

*Review*

## **Viruses of Fish: An Overview of Significant Pathogens**

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**Abstract:** The growing global demand for seafood together with the limited capacity of the wild-capture sector to meet this demand has seen the aquaculture industry continue to grow around the world. A vast array of aquatic animal species is farmed in high density in freshwater, brackish and marine systems where they are exposed to new environments and potentially new diseases. On-farm stresses may compromise their ability to combat infection, and farming practices facilitate rapid transmission of disease. Viral pathogens, whether they have been established for decades or whether they are newly emerging as disease threats, are particularly challenging since there are few, if any, efficacious treatments, and the development of effective viral vaccines for delivery in aquatic systems remains elusive. Here, we review a few of the more significant viral pathogens of finfish, including aquabirnaviruses and infectious hematopoietic necrosis virus which have been known since the first half of the 20th century, and more recent viral pathogens, for example betanodaviruses, that have emerged as aquaculture has undergone a dramatic expansion in the past few decades.

**Keywords:** aquabirnavirus; betanodavirus; infectious hematopoietic necrosis virus; salmonid alphavirus; epizootic hematopoietic necrosis virus; infectious salmon anemia virus; viral hemorrhagic septicemia virus

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## 1. Introduction

While early studies (pre-1950s) of fish pathology indicated the presence of ‘filterable agents’, *i.e.*, viruses [1], the viral etiology of these previously recognized diseases such as infectious pancreatic necrosis, Oregon sockeye disease, although suspected, was not proven until the use of fish cell lines for the isolation of piscine viruses was established [2,3]. Over the following three decades, the availability of fish cell lines for virus isolation provided the stimulus for the development of “modern fish virology”. The ability to isolate and expand fish viruses *in vitro* not only facilitated research on viral diseases but also led to virus isolation becoming the “gold standard” for the detection of viruses in the important aquaculture species such as carp, rainbow trout and Atlantic salmon. Even in the modern molecular era virus isolation remains an important tool for research and diagnosis. Thus, over the past decade, through the use of cell culture and molecular approaches our knowledge of the biology of fish viruses has grown exponentially. Coincidentally, fish farming has expanded globally with an increase not only in absolute production (kilotonnes/year) but also in the number of fish species being cultured in both freshwater and marine systems. The increase in aquaculture operations world-wide has provided new opportunities for the transmission of aquatic viruses and the occurrence of viral diseases remains a significant limiting factor for aquaculture production and for the sustainability of biodiversity in the natural environment. Here we provide an overview of some of the significant viral pathogens affecting finfish species.

Diagnostic techniques for viral diseases of fish will not be discussed since these have become relatively standard and include pathological and histopathological examination, virus isolation on cell culture (where cell culture systems exist), molecular techniques including conventional and real-time polymerase chain reactions, *in situ* hybridization and various immunodiagnostic techniques [4].

## 2. Aquabirnavirus

*Aquabirnavirus* is the largest and most diverse of the three genera within the family *Birnaviridae*—non-enveloped viruses with a bi-segmented, double-stranded RNA genome. The type species, infectious pancreatic necrosis virus (IPNV), was the first fish virus isolated in cell culture [5] and until recently has remained one of the most intensely studied viruses of fish. The associated disease in farmed trout was recognized as early as the 1940s but was not named infectious pancreatic necrosis (IPN), based on histopathological findings, until the mid-1950s [6]. The virus isolated from a disease outbreak causing 50% mortality of rainbow trout fingerlings is the archetype IPNV strain VR-299 [1]. Since that time a vast range of IPNV and IPN-like viruses has been isolated from a very wide host range of diseased and non-diseased salmonid and non-salmonid fish species and invertebrates world-wide [7,8]. An example of a pathogenic marine aquabirnavirus (MABV) is yellowtail ascites virus (YAV), which was the first aquabirnavirus isolated from marine fish, yellowtail (*Seriola quinqueradiata*) in Japan [9]. Since then MABV have been detected in various marine hosts [10]. This diversity within the *Aquabirnavirus* genus makes classification down to the species level difficult.

