REVIEW

# Immunological Control of Fish Diseases

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**Abstract** All metazoans possess innate immune defence system whereas parameters of the adaptive immune system make their first appearance in the gnathostomata, the jawed vertebrates. Fish are therefore the first animal phyla to possess both an innate and adaptive immune system making them very interesting as regards developmental studies of the immune system. The massive increase in aquaculture in recent decades has also put greater emphasis on studies of the fish immune system and defence against diseases commonly associated with intensive fish rearing. Some of the main components of the innate and adaptive immune system of fish are described. The innate parameters are at the forefront of immune defence in fish and are a crucial factor in disease resistance. The adaptive response of fish is commonly delayed but is essential for lasting immunity and a key factor in successful vaccination. Some of the inherent and external factors that can manipulate the immune system of fish are discussed, the main fish diseases are listed and the pathogenicity and host defence discussed. The main prophylactic measures are covered, including vaccination, probiotics and immunostimulation. A key element in the immunological control of fish diseases is the great variation in disease susceptibility and immune defence of different fish species, a reflection of the extended time the present day teleosts have been separated in evolution. Future research will probably make use of molecular and proteomic tools both to study important elements in immune defence and prophylactic measures and to assist with breeding programmes for disease resistance.

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## Introduction—the Immune System

The immune system protects an organism against diseases by identifying and eliminating the pathogen and suppressing the emergence of tumors. Another important role of the immune system is to participate in processes that maintain stable conditions (homeostasis) during development and growth and following inflammatory reaction or tissue damage.

The classical division of the immune system is into the innate and the adaptive systems. The innate system is an evolutionary ancient system present in both invertebrates and vertebrates. It is composed of germ-line encoded, relatively non-specific recognition parameters (although this is debatable), showing instant action but of short duration. The innate system's response to pathogens is determined by the evolutionary lineage and genetic make-up and has been tailored through time by environmental factors and pathogenic associations. The specificity of the innate defence is therefore an inheritable trait (Janeway and Medzhitov 1998; Carroll and Janeway 1999; Du Pasquier 2001; Du Pasquier 2004; Alvarez-Pellitero 2008).

The adaptive arm is relatively recent development in evolutionary time, assumed to appear in jawed vertebrates (gnathostomata), i.e. in primitive true fishes, about 400–500 million years ago. The key elements in the evolution of the adaptive system are the appearance of the thymus, the B- and T-lymphocytes and of the RAG (recombination activation gene) enzymes, which through gene rearrangement generate the great diversity of the immunoglobulin superfamily (B- and T-cell receptors (TCR) and the major

histocompatibility complex (MHC)). These are not germ-line encoded but are generated somatically, primarily during ontogeny. The result is practically unlimited diversity of the pathogen recognition repertoire. The specific activity of adaptive response is therefore not an inheritable trait but reflects the immune experience of each individual. Activation of the adaptive immune system is relatively slow, requiring specific receptor selection, cellular proliferation and protein synthesis but it is long lasting. (Dixon et al. 1995; Du Pasquier 2000; Bowden et al. 2005; Harding and Neefjes 2005; Huttenhuis et al. 2005; Randelli et al. 2008).

The "sudden" appearance of the adaptive immune system with the emergence of the gnathostomata is a twofold mystery: what were the selection pressures that called for its evolution and where are the roots in the agnatostomata or the prochordata?

It has been suggested that the primary selection pressure was development of the jaw resulting in greater food intake (and possibly increased injuries of the alimentary tract), increased metabolic rate, higher mobility and also increased exposure to parasites, possibly another key element in the development of the adaptive immune system (Matsunaga 1998; Rolff 2007). The roots of the adaptive system in the immune system or other biological parameters of the invertebrates are also unclear. Possible candidates may be virus receptors and lymphocyte-like cells, which have been described in prochordata (Matsunaga and Andersson 1994; Matsunaga 1998; Du Pasquier 2004; Pang et al. 2006; Rolff 2007).

In recent years fish immunological research has been mainly focused on two aspects.

Firstly, comparative and developmental studies have contributed to a better understanding of the structural and functional evolution of the immune system from invertebrates, through fish to mammals. Fish provide an important model for studying the evolution of the adaptive immune system and due to the often extended period from the start of infection till the appearance of adaptive response, fish also provide an interesting model to study the communication between innate and adaptive arms of the immune system (Du Pasquier 2001; Du Pasquier 2004, Flajnik and Du Pasquier 2004; Sullivan and Kim 2008).

The second aspect, and one that has received the major funding, is the requirement of the fish farming industries. The world-wide growth in aquaculture in the past 2 – 3 decades has demanded the development of a comprehensive knowledge of the immune system of some commercially important fish species. The aim has been twofold: to secure the optimum activity of the natural immune defence of the fish through cultural conditions and the choice of fish stock (breeding) and also to develop and improve prophylactic measures such as vaccination and probiotics (Vadstein 1997; Ellis 2001; Alvarez-Pellitero 2008; Van Muiswinkel 2008).

The aim of the present review is to examine the immune system of fish (in this case primarily the teleost species), the inherent and external factors that influence its competence, the main pathogenic threats and immuno-prophylactic manipulations.

Several comprehensive reviews have been published in recent years dealing with the main headings of this paper and will be referred to below. Emphasis will be put on papers published within the last decade.

## The Immune System of Fish

### Innate Factors

The innate immune system is of prime importance in the immune defence of fish. It is commonly divided into 3 compartments: the epithelial/mucosal barrier, the humoral parameters and the cellular components. The epithelial and mucosal barrier of the skin, gills and alimentary tract is an extremely important disease barrier in fish, being constantly immersed in media containing potentially harmful agents. As well as providing physical and mechanical protection the fish mucus contains several immune defence parameters including antimicrobial peptides, complement factors and immunoglobulins (Aranishi and Mano 2000; Smith et al. 2000; Ellis 2001; Hatten et al. 2001; Fast et al. 2002; Suzuki et al. 2003; Magnadottir 2006; Whyte 2007; Subramanian et al. 2007; Subramanian et al. 2008).The humoral parameters are either expressed as cell receptors or as secreted soluble forms. These include the complement system, which is well developed in fish and comprises the alternative, lectin and classical pathways. The three pathways can terminate in membrane attack complex and cell lysis or enhance phagocytosis by opsonisation of the pathogen and activation of the adaptive immune response through the classical pathway (Nonaka and Smith 2000; Boshra et al. 2006). Sponatneous haemolytic activity, attributed to the alternative complement pathway (SHA or ACP), is commonly high in fish serum (Lange et al. 2001) and many fish sera also show strong lysozyme activity, which is an important bactericidal enzyme (Grinde et al. 1988; Saurabh and Sahoo 2008). Other important parameters of innate humoral defence include lectins, like the mannose binding lectin (MBL), which can act as bacterial agglutinins or opsonins (Russell and Lumsden 2005), and the pentraxins (C-reactive protein (CRP) and Serum amyloid P (SAP)), which are central parameters of acute phase response and important pathogen recognition proteins (Bayne and Gerwick 2001). Antimicrobial peptides are key elements in innate defence (Smith et al. 2000; Fernandes and Smith 2004; Maier et al. 2008), also protease inhibitors like $\alpha$2-macroglobulin and $\alpha$1-antitrypsin (Bowden et al.

