against *Aeromonas* bacterial infections [55]. The application of adjuvants and immunostimulants in fish vaccines, along with their delivery methods have been identified by some key researchers working in this area. The data was obtained based on alternative methods (other than injection) for vaccine delivery, and the protective efficacies of traditional and promising new-generation adjuvants [56,57]. Tafalla et al. [58] defined and perceived the commercially available fish which evolved over time. More than 26 licensed fish vaccines are available commercially and globally in the current scenario [33]. Vaccines have been approved for use by the United States Department of Agriculture (USDA) for diverse species of aquaculture, and most of them are produced by conventional methods which culture target pathogens. The appropriate collection of vaccines has successfully protected fish against some of the severe fish diseases up to an extent.

Some of the vaccines available for infectious diseases are inactivated (IPNV, ISAV), nucleic acid (DNA, RNA) vaccines and attenuated live vaccines. DNA vaccines are studied to be effective against viral infections and are developed for a series of pathogens in the water [59]. Another interesting exploration was the discovery of RNA vaccines which are self-replicating based on the alphavirus genome [60]. Even though numerous types of vaccines have been explored, tested and controlled successfully for many diseases, huge challenges persist in delivering an effective immunization in fish.Viral disease outbreak, mitigatory species of fish, anthropogenic activities, and morbidity rate increase are the challenges being faced by the farming and trading of aquatic species. Some of the activities such as mining and construction works in near by area lead to viral infections in marine ecosystems. Moreover, consumption of infected fish, used as a protein source for farm fish, result in the infection of farm fish species. Another major drawback is the lack of disease diagnosis tools and disease surveillance measures, especially in the underdeveloped countries [61–63]. Different management strategies and policies should be designed and developed to manage aquaculture trading and diseases. A multifaceted approach needs to be developed for further prevention of emerging etiological agents and infectious diseases caused by them. (Table 3).

5. Fish Vaccine Production against Various Pathogens

The discovery and subsequent production and commercialization of vaccines against infectious diseases in fish are commercially not available. The processes use multiple sources and steps. Each vaccine undergoes the steps of identification of the pathogen/disease, process development, production, validation with multiple individual fish, documentation and licensing of the vaccine for commercialization (Figure 4). Various sources are used to achieve these steps.

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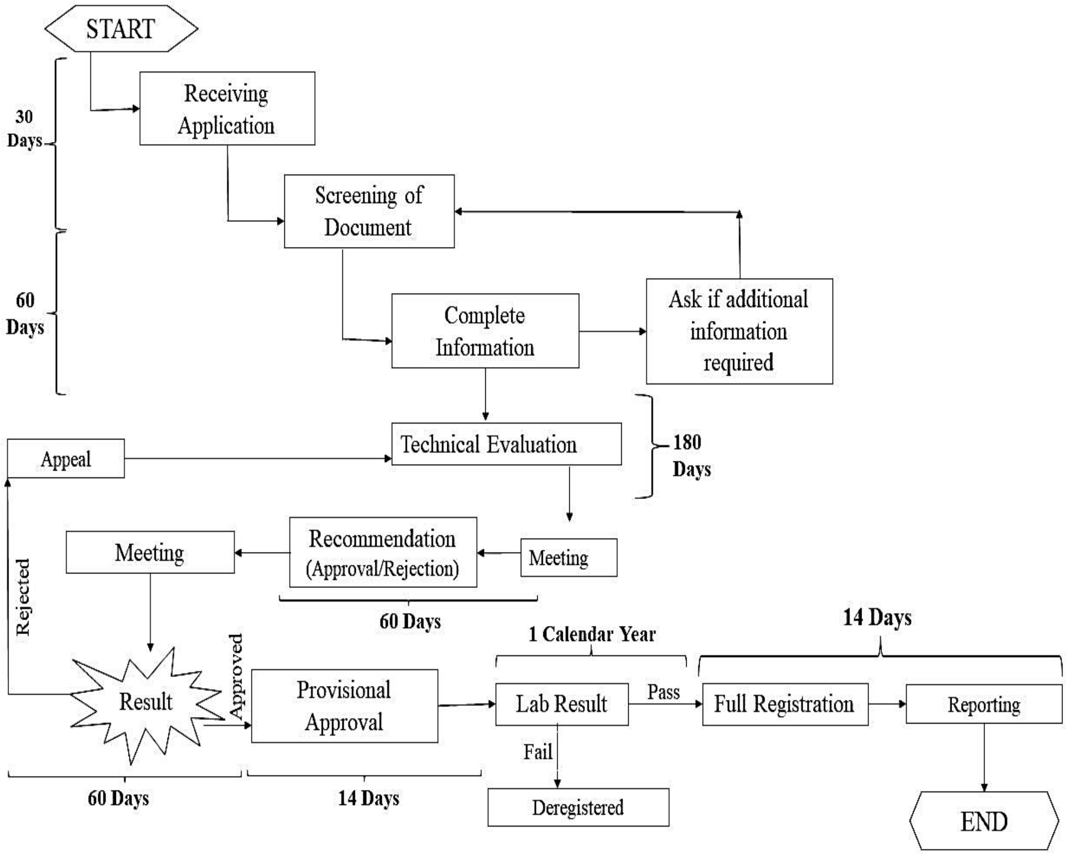

Figure 4. Schematic diagram for fish vaccine regulatory approval.