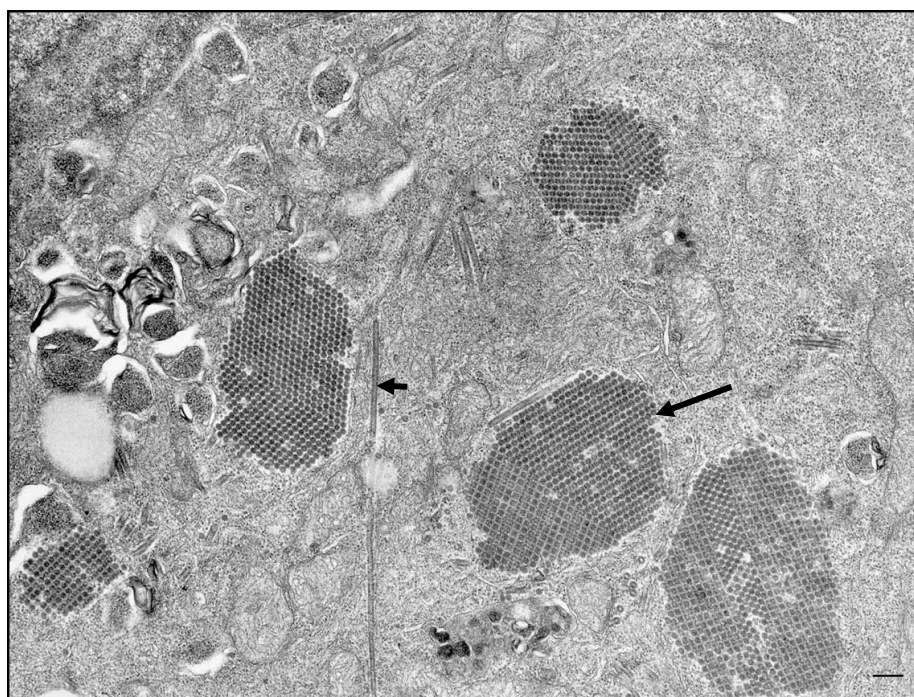
IPN was first recognized as an acute contagious disease of young salmonid fry in the freshwater phase of production that could cause up to 100% mortality. More recently, disease associated with

significant mortality has emerged in the post-smolt, seawater stages [11,12]. Aquatic birnaviruses that cause disease in salmonids (IPNV) are distinguished from other viruses that are serologically related to IPNV but are apparently avirulent, isolated from non-salmonid fish species and invertebrates and are named IPN-like or aquatic birnaviruses.

To date, 4 serogroups, A, B, C, D [7,13,14] have been proposed with most aquabirnaviruses comprising 9 serotypes (A1–A9) within serogroup A. These serotypes appear to correlate with geographical regions rather than host species. Viruses within the other 3 serogroups are less well studied. Genetic analysis indicates the clustering of 7 genogroups [15,16] which tend to correlate with geographical and serological characteristics [17].

Aquabirnavirus particles are non-enveloped icosahedrons, 60 nm in diameter (Figure 1), containing a genome consisting of two segments (A and B) of dsRNA. Segment A encodes a polyprotein which is post-translationally cleaved to form three viral proteins VP2, VP3 and VP4, with VP2 epitopes being responsible for serotype specificity and the target for neutralizing antibodies [18]. Segment B encodes VP1, an RNA-dependent RNA polymerase [19].

**Figure 1.** Transmission electron micrograph of a fathead minnow cell (FHM cell line) infected with infectious pancreatic necrosis virus (IPNV). Note the presence of virus-specific tubules (short arrow) and crystalline arrays of virions (long arrow). Scale bar represents 200 nm.