1997), which block lytic bacterial enzymes and growth inhibitors like transferrin (Stafford and Belosevic 2003), which block or delay bacterial growth and interferon, which acts against viral infections (Ellis 2001; Schultz et al. 2004; Furnes et al. 2009).

The general term for these innate parameters is pattern recognition proteins or receptors (PRP/R). These parameters recognise pathogen associated molecular patterns (PAMPs) associated with microbes and also inherent danger signals from malignant tissues or apoptotic cells. Typical PAMP are various polysaccharides and glycoproteins like bacterial lipopolysaccharide (LPS), flagellins, teichoic acid and peptidoglycan, DNA CpG motifs and virus associated double stranded RNA (dsRNA) (Janeway 1989; Medzhitov and Janeway 2002).

Important PRRs are the toll-like receptors (TLRs), which has received some attention in fish research in recent years (Akira and Hemmi 2003; Heine and Lien 2003; Takeda and Akira 2004). Studies of TLRs have revealed a remarkable specificity of the innate immune response, perhaps not appreciated before. TLRs have been identified in several species like zebrafish (*Danio rerio*), goldfish (*Carassius auratus*), pufferfish (Tetraodontidae sp.), flounder (*Paralichthys dentatus*), Atlantic salmon (*Salmo salar* L.) and rainbow trout (*Oncorhynchus mykiss*) showing similar organisation, expression and ligand characteristics as seen in mammalian species (Bricknell and Dalmo 2005).

Some of the innate parameters mentioned above show greater structural and functional diversity than seen in the mammalian counterparts. Examples are the multiple forms of different complement proteins, seen in several fish species (Sunyer et al. 1997) and the heterogeneity of CRP described in cod (*Gadus morhua* L.; Gisladottir et al. 2009). Such diversity may be important in increasing the recognition ability of the immune system.The innate cellular defence of fish involves primarily phagocytic leukocytes and non-specific cytotoxic cells. Leukocytes (white blood cells), are mobile cells that scout the organism for foreign invaders or danger signals marked by the PRP/Rs. The main immune cells of the innate system of fish are the granulocytes (in fish probably only neutrophils) and the monocytes/macrophages both types with phagocytic activity. Fish also have tumor attacking non-specific cytotoxic cells (Ellis 2001; Fischer et al. 2006) believed to be equivalent to mammalian natural killer cells. Phagocytes, when stimulated by linking with PAMPs through receptors or by the uptake of a pathogen, will show so called respiratory or oxidative burst activity indicated by the release of bactericidal reactive oxygen species, nitric oxide and other detectable factors. Stimulation also induces the production of cytokines, the signal molecules of cellular communications and an essential factor for the functioning of innate and adaptive immune response. Cytokines identified in fish either through gene expression or functional activity include cytokines involved in anti-bacterial activity like interleukin (IL)-1β, tumor necrosis factor-α and IL-6, and anti-viral cytokines like interferons (IFNs). Cytokines involved in T-cell differentiation during adaptive immune response (see below) are also present in fish-like type I and type II IFN, IFN-γ, IL-18 and IL-2, all Th1-type cytokines, and IL-4, a possible Th2-type cytokine (Secombes 2008).

The production or expression of both humoral and cellular innate parameters is commonly amplified or up-regulated during immune response but there is believed to be no memory. This means that a second encounter with the same pathogen will not result in enhanced response as is seen in adaptive immune response.

Adaptive Factors

The key humoral parameter of the adaptive system is the immunoglobulins (antibodies), expressed either as B-lymphocyte receptor or secreted in plasma. Effectively only one functional immunoglobulin class, a tetrameric IgM, is present in teleosts. This is in contrast to the 5 immuno-globulin classes and several sub-classes of mammals. Other Ig-like molecules have been described in some fish species, which may increase the diversity of the B-cell recognition capacity (Wilson et al. 1997; Randelli et al. 2008).

The lymphocytes, the B- and T- cells, are responsible for specific pathogen recognition and initiation of the adaptive immune response. The B-cells are involved in the humoral response while the T-cells are responsible for the cell-mediated response. Following activation by a specific antigen, either in soluble form or in association with the MHC marker on antigen presenting cells (APC), the B-cells proliferate and differentiate into long lasting memory cells and plasma cells, which secrete the specific antibody. Teleost B-cells are similar to the B1-subset of mammalian B-cells in that they express on their surface and secrete antibodies only of the IgM class (as mentioned above).

T-cells, using a specific receptor, recognise pathogen only in association with the MHC marker on APCs. Recognition leads to the production of memory T-cells, which will persist after infection and are ready to expand on re-encounter. In mammals there are several subsets of T-cells with different functional roles. The expression of TCR has been demonstrated in several fish species and different functional studies have shown the presence of different T-cell types in fish. However, only one or two monoclonal antibodies against putative T-cell markers (in sea bass and carp) have so far been made available and this paucity of tools to identify specific T-cell markers has greatly handicapped research in this area (Randelli et al. 2008).

The MHC cell surface structure is the key tool involved in the rejection of a pathogen. MHC class I is expressed on nearly all cells and is primarily involved in presenting intracellular viral proteins to specific T-cells while MHC class II is expressed by specific APC and is involved in presenting opsonised and degraded pathogen components to B- and T-cells. The expression of these molecules has been established in several fish species and unlike the situation in mammals they appear to be present on different chromosomes in fish. This suggests a separate evolutionary lineage of the traits for immune defence against viral infection (class I) and bacterial infection (class II, Van Muiswinkel et al. 1999). Macrophages are the main APC in fish but dendritic cells, which are important APC in mammals, have also been described in some species (Ganassin and Bols 1996; Harding and Neefjes 2005; Rakus et al. 2009b).

