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Understanding Fish Immunity and Innovative Vaccination Approaches in Aquaculture

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Fish possess a unique immune system that, while somewhat similar to mammals, exhibits distinct characteristics. This review paper explains the complexities of fish immunity, highlighting the innate and adaptive immune responses that protect against various pathogens, including bacteria

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(*Aeromonas* spp, *Flavobacterium columnare*, *Mycobacterium marinum*, *Streptococcus iniae*, *Edwardsiella tarda*, *Pseudomonas aeruginosa* etc), viruses (*Infectious Hematopoietic Necrosis Virus* (IHNV), *Viral Hemorrhagic Septicemia Virus* (VHSV) etc.), fungi and parasites (*Dioctophyma renale* etc). Host-pathogen interactions are dynamic and critical for understanding the immune evasion strategies employed by pathogens, such as antigenic variation, molecular mimicry and biofilm formation. Vaccination is crucial in aquaculture, enhancing fish immunity against diseases through various vaccines, including inactivated, live, subunit, and nucleic acid vaccines. Various delivery methods are employed to maximize immunogenic responses, such as injection, immersion, and oral administration. Additionally, advancements in science and technology have led to innovative techniques to increase vaccine efficacy, including nanoparticle delivery and microencapsulation. Successful vaccination strategies have been adapted to combat significant fish pathogens, demonstrating the potential for enhancing disease resistance in aquaculture. This comprehensive overview underscores the importance of understanding fish immune systems and developing effective vaccination strategies to ensure fish health and sustainability in aquaculture practices.

Keywords: Immune system; vaccination; disease; pathogen; aquaculture.

1. INTRODUCTION

Fish are cold-blooded animals that appeared during the Devonian period. They are the most diverse vertebrates and have organs for immunity similar to those in the mammalian immune system. The immune system is a network within an organism that detects various agents, from viruses to parasitic worms, protects against diseases, and differentiates between harmful and non-harmful agents. The study of immunology in aquatic organisms began with Metchnikoff in 1893, who observed the wounded larvae of starfish and later explored the cellular basis of the interaction between host and pathogen (Coates et al., 2022). Organisms have outer and inner epithelial surfaces that help defend against microorganisms and contain lectins, complement proteins, lysozyme, and antimicrobial peptides (Quyoom and Iqbal 2023). Fish immune systems represent important comparative outgroups for understanding the evolution of the immune system (Lieschke and Trede 2009). Most secondary lymphoid organs in fish are similar to those in mammals; however, differences in lymphatic nodules and bone marrow organs contribute to a less robust adaptive immune response (Mokhtar et al., 2023). The immune system of fish contains both innate and adaptive immunity. Innate immunity acts as the primary defence line against pathogens and is non-specific, whereas adaptive immunity is specific and targets particular pathogens. Physical parameters, humoral parameters, and cellular factors are the three components of the innate immune system. The fish kidney contains two parts: the anterior kidney, also called the head kidney, which is aglomerular and contains B lymphoid cells, and the posterior kidney. Antigen-presenting cells (APCs), such as macrophages or monocytes, are crucial for distinguishing between self and nonself-cells and inhibiting foreign agents accordingly (Rauta et al., 2012).

Various types of pathogens affect the health and growth of fish. These pathogens include bacteria (*Aeromonas* spp., *Vibrio* spp., *Flavobacterium* spp., *Yersinia ruckeri*), viruses (*Infectious Pancreatic Necrosis Virus* [IPNV], *Spring Viremia* of Carp Virus [SVCV], *Koi Herpesvirus* [KHV], Channel Catfish Virus [CCV]), fungi (*Branchiomyces* spp (Iqbal (n.d.); Mushtaq (n.d.), *Saprolegnia* spp.), and parasites (*Ichthyophthirius multifiliis*, *Dactylogyrus* spp., *Gyrodactylus* spp., *Trichodina* spp.) (Mondal and Thomas 2022 Iqbal, 2023). Bacterial pathogens have developed various mechanisms to evade or neutralize host defences, thereby ensuring their survival within a host (Celli and Finlay 2022). These strategies include biofilm formation, surface modulation, cytokine inhibition, blockade of acquired immunity, and the utilization of specific virulence factors such as type III secretion systems and pore-forming toxins. Biofilm formation enables bacteria to create a protective matrix that shields them from immune cells and antibiotics, enhancing their resistance (Finlay and McFadden 2006).