Infectious pancreatic necrosis in its acute form can cause up to 100% mortality in young salmonids and remains one of the most significant diseases of major concern to the salmonid aquaculture industry. Of further significance, the majority of fish that survive a disease outbreak become sub-clinical carriers—fish that are persistently infected with no clinical signs. These sub-clinical carriers are a source of horizontal transmission, shedding virus in their feces particularly under stressful conditions such as spawning.

Mortality rates associated with disease outbreaks can be quite variable (5–100%) and it is probable that various host, viral and environmental factors influence the severity of the outbreak [20]. While some host (e.g., nutritional status) and environmental factors (e.g., water quality) can be controlled little is known about viral virulence factors [17,21–23]. The vast diversity within this group of viruses and the broad host range has hindered progress in this area.

As with all viral diseases of finfish, avoidance is an important control strategy through the use of good bio-security measures that have been developed over the decades and are now well-established [4]. However, disease outbreaks still occur and much current research is aimed at vaccine development for viral diseases of finfish including IPN. While the lack of a reliable challenge model has slowed research on immunity to IPNV infections [24–26], there are a number of vaccines available and in use [27].

### 3. Betanodavirus

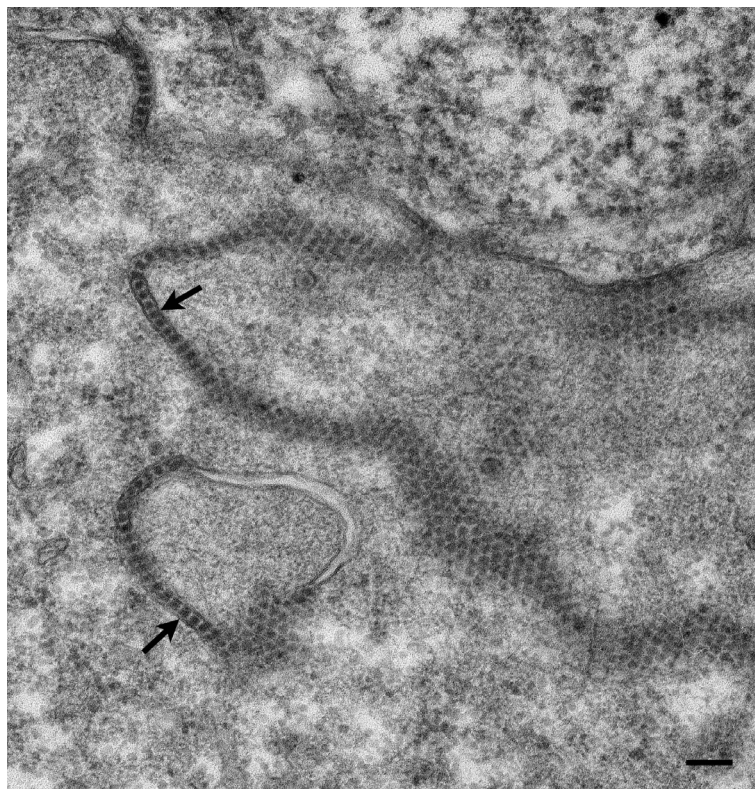
*Betanodavirus* [28] is one of the two genera making up the family *Nodaviridae* and is the etiological agent of viral nervous necrosis (VNN, also known as viral encephalopathy and retinopathy—VER). The disease was first reported in barramundi (*Lates calcarifer*) farmed in Australia [29,30], Japanese parrotfish *Oplegnathus fasciatus* [31] followed a year later in turbot *Scophthalmus maximus* [32], European sea bass *Dicentrarchus labrax* [33], redspotted grouper *Epinephelus akaara* [34] and striped jack *Pseudocaranx dentex* [35]. The disease is characterized by vacuolating necrosis of neural cells of the brain, retina and spinal cord and causes up to 100% mortality in larval and juvenile fish, and can cause significant losses in older fish. The pathology has been well-described [30,36] but research on viral characterization was delayed until the virus was eventually isolated and expanded in the SSN-1 cell line [37] and since then our knowledge on the biology of this virus has expanded rapidly.