All the basic features of the adaptive immune system are therefore present in fish. However, compared with mammalian species, the antibody repertoire of fish is more restricted. This is due to, for example, limitations in the genetic machinery, slower metabolic rate of a poikilothermic animal (Du Pasquier 1982), the organisation of clonal selection is limited, fish having no lymphnodes or germinal centres, memory is restricted and enhanced secondary response (in mammals basically through Ig class switch) is limited or absent (Kaattari et al. 2002). In addition, the adaptive system of fish deviates in some interesting aspects from the mammalian system, which may to some extent compensate for these limitations. For example, compared with the mammalian pentameric IgM, teleosts have a more flexible, loosely associated, tetrameric IgM (Kaattari et al. 1998). Fish IgM can also be present in relatively high concentration in fish serum as natural antibodies, which are believed to have PRP properties (Magnadottir et al. 2009). Another interesting deviation from the mammalian adaptive system is the apparent phagocytic activity of B-lymphocytes described in some fish, which may indicate a multiple role of fish lymphocytes (Li et al. 2006).

During infection the fast but generally short-lived innate immune response precedes the longer lasting more specific adaptive immune response. In fish this lag period can be as much as 10 – 12 weeks, which has to be kept in mind when considering vaccination as a prophylactic measure in fish aquaculture.

## Inherent Factors that Affect the Immune System of Fish

There are several inherent factors that can affect the immune system of fish resulting in variation in disease resistance between different species and between different individuals. These include evolutionary status, genetic variations, age, sex and maternal effects.

### Evolutionary Lineage

The evolutionary lineage of present day teleosts goes back to Jurassic time separating the different orders of modern teleosts by up to 100–200 million years. Teleosts have also adapted to very varied environments and their feeding and breeding habits vary extensively. It follows that the selective pressures during evolution must vary considerably and influence their immune system and immune response. Comparing the immune response of the gadidae and salmonid species there are even indications that different lines of immune defence have been "tested out" through evolutionary time independently of the general physiological and anatomical progress of fish evolution (Pilstrom et al. 2005).

### Genetic Make-Up

Several studies have shown that the activity of different immune parameters can vary greatly between individual fish of the same species and that resistance to pathogens shows marked individual diversity. This diversity strengthens the survival of the species in its entirety especially under natural conditions. In aquaculture based primarily on out bred fish, this can cause problems of unpredictability in some research programmes, evaluations of husbandry practices or prophylactic methods. Selective breeding employed in aquaculture to select for favourable traits like disease resistance, has been problematic possibly due to the inherent diversity and often obscure correlation between immune parameters and disease resistance (Roed et al. 1993; Van Muiswinkel et al. 1999; Olesen et al. 2007; Ødegård et al. 2007; Mahapatra et al. 2008; Robinson and Hayes 2008).

### Age and Sex

Age and sexual maturation are important inherent factors that influence the immune system and immune response of fish. Considerable attention has been paid to the development of the immune system of fish from fertilized egg to a fully immuno-competent stage (Zapata et al. 2006). During ontogeny components of the innate system generally appear before adaptive immune parameters. Commonly present at hatching are phagocytes, lysozyme activity and complement proteins (Lange et al. 2004; Magnadottir et al. 2005). In general adaptive immune parameters appear later in marine species than in fresh water species but the order of appearance of the different organs and components of the immune system varies from one species to another. These

variations play a crucial role in larviculture management and determine when vaccination is a valid prophylactic measure (Zapata et al. 2006).

In fully developed fish, immune parameters can change with increasing age and vary between males and females. For example, the immunoglobulin concentration in serum (and natural antibody activity) increases with increasing age. In some species, like the cod, this increase continues throughout life, in other species maximum level is reached at sexual maturation (Klesius 1990; Nagae et al. 1993; Magnadottir et al. 1999b).

Interaction between the immune system and the endocrine system are well documented in fish. This interaction has been mainly studied with reference to stress hormones (see below) but male and female sex hormones, testosterone and estradiol-17β, have also been shown to effect immune parameters directly during sexual maturation and spawning (Maule et al. 1996; Cuesta et al. 2007). Again, the effects vary depending on the fish species and the parameter studied. Suppression of plasma IgM levels was, for example, observed in rainbow trout following administration of sex hormones (Hou et al. 1999), while male and female sex hormones had different but not suppressive effects on phagocytic and complement activity and IgM levels in gilthead sea bream (*Sparus aurata*; Cuesta et al. 2007). In aquaculture, measures are frequently taken to control, delay or impede sexual maturation and spawning to avoid threats to fish health during this period, for example, by inducing sterility through polyploidy (Piferrer et al. 2009).

Maternal Effects

It is an accepted paradigm that maternal health is important to the welfare of the offspring and this also applies to fish. In aquaculture the health status of the brood fish before and at the time of spawning is commonly reflected in the fitness and survival of the larvae. Maternal transfer of immune parameters to the offspring (eggs) can reduce the vulnerability of the larvae during the immediate period after hatching (Mousseau and Fox 1998; Hanif et al. 2004; Mulero et al. 2007; Nye et al. 2007; Swain and Nayak 2009).

There are examples of both innate and adaptive immune parameters being transferred from mother to the egg. Vitellogenin, the egg yolk protein, has been shown to have bactericidal effects (Shi et al. 2006) and maternal transfer of complement proteins, lysozyme and antibacterial peptides has been described in several fish species (Ellingsen et al. 2005; Lange et al. 2005; Magnadottir et al. 2005; Seppola et al. 2009). Most studied is the maternal transfer of immunoglobulin (IgM), this being of particular interest in view of the often delayed ability of fish larvae to produce antibodies. There are several examples of maternal transfer

of IgM in fish, for example, in Atlantic salmon, plaice (*Pleuronectes platessa*), sea bass (*Dicentrarchus labrax*) and tilapia (*Oreochromis mossambicus*; Bly et al. 1986; Breuil et al. 1997; Olsen and Press 1997; Takemura and Takano 1997) while no maternal transfer of IgM has been detected in cod and haddock (*Melanogrammus aeglefinus*; Magnadottir et al. 2004; Corripio-Miyar et al. 2007a; Seppola et al. 2009). In some instances passive protection against specific diseases has been demonstrated in juvenile fish following the transfer of maternal antibodies from brood fish (sea bream) vaccinated against the disease (Hanif et al. 2005). In other instances (Atlantic salmon) such protection was not obtained (Lillehaug et al. 1996). In general the maternal antibodies are of low concentration and short duration suggesting that their primary role might be protection against vertical transmission of infection (Swain and Nayak 2009). A different form of maternal effect on the immunity of the offspring has been described in discus fish (*Symphysodon aequifasciata*) and other fish that care for their eggs and larvae. The discus fish secretes substances from the epidermal mucus, which provides nutrition for the larvae and plays a protective role against infections (Schardin and Anzenberger 1999; Chong et al. 2005).

## External Factors Affecting the Immune System of Fish

The immune system and response of fish can be greatly influenced by various external factors like temperature, light, water quality, salinity and different stress inducers. Only the effects exerted by temperature and stress will be reviewed here.