There is a dynamic interaction between the host immune system and pathogens, making it essential to understand the relationship between host and pathogen to study the effects of pathogens on the host. Host-parasite interactions are intricate and influenced by various factors

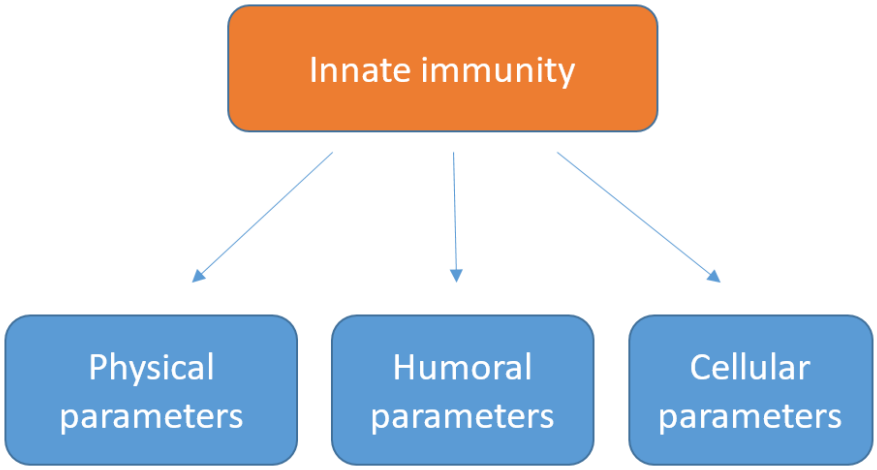

Fig. 1. Components of Innate immune system in fish

that can alter the dynamics in either direction. The age, behaviour, immunological condition, and environmental changes affecting the host can impact the relationship in a way that may benefit the host. Conversely, when a parasite successfully evades the host's immune response, it gains an advantage. Pathogens can enter the fish through various routes, such as the skin, gills, and alimentary canal, and can invade the immune system. Fish immune systems recognize pathogens using pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs). This recognition triggers an innate immune response that involves physical barriers (skin, mucous membranes) and antimicrobial substances (peptides, lysozymes, complement proteins). Immune cells then engulf foreign agents. However, pathogens have adopted various strategies to evade the immune response, such as biofilm formation and manipulation of host cells (Khan, 2012).

2. IMMUNE EVASION MECHANISMS OF BACTERIA

Antigenic variation in bacteria: Antigenic variation is a common strategy employed by bacterial pathogens to evade immune responses. By changing the antigens on their surface, bacteria can avoid recognition by the immune system and establish chronic infections (Palmer et al., 2016). This can be achieved through various mechanisms, such as having multiple copies of a molecule with independent on/off switches, expressing different genes from a pool of silent copies, or constantly changing a highly variable region in a molecule.

Molecular mimicry: Bacteria can hide themselves by expressing host-like molecules on their surface, leading to reduced recognition by the immune system. By molecular mimicry, bacteria can prevent detection by antibodies and other molecules of the innate and adaptive immune systems that have evolved to recognize foreign invaders. In some cases, it may trigger autoimmune or inflammatory responses by cross-reacting with self-antigens over time. Bacteria that employ molecular mimicry include *Streptococcus pyogenes*, *Salmonella, Helicobacter pylori* and *Mycobacterium tuberculosis* (Moran et al., 1996).

Biofilm formation: Biofilms are complex communities of bacteria encased in a slimy extracellular matrix, protecting the host immune system Within biofilms, bacteria exhibit increased resistance to antibiotics and immune cells. Mature biofilms are highly resistant to phagocytosis. Detached biofilm fragments can spread infection by evading immune clearance (Johnson, 2008).

Bacterial surface modulators: Pathogens can alter their surface structures, such as expressing a carbohydrate capsule or modifying lipid A, to hide from immune surveillance systems and avoid recognition by Toll-Like Receptors (TLRs). This allows them to evade immune recognition and phagocytic killing. Examples of bacterial surface modulators that play a role in immune evasion are Capsular polysaccharides, LPS, Protein A, Pili/fimbriae, O-antigen capsule, Teichoic acid, etc (Kaparakis-Liaskos and Ferrero 2015).

Inhibition of phagocytosis: Phagocytosis is a crucial immune mechanism where specialized cells engulf and digest bacteria. Some bacteria have developed mechanisms to evade phagocytosis. For instance, Staphylococcus aureus produces proteins that interfere with the opsonization process, where antibodies or complement proteins coat bacteria to enhance their recognition by phagocytes. By inhibiting opsonization, S. aureus can avoid detection and destruction by immune cells.