The virus infects a large range of host species—at least 40 species of marine and freshwater fish world-wide [30]—and the known host range continues to expand as new species of fish are used for aquaculture [38,39]. Of further interest is the potential of wild fish to become sub-clinical carriers as virus-contaminated water spreads from aquaculture enterprises into the marine environment particularly for those countries with large mariculture industries [40].

Viral nervous necrosis has a wide geographical distribution and includes south and east Asia, Oceania, Mediterranean Europe and Tunisia, UK, Norway and North America. To date, the virus has not been reported from South America.

Virions of nervous necrosis virus (NNV) are small (25–30 nm in diameter), spherical and non-enveloped (Figure 2) with a genome consisting of two molecules (RNA1 and RNA2) of +ve sense ssRNA, the complete sequences of which have been determined [41]. RNA1 encodes a non-structural protein and RNA2 encodes the coat protein [35,42,43]. Based on the coat protein gene sequence, betanodaviruses have been classified into a number of genotypes; the number of genotypes has increased from the initially proposed four [44] to at least five genotypes [45,46], and several sub-genotypes [39], which appear to be restricted to geographical locations relating to water temperatures [47].

**Figure 2.** Transmission electron micrograph of an infected retinal cell with nervous necrosis virus. Virions (arrows) are located within the smooth endoplasmic reticulum. Scale bar represents 100 nm.



Current research is focused on vaccination as a potential means of control. While protection has been demonstrated in various host species using a number of different vaccination schemes [48–53], a commercially available vaccine is yet to be developed. It is likely that one vaccine will not be sufficient for the control of this disease. There are a number of considerations to be addressed including the number of different genotypes/serotypes of the virus, the relatively large number of susceptible aquaculture species, the range of environmental factors (e.g., water temperature and husbandry practices) involved with aquaculture in the different geographical locations around the world.

#### 4. Infectious Salmon Anemia Virus

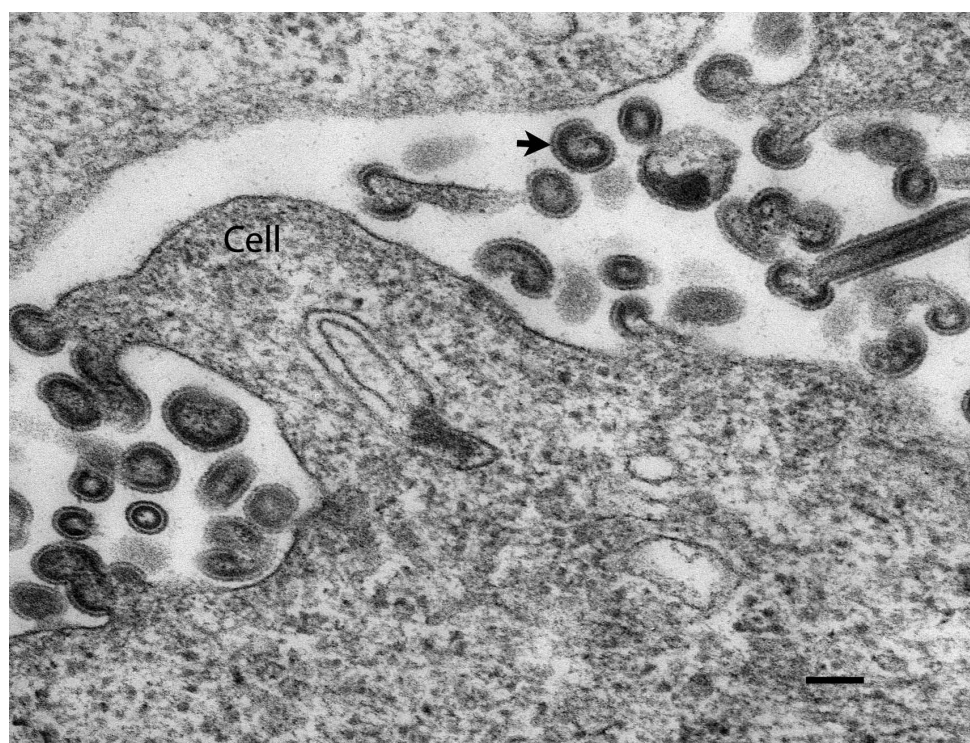
The orthomyxovirus, infectious salmon anemia virus (ISAV), is the causative agent of infectious salmon anemia (ISA), a disease of sea-farmed Atlantic salmon (*Salmo salar*). The disease initially reported in Norway [54] had been known for some time before its viral nature was confirmed when a new salmon cell line (SHK-1), susceptible to infection, was developed [55]. Since that time, with the ability to expand the virus *in vitro* and obtain purified virus, research accelerated and the virus is now well-characterised [56].