Environmental Factors

In ectothermic or poikilothermic animals like fish, environmental changes can have significant effects on the immune system. Seasonal and diurnal changes in immune response and disease prevalence have been reported in wild fish, the ruling factors being changes in temperature and light density (Zapata et al. 1992; Collazos et al. 1995; Hutchinson and Manning 1996; Bowden et al. 2007; Bowden 2008; Hayward et al. 2009). In land-based (indoor) fish farms, factors like temperature, light and salinity as well as water quality can be controlled and optimum conditions maintained. This is frequently at considerable expense. Fish reared in open air tanks or ponds and in sea cages are subjected to greater environmental variations resulting in complex interaction between thermal effects *per se* and temperature-induced stress.

This was demonstrated by Pérez-Casanova (Pérez-Casanova et al. 2008) in a study on the immune and stress

response of cod reared at temperatures from 10°C to 19°C. While plasma cortisol level and some immune parameters like the expression of β₂-microglobulin, MHC Class I and IgM light chain peaked at 16°C and then returned to basal level, the expression of cytokine IL-1β only reached maximum at 19°C while the temperature change had no effects on phagocytic respiratory burst activity.

The temperature effects on disease resistance also depend on characteristics of the pathogen involved. In some cases increased disease prevalence in winter coincides with a lower level of certain innate parameters, seen, for example, in a higher incidence of haemoflagellate (*Trypanoplasma bullocki*) infection in flounder in winter (Fletcher 1986). However, the opposite is observed in the increased prevalence of proliferative kidney disease (PKD, *Tetracapsula bryosalmonae*) of rainbow trout with increasing temperature, possibly because the immune system cannot cope with the increased prevalence of the parasite favoured at higher temperature (Morris et al. 2005).

Regardless of the influence of stress or pathogen it is commonly stated that innate parameters are more active at low temperatures while parameters of the adaptive system tend to be suppressed at low temperature (Bly and Clem 1992). This statement is supported by several experiments. For example, in cod acclimatised at different temperatures for 12 months, innate parameters like spontaneous haemolytic activity decreased while the IgM serum concentration and natural antibody activity increased with increasing temperature (Magnadottir et al. 1999a). Other studies have also demonstrated that low temperature will suppress T- cell activity and delay antibody response (Cecchini and Saroglia 2002; Hoare et al. 2002; Langston et al. 2002). Several studies have also shown that this state of affairs is by no means the general rule in fish. It was, for example, shown by Nikoskelainen et al. (2004) that after acclimatising rainbow trout for 57 days at temperatures from 5°C to 20°C, phagocytic activity as well as the serum complement activity increased with increasing environmental temperature while the natural antibody activity was not affected.

In vitro studies have shown that many innate parameters of fish, like complement-, lysozyme-, phagocytic- and NCC-activity, are active at a wider temperature range and show higher activity at low temperatures than the corresponding parameters of endothermic organisms (Ainsworth et al. 1991; Dexiang and Ainsworth 1991; Lange et al. 2001; Lange and Magnadottir 2003; Magnadottir et al. 2005).

Stress

Another generally accepted paradigm is that stress, especially chronic stress, will suppress immune response and lower the disease resistance.

Numerous experiments have been conducted on different fish species to examine the effects of stress on the immune system. In these experiments stress hormones like cortisol and adrenaline or other stress related proteins like heat shock proteins and plasma glucose levels have been monitored, as well as innate and adaptive immune parameters and the effects on disease resistance (Demers and Bayne 1997; Gornati et al. 2004a; Fast et al. 2008). Genetic analysis of immune and stress parameters and proteomic studies have also been carried out (Gornati et al. 2004b; Kumar et al. 2009; Talbot et al. 2009). These studies have demonstrated a close interaction of the neuroendocrine and the immune systems in fish and the regulation of these interactions by cytokines and neuropeptides (Weyts et al. 1999; Harris and Bird 2000; Watanuki et al. 2000; Castillo et al. 2009).

Confinement, high density, handling and transport are stress inducers which are highly relevant to aquaculture and have received considerable attention (Saeij et al. 2003; Binuramesh et al. 2005; Brydges et al. 2009; Ramsay et al. 2009). Long term exposure to these stressors has generally suppressive effects on the immune system and disease resistance of fish. Some examples of initial stimulation have been reported, for example, following short exposure to handling stress of Atlantic salmon (Fast et al. 2008) and rainbow trout (Demers and Bayne 1997). Recovery to basal levels is also commonly seen during chronic stress induction (Tort et al. 1996; Pérez-Casanova et al. 2008). Similarly, fish in aquaculture appears to adapt to confinement and show lower stress response than the wild type (Barnett and Pankhurst 1998). In confinement studies, gender, sexual maturation and spawning as well as social status are influential factors reflecting the effects other endocrine parameters like sex and growth hormones can have on the immune system (Peters et al. 1991; Schreck et al. 2001; Binuramesh et al. 2005; Yada 2007).

Direct administration of stress hormones or neuropeptides in in vivo or in vitro studies has similarly demonstrated varied but generally the suppressive effects on immune parameters of fish (Espelid et al. 1996; Hou et al. 1999; Harris and Bird 2000; Watanuki et al. 2000; Castillo et al. 2009). For example, in a study of Atlantic salmon, Ig-positive lymphocytes were down regulated following cortisol injection and mitogenic stimulation of lymphocytes was suppressed when incubated with cortisol (Espelid et al. 1996). On the other hand, β-endrophin was shown to stimulate in vitro phagocytic activity of leukocytes (macrophages) isolated from kidneys from both rainbow trout and carp (*Cyprinus carpio*) (Watanuki et al. 2000).

In aquaculture, selective breeding of low cortisol responders has been considered (Del Valle and Taniguchi 1995; Tanck et al. 2002) and modulating stress response through feeding regimes has also been suggested (Jeney et

al. 1997; Montero et al. 2001; Vielma et al. 2003; Welker et al. 2007).As well as affecting the immune system and disease resistance of fish stress also affects other factors like growth, sexual maturation, gamete quality and larval health. (Schreck et al. 2001; Varsamos et al. 2006). Because of these wide reaching effects, husbandry practises in aquaculture aim at avoiding stress by maintaining steady environmental conditions, rearing at optimum density, controlling sexual maturation and avoiding excessive handling.