Manipulation of host signalling pathways: Bacteria can interfere with host signalling pathways to subvert the immune response. Some bacteria produce effector proteins that manipulate host cell signalling, inhibiting the production of antimicrobial peptides and interfering with cytokine signalling (Bhavsar et al., 2007). Bacteria can create a favourable environment for their survival and replication by disrupting these essential communication pathways.

Inhibition of complement system: The complement system is a part of the innate immune response that helps clear pathogens. Bacteria like *Streptococcus pneumoniae* produce proteins that interfere with complement activation, preventing opsonization and subsequent phagocytosis (Blom et al., 2009).

Intracellular survival: Many bacteria, such as Mycobacterium tuberculosis, have evolved to survive and replicate within host cells, particularly macrophages, shielding them from extracellular immune attacks like antibodies and complement proteins.

Modulation of host cell death: Bacteria can induce or inhibit apoptosis in host cells to their advantage. Inducing apoptosis in immune cells can eliminate key effector cells, while inhibiting apoptosis in infected cells can prolong the survival of a niche for bacterial replication (Gao and Kwaik 2000).

Secretion systems: Bacterial secretion systems, such as the Type III secretion system (T3SS), directly inject effector proteins into host cells. These proteins can manipulate host cell functions, helping bacteria evade detection and destruction.

Blockade of acquired immunity: Bacterial pathogens can interfere with the activation and function of B and T cells, key players in adaptive immunity. This can be achieved through various mechanisms, such as disrupting antigen presentation or inhibiting the activation of immune cells (Zhou et al., 2021).

Resistance to antimicrobial peptides: Bacteria have developed resistance mechanisms to antimicrobial peptides, an important part of the innate immune defence. Alterations in membrane composition or secretion of proteases that degrade these peptides help bacteria resist this line of defence (Joo et al., 2016).

3. VACCINATION IN AQUACULTURE

Diseases significantly impact the aquaculture industry, affecting socio-economic conditions in many Asian fish-producing countries (Ranjan et al., 2024). A vaccine is a biologically derived preparation designed to enhance immunity against a specific disease or a group of diseases. Vaccines work as biological agents to activate the body's defences against a particular antigen that is obtained from disease-causing infectious organisms (Czochor and Turchick 2014). Common fish vaccination either produces or contains an antigen-binding material. This binding materials triggers the fish immune system and response against a particular disease (Ma et al., 2020).

3.1 Types of Vaccines

A. Inactivated or killed vaccines

Vaccines that are inactivated or destroyed are typically created from major disease-causing microbes that are physically, chemically, or radiation-treated to make them non-infectious and incapable of replicating within or outside a host. These alterations are made without affecting the microbial agent's antigenic qualities (Tlaxca et al., 2015).

B. Live or attenuated vaccines

Live vaccinations are produced using one or more bacteria or viruses that inherently possess low virulence or are attenuated to be less harmful to the desired fish species. Disease-causing agents can be altered or made less potent by employing chemical or physical interventions, repetitive passage in cell cultures, typical conditions during culture, or genetic engineering (Desmettre and Martinod 1997). Live vaccines generally exhibit higher immunogenicity than inactivated preparations, as they can replicate or enter the host, leading to more robust cellular responses associated with innate and adaptive immunity (Levine and Sztein 2004). Strong

antibody responses are produced by these cell-mediated immune responses, which closely resemble a pathogen's natural infection (Collins, 1974). This provides a significant advantage for species in agriculture and aquaculture (Shoemaker et al., 2009).

C. Subunit vaccine

Subunit vaccines use purified fragments from microorganisms that are inherently immunogenic, enabling them to elicit immune responses in hosts when administered (Ma et al., 2020). As subunit vaccines cannot multiply within the host, there is no chance of infection to either the host or non-target species. Instead, they are made completely of antigenic compounds (Dungu, 2011). These vaccines can be produced under strictly regulated circumstances and freeze-dried for convenient handling, storage, and transportation without refrigeration. In addition, they effectively target immune reactions on specific microbiological factors (Hansson et al., 2000).