Since initial reports in Norway, ISA in Atlantic salmon has been reported in Canada [57–59], where it was originally designated hemorrhagic kidney disease, UK [60,61], Faroe Islands [62], USA [63]

and Chile [64]. Virus has also been isolated (in the absence of ISA) from rainbow trout in Ireland [65] and Coho salmon in Chile [66].

The genetic and phenotypic characteristics of ISAV place it in the *Orthomyxoviridae* [67] and it is the type species of the genus *Isavirus* [68]. ISAV virions are pleiomorphic and enveloped with a diameter of 100–130 nm and 10–12 nm surface projections (Figure 3). The genome consists of eight negative-sense ssRNA molecules which encodes at least 10 proteins including the two main surface glycoproteins, the hemagglutinin-esterase (HE), responsible for receptor-binding and receptor-destroying activities and a fusion protein [56].

**Figure 3.** Transmission electron micrograph of a cultured cell (SHK-1 cell line) infected with infectious salmon anemia virus (ISAV). Arrow indicates an extracellular virion. Scale bar represents 100 nm.



The ISAV genome has been fully sequenced [69]. Based on sequence differences of the HE gene, ISAV isolates have been divided into two major groups—the European group and the North American group [70–72]. Within these two major groups, isolates can be typed according to variations within a small, highly polymorphic region (HPR) of the hemagglutinin gene [73–76]. The HPR is characterised by the presence of gaps rather than single nucleotide mutations and, together with the fusion protein, has been implicated in viral virulence [77–80].

While fish species other than Atlantic salmon are susceptible to infection with ISAV, only Atlantic salmon develop ISA disease following infection with ISAV. Of interest, a survey of wild fish undertaken following the 1998 outbreak in farmed salmon in Scotland [60] revealed sub-clinical infections of sea trout (*S. trutta*) from which virus was isolated (5 fish positive out of 203 tested). In addition, ISAV was isolated in cell culture inoculated with one of 24 tissue pools (5 fish/pool) from cod (*Gadus morhua*) sampled from a well-boat that contained ISA-diseased salmon.

Experimental infections have demonstrated that herring (*Clupea harengus*) can be infected after immersion in ISAV-contaminated water [81], and rainbow trout (*Oncorhynchus mykiss*) by co-habitation with ISAV-infected salmon [82]. Experimental infection by intraperitoneal injection has been reported for sea/brown trout (*S. trutta*), Arctic char (*Salvelinus alpinus*) and rainbow trout [83,84]. No mortalities were associated with infection. ISAV has also been isolated from farmed Coho salmon (*O. kisutch*) in Chile [66] even though experimental studies indicate that Pacific salmon are relatively resistant to the virus [85]. Thus these fish species in which natural and/or experimental infections have been demonstrated can be considered potential carriers/reservoirs for ISAV.