## Fish Diseases

In the wild, under normal conditions fish is an extremely successive animal sub-phylum and are not considered to be particularly disease susceptible. However, as commonly pointed out fish are in close contact with their environment and are thus exposed to a variety of both harmless and potentially pathogenic microbes often in high concentration (Ellis 1999; Ellis 2001). Mortalities in wild fish populations caused by infectious diseases may therefore be significant but are probably hidden by environmental and behavioural factors and also by poor documentation. On the other hand, several reported cases of mass mortalities in both marine and fresh water populations, attributed to specific disease outbreaks or epizootics, have drawn attention to this phenomenon and warranted closer examination. Examples include the periodic epizootics in herring (*Culpea harengus* L.) in the coastal waters of Norway, Sweden and Iceland caused by the flagellate, *Ichthyophonus hoferi* (Rahimian 1996; Mellergaard 1997; Hershberger et al. 2009), recurring herpesvirus epidemics causing mass mortality in Australian pilchard (*Sardinops sagax*; Hershberger et al. 2009) and the viral haemorrhagic septicaemia outbreaks currently sweeping the great lakes and Mississippi basin of North America affecting various fresh water species (Groocock et al. 2007; Lumsden et al. 2007; Elsayed et al. 2006). Mass mortalities of this nature can sometimes be attributed to known environmental or behavioural changes but in other cases no obvious explanations are available.

Intensive culture systems with associated stress and other husbandry risks greatly increases the threat of infection. In addition, the high density of fish in aquaculture augments the disease propagation.

Infectious fish diseases can be caused by pathogenic and in some cases opportunistic bacteria, viruses, parasites or fungi. Some of the main diseases will be listed below.

### Parasitic Infections

Fish are hosts to various parasites spanning numerous invertebrate or fungal taxa, for example, protozoan flagel-late and coccidian species, metazoan cestoda, nematode and copepoda species and fungi or fungi related species like Saprolegniaciae and Loma (see reviews by Wiegertjes et al. 2005; Bricknell et al. 2006; Alvarez-Pellitero 2008; Sitjà-Bobadilla 2008). Some parasites have complex life cycle embracing several stages of development and more than one host (like flukes, tapeworm) while others are only passed from one fish to another (like some ciliates and copepodian sea lice). Parasites can be host specific or infect a variety of fish species. Some fish, like the cod are known for their infestation from early age by a broad parasite fauna. Over 100 parasite species have been described in cod some of which are specific to cod (Hemmingsen and MacKenzie 2001).

Economically important parasitic infections associated with both wild fish and fish in aquaculture include the sea lice (*Lepeophtheirus* and *Caligus* ssp.), arthropodan ectoparasites, which have caused serious problems in both wild and farmed salmonid and gadidae species (Costello 2009), the *Trichodina* ssp., which cause problems in both freshwater and marine hatcheries (Kristmundsson et al. 2006), proliferative kidney disease (PKD) of salmonids caused by *Tetracapsula* ssp. (Wahli et al. 2002) and Loma, an intracellular fungal parasite infecting the gills of salmonids and other species (Bader Jr et al. 1998; Bricknell et al. 2006).

### Bacterial Infections

Serious losses in aquaculture are attributed to outbreaks of bacterial diseases in spite of considerable success in vaccine development in this field. Various reviews have listed the main bacterial diseases affecting aquaculture today (see reviews by Ellis 1999; Ellis 2001; Sommerset et al. 2005a; Toranzo et al. 2005; Bricknell et al. 2006). Only a few examples will be mentioned. These include vibriosis caused by *Vibrio anguillarum* infecting a variety marine species but also some fresh water species, redmouth disease caused by *Yersinia ruckeri* mainly associated with rainbow trout but also seen in turbot, sea bass and sea bream, enteric septicaemia caused by *Edwardsiella ictaluri* afflicting primarily channel catfish, typical and atypical furunculosis infecting a variety of species, the typical disease being caused by *Aeromonas salmonicida* ssp. *salmonicida* and the atypical by, *A. salmonicida* ssp. *achromogenes*, bacterial kidney disease caused by *Renebacterium salmoninarum* mainly associated with wild and cultured salmonids, winter ulcer disease caused by *Moritella viscosa* also primarily associated with salmonids, bacterial gill disease caused by *Flavobacterium branchiophilum* a widespread disease of salmonids, carp and other species, pasteurellosis caused by *Photobacterium damselae* infecting Japanese yellowtail (*Seriola quinqueradiata*) and Mediterranean sea bass and

sea bream and *Francisella* sp. infecting, for example, cod in Norwegian aquaculture (Schrøder et al. 2009).

Viral Infections

The main viral fish diseases in aquaculture have been listed in several reviews (Jeney and Jeney 1995; Ellis 2001; Sommerset et al. 2005a; Bricknell et al. 2006; Samuelsen et al. 2006). For example, IPN, is a highly infective disease of near global distribution caused by infectious pancreatic necrosis virus (IPNV). Although associated with young salmonids in intensive aquaculture it is also a concern in other species. Infectious salmon anaemia virus is primarily found in salmonids as is the infectious hematopoietic necrosis virus (IHNV). Strains of viral hemorrhagic septicaemia viruses (VHSV) infect various fish species, both marine and fresh water, including salmonid and gadoid species. Spring viraemia of carp is caused by *Rhabdovirus carpio* or SVCV and infections due to Koi herpesvirus and cyprinid herpesvirus-3 (CyHV-3), are also well known viral infections in cyprinid and other species (Jeney and Jeney 1995; Rakus et al. 2009a).

Pathogen–Host Association

The susceptibility and the clinical signs of infection caused by a pathogen can vary considerably from one fish species to another. A key element in these variations lies in differences in the immune defence of the fish. An example of this is the different histopathological response of Atlantic salmon and cod to atypical furunculosis. Widespread granuloma formation is characteristic of cod's response while in salmon haemorrhage and localized cellular necrosis is typical (Gudmundsdottir 1998; Wiklund and Dalsgaard 1998; Magnadottir et al. 2002). Atlantic salmon, like other salmonids, will also show good specific antibody response to a variety of bacterial infection while cod shows limited or no antibody response (Solem and Stenvik 2006; Lund et al. 2008).

These and several other studies have emphasised the paradigm that what we know of the pathogen–host association in one species can seldom be transferred to another fish species.

There is a fine balance between the pathogen's mechanisms of infection and the host's defence response. In some cases, the evolutionary pressure is on the pathogen to cause minimal harm as well as avoiding or coping with the immune response of the host. Hence, the greatest mortalities may occur when the pathogen-host association is relatively new or when the immune defence of the host is compromised as is often the case in intensive aquaculture.

In other instances, even a long standing host–pathogen association does not appear to be directed towards commensalism or symbiosis, hence, the survival of some pathogens may be attributed to a rapid proliferation and even killing of the host, for example, as seen in *Enteromyxum scophthalmi* infection of turbot (*Scophthalmus maximus* L.; Sitjà-Bobadilla et al. 2006).