D. Nucleic acid vaccines

DNA or RNA encoding the target antigen(s) makes up nucleic acid vaccinations. Since they cannot convert to a pathogenic state, they are thought to be quite easy to manufacture and safe to employ (Ulmer et al., 2012). DNA vaccines insert genetic material into the host that encodes certain pathogen antigens. This genetic material can induce protection by establishing an effective immune response in the host's cells and promoting the generation of the appropriate targeted antigens. DNA-based vaccines comprise an expression plasmid with a particular genome that codes for a particular antigen protein. A strong immunological response is anticipated when the host expresses this protein. Plasmid production is enhanced in bacterial cells, where the target gene is surrounded by components that facilitate and control its expression in eukaryotic cells (Kurath, 2008). DNA vaccines can effectively stimulate both humoral and cellular immunity. DNA vaccines can be developed more quickly and easily once a protective antigen has been found because they use molecular mechanisms similar to those employed by viruses to penetrate host cells (Reyes-Sandoval and Ertl 2001). These vaccinations have shown to be especially efficient against fish rhabdoviruses and are often more successful in avoiding viral infections (Hølvold et al., 2014).

The RNA vaccine has the necessary molecular building blocks for a messenger RNA molecule, allowing translational expression in the cell's ribosome. These elements include the targeted antigen's open reading frame (ORF), surrounded by the 3′ and 5′ untranslated regions (UTRs), one 5′ cap, and a terminal polyadenylate tail. The mRNA vaccine is administered and then translated into the cell's ribosomes to produce the target antigen (Kairuz et al., 2022). Even while an individual messenger RNA molecule only encodes one particular antigenic substance, it can be translated to produce a significant amount of that antigen (Liu, 2019). RNA vaccines are evolving rapidly and offer several benefits, including safety due to RNA's non-contagious nature and its breakdown by cellular functions, as well as eliminating the risk of infection or insertional mutagenesis (Pardi et al., 2018).

3.2 Delivery Methods

The choice of the right delivery route and technique significantly impacts an aquaculture vaccine's efficacy. The successful administration of vaccination is just as important as its design. Therefore, accurate administration is essential in aquatic species to attain maximum immunological responses (Siskind and Benacerraf 1969). Throughout aquaculture vaccinations' research and development phase, specific vaccine delivery strategies are required due to several factors, including vaccination technology, the species and stage of reproduction of the organism, knowledge of the pathogen's characteristics and infection pathways, and financial considerations (Mondal and Thomas 2022). The main immunization delivery methods used in the aqua-culture field today are as follows:

3.2.1 Vaccination via injection

The majority of aquaculture vaccinations are administered intramuscularly or intraperitoneally via injection. This technique guarantees precise and regulated vaccination antigen delivery within the targeted organism (Tammas et al., 2024). Among the various administration methods, intraperitoneal injections offer the most effective and durable immunization (Dalmo et al., 2016). Injection vaccination effectively bypasses natural barriers that could prevent the vaccine from being distributed and absorbed uniformly, allowing for the precise administration of vaccine antigens in precise quantities. This method also facilitates the incorporation of adjuvants, which enhance the immunization process (Assefa and Abunna 2018).

3.2.2 Vaccination via immersion

During immersion vaccination, aquatic species are submerged in a specially prepared vaccine solution, allowing antigens to be absorbed through the mucosal surfaces of their skin, gills, gut, and nasal passage (Muñoz-Atienza et al., 2021). This strategy simulates natural infection pathways and builds an effective defensive network against common aquatic pathogens by promoting the immune system's mucosal and systemic responses.

3.2.3 Oral vaccination

Oral administration of aquaculture vaccines can be accomplished by either directly adding or combining vaccination antigens with feed (Mondal and Thomas 2022). With this method, vast numbers of animals can be mass vaccinated without requiring specific treatment, thereby reducing labour costs and minimizing stress, enhancing organisms' welfare (Lillehaug, 2014). It is also adaptable for animals of all sizes, making it particularly suitable for applications like vaccinating fish fry requiring prompt immunization (Wang et al., 2020).

3.3 Innovations in Vaccine Delivery

A. Nanoparticle delivery

A nanoparticle is a very small particle of 1 to 100 nm, which provides a flexible way to administer vaccines (Zhao et al., 2014). Nano polymers are the most widely employed class of nanoparticles (NPs) in aquaculture vaccinations due to their biological compatibility and ability to degrade within the hosts. Lipid-based nanoparticles, which also serve as an adjuvant to produce a polymer for targeted antigen delivery, are an efficient means of delivering nanoparticles and enhancing immune responses. This tactic is commonly referred to as immunostimulating complexes (ISCOMs). Saponins and lipids like cholesterol or phospholipids combine to form these complexes, which self-assemble into structures about 40 nm in size (Vinay et al., 2018).