As with many infectious diseases of fish, ISAV-infected fish may not necessarily exhibit clinical signs but the onset of disease may be precipitated by adverse environmental conditions or stress such as increased water temperature or poor water quality [86]. Stress factors (e.g., rising or falling temperatures) appear to play an important role in precipitating disease outbreaks in sub-clinical carrier fish; ISA outbreaks tend to occur during the spring (rising water temperatures) or with onset of winter (falling water temperatures). Cumulative mortality during an outbreak appears to be variable (from insignificant to >90%). Epidemiological studies have indicated that ISAV is transmitted from infected sources horizontally via seawater [87]. Significant risk factors include geographical proximity to infected marine sites or slaughterhouses/processing plants releasing unprocessed, contaminated water, and sharing of staff and equipment between sites. It is interesting to note that ISAV nucleic acid has been detected by RT-PCR in water samples taken up to 1.5 km away from infected sites. Thus prompt disinfection of affected and contaminated sites is likely to mitigate the risk of transmission [88].

Atlantic salmon survivors of an ISAV infection appear to be less susceptible to re-infection indicating the presence of a protective immune response [89]; in addition, convalescent antiserum has ISAV-neutralising activity [90]. For the development of vaccines the existence of different ISAV strains needs to be taken into consideration. Inactivated viral [91,92] and DNA vaccines [93] have been investigated and shown not to be 100% protective. Nevertheless, vaccines are available and have been used in North America, Faroe Islands and Norway [4].

## 5. Salmon Alphavirus

Pancreas disease (PD) has been recognized in farmed Atlantic salmon since the 1970s but the infectious nature of the disease was not proven until a toga-like virus was isolated two decades later from an outbreak in Ireland [94] and, subsequently, from outbreaks in Norway [95] and Scotland [96]. Sequence analyses [97] demonstrated that this new virus was related to the alphaviruses. Thus, Salmon alphavirus (SAV) is a relatively new species of the genus *Alphavirus* within the family *Togaviridae*. It is only recently that the relationship between salmon pancreas disease virus (SPDV) and sleeping disease virus (SDV) has been clarified. At least six subtypes of SAV (Table 1), based on analyses of partial E2 and nsP3 gene nucleotide sequences [98], have been described that are the causative agents of significant diseases of farmed Atlantic salmon and rainbow trout in Europe [99]. SAV1 or SPDV causes PD in farmed Atlantic salmon in Ireland. SAV2 or SDV causes sleeping disease in England, France, Germany, Italy, Scotland and Spain. SAV3 or Norwegian salmon alphavirus is responsible for PD in Norway, exclusively [100]. SAV4 consists of Atlantic salmon strains from Ireland, SAV5

consists of Scottish strains only and SAV6 contains one virus only, isolated from Atlantic salmon in Ireland [98].

Typical alphaviruses are transmitted by arthropods or insects, usually mosquitoes [101]. While an invertebrate vector for SAV has not been identified and direct horizontal transmission has been demonstrated [102], it is not known whether aquatic invertebrates play a significant role in the epizootiology of the SAV-associated diseases.

**Table 1.** Summary of Salmon Alphavirus (SAV) Subtypes.

<b>Virus Subtype</b>	<b>Host Range</b>	<b>Disease</b>	<b>Geographical Range</b>
SAV1	Marine Atlantic salmon	Pancreas disease	Ireland
SAV2	Freshwater rainbow trout	Sleeping disease	England, France, Germany, Italy, Scotland, Spain
SAV3	Sea-reared Atlantic salmon, rainbow trout	Pancreas disease	Norway
SAV4	Marine Atlantic salmon	Pancreas disease	Ireland, Scotland
SAV5	Marine Atlantic salmon	Pancreas disease	Scotland
SAV6	Marine Atlantic salmon	Pancreas disease	Ireland

Alphaviruses are enveloped, spherical (*ca.* 60 nm diameter) viruses with a ssRNA genome (11–12 kb in size) the coding sequences of which are organized into two large, non-overlapping open reading frames [103]. The genomes of the reference strains of SPDV (F93-125) and SDV (S49P) have been sequenced and compared demonstrating that these strains are subtypes of the same virus [104], as indicated by an earlier comparative histopathology study [105].

Early studies suggested that pre-exposed fish developed resistance to re-infection [106]. Subsequent studies have shown that inactivated virus [107] and a recombinant, attenuated salmonid alphavirus [108] could provide good protection against PD, indicating that development of a commercial vaccine should be possible.

## 6. Infectious Hematopoietic Necrosis Virus

Infectious hematopoietic necrosis virus (IHNV) is one of three rhabdoviruses of finfish listed by the OIE (the World Organisation for Animal Health), the other two being viral hemorrhagic septicemia virus (VHSV) and spring viremia of carp virus (SVCV). It is the causative agent of infectious hematopoietic necrosis (IHN) which affects most salmonid fish species [109]. First described in the 1950s, IHNV caused severe losses in salmonid hatcheries in the Pacific Northwest of the USA and since then has spread throughout North America (USA and Canada) and overseas to Asian (PR China, Iran, Japan, Rep of Korea, Russia) and European (Austria, Croatia, Czech Republic, France, Germany, Italy, Netherlands, Poland, Slovenia, Spain) countries [4] through the movement of infected eggs and/or fish [110]. Moreover, recent studies have demonstrated that spread through Europe in recent times has occurred via trade in infected fish [111]. Following introduction to a new environment with host fish of different genetic backgrounds representing new selection pressures, studies both in Europe [111] and in Japan [112] have indicated a relatively rapid evolution of IHNV.



The virus has the typical bullet shape of members of the *Rhabdoviridae* and the genome consists of a single molecule of negative-sense ssRNA (ca. 11 kb) encoding six proteins: a nucleoprotein, a phosphoprotein, a matrix protein, a glycoprotein, a non-virion protein and a polymerase [113,114]. IHNV is the type species of the genus *Novirhabdovirus* which also contains VHSV.

Originally, the host range was thought to be restricted to species within the genus *Oncorhynchus*, until in 1984 when an outbreak in Atlantic salmon (*Salmo salar*) occurred for the first time [115]. Since then, in addition to most salmonid species [109], several non-salmonid species are known to be susceptible. For example, studies with white sturgeon (*Acipenser transmontanus*) demonstrated this species susceptibility to IHNV and suggested that it represented a potential virus vector [116]. Of further interest, HIRRV, a cold water virus isolated from flounder (*Paralichthys olivaceus*) and ayu (*Plecoglossus altivelis*) in Japan [117], has been shown to be closely related to IHNV and is also a member of the genus *Novirhabdovirus* [118].

The clinical signs and histopathology have been well-documented [1]. Risk factors include fish species and fish age—as with many viral diseases of finfish, younger life stages are more susceptible and losses during acute outbreaks can reach 95% [119]. There are 4 genogroups based on nucleotide sequence variation within the G gene that encodes the viral glycoprotein [112,120] and these genogroups demonstrate differential host-specificity [121] and virulence [122]. As with most other infectious diseases of farmed fish, fish density, temperature, water quality and nutritional status of the host, and virus strain influence susceptibility to IHNV [119]. Recent studies have demonstrated that the basis for viral host-specificity and virulence are, in part, due to fish host entry and kinetics of viral replication [123].

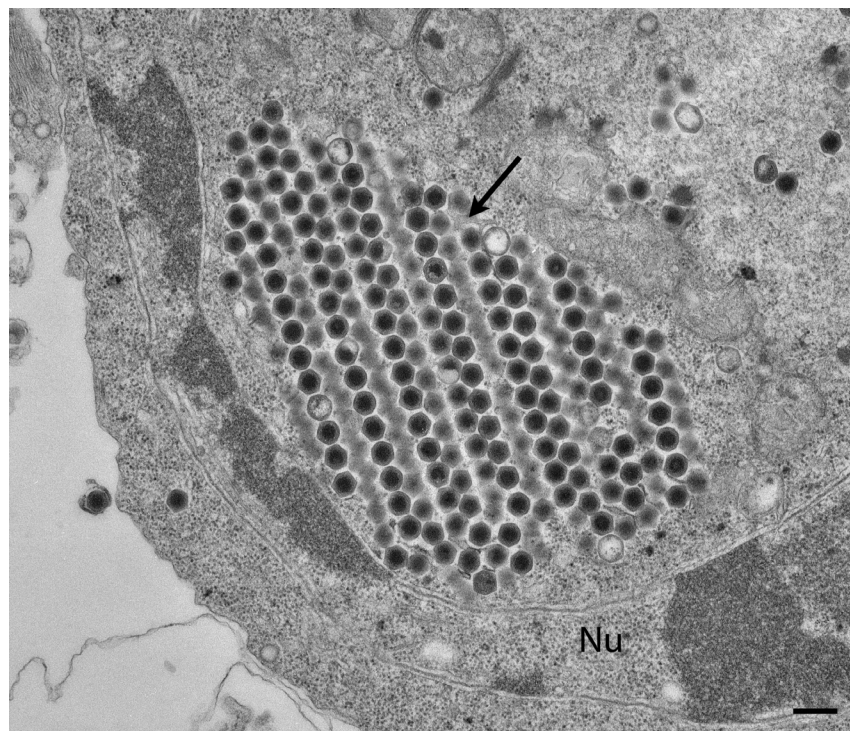
Due to the severe losses caused by IHN [109] there has been a long interest in the development of a vaccine [124–126]. While research on inactivated [127], recombinant [128] and DNA vaccines [129–131] have demonstrated that protective vaccination against IHN is readily achievable, further research is required to address practical and regulatory issues with respect to vaccine delivery and safety [132].

## 7. Epizootic Hematopoietic Necrosis Virus

Epizootic hematopoietic necrosis virus (EHNV) is a member of the genus *Ranavirus* in the family *Iridoviridae*; other genera in the family include *Iridovirus*, *Chloriridovirus*, *Lymphocystivirus* and *Megalocytivirus*. There are six viral species within the genus (*Ambystoma tigrinum virus*; *Bohle iridovirus*; *Epizootic hematopoietic necrosis virus*; *European catfish virus*; *Frog virus 3*; *Santee-Cooper ranavirus*). Species can be differentiated via RFLP profiles, virus protein profiles, DNA sequence analysis and host specificity, however none can be differentiated via classical antigen-antibody interactions (e.g., antigen capture ELISA) [4].

EHNV is a large icosahedral virus, approximately 175 nm (Figure 4) with a double-stranded DNA genome of 127 kb. It replicates in both the nucleus and cytoplasm with intracytoplasmic assembly. The virus obtains its outer limiting membrane via budding from the host cell plasma membrane. The inner capsid is surrounded by an internal lipid bilayer similar to that described for FV3 [133] and contains a nucleoprotein core consisting of a genome that is circularly permuted and terminally redundant.

**Figure 4.** Transmission electron micrograph of a fathead minnow cell (FHM cell line) infected with epizootic hematopoietic necrosis virus (EHNV). Paracrystalline arrays are indicated by the arrow. An enveloped virus that has budded from the host cell plasma membrane can also be seen. Nu = nucleus. Scale bar represents 200 nm.



EHNV was first isolated in 1985 from fatalities of juvenile redfin perch (*Perca fluviatilis*) in Victoria, Australia. It was the first virus isolated from freshwater finfish in Australia [134,135]. Since then it has been isolated from farmed rainbow trout (*Oncorhynchus mykiss* (Walbaum)) [136]. To date these are the only teleost species known to be naturally infected by EHNV with redfin perch being highly susceptible compared to rainbow trout which