The route of infections is a determining factor in the infectivity of pathogens in different fish species and will call on diverse host response (Quillet et al. 2007). Some pathogens may also augment their infectivity by employing vertical transmission from the brood fish to the eggs as well as horizontal transmission, seen, for example, in BKD (Pascho et al. 1993) and parasitic vector may be important in the etiology of some viral diseases (Jeney and Jeney 1995; Petterson et al. 2009).

However, there are some general ways by which the different pathogens escape or delay the immune response of the fish. These mechanisms are commonly directed against the innate arm of the immune system, this being in the front line of the immune defence of fish. Sitjà-Bobadilla (2008) lists ten mechanisms by which parasites are known to escape or delay host's immune response and several papers have discussed the evasive mechanisms of pathogenic bacteria (Ellis 1999; Ellis 2001; Hornef et al. 2002; Basset et al. 2003; Portnoy 2005). Similar mechanisms will also apply to viral infections. For example, the pathogens may limit their infection to sites where immune response is naturally suppressed. This includes sites like the central nervous system (including the brain), gonads and the eyes. Antigen-based strategies through antigen mimicry, masking or rapid variations (e.g. viral polymorphism) or by avoiding or inactivating humoral defence parameters are also known. A recent review paper focuses, for example, on how metazoan parasites escape being attacked by the complement system through a variety of mechanisms, which obstruct or hold up the complement cascade at different stages (Schroeder et al. 2009).

The ability to pass through the integument system of fish is an important factor in the pathogenisity of many bacteria. Bacteria may produce adhesive molecules or excrete proteases that can digest the mucus as seen in *Aeromonas hydrophilia* (Fang et al. 2004; Angka et al. 1995). Another example is a protective external capsule of *A. salmonicida* ssp. *salmonicida*, which protects against various humoral defences and opsonisation and also hides important virulence factors and thus assists the spreading within the host. *A. salmonicida* ssp. *salmonicida* also has high iron-uptake system that diminishes the defence action of the host's transferrin and it produces enzymes that confer resistance to the bactericidal activity of phagocytes (Ellis 1999). In vitro studies have shown that *E. ictaluri* survives phagocytosis and can multiply inside macrophages. *R. salmoninarum* also survives within phagocytes by neutralizing the products of macrophages respiratory burst

(Gutenberger et al. 1997). Overcoming the integumental innate parameters is a key element for the infectivity of e.g. VHSV and IHNV in rainbow trout (Quillet et al. 2007; Ellis 2001) and cell adhesive properties have been demonstrated between IHNV, VHSV and IPNV and host cells (Heras et al. 2008). Entering the host cell via binding to sialic acid cell surface residue has also been described (Eliassen et al. 2000).

In spite of the evasive measures of the pathogen several studies have shown that the adaptive arm of the immune system is primed during the initial stages of infection and can in many cases successfully eliminate or at least limit ardent pathogens in the late stages of infection or when re-encountered i.e. provide protection (Sitjà-Bobadilla 2008; Raida and Buchmann 2009; Buchmann et al. 2001; Alvarez-Pellitero 2008; Joerink et al. 2007; Fast et al. 2002). For example, in an experiment on rainbow trout infected with *Y. ruckeri* both the bacterial load and the innate response were much lower when survivors from the first infection were re-infected (Raida and Buchmann 2009). This improved survival was not believed to be mediated by specific antibodies but by adaptive cellular response through specific antigen stimulated T-cells and cytokine expression (Secombes et al. 1996). In other instances, specific antibodies are the key element in protection. For example, specific anti-adhesins antibodies are believed to be an important defence against bacterial gill disease (*F. branchiophilum*) in rainbow trout (Lumsden et al. 1995).Several experimental infections and vaccination trials have shown that the Type I interferon and natural cytotoxic cells, are the prime players in the initial defence of fish against viral infections (Fischer et al. 2006; Ellis 2001; Robertsen 2006). The anti-viral response of these parameters appears to be quick, even within hours while specific antibodies may be produced later (10 days; Utke et al. 2008; Lorenzen et al. 2002; Milev-Milovanovic et al. 2009; Pakingking et al. 2009).

## Immuno - Prophylactic Control of Fish Diseases

Antibiotics have been used extensively in aquaculture in the past but the present consensus is that this should be kept at a minimum. Excessive use of antibiotics is known to produce resistant bacteria, which are considered a major threat to animal (and human) health (Gudding et al. 1999). With the development of immunoprohylactic control measures, the use of antibiotics in aquaculture has been greatly reduced in the past 20 years (Gudding et al. 1999; Gudmundsdottir and Björnsdottir 2007).

Immunoprophylactic control of fish diseases involves classical vaccinology, pro- and prebiotic treatments and immunostimulation, all preventive measures aimed at priming the innate and/or the adaptive immune system ahead of infection.

## Vaccines

Many experiments have shown that fish, which survive infection, will show enhanced disease resistance or complete immunity on second encounter. A key element, as mentioned above, is the adaptive immunity, the appearance of memory cells and specific antibodies. The basic aim of vaccination is to imitate this process. Vaccination should thus activate both the innate and the adaptive system and lead to lasting protection. The vaccine efficacy in fish is generally established by challenge experiments. In mammals specific antibody response is a good indicator of vaccine efficacy but in fish this is unreliable. Some fish species will produce protective antibody response to vaccination (Erdal and Reitan 1992; Pakingking et al. (2010)) while others, notably the gadidae species, will show varied or no antibody response (Samuelsen et al. 2006; Corripio-Miyar et al. 2007b; Schrøder et al. 2009).

Fish vaccination has a long history (Van Muiswinkel 2008) but only in the last 10–20 years has vaccination against common bacterial infections in aquaculture become a well established and on the whole a successful prophylactic measure. Fish vaccines administrated by injection, immersion or in the feed are now routinely used in a wide variety of farmed species commonly employing polyvalent vaccines.

Commercial vaccines are available for more than half of the major bacterial and viral diseases of aquaculture. However, no commercial vaccines have so far been produced against parasitic infections (Sommerset et al. 2005a).

Common anti-bacterial vaccines like those produced against *Yersinia ruckerii*, *V. anguillarum*, *Vibrio salmonicida* and other *Vibrio* species are based on inactivated bacterial suspension (bacterin). Generally these have given good or adequate protection with little or no side effects and can be used as immersion vaccines, useful for younger fish. In some instances immersion or bath vaccination results in the appearance of specific antibodies in the skin mucus before the systemic production. This may be important in circumstances when the key to the bacterial infectivity is passing the integumental defence.