B. Reverse vaccinology

Reverse vaccinology is an alternative method in vaccine development that derives genetic information from a pathogen to identify potential vaccine candidates. This method is often more effective than traditional approaches involving live or inactivated pathogens (Patil and Shreffler 2019). This technique has been applied in aquaculture to control various diseases. Vaccine development against *Vibrio anguillarum*, a pathogenic bacterium responsible for vibriosis in various fish species.

C. Microencapsulation

In aquaculture, microencapsulation has become a widely used technology to manufacture potent oral vaccinations (Radhakrishnan et al., 2023). This methodology includes the application of polymers, which might be synthetic or natural. Historically, chitosan, alginate, and PLGA polymers have been used. The adjuvant features of nanoparticles enhance immune function while enabling the extremely selective and targeted delivery of antigens within hosts (Jazayeri et al., 2021). Another intriguing and very promising encapsulation technique being researched in the field of oral vaccination for aquaculture is bio encapsulation. Introducing living things as biological carriers to deliver vaccination antigens is a unique strategy that often uses organisms fed to aquatic species for nutrition (Ma et al., 2020). The bio encapsulated antigens are absorbed entirely upon ingesting these organisms, promoting immune response development on the mucosa and systemic levels (Radhakrishnan et al., 2023).

4. CASE STUDIES

Ravid-Peretz et al. (2019) described a vaccine developed against *Mycobacterium marinum*, the primary etiological agent of mycobacteriosis in *European sea bass*, targeting bacterial disease. The vaccine utilized an avirulent strain of *M. marinum* that was heat-inactivated and combined with 70% Montanide™ ISA 760 VG adjuvant. A booster was administered 30 days post-vaccination. The challenge involved a virulent strain *of M. marinum*. The only group with a distinct IgM response was the one receiving the single adjuvanted vaccine. Pridgeon et al. (2011) reported on attenuated vaccines developed against *Streptococcus iniae* for Nile tilapia (*Oreochromis niloticus*). A formulation cultivated on novobiocin medium was administered via intraperitoneal (IP) injection, achieving relative percent survival (RPS) rates of 100% against the parental strain and 79–100% against heterologous strains. When delivered through immersion, the vaccine produced an RPS of 86% against the homologous strain. In contrast, high mortality rates of 80–100% were observed for IP injections and 64% for immersion in unvaccinated controls.

Smage et al. (2018) formulated a vaccine against *Tenacibaculum finnmarkense* in Atlantic salmon (*Salmo salar*), using a 0.4% formalin-inactivated HFJT strain combined with mineral oil as an adjuvant. Fish at the parr stage received IP injections of the bacterin at concentrations of 1× and 0.06×. After smoltification, all groups were challenged with either the homologous HFJT strain or the heterologous Tsp.2 strain. Although the higher concentration induced a stronger antibody response at 8 and 12 weeks' post-vaccination, it did not provide adequate protection for the fish. The HFJT strain proved to be highly pathogenic, resulting in 90–100% mortality. Surprisingly, controls challenged with Tsp.2 exhibited lower mortality rates (30–65%) compared to vaccinated fish (25–84%) in three out of four trials, regardless of vaccine concentration. Xu evaluated the effectiveness of different doses and schedules of a pcDNA3.1-IAg52b plasmid DNA vaccine against *Ichthyophthirius multifiliis* in channel catfish. Six groups were tested: 10 μg, 20 μg, two doses of 10 μg, a mock control, a positive control with live theronts and a non-vaccinated control. Fish immunized with 20 μg or two doses of 10 μg showed significantly greater anti-Ich antibody concentrations and survival rates (35.6% and 48.9%, respectively) compared to the sham controls (0%), which received a 10 μg dose Xu et al., 2020).

5. CONCLUSION

The immune system is a network within an organism that detects various agents, from viruses to parasitic worms and protects against diseases. Understanding fish's immune system and developing effective vaccination strategies are critical for ensuring fish health and sustainability in aquaculture. As pathogens evolve, ongoing research and innovation in vaccine technology and delivery methods will enhance disease resistance in aquatic species. Vaccines play a key role in protecting against disease in aquaculture, reducing infection, improving immunity, and increasing productivity. It helps to reduce the usage of antibiotics and also supports fish welfare by reducing disease-related stress. Further studies will provide deeper insights into host-pathogen interactions and the development of novel vaccines to protect fish against various types of pathogens.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

We declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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