5.1. Nocardiosis

Nocardiosis, which is caused by *Nocardia seriolae*, was first discovered in Japan's central region [64]. It swiftly expanded to the country's western regions and resulted in widespread Seriola fish mortality. Nocardiosis initially did not have a large negative economic impact but now has been considered to be a major cause of mortality in fish [65]. Although Seriola fish get easily infected by *Lactococcus garvieae*, nocardiosis has replaced it as the disease that causes the most economic harm to Japan's aquaculture sector due to the development of a vaccine to control the bacteria [66]. Nocardiosis is distinguished by tubercles on the kidney and gills, as well as ulcers on the body's exterior [67,68]. The creation of a vaccination against this illness is eagerly awaited. The administration of Freund's incomplete adjuvant or formalin-killed cells of *N. seriolae* generated a humoral immune response but th evaccine does not have a protective role against infectious diseases [69]. Numerous studies have documented that *N. soli, N. fluminea*, and *N. uniformis* could be vaccinated using live vaccines, such as in *N. seriolae* a "codon-optimized antigen-85- like gene" [70]. Kato et al. [70] insisted-on "DNA vaccines encoding the codon-optimized antigen-85-like" genotype of *N. seriolae*, and malin-killed cell vaccine augmented with hybrid interleukin-12.

5.2. Bacterial Hemolytic Jaundice

It was documented that bacterial hemolytic jaundice in farmed yellowtail causes 5%–20% overall loss in cultured fish, like Japanese amberjack population [72]. The hemolytic activity of the bacteria causes the skin and muscle tissue of the infected fish to turn yellow [72]. The illness originally surfaced in the 1980s and has since spread rapidly over western Japan [73,74]. In addition to the losses caused by nocardiosis, a silent infection in yellowtail culture, the illness also results in considerable economic losses as it affects large number of fishes before shipping. *I. seriolicida* exhibits a low pathogenicity for greater amberjack and yellowtail kingfish [75].

Matsuyama et al. [74] reported that those fish survive against naturally occurring contagions with *Ichthyobacterium* exhibit strong immunity and antibody-mediated death of the pathogen. Even though the bacterial serotype has not been identified, molecular epidemiological studies have shown that *Ichthyobacterium* populations are clonal populations with few variations. Furthermore, if low-cost growth techniques can be created and bacterial quality is steady, it would be possible to develop an effective vaccine. Takano and team [76] sequenced *Ichthyobacterium seriolicida* isolated from *Seriola quinqueradiata*. This genome data of JBKA-6T sp. is being used in research to create a recombinant vaccine [76].

5.3. Bacterial Cold-Water Disease

Fish that live in cold, fresh waters with temperatures of 16 °C or lower are susceptible to one of the bacterial diseases known as coldwater disease (CWD). *Flavobacterium psychrophilum* causes bacterial CWD [77] and rainbow trout fry disease [78]. In 1990 and 1993, Japanese researchers documented the presence of bacterial CWD in farmed coho salmon and in natural sweetfish, respectively [79,80]. It has significantly harmed the abundance of sweetfish in numerous rivers. Genomics, serotypes and lethal studies indicated different strains of *F. psychrophilum* in sweetfish and other species [81,82].

Antiserum obtained from bacterial CWD infected fish used for the process of passive immunization helped to battle the illness and can be used for the development of an efficient vaccine [83]. The use of an oil-based adjuvant, formalin killed cell vaccine has also demonstrated a protective effect [84]. This oil-based adjuvant takes a minimum of two months to get completely washed off from the body of the sweet fish. Since sweet fish is annual and all of its organs are edible, this long-term residual adjuvant vaccine is not a suitable choice of vaccine [85]. Further developments of a water-soluble adjuvant and its effectiveness with a short residence period have also been demonstrated [86–88].

Unfortunately, the adjuvant's toxic properties prevented the vaccine from being marketed. No permanent impact has been attained despite studies on enteric micro-capsulated oral vaccinations and oral vaccines employing formalin-killed cells from logarithmic bacterial colonies [89]. Researchers have focused on recombinant vaccines of antigenic proteins against *F. psychrophilum* in sweet fish [90]. Though these antigenic proteins are promising candidates in the creation on bacterial CWD vaccines, further research is required to improve efficacy of these vaccines [91].

5.4. Erythrocyte Inclusion Body Syndrome

The etiologic agent of EIBS in *Oncorhynchus kisutch* is porcine orthoreovirus 2 [92]. The illness strikes when the water temperature is below 10 °C, and it results in anemia and widespread deaths. PRV-1 is shown to be linked with PRV-2 [93,94] and PRV-3 [95], which are infections that cause HSMI in *Salmo salar* and an infection that resembles HSMI in rainbow trout [96]. Although there have been no serious attempts to culture porcine orthoreovirus 2, a DNA based genetic approach may help to develop a vaccine. Haatveit et al. [97] studied PRV-1 DNA vaccine in experimental fish had shown a moderate protective effect. Making a recombinant vaccine might work for EIBS due to correlation found between PRV-1 and PRV-2.

5.5. Parasitosis

In Japan, farmed marine fishes are plagued by the "skin-parasitic capsalid monogeneans, *Neobenedenia girellae* and *Benedenia seriolae*". The latter has strong host specificity for *Seriola* species while the former parasitizes a variety of fish species and exhibits moderate host specificity [98]. Even though praziquantel oral administration and bath treatments with freshwater or hydrogen peroxide solutions are successful in controlling the parasite, they involve significant costs or work [99]. In numerous marine fish species, including the Japanese flounder (*Paralichthys olivaceus*), the ciliate *Miamiensis avidus* causes scuticociliatosis [100]. No effective treatment made a vaccine compulsory for scuticociliatosis infection in several countries, like Malaysia and Japan [101]. In experimental infections with ciliate, *P. olivaceus* immunized with formalin-killed paracetic *M. avidus* displayed reduced deaths [100]. However, in a vaccination study with *Philasterides dicentrarchi* or *M. avidus* in Spanish turbot, indicated an effective protection when it was used as a vaccine [102,103], and at least three different *M. avidus* or *P. dicentrarchi* serotypes happened to be present in Malaysia and Japan [101].

Surface antigens implicated in *M. avidus* immobilization have been identified as highly antigenic short, linear peptide fragments of proteins that could be associated with three serotypes [103]. As a result, it is believed that a combination of different immobilized *M. avidus* serotypes or polypeptides generated from different serotypes are potential antigens for vaccines.

5.6. Vaccines Other Than Inactivated Vaccine

Eel, Japanese flounder, and red sea bream aquaculture in Japan suffer commonly from edwardsiellosis [104]. It was already established that cultured yellowtail and greater amberjack are both negatively impacted by infectious diseases brought on by *Mycobacterium* spp. and *N. seriolae* [105–107].

Mochizuki et al. [108] specified that the nucleotide of IHNV isolates mutates quickly. It modulates its virulence capacity in rainbow trout farms as observed in different countries such as Japan and Malaysia. Various scientists in the world are working to develop preventative measures against these intracellular infections. *Edwardsiella*, *Mycobacterium*, *N. seriolae* and IHNV are infections occurring within a cell. To prevent these intracellular infections, a live-attenuated vaccine or a cytokine adjuvant-basedsed vaccine has been established [70,109]. A DNA vaccine for IHNV infections has been approved against intracellular pathogens of fish in the USA and Canada, respectively. The rules for the introduction of additional vaccinations in fish have not yet been studied. In Japan, all known licensed fish vaccines are inactivated ones. Therefore, it is essential to build an administrative structure that can integrate live-attenuated, or DNA based vaccines into Japanese aquaculture in addition to confirming their safety and efficacy [110]. Major disease prevention could be achieved using full vaccination protocols in aquaculture. Major vaccination is used in commercial aquaculture of species like barramundi, rainbow trout, Atlantic salmon, sea bass, sea bream, tilapia, turbot and yellowtail. Currently, available vaccines for commercial aquaculture are listed in Table 4.

Table 4. Major vaccination is used in the commercial aquaculture systems.

S. No.	Species	Vaccination against	Reference
1	cold-water vibriosis, classical vibriosis,	*Listonella anguillarum, Vibrio ordalii*	[111]
2	furunculosis	*Aeromonas salmonicida* subspecies *achromogenes*	[112]
3	Vibriosis	*Vibrio salmonicida* *Vibrio anguillarum*	[112]
4	yersiniosis	*Yersinia ruckeri*	[111]
5	pasteurellosis	*Photobacterium damselae* subspecie *piscicida*	[111]
6	edwardsiellosis	*Edwardsiella ictaluri*	[111]
7	winter ulcer	*Moritella viscosa*	[111]
8	*Streptococcosis/Lactococcosis*	*Streptococcus iniae, Lactococcus garviae*	[111]

Additionally, experimental vaccinations are used to prevent illnesses including *Vibrio harveyi* infection in barramundi and *Photobacterium damsela* subsp., damsela infection in salmonids, piscirickettsiosis, bacterial kidney disease in salmonids, as well as *Flexibacter maritimus* infection in turbot. However, non-licensed vaccines remain utilised in industrial fish farms. Many approved

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bacterial vaccines are inactivated products, and only a small amount of recombinant vaccine technology has been applied thus far. Typically, intraperitoneal injections of multivalent vaccinations are used to immunize salmonid fish. Although booster vaccination is increasingly used predominantly in the Mediterranean province, immersion vaccination remains the standard method of immunization for marine fish species [30,113,114].

5.7. Autogenous Vaccines

Japan forbids the use of autogenous vaccinations in aquaculture. Inactivated immunological VMPs made from pathogens and antigens taken from an animal or animals at a particular facility and used to treat that animal or those animals in the same area are known as autogenous vaccines [115]. A public funded facility working on a specific disease can produce an autogenous vaccine faster than a commercial vaccine which can be created and granted a license [116] (Figure 3). Therefore, when there are no reports of effective commercial fish vaccines, these autogenous vaccines prepared from the pathogen strains in a precise fish farm may provide protection. In general, different diseases and their variations may appear when different fish species are cultivated. The advancement of generating a fish vaccine may be aided properly by the introduction of autogenous vaccines in nations like Japan, where a variety of fish species are cultured [117–120]. Therefore, more research on fish vaccines are now needed.

6. Need for Fish Vaccines

6.1. Status of Fisheries Product

Although crops provide food supply to mankind, additional animal based nutrition is also required to feed the growing world human population. So, we must search for a new source of food to meet the demands of the human population. Depending on the food source for fish, as long as the fish get plant-based food,alternate hope is aquaculture because it not only feeds the population but also provides by-products like fish oil, liver oil, fish meal, fish protein, fish flour, fish roes, fish selage, fish fertilizers, isinglass and scientific study. Fish are also important for ecosystem balance, economic contribution, prevention of water pollution and disease control etc. [16]. There are some threats to fish like climate change, habitat loss, overfishing, illegal fishing [121], ocean pollution and disease. It is essential to protect them from these threats, and in this concern, vaccination strategies must be developed to safeguard their existence.

According to the FAO, 2022 world fisheries and aquaculture production increased from 110.7 metric ton to 178.9 metric ton in the years from 1990 to 2018, but slightly decreased in the production of aquaculture and fisheries in the year of 2019 (1.5 Metric ton), and 1.1 metric ton in 2020. Human consumption of fisheries and aquaculture has also increased from 86.6 metric ton to 158.1 metric ton from the year of 1990 to 2019 but reduced in 2020 up to 0.7 metric ton. The trade (export) of fisheries and aquaculture also increased in the year of 1990 to 2108, from 39.6 metric ton to 66.8 metric ton, but decreased up to 0.2 metric ton in 2019, and 6.8 metric ton in 2020.

India is the second largest fish producing country after China. China produces 58.8 million metric ton (one third of total world fish production) while India produces 9.46 million metric tons annually, although aquaculture industry was established in the 19^{th} century in India [122]. According to the Ministry of Fisheries, Animal Husbandry and Dairy, Government of India, fish production has been increased from 63,05,000 matric tons to 141,64,000 matric tons in just 16 years i.e. from the year form 2004 to 2020 [122].

Communicable and infectious diseases are still a major threat to the development of aquaculture industry in the world. Fish are vulnerable to many bacterial, viral, fungal, protozoan and parasitic diseases like red pest, fungus, tuberculosis, argulus, velvet or rust, anchor worm, costia (*Ichthyobodo*), lymphocytis, etc. Some communicable diseases along with their pathogens, symptoms and treatments are given in the Table 5.

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Table 5. Communicable diseases, their pathogen, symptoms and treatment in different fishes.

S. No.	Disease	Pathogen	Symptoms	Treatment	References
1	Columnaries Disease	*Flavobacterium columnare*	Lesions in skin, finerosion, nacrosis in gill	Amphenicol. Nifurpirinol, Nifurprazine, Oxolinic acid	[123–129]
2.	Epizootic ulcerative syndrome (EUS), or 'red spot disease	*Aphanomyces invadens*	red lesions (sores) or deep ulcers	No effective treatment but can be treated with different parts of *Azadirachta indica*	[130]
3.	Spring viremia of carp	rhabdovirus, spring viremia of carp virus	destruction of kidney, spleen and liver tissues	DNA vaccination may be protectable in fish	[131–133]
4.	Lymphocystis	*Lymphocysti* virus or *Lymphocystis* disease virus	Pebble or wart-like nodules mostly on the fins, skin, gills etc	No effective treatment	[134,135]
5.	Carp Pox	Cyprinid herpesvirus-1 (CyHV-1)	Milky skin lesions, Thickening of fins	No effective treatment	[136–138]

6.2. An Emergency Need in Fish Vaccines

Aquatic foods like sea plants, fish and crustaceans are one of the largest sources of food protein for humans. However, the aquaculture industry faces huge economic losses due to infectious diseases. In the aquaculture industry, bacteria accounts for more than 50% of infectious diseases, followed by viruses, parasites, and fungi [139]. These diseases have an impact on fish both internally and topically, including their gills, fins, and body surface. In general, fish farmers used a variety of strategies such as biosecurity controls, better settings, and feeding the fish special diets to manage the diseases that affected the fish. The use of disinfectants, addition of antibiotics, and treatment with pharmaceuticals like therapeutic treatments are a few examples of synthetic methods [16]. Although antibiotics and chemotherapeutics were used to treat diseases, there are some downsides such as problems with drug resistance and consumer safety concerns [140–144]. Neverthless, few fish vaccines are being studied and available in litarature (Table 6).

Table 6. Commercial names of few fish vaccines and their mode of administration.

Species	Disease	Organism	Name of the vaccine	Mode of administration	Type of vaccine	Reference
Salmon	Infectious hematopoietic necrosis	Infectious hematopoietic necrosis virus	APEX-IHN®	IM	IHNV plasmid vaccine	[145]
	Enteric Redmouth disease Yersiniosis	Yersinia *ruckeri* serotype O1b	Alpha ERM Salar	IP	Inactivated bacterial vaccine	[146]
			Aquavac YER knows	IP	Inactivated bacterial vaccine	[147]
	Pancreatic disease	Salmon pancreas disease virus	ALPHA JECT micro 1 PD	IP	Inactivated viral vaccine	[146]
		salmonid alphavirus	Clynav PD	IM.	DNA plasmid	[148]
		Salmon alphaviruses (SAV)	Norvax® Compact PD	IP	Inactivated viral vaccine	[147]
	Infectious salmon anemia	Infectious salmon anemia virus (ISAV)	ALPHA JECT® micro 1 ISA	IP	Inactivated viral vaccine	[146]

Tilapia	Streptococcosis	*S. agalactiae* serotype lb	AQUAVAC® Strep Sa	IP	Inactivated viral vaccine	[149]
		S. agalactiae serotype Ia & serotype III	AQUAVAC® Strep Sa1	IP	Inactivated viral vaccine	[149]
Tilapia, seabass		*S. iniae*	AQUAVAC® Strep Si	dip immersion/ IP	Inactivated viral vaccine	[149]
		Streptococcus agalactiae Ib	ALPHA JECT® micro 1 Tila	IP	Inactivated viral vaccine	[146]
Koi	Koi herpes virus disease	Koi herpes virus (KHV)	KV-3	Immersion/ Injection	Attenuated viral vaccine (not used because of its safety issues)	[149]
Sea bass	Viral Nervous Necrosis	Nodavirus	ALPHA JECT micro® 1 Noda	IP	Inactivated viral vaccine	[146]
	Aeromonas veronii infection	*Aeromonas veronii*	Autogenous *Aeromonas veronii* vaccine	IP	inactivated bacterial culture	[146]
	Vibriosis	*Listonella anguillarum*	ALPHA DIP® Vib	Dip vaccine	inactivated bacterial vaccine	[146]
Asian seabass	Epizootic Haematopoietic Necrosis	Iridovirus	AQUAVAC® IridoV	IP	Inactivated viral vaccine	[149]
Seabass	Infectious pancreatic necrosis	Infectious pancreatic necrosis virus (IPNV)	AquaVac® IPN Oral	Oral	Inactivated viral vaccine	[147]
Rainbow trout			Alpha Jects® 1000	IP	Inactivated viral vaccine	[146]
Pangasius	Enteric Septicaemia disease Motile Aeromonad Septicaemia	*Aeromonas hydrophila* and *Edwardsiella icataluri*	ALPHA JECT® Panga 2	IP	inactivated bacterial VACCINE	[146]

In the Table 6, we can see that the majority of vaccines are produced by inactivating bacterial and viral cultures, which are injected intra-peritoneally for emulsion-based injectable vaccines and intramuscularly for DNA plasmids [151], which produce higher protection against diseases for fish. However, using an injection to administer the vaccines in fish, even in fingerlings are tricky. Even with automation of the vaccination process in fish, they still experience stress. However, economically important fishes can be vaccinated [152]. Different environmental conditions such as pH, presence of organic matter and temperature can have an impact on a drug's efficacy [153,154]. Viral infections are more challenging to control due to the lack of antivirals or efficient viral vaccinations [155]. Only a few viral vaccines have acquired licences despite the fact that companies and academic institutions have carried out numerous research investigations to create viable viral vaccines [156].

Vaccination is an effective method to improve the immune response and is cost-effective for aquaculture but should be developed to meet the above-mentioned hurdle. Aquatic vaccines are likely to foresee advancement in the following years because of increased technological inventions like sequencing, antigen screening, development of fish cell lines, development of innovative vaccine protein expression and delivery systems and increased fundamental knowledge about fish mucosal immunity. Future research should concentrate on developing highly effective vaccines with appropriate adjuvants, and improving vaccine delivery will undoubtedly result in novel immunization strategies.

7. Plant-Derived Fish Vaccines, a New Perstective in Immunology

An emerging expression system through which recombinant genes are expressed in plant cells, is called plant molecular farming. In this technique, foreign proteins are expressed in plants with the

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purpose of using only the protein rather than the plant [157]. In the late 1980s, attempts were made to express recombinant proteins in plants [158,159]. Initially plants were used to express pharmaceutically important proteins. In 2012, a plant produced enzyme Glucocerebrosidase was the first plant expressed product to be commercialized for human use [160]. Since then, numerous research has been carried out for production of human and animal recombinant proteins in plants. Three different platforms are used to express recombinant protein in plants viz., stable nuclear expression, stable expression of transgenes in chloroplasts and transient expression of transgenes [161] (Figure 4). Each approach has benefits and drawbacks, and the choice of platform is mostly determined by the amount of required protein.

Currently, good manufacturing practices and the regulatory concerns with plant-made recombinant proteins have also been thoroughly developed. Plant molecular farming may utilize a wide range of plant species. In lettuce, tomato, potato, cabbage, and other edible plants, nuclear and plastid genome engineering has been used to produce a variety of recombinant proteins. It has been suggested that a chloroplast expression system is a promising method of producing oral vaccinations. Vaccines against viruses, bacteria, and parasites have been made using transgenic plants [161].

7.1. Advantages of Plant Derived Fish Vaccines

Plant derived vaccines have been used for their multi-fold advantages such as 1) Plant expression system is safe, and the vaccines do not have any toxic metabolites and hyperglycosylated proteins, 2) Plants have greater capacity for biosynthesis of proteins in a large scale, and performs complex assembly and folding of proteins, 3) Plants are environmental friendly, cost effective and sustainable when compared to existing expression systems and 4) Plant-derived vaccines can be effectively used for oral delivery without the requirement of sophisticated and time-consuming downstream processes.

7.2. Prospective Plant-Derived Fish Vaccines

Financial cost is one of the crucial factors that needs to be considered while developing vaccines for the aquaculture industry. The plant expression system for vaccine production provides cost-effectiveness, safety and efficacy. The plant-derived fish vaccines will provide increased and sustainable fish health in flourishing global aquaculture industry. Research in the field of plant derived fish vaccines is few but now the numbers are increasing [162]. In aquaculture there is a lot of potential for oral vaccinations for fish, made from edible plants. Additionally, a plant-generated recombinant vaccine can deliver multiple antigenic proteins simultaneously [163]. Table 7 shows some plant-derived vaccines in fishand other animals. However, no fish vaccine made in plants has yet been made commercially available (Figure 4). Therefore, it is vital to conduct more study on the development of fish vaccines employing plants as an important platform [164].

Table 7. List of plant-derived vaccines in fish and other animals under development.

S. no	Protein Expressed	Expression system	Treated animals	Reference
1.	Recombinant major capsid protein (rMCP) of iridovirus	Rice callus	*Neoscorpis lithophilus*	[156]
2.	Nervous necrosis virus (NNV) coat protein	Tobacco chloroplast	Grouper fish	[152]
3.	AcrV and VapA Antigens from Aeromonas salmonicida	Chloroplasts of *Chlamydomonas reinhardtii*	Salmon	[165]
4.	VP28 from White Spot Syndrome Virus	*Chlamydomonas reinhardtii*	*Penaeus monodon*	[166]
5.	VP28 from White Spot Syndrome Virus	*Dunaliella salina*	Cray fish	[167]
6.	Virus-like -particle from Atlantic cod nervous necrosis virus (ACNNV)	*Nicotiana benthamiana*	Salmonids	[168]

7.	ORF1 from Cardiomyopathy syndrome (PMCV)	*Nicotiana benthamiana*	Salmonids	[163]

Oral immunization offers a stress-free, time-saving delivery, with less labor costs and minimizes the need for expensive downstream processing, purification, and cold storage while transporting [169]. By using plant as an expression system, recombinant major capsid protein (rMCP) from iridovirus affecting *Neoscorpis lithophilus* was successfully expressed in rice callus. The rMCP was able to provide immune protection from iridovirus [156]. Likewise, nervous necrosis virus (NNV) coat protein was stably transformed into *N. tabacum* chloroplasts [152]. AcrV and VapA antigens from *Aeromonas salmonicida* affecting salmon were stably expressed in chloroplasts of *Chlamydomonas reinhardtii*, showing elevated immune production during infection [165]. White Spot Syndrome Virus (WSSV) affecting crustaceans causes huge economic loss, and the VP28 protein from WSSV was successfully expressed in *Chlamydomonas reinhardtii* and *Dunaliella salina* [166,167]. Successful transient expression of Atlantic cod nervous necrosis virus (ACNNV) VLPs in *N. benthamiana* was demonstrated, and immunization study showed effective defense against virus challenge [168]. Plant-based Virus like particle (VLP) against piscine myocarditis virus (PMCV) causing cardiomyopathy syndrome in wild Atlantic salmon, was transiently expressed in *N. benthamiana*. Limited immune protection was induced by plant derived PMCV VLP vaccine against PMCV infection [163].

To elicit effective immune responses in fish, studies on plant derived vaccines primarily focus on enhancing the quantity and purity of the produced antigens in the expressing plants (Figure 5). For the maximum quantity and quality of antigens, it is crucial to target the most appropriate subcellular compartment in plant cells. While there are many challenges in the way of plant-derived vaccine manufacture and use, the possibility and promise of improved plant-based vaccinations is alluring. In conclusion, plant biotechnology offers a good choice to produce future aquatic vaccines.

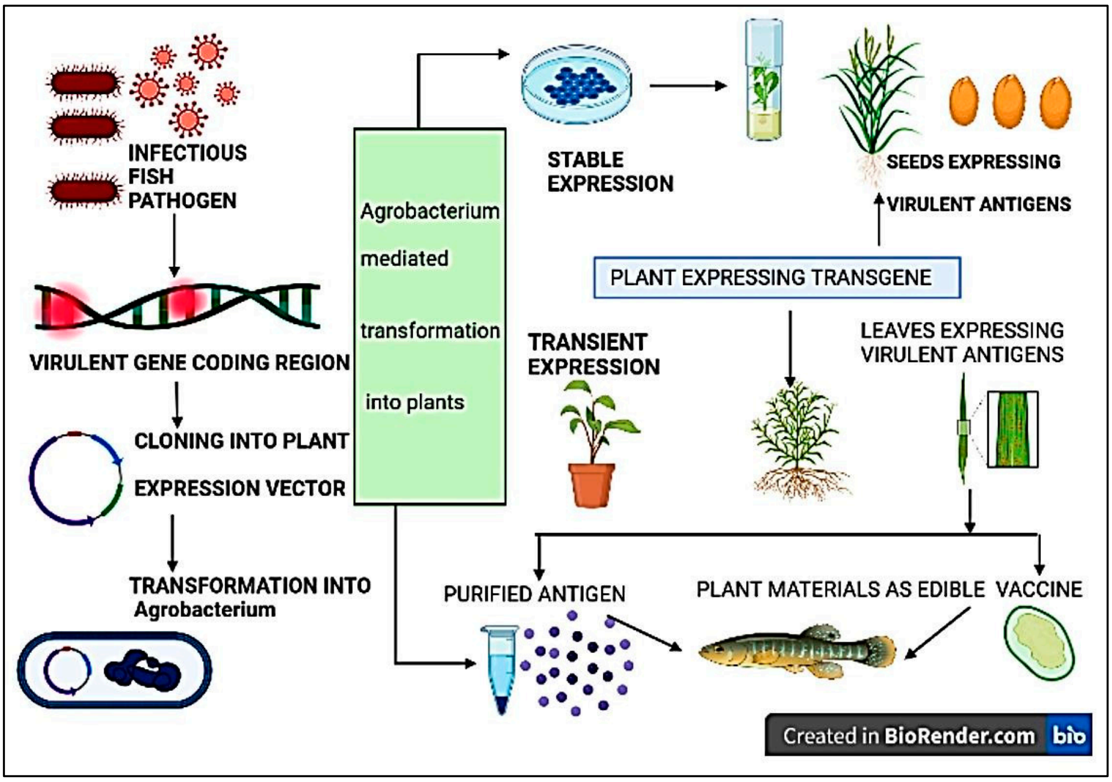

Figure 5. Schematic representation of steps involved in plant-based fish vaccine development.

8. Updates on Strategies to Develop Fish Vaccines

A vaccine should be safe for the fish, and the mode of administration if it is oral mode would be better and provide 100% protection as long as production cycle. The main challenge to produce and

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develop vaccines stay in a sequence of events starting from manufacture to marketing. Another important challenge is to provide a cost-effective vaccine and a readily available one [170]. A major restriction is to commercialize the oral vaccines and preserve the antigens. Licensing of vaccines also is not practically applicable for all fish antigens. Autogenous vaccines can be used as an alternative. Brooker et al. [172] have studied on autogenous vaccine and it was shown to be effective in controlling the A*eromonas salomonicida* when administered via injection in cleaner fish. Adjuvants are limited for mucosal vaccines and adjuvant usage modulates the immunogenicity of an antigen [7]. Vaccines need to be designed according to the type of fish species, production cycle, farming technology, environment etc. Strategies must be developed based on the genomes of a variety of fish, and the epidemiology with multi approach strategies need to be taken care of for better production (Figure 5) [7].

Kole et al. [172] proposed that a trivalent oral vaccine consisting of attenuated viral hemorrhagic septicemia virus (VHSV), *S. parauberis* serotype I and antigens of *M. avidus*, encapsulated in a chitosan-PLGA complex, could be an assuring strategy to prevent the outbreak of diseases in olive flounder. In addition to this, various other vaccination approaches are in their developmental phases such as algal-enclosed oral vaccines, bacterial biofilm-based antigens and exosome-derived vaccines [173–175]. The partial immunization in the fish led to the utilization of epitope-based vaccines, where one could, with the help of bioinformatics, formulate an antigen with multiple epitopes that would be of potential benefit in creating effective vaccines [176]. Orally delivered vaccines have a disadvantage of being disintegrated in the (acidic) gut of fish. As mentioned earlier, these vaccines or recombinant proteins, when encapsulated by a microalgal cell wall, is protected from such harsh environments and is also delivered to the system very easily via cell wall degradation [173].

Control and prevention strategies need to be designed for the appropriate treatment of infectious diseases in fish. One of the strategies for control and prevention of vibriosis in Asian fish culture by Xu et al. [177] has been established. As per their review, even though applicable measures are identified, less numbers of vaccine are available to treat the diseases in fish. General prevention strategies are highlighted in Figure 6. Another major challenge in developing novel techniques is antibiotic resistance by microorganisms in fish.

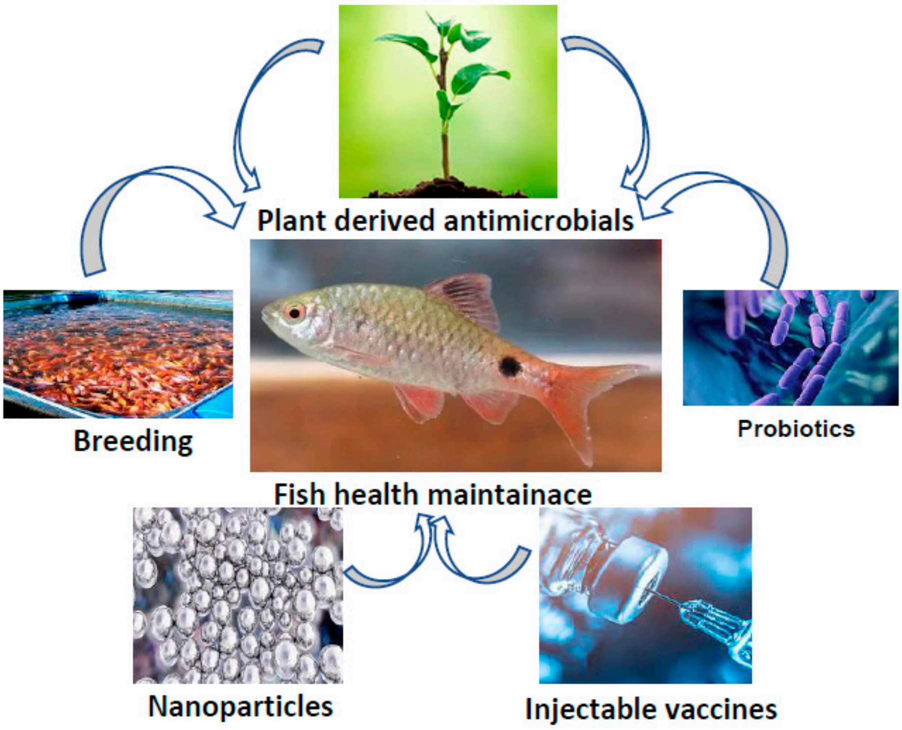

Figure 6. Control and prevention strategies for fish infectious diseases [32,177]. Different approaches such as nano-based drugs/vaccines or injectable vaccines or even probiotics or plant based medicines or edible vaccines are used to fish helath.

The world need of fish is increasing everyday and the estimated demand of fish by 2050 is presented in Table 8. Therefore, the loss due to infectious diseases in fisheries industries must be controlled. Various vaccines which have been proven to have a positive impact on reducing fish mortality were outlined in this review. However, the most effective vaccines are necessary to address the increased demand of fish and fisheries as well as the need for management of large-scale fish farming, which is discussed below.

Table 8. Prediction about fish demand for human consumption in 2050 in top ten countries.

World number	Position	Country	Total consumption (Million tonnes)
1		China	99875
2		India	24601
3		United States	10423
4		Mexico	6061
5		Brazil	5460
6		Nigeria	5359
7		France	3494
8		Spain	2529
9		Peru	23331
10		Ghana	9121

The worldwide capture fisheries production has been recorded throughout various time periods in different nations (Figure 7 and 8) reveals a slight decline in production in 2020 in inland fisheries system. Moreover, concerns about food security and sustainability will increase as the world population approaches 9 billion by 2050 (Table 8) [178]. Therefore, economic expansion, job growth, nutritional profile and gender empowerment are a few of the variables that have contributed to an increase in demand for fish and fisheries. The market expanded approximately 20 folds in 2020, compared to production in 1976. Billions of people depend on fishing and its allied sectors to meet their financial and health needs. Increase in fish consumption is largely driven by technological developments in processing and distribution, which has a direct effect on the increased demands for fish and fish products. Good management practices are crucial to reduce stress and minimize the prevalence of diseases (Figures 5 and 6). Marine ecosystems are constantly bombarded with challenges that pose a serious threat to their sustainability. Several studies assert that climate change is the major player amongst all other factors [179]. Currently, there seem to be no climate-change measures that have been added to the fisheries management policies [180]. A shift in the regulatory guidelines of fisheries has only occurred recently, with governments opting for a more Ecosystem based approach to Fisheries Management (EAF). In simple terms, EAF considers all the species of a particular marine ecosystem, rather than focusing on one single species in isolation. Other components such as climate change, co-interaction with other species and pollution also come into picture (*Understanding Ecosystem-Based Fisheries Management, NOAA)*. Understanding the role of each of these factors helps in maximizing the benefits of fisheries and other marine ecosystems, by avoiding over exploitation of the available resources. It is vital to ensure that fisheries are managed appropriately to attain the goals of food security, employment and nutritional benefits. Apart from EAF, other existing strategies for management of fisheries include Rights-based Management and Management for Resilience [181]. So, fish vaccination is one of the major tools for the management of aquaculture health, hence a need to move away from conventional vaccines and concentrating on novel fish immunization techniques are essential. Vaccine development employing advanced technologies like 'Omics based' [182,183] and nano carriers-based adjuvants [184,185] environmentally friendly vaccines like plant based vaccines [186,187], which are efficient, cost-effective, require small doses, and do not require the use of antibiotics, arises in light of the increasing importance that fish and fisheries are receiving globally in recent years.

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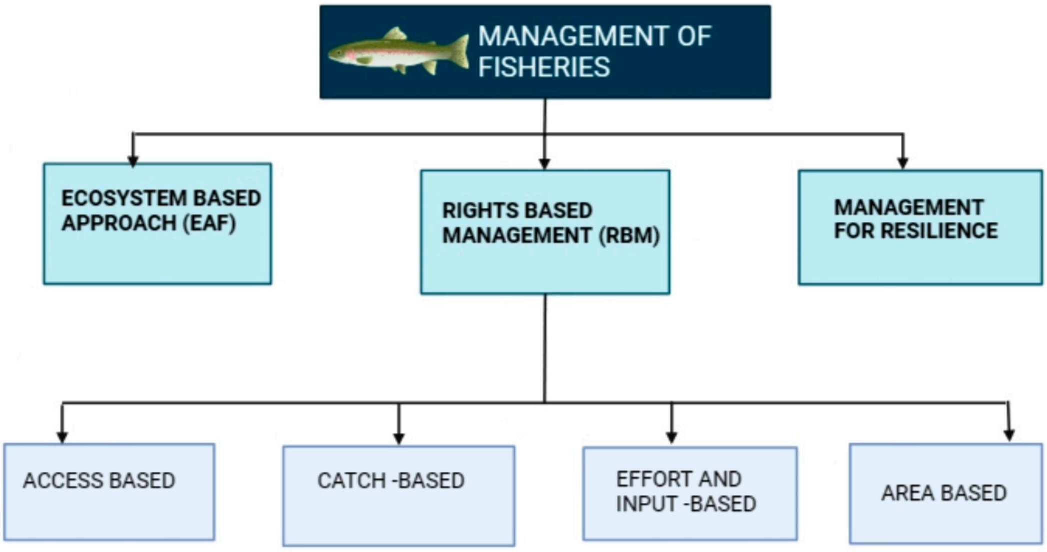

Figure 7. Overview of management of fisheries, modified after Holsman et al. [179].

Figure 8. Five main steps of process of fisheries management.

9. Conclusion

As shown in Table 8 and Figure 6 and 7, the demand for fisheries products is growing faster than expected internationally. With the ever-growing demand of fish food in world markets, their management in aquaculture by preventive measures against contagious diseases is one of the challenging areas. Therefore, modern technology is currently being used in the creation of unique and alternative fish vaccines, for example plant derived vaccines, which are useful to develop immune response beneficial to fish health. The industry requires a reliable aquaculture vaccine for economic success. The inefficient steps of conventional vaccine developing methods require to be modified for fighting against emerging disease concerns. These research protocols for producing fish vaccines that employ newer technologies may be expensive but are essential. It will be crucial to leverage the abundance of biotechnology that is now available to address emerging disease concerns due to the continual demand for novel vaccines induced by the global development of aquaculture. Especially vaccination in in brood stocks is important for fish seed production. The development of fish vaccines is known to use either whole killed pathogens, subunit of a protein, peptide or a recombinant protein, DNA vaccines or live attenuated vaccines via different modes of administration. More research is expected to come up with strategies regrading mode of administration and use of adjuvants.

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