Live attenuated bacteria have also been used successfully in vaccine preparations, for example, against *E. ictaluri* infection (Shoemaker et al. 1999). However, associated risks of reversion to virulent forms will limit the general use of such vaccines in aquaculture.

Other vaccines, like those against furunculosis, make use of whole bacteria or bacterial antigens mixed with adjuvants to enhance and prolong the vaccination effects. Most commonly used are oil-based adjuvants but other

types, like aluminium-, glucan- alginate- or chitosine- based adjuvants have also been tested (Kamilya et al. 2006; Ravelo et al. 2006). These vaccines are normally administrated by injection and are often more efficient and with longer lasting effects than immersion vaccines. This method of administration is, however, stress inducing and side effects signified by abdominal adhesion and reduced growth have been attributed to the use of some adjuvants (Afonso et al. 2005; Mutoloki et al. 2006; Berg et al. 2007; Aunsmo et al. 2008; Treasurer and Cox 2008). Oral vaccination i.e. with the feed, although an attractive method in theory, has so far not found general application in aquaculture.

Bacterial vaccines based on molecular technology, including DNA vaccines and the use of recombinant protein antigens have in many cases given promising results but are faced with the same uncertainties as the viral DNA vaccines, which will be discussed below (Gudding et al. 1999; Pasnik and Smith 2005; Kumar et al. 2007; Gillund et al. 2008; Secombes 2008; Tonheim et al. 2008).

Practical and ethical considerations have so far hindered the general use of anti-viral vaccines in aquaculture. Those approved for commercial use are primarily based on inactivated viral preparations. Vaccines based on molecular technology, make use of either recombinant proteins, mainly surface viral glycoproteins, produced in *E. coli* (or other bacteria) or of intra muscular injection of plasmid DNA encoding the antigen of interest. Many of these experimental DNA vaccinations have given relatively fast, specific and long lasting protection in challenge trials. On the negative side is the ethical question of what happens to the bacterial plasmid DNA in the organisms. Experiments have shown that this is not completely degraded at the injection site and may reach other tissues or even be secreted. This introduces the danger of the plasmid being introduced to another unrelated host with unforeseeable consequences for the environment (Lorenzen et al. 2002; Lorenzen et al. 2005; Sommerset et al. 2005b; Kanellos et al. 2006; Kurath et al. 2006; Kumar et al. 2007; Gillund et al. 2008; Pakingking et al. 2009).

Anti-parasite vaccines are also called for by the fish farming industry. The production of commercial anti-parasite vaccine is basically delayed by the often complex structure and life cycle of the parasites and the difficulties in cultivating the parasite in sufficient, homologous quantity for vaccine production. Identification of the parasite antigen or antigens that will induce protective immunity is also needed. This is especially important when considering recombinant protein production, which is an attractive approach in anti-parasite vaccine preparations (Gudding et al. 1999; Buchmann et al. 2001; Chettri et al. 2009).

Vaccine effectiveness varies considerably depending on the fish species, the age of the fish and cultural condition (Sommerset et al. 2005a; Gudmundsdottir and Björnsdottir 2007).

The species difference, as discussed above, is basically due to the complex and varied interaction of pathogen and the host's immune response. The efficacy of vaccines against typical and atypical *A. salmonicida* and against *V. anguillarum* serotypes in salmonids, gadoids and other species has, for example, received considerable attention in the litterature (Eggset et al. 1997; Gudmundsdottir et al. 1997; Ellis 1999; Lund et al. 2002, 2003, 2006; Gudmundsdottir and Björnsdottir 2007; Mikkelsen et al. 2007; Lund et al. 2008).

The age of the fish at vaccination is another important factor. Fish larvae and fry need to have fully developed adaptive system before vaccination is attempted. In marine species, this can be several weeks after hatching as mentioned above. Some studies have also shown that a fully developed adaptive system does not necessarily signify full immunological competence with respect to vaccine efficacy (Schrøder et al. 2006; Mulero et al. 2008). In addition, vaccine efficacy and possible side effects may be influenced by the age of the fish (Berg et al. 2007).

Another critical factor for successful vaccination is the environmental temperature. An experiment by (Raida and Buchmann 2008), for example, has shown that bath vaccination of rainbow trout against enteric red mouth disease is only successful at 15°C but not at temperatures below or above this (5°C, 25°C). Variations in temperature can also affect both the magnitude and duration of adaptive response following vaccination (Eggset et al. 1997).

Probiotics and Immunostimulation

Another approach to immunoprophylactic control is the use of probiotics and immunostimulants including specific dietary manipulation.

The classical definition of the term probiotics is: "a live microbial feed supplement which beneficially affects the host by improving its intestinal balance" (Fuller 1989), the emphasis being on "live" and "intestinal". In practice, however, the term has also been applied to non-viable microbes, not necessarily restricted to the intestinal balance. An immunostimulant has been defined by Bricknell and Dalmo (2005) as: "a naturally occurring compound that modulates the immune system by increasing the host's resistance against diseases that in most circumatnces are caused by pathogens" (Irianto and Austin 2002a; Irianto and Austin 2002b; Bricknell and Dalmo 2005; Balcázar et al. 2006; Kesarcodi-Watson et al. 2008).

These treatments are primarily aimed at enhancing the innate system and therefore of value as general preventive measures in aquaculture. They are of special value in larviculture, especially of species that show late appearance

of the adaptive system like many marine species (Vadstein 1997; Bricknell and Dalmo 2005) but beneficial effects on adaptive parameters and on the antibody response of immunocompetent fish have also been demonstrated (Reyes-Becerril et al. 2008; Nikoskelainen et al. 2003; Picchietti et al. 2009). The administration is generally in the feed, in the case of larvae cultures in rotifers or Artemia. Immersion or bathing is also employed or inoculation, sometimes as an adjuvant for vaccine preparation (Vadstein 1997; Skjermo and Bergh 2004; Bricknell and Dalmo 2005; Kamilya et al. 2006; Planas et al. 2006; Picchietti et al. 2009). Immunostimulants and probionts can also be of value during periods of stress in aquaculture i.e. during sexual maturation and spawning or transfer to sea cages etc. (Jeney et al. 1997; Bagni et al. 2005).

## Probiotics

The use of probiotics is well established in domestic animal farming and has in recent years also been used in aquaculture (Olafsen 2001; Irianto and Austin 2002a; Wang et al. 2008; Qi et al. 2009; Sharifuzzaman and Austin 2009).

Commercially available probiotics, for example, lactic acid bacteria, Bacillus ssp. and yeasts, are common ingredients in human health food and in domestic farming. Some of these have been tested in aquaculture with generally good results (Nikoskelainen et al. 2003; Li and Gatlin III 2005; Panigrahi et al. 2005; Aly et al. 2008; Ma et al. 2009).

A few commercial probiotic preparations have also been developed specially for use in aquaculture like MacroGard (β-glucans) and Ergosan (polysaccharide from seaweed; Bagni et al. 2005).

A search for probiotic bacteria in aquaculture involves the screening of the bacterial flora associated with the fish under study and/or its environment. The anti-microbial activity against fish pathogens is then tested, the pathogenicity in the host fish is examined and finally the effects on growth and survival of larvae or challenged fish are examined (Kesarcodi-Watson et al. 2008). Several experiments of this nature have been described in the literature where the end product has proved beneficial for the fish (Fjellheim et al. 2007; Gatesoupe 2007; Lauzon et al. 2008; Lauzon et al. 2009; Sharifuzzaman and Austin 2009). Sharifuzzaman and Austin (2009), for example, included probiotic bacteria isolated from the intestines of rainbow trout in the diet of rainbow trout and found significant reduction in mortality when challenged with V. anguillarum. There is also some evidence that probiotic bacteria isolated from the host or its environment are more beneficial than commercially available products (Lauzon et al. 2009).

How probiotic bacteria work is not always fully understood. Live probiotic bacteria are believed to affect the intestinal flora, their antagonistic activity and/or competition for nutrients and space reducing the number of pathogenic bacteria. They are also thought to improve appetite and hence increase growth. There are examples of probiotic treatment enhancing cellular and humoral immune parameters (Irianto and Austin 2002b). Probiotics may also stimulate innate defence through TLR, other cellular receptors or humoral factors but for this to take place the probiotic bacteria or its products would have to pass the mucosal and epithelial barrier of the alimentary canal and prime the normal defence mechanisms of the fish. When the inclusion of probiotic bacteria, for example, in the feed ceases these disappear from the host digestive system within days or few weeks. However, the beneficial effects can be long lasting (Robertson et al. 2000; Nikoskelainen et al. 2003; Planas et al. 2006).

## Immunostimulation

The term immunostimulant covers a wide range of substances that activate the immune system through pattern recognition proteins/receptors and TLRs and enhance overall resistance to various diseases. Immunostimulatns can be bacterial, viral, plant or parasitic derivatives as well as some synthetic compounds (Raa 1996; Vadstein 1997; Sakai 1999; Robertsen 1999). One of the most used substances in immunostimulation experiments in fish are various forms of β-glucans from different sources, normally introduced in the feed but also by intraperitoneal injection or as vaccine adjuvant (Dalmo and Bøgwald 2008). For example, Ai et al. (2007) fed β-1,3 glucan from the cell wall of Saccharomyces cerevisiae (yeast) to yellow croaker (Pseudosciaena crocea) and demonstrated significant increase in lysozyme, phagocytic and respiratory burst activity and reduced mortality during Vibrio harveyi infection. These effects were dose-related, low glucan content being beneficial whereas high glucan content had limited effects (Ai et al. 2007).

Other types of promising immunostimulants in aquaculture include synthetic double stranded RNA, referred to as Poly I:C, which is thought to stimulate anti-viral defences through binding to TLR-3 analogue in fish (Jensen et al. 2002; Lockhart et al. 2004; Bricknell and Dalmo 2005; Fernandez-Trujillo et al. 2008; Das et al. 2009) and synthetic oligodeoxynucleotides (ODNs) or CpG, which through binding to TLR-9 is thought to simulate the activity of intracellular bacterial DNA and trigger innate and adaptive response (Jorgensen et al. 2003; Bricknell and Dalmo 2005; Tassakka and Sakai 2005). As with DNA vaccines there are ecological and ethical questions that need to be addressed when using these immunostimulants in aquaculture (Myhr and Dalmo 2005).

Some concern has been expressed over the possible side effects that immunostimulants might have on the immune system of fish, especially on the developing immune system of fish larvae (Bricknell and Dalmo 2005). A build up of tolerance to the immunostimulant and related PAMPs is a possibility and prolong treatment may also have unforeseeable effects on the development of the adaptive system of the larvae. This problem has not been experimentally addressed but it is generally recommended that pulse application should be practiced rather than the constant inclusion of the immunostimulant in the feed.

The addition of various food additives like vitamins, carotenoids and herbal remedies to the fish feed have been tested in aquaculture. Overall the effects have been beneficial, for example, reducing stress response, increasing the activity of innate parameters and improving disease resistance (Ai et al. 2004; Amar et al. 2004; Puangkaew et al. 2004; Cerezuela et al. 2009; Yin et al. 2009).

## Concluding Remarks

In this review some of the main components of the fish immune system were described and the influence of inherent and external factors on the immune system and immune response of fish were discussed. Some of the main fish diseases were listed and the association between the host and the pathogen examined. Immuno-prophylactic control through vaccination, probiotics and immunostimulation were also examined.

Various aspects of this subject have, for the sake of brevity, been left out or only briefly mentioned. For example, there is an ongoing interest in genetic breeding programmes in aquaculture. Although mainly applied to cultural traits such as growth and feed conversion these programmes have also included selecting traits for disease resistance, especially of commercially valuable species like salmonids, sea bass, sea bream, catfish (*Ictalurus punctatus*), flounder, tilapia and cod (Cipriano et al. 2002; Henryon et al. 2002; Henryon et al. 2005; Sahoo et al. 2008).

An increased awareness of animal welfare has placed restrictions on large scale experiments with live fish. For example, large scale challenge tests associated with vaccine trials are presently coming under critical scrutiny. This has called for the use of molecular tools, such as microarray, to identify genetic differences that might affect disease resistance. This approach is also of interest in breeding experiments (marker-assisted breeding). However, it calls for the availability of genetic maps and these are still lacking or limited when it comes to fish species used in commercial aquaculture. Until these are available, geneti-

cally well defined and easily manageable species such as zebrafish, medaka (*Oryzias latipes*), fugu (*Takifugu rubripes*), pufferfish species, guppy (*Poecilia reticulate*) and stickleback (*Gasterosteus aculeatus*) are being used as possible models (Dahm and Geisler 2006).

Changing attitudes to environmental issues have also demanded examination of the effects the aquaculture industry might have on the environment and on wild fish (Ashley 2007). Monitoring and evaluating changes in immune parameters and the disease resistance of wild and cultured fish as well as of changing water quality are therefore other issues that have to be addressed (Gornati et al. 2005).

Important progress has been made in recent years in our knowledge of the immunological control of fish diseases which has benefitted the growing aquaculture industry worldwide and also provided better understanding of some basic immunological phenomena. Two critical elements in this area of research have been established and repeatedly confirmed: the influence of external and inherent factors like temperature and stress on the immune response of fish and the varied response of different fish species to the same or different pathogens.

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