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Fin fish vaccination as prevention in aquaculture: A review

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ABSTRACT

Fisheries and aquaculture are notably known as the most important sources of protein that can provide food for billions of people worldwide. The aquatic farming production keeps expanding gradually in recent years professing that fisheries and aquaculture has become the fastest growing food-producing market. This sector continues to attract great interest from everyone due to its promising contribution in global food security, economic and social development. However, growing high density of marine culture to maximize the production has caused the aquatic animals to be vulnerable to diseases. Various infectious fish diseases have led to high fish mortality that later poses a significant threat to companies' long-term viability and countries' socio-economic development. Therefore, this review discusses fish diseases and the overview of fish vaccines as one of the approaches to ensure a sustainable future for aquaculture.

Keywords: Aquaculture, fish disease, fish vaccination

INTRODUCTION

Global aquaculture is still growing rapidly today as one of the highest protein sources worldwide. Demands of protein for food consumption along with the uprising of world population undoubtedly has driven this trend to keep increasing at an impressive rate. According to data collected by Food and Agriculture Organization (FAO) (2020), consumption of food fish worldwide from 1961 to 2017 has risen at a regular annual rate of 3.1%. Therefore, the global capture fisheries and aquaculture fish production were expected to increase in 2018. The inclination can be seen recently where capture fisheries worldwide have recorded 96.4 million tonnes of production in 2018 contributed mostly by marine capture fisheries. On the other hand, the global aquaculture sector has also produced around 114.5 million tonnes fish in 2018 where finfish, molluscs and crustaceans have dominated (FAO, 2020).

However, it is unfortunate that fisheries and aquaculture catches declined 1% in 2019 before increasing barely 0.2 % in 2020 (FAO, 2022). Lockdowns and movement restrictions during a Covid-19 pandemic in 2020 had severely impacted the fisheries supplies and also aquaculture operations. This trend roughly describes that between fisheries and aquaculture exists economic interactions and dependency to each other at the food market level (Natale *et al.*, 2013). Globally, China is the main fish producer in Asia followed by few countries in Americas, Europe, Africa and Oceania (FAO, 2020). In 2020, despite the 2020 pandemic waves, China continued to be the major supplier as reported by FAO (2022).

Diseases of farmed fish

Aquaculture, a rapidly growing industry, significantly contributes to global economic growth. However, high yields in fish farming come with considerable risks. Outbreaks of infectious fish diseases lead to economic losses and high fish mortality rates in large-scale commercial fish farming. Additionally, cultivating fish in high density has detrimental effects on the environment, causing natural land destruction, loss of amenity value and water pollution (Witus and Vun, 2016; Dadar *et al.*, 2017; Zhang *et al.*, 2022). Furthermore, unsustainable practices implemented in marine culture farms such as poor water treatment systems and unrestricted escape of invasive or non-native fish species may affect the biodiversity and natural balance of ecosystems (Witus and Vun, 2016; Schulz *et al.*, 2020).

FAO (2018) stated irresistible increasing fish production by the intensification of aquaculture along with the adverse effects it poses upon the environment has seriously promoted the development of various infectious fish diseases. Moreover, stressors like poor water quality, poor handling practices and sudden changes in water temperature can also trigger disease infection (Schulz *et al.*, 2020). Reviews demonstrated bacteria are the most common pathogens accounting for nearly 55% of disease outbreaks in fish cultures, in addition to the fact that 10% of all marine culture animals likely die from infection almost every year (FAO, 2020; Zhang *et al.*, 2022). This scenario possibly shows that the costliest epidemics are those affecting marketable species.

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Table 1: Overview of fish diseases causing economic impact in fin fish aquaculture.

Diseases	Pathogen	Susceptible fish host	Reported by
Nervous necrosis virus disease	Nodavirus	*Epinephelus* sp., *Dicentrarchus labrax*, *Anguilla anguilla*, *Clarias fuscus*	Yong *et al.* (2017)
Viral hemorrhagic septicemia	Viral Hemorrhagic Septicemia Virus	*Oncorhynchus mykiss*, *Scophthalmus maximus*, *Paralichthys olivaceus*	Baillon *et al.* (2020)
Red sea bream iridovirus disease	Red Sea Bream Iridovirus	*Oplegnathus fasciatus*, *Dicentrarchus labrax*, *Scomber scombrus*, *Epinephelus* sp.	Novitasari *et al.* (2019); Kurniasih *et al.* (2019)
Infectious salmon anemia (ISA)	Virulent HPR-deleted strains of ISA virus	*Salmo salar*	Qviller *et al.* (2020)
Koi sleepy disease	Carp Edema Virus, Flavobacteria	*Cyprinus carpio*	Adamek *et al.* (2018); Kushala *et al.* (2022)
Rainbow trout fry syndrome	*Flavobacterium psychrophilum*	Salmonids	Hoare *et al.* (2017)
Vibriosis	*Vibrio harveyi*, *V. alginolyticus*, *V. corchariae*, *V. parahaemolyticus*, *V. angullarum*	*Epinephelus coioides*, *Mycteroperca tigris*, *Larimichthys crocea*, *Scophthalmus maximus*	Ilmiah *et al.* (2013); Xu *et al.* (2019); Deng *et al.* (2020); Mohamad *et al.* (2021)
Pseudomonadosis	*Pseudomonas* spp.	Salmonids	Schulz *et al.* (2020)
Francisellosis	*Francisella noatunensis*	*Oreochromis niloticus*	Fernandez-Alarcon *et al.* (2019)
Streptococcosis	*Streptococcis iniae*, *S. parauberis*, *S. agalactiae*, *S. dysgalacties*	*Oreochromis* sp., *Oncorhynchus mykiss*, *Dicentrarchus labrax*, *Lutjanidae* sp.	Mishra *et al.* (2018); Mohamad *et al.* (2021)
Mycobacteriosis	*Mycobacterium* spp.	*Danio rerio*	Martínez-Lara *et al.* (2020)

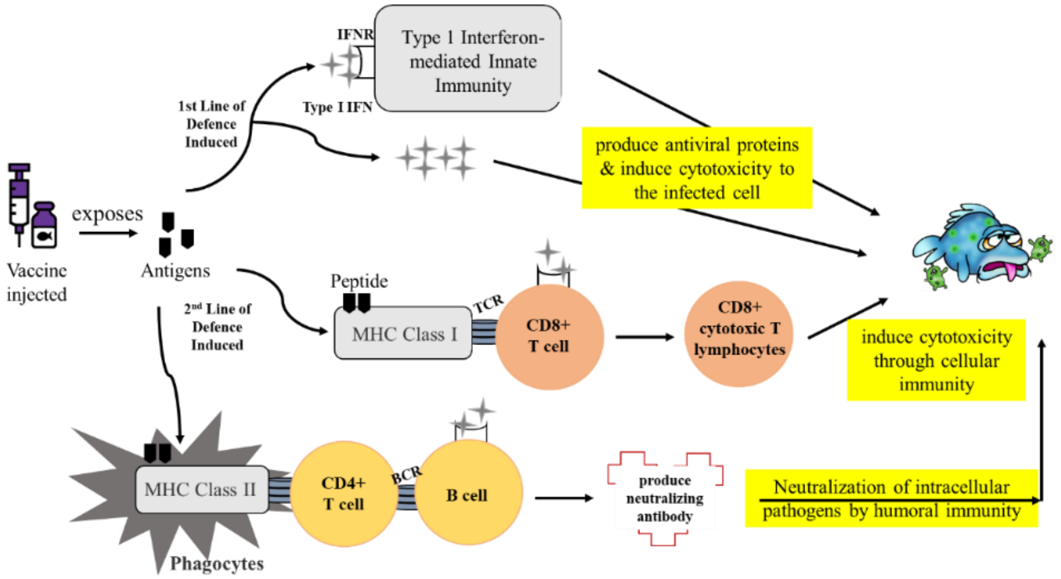
From a different angle, aquatic infectious diseases may create social implications too such as hampering public safety and intimidating human health as well as impacting food security (Groner *et al.*, 2016; Lafferty and Hofmann, 2016; Ziarati *et al.*, 2022). This is because humans may acquire infections through consuming seafood in a matter of expanding human reliance on resources obtained from the ocean. For instance, the pathogenic transmission of *Vibrio parahaemolyticus* and *V. vulnificus* through ingestion of marine organisms can cause human gastrointestinal ailment, septicaemia and in worst cases, death (Groner *et al.*, 2016). Besides, there is the possibility of diseases spreading as aquaculture products are transported around the world and this might lead to the accidental release into the environment (Lafferty and Hofmann, 2016). In short, such infectious diseases might cost billions of dollars to the global economy.

Some of the examples of fish diseases reported in aquaculture that probably leads to huge economic losses are summarized and listed in Table 1.

Fish immune responses

Generally, the piscine immune system is composed of two main components named, the innate immune responses and the adaptive immune responses (Thompson, 2017; Ashfaq *et al.*, 2019; Smith *et al.*, 2019). Substances like antitoxins, agglutinins and lysins were known in the 1920s and 1930s to be involved in mammals' defence mechanisms together with phagocytes. Yet, there was limited scientific explanation behind this humoral immunity working (Van Muiswinkel, 2008). The difference can be seen in this day and age, where research on fish immune systems constantly increases as the science field to be explored is getting wider.

As stated by Thompson (2017), Smith *et al.* (2019) and Kushala *et al.* (2022), the innate immune system is the first line of defences to recognize and respond immediately to invading bacteria, virus or other microorganisms, but this system does not offer long-lasting or specific immunity and also does not keep the memory of previous responses.



IFN: Interferon, IFNR: Interferon receptor, MHC: major histocompatibility complex, TCR: T-cell Receptor, BCR: B-cell Receptor

Figure 1: Overview of the innate and adaptive immune mechanisms of fish induced by vaccination to eliminate the invaded pathogens. Adapted from Aoki *et al.* (2015).

Physical barriers such as skin, gills and gut are examples of the front line in fish body defense mechanisms (Smith *et al.*, 2019). Thompson added that the next step is when the exterior barriers of the fish are finally encountered and breached by harmful microorganisms, then cellular and humoral components of the innate immune system will be activated (Smith *et al.*, 2019).

All of these interconnecting networks (as simplified in Figure 1) not only will help in terminating pathogens and controlling infections but also can stimulate the subsequent second defences line when infections are out of control (Thompson, 2017; Ashfaq *et al.*, 2019; Tian *et al.*, 2022). Unlike the innate immune system, Smith *et al.* (2019) and Thompson mentioned that the adaptive immune response is specific and can retain memory of the former pathogens invasion making it capable of quickly eliminating pathogens upon reencountering.

Current aquaculture has offered various approaches to strengthen the fish immune system and the disease resistance of fish. Vaccines, for instance, are immunostimulants that are able to trigger the fish's immune responses via inducing or increasing fish defenses mechanisms (Thompson, 2017; Adams, 2019). Moreover, immunization or vaccination has been implemented as a crucial disease management plan as stated by Nayak and Nakanishi (2016). So, more studies and knowledge in regard to fish body responses are needed to aid in the optimization of fish protection against harmful pathogens or infectious diseases. It also shows how imperative the adaptive immune system of fish is to be explored for potential vaccine development.

Types of fish vaccines

Mohamad *et al.* (2021) affirmed that the development of aquaculture vaccines must be safe for both fish farmed and consumers. Besides, it is economical, convenient and efficient in the long term. So, from the economic and ethical grounds perspective, vaccination is seen as the most applicable and relevant choice for controlling diseases due to its environmentally friendly approach compared to another method like antibiotics (Thompson, 2017; Adams, 2019). According to Thompson, vaccines are defined as non-pathogenic preparations of the causative agent of a particular disease that acts as an antigen, capable to induce the host's adaptive immune system as well make it able to recognize and kill the invader when it encounters it later.

Thompson (2017) added there are a vast number of vaccine types that have been studied for use in aquaculture. For instance, inactivated whole-cell bacterial products are the most common vaccines used for aquaculture, created from a virulent pathogen causing infections through physical (heat), chemical (formalin or chloroform) or radiation (mutagenesis) processes that made the pathogenic microbes unable to invade or replicate in or outside of a host (Thompson, 2017; Ma *et al.*, 2019; Mohd-Aris *et al.*, 2019). Some of the examples of inactivated whole-cell vaccines studied are formalin-killed *Vibrio harveyi* against vibriosis in torbut and *Aeromonas hydrophila* against bacteriosis in pacu, respectively (Xu *et al.*, 2019; Vaz Farias *et al.*, 2020). Both these studies show a promising result where both vaccines induce effective immunoprotection by enhancing not only the innate immune response but also the adaptive immune system.

Live-attenuated vaccine such as *Flavobacterium* B.17-ILM that has been tested in rainbow trout is another type of vaccine that carries a native antigenic form that are usually expressed by microbes *in vivo*. It can mimic real infections promoting the induction of natural body defences responses similar to those in natural exposure and normal infection. Hence, it starts to gain attention from scientists due to the presence of virulent factors on the surface, easy to culture and the production cost is cheaper (Ma *et al.*, 2019; Mohd-Aris *et al.*, 2019).

Ma *et al.* (2019) has mentioned that deoxyribonucleic acid (DNA)-based vaccines can also be developed rapidly and somewhat straightforwardly if the protective antigen is already known. DNA vaccine refers to the incorporation of an expression plasmid containing a specific gene encoding a selected antigen, which later is thought to evoke strong antibodies (cellular and humoral immunity) when expressed in the host cells (Aoki *et al.*, 2015; Ma *et al.*, 2019). Forkhead-associated (FHA) domain-containing protein or termed as pcDNA-FHA was examined against fish nocardiosis in hybrid snakehead in a study done by Chen *et al.* (2019).

Based on Wang *et al.* (2016) and Ma *et al.* (2019) studies, there is also a recombinant protein subunit vaccine made up of at least one type of microbial component that is able to be created in heterologous expression systems. In other words, this subunit vaccine uses only antigenic constituents or fragments that present no risk of pathogenicity to the targeted or non-targeted host. These subunit vaccines have several desirable qualities such as safety, can be freeze dried and allow the integration of unnatural elements, however, in many cases, it poses weaker stimulation of potent immune response than inactivated or live-attenuated pathogens. Thus, it sometimes required additional adjuvants (Ma *et al.*, 2019). A study done by Sun *et al.* (2020) has constructed a recombinant subunit vaccine based on the *Vibrio harveyi* antigen TssJ resulting that rTssJ can actually act as an immune protector that is able to confer different immune responses.

Recent advancements in immunoinformatics have opened up new approaches for combating infectious diseases in aquaculture. It started in late 2020 during Covid-19 pandemic where a messenger ribonucleic acid (mRNA) vaccine, Tozinameran INN, has received primary approval from the United Kingdom for SARS-CoV-2 infection prevention (Aida *et al.*, 2021). This indicates the beginning of novel and third generation vaccines, in other words, gene-based technology to be licensed and endorsed for a disease-causing agent. RNA-based vaccines are similar to DNA-based vaccines where both are non-infectious, thus safe to be used (Kembou-Ringert *et al.*, 2023). This type of vaccine has also shown outstanding results in case of coronaviruses proving it to be a potent immunostimulatory. Basically, RNA replicon vaccines utilize an mRNA molecule containing the desired antigens enclosed within a vesicle carrier. The RNA will be translated promptly when it reaches the host's cell and subsequently expresses the target antigen (Aida *et al.*, 2021; Kembou-Ringert *et al.*, 2023). According to Kembou-Ringert *et al.* (2023), it is challenging to develop mRNA vaccines as naked mRNA is susceptible to degradation by nucleases. Besides, the size of mRNA is too large and highly negatively charged, making it incapable of passively entering the cell membrane. Consequently, it reduces the rate of cellular uptake since repulsion with anionic cell membrane may occur too.

In short, fish vaccines presently have been available for a variety of species, even some of them are commercially accessible and have been marketed globally (Brudeseth *et al.*, 2013; Adams, 2019). Several of the commercially available vaccines that recently can be accessed globally are listed in Table 2 below.

Delivery of fish vaccines

According to Thompson (2017), immunization administered by injection is the typical approach chosen, with the help of automated vaccination machines to inject mass fish. Besides, vaccination through immersion is usually applied on smaller fish while some oral immunization is also presently commercially available but are limited due to several challenges, for instance the possibility of denaturation in the gut (Munang'andu *et al.*, 2015; Thompson, 2017; Adams, 2019). Afterwards, Adams mentioned that existing immunization methods of delivery and strategies may have not been at optimized efficacy though some novel vaccines show significant protection.

As stated by Plant and LaPatra (2011) and Dalmo *et al.* (2016), immersion is the simplest method to apply as it can be done using a spray, direct immersion (DI) or hyperosmotic infiltration (HI). Nevertheless, this method may only be applicable and effective for certain antigens or farming situations. In addition, oral vaccination is seen as the most practicable, realistic and versatile approach because vaccines can be administered together with feed to large quantities of fish at one time without risking them to stress as the oral vaccine is generally created by top coating the fish feed with antigen or mixing the antigen into the feed (Plant and LaPatra, 2011; Dalmo *et al.*, 2016; Gonçalves *et al.*, 2022).

Besides, injection vaccines are usually multivalent, incorporating different bacterins or a combination of bacterins and killed virus or viral proteins which are reliably administered in small, known quantities of antigen directly to the fish. This method has the advantage of improving vaccine immunogenicity by adding an adjuvant, however, the injecting process is laborious and costly, also anesthetizing may impose stress on the fish and may visibly cause injuries on the injection sites. If manually shot, the fish first needs to be anesthetized and injection is typically accomplished using air-powered syringes through intraperitoneal (IP) injection or intramuscular (IM) injection. Currently, machines have been introduced to vaccinate vast amounts of fish per hour but need the fish size to be similar and larger than for manual vaccination

Table 2: Example of commercially available vaccines for the immunization of fin fishes.

Disease	Pathogen	Common fish host	Vaccine type	Brand/Manufacturer	Produced by
Infectious Hematopoietic Necrosis (IHN)	IHN virus *Rhabdovirus*	Salmonids	DNA	APEX-IHN	Fisheries and Oceans Canada (2007)
Infectious Spleen and Kidney Necrosis (ISKN)	ISKN virus *Iridovirus*	*Lates calcarifer*, *Epinephelus* sp., *Seriola quinqueradiata*	Inactivated ISKN virus	AQUAVAC IRIDOV	MSD Animal Health (2023)
Enteric Red Mouth Disease	*Yersinia ruckeri* serotype O1b	*Salmo salar*	Inactivated	Alpha ERM Salar	Pharmaq (n.d.); Gudding and Goodrich (2014)
Furunculosis, Vibriosis, Coldwater vibriosis, Winter sore, Infectious Pancreatic Necrosis (IPN)	*Aeromonas salmonicida*, *Vibrio salmonicida*, *Listonella anguillarum* serotype O1 and O2a, *Moritella viscosa*, IPN virus	*Salmo salar*	Inactivated	ALPHA JECT micro 6, Norvax® Minova 6	Pharmaq (n.d.)
Flavobacteriosis	*Flavobacterium psychrophilum*	*Salmo salar*	Inactivated	ALPHA JECT® IPNV-Flavo 0,025	Pharmaq (n.d.)
Steptococcosis	*Streptococcus agalactiae*	*Oreochromis niloticus*	Inactivated	ALPHA JECT® micro 1 Tila	Pharmaq (n.d.)
Furunculosis, Vibriosis	*Aeromonas salmonicida*, *Listonella anguillarum* serotype O1 and O2a	*Salmo salar*	Inactivated	ALPHA JECT® 3000	Pharmaq (n.d.)
Vibriosis	*Listonella anguillarum* serotype O1	*Dicentrarchus labrax*	Inactivated	ALPHA DIP® Vib	Pharmaq (n.d.)
Vibriosis	*Vibrio anguillarum*, *V. ordalii*	*Oncorhynchus mykiss*, *Dicentrarchus labrax*	Inactivated	AQUAVAC® Vibrio	MSD Animal Health (2023)

(Plant and LaPatra, 2011; Evensen and Leong, 2013; Munang'andu *et al.*, 2015; Mutoloki *et al.*, 2015).

Biosafety and biosecurity measures and its implementation in Australia as an example

Implementation of biosafety and biosecurity measures is crucial when testing and deploying fin fish vaccines to ensure the protection of marine ecosystems. Biosafety and biosecurity in the context of fish vaccination refer to the set of practices, protocols and measures designed to secure the safety of handling, testing, deployment and disposal of fish vaccines while mitigating the risk of introduction or spread of diseases and pathogens to aquatic environment, human health and the surrounding ecosystem (National Academy of Sciences, 2015; Assefa and Abunna, 2018; World Organisation for Animal Health, 2019).

Australia, for instance, has enacted regulations on biosecurity practices in aquaculture, emphasizing the need for disease prevention and control, including those associated with vaccine testing and deployment (Barnes *et al.*, 2021). Their development and authorization of animal vaccines' laws aimed to license immunological veterinary medicinal products that are proven for their purity, safety, potency and effectiveness (Adam, 2014). Australian Pesticides and Veterinary Medicines Authority (APVMA) is Australia's national regulator for agricultural and veterinary chemicals that acts following what has been written in the Agricultural and Veterinary

Chemicals (Administration) Act 1992 and the Agricultural and Veterinary Chemicals Code Act 1994. APVMA cooperated with the Department of Agriculture, Fisheries and Forestry (DAFF) and other partner agencies as well as governments' in improvising the detection, surveillance and response to potential biosecurity issues (APVMA, 2023).

Tasmania is known as Australia's largest aquaculture industry and the salmonid marine culture was a pioneer in adopting vaccination and was the first in vaccine deployment against vibriosis in 1988. Currently, they have five registered and three permitted vaccines locally produced for salmonids where these micro-producers are supported by native production of auto vaccines deployed under low usage licenses with veterinary stewardship (Barnes *et al.*, 2021). According to APVMA (2021), there are no antibiotics officially approved for use in Australian marine culture, yet in certain state jurisdictions, registered veterinarians have the authority to prescribe off-label antibiotics and for this purpose, APVMA will give occasional issues of minor usage. Adam *et al.* (2019) stated that many countries have been using commercially licensed and registered vaccines for their farmed fish, nonetheless, commercial vaccines are costly and take a longer time to develop. Besides, it is impractical to establish authorized vaccines against all fish pathogens as there is a wide range of fish species being cultured that are vulnerable to several diseases.

Due to a lack of locally produced fish vaccines, Australia's national regulator has allowed fish farmers to import veterinary vaccines to help them tackle infectious disease outbreaks. Despite that, importers must first apply for an import permit to bring animal vaccines into Australia that is issued by DAFF (DAFF, 2023). However, a comprehensive assessment of the efficacies of those vaccines against the diversity of native prevalent strains in the field is still scarcely recorded. Barnes *et al.* (2021) explained there was a case that happened in Australia where fish were administered with a commercial vaccine, unfortunately causing vaccine failure in streptococcosis outbreaks caused by *Streptococcus iniae* due to serological diversity between vaccine and local strains. This evidence highlights the significance of incorporating the right antigens and protecting commercial vaccines in field application.

Moving forward to enhance existing capacities in safeguarding fish sector from new emerging diseases risk, Australia established the Australian Aquatic Animal Health and Vaccine Centre in 2014, based at the Fish Health Unit in Launceston. The purpose of this centre is so that researchers can test organisms and do a lot of tank trials safely under biosecure conditions ensuring vaccine efficacies for native environments and diseases (FRDC, 2014; Huon Aquaculture, 2020).

Australia's national regulator requires vaccine owners to provide clear data justifying efficacy claims, including specific antibodies related to the vaccine component(s) in immunized animals. Supportive findings from challenge trials are necessary, along with demonstrating the presence of specific antibodies and the duration of protection. These guidelines ensure product quality and safety for humans, animals, and the environment, aligning with Australian laws and regulations. (APVMA, 2020; Holdsworth and Fisher, 2022; APVMA, 2023).

Manufacturing and deploying fish vaccines involve complex and risky biosafety and biosecurity measures due to biological and physical variability challenges. Even subtle changes in the manufacturing process can affect the final product's purity, safety or efficacy. To authorize a new process, a clinical study may be necessary, which slows down the production and contributes to its low success despite high global demand for vaccines (Plotkin *et al.*, 2017). Therefore, Adams (2019) suggested that autogenous vaccines can be another applicable option. An autogenous vaccine, also known as a custom vaccine, is created from microorganisms isolated from animals assumed to cause diseases on a specific farm. The veterinarian identifies these causative agents. APVMA provides regulatory and production guidelines for local autogenous vaccine permits, offering a cost-effective and swift minor use permit process. These vaccines, developed from site-specific pathogens, offer flexibility in production regulation and are implemented within a cooperative veterinary-client-patient relationship (Ma *et al.*, 2019; APVMA, 2021). As stated by APVMA (2020), autogenous vaccines are typically omitted from biosecurity guidelines since they are generally not registered, but the agency will issue several permits for their production, distribution and utilization.

At present, agencies and regulators globally are gradually using new approach methodologies (NAMs) which are new modern and innovative scientific approaches such as *in vitro* testing and *in silico* modelling software. NAMs has been prioritized for regulatory decision making because of their ability to reliably, accurately and efficiently generate information which are seen as a more ethical way and faster in doing safety assessment and testing in fields while it also able to minimise or substitute the reliance on conventional animal testing methods (Stucki *et al.*, 2022; APVMA, 2023). Hence the APVMA is collaborating with industry and other regulatory bodies to maximize the implementation of NAMs as well to achieve a sustainable aquaculture (APVMA, 2023).

CONCLUSION

Infectious diseases caused by various pathogenic microbes are pervasive in fish farms affecting many aspects including social, cultural, and especially economic. The impacts can sometimes be unbearable as it brings huge losses to the respective countries. Therefore, it is imperative for us to study more and understand the possible consequences of high-density marine cultures so that diagnosis can be done effectively, and relevant approaches can be quickly implemented to manage aquaculture-associated diseases. Fish vaccine and vaccination are proven to be realistic and applicable for a sustainable marine culture industry. Nonetheless, further studies on searching for protective antigens, adjuvants that can maximize immunogenicity as well as proper route chosen for immunization are essential and required to optimize immune responses. The combination of all scientific knowledge and information gathered together with the current vaccine technology and delivery system available can also be utilized in developing successful vaccines. Besides, most of the commercialized vaccines used in aquaculture today tend to be specific towards one pathogen and only very few polyvalent vaccines are produced. This suggests us to find another alternative strategy contributing to immune advancement so that fish vaccines are still relevant when someday fishes are expected to be immunocompromised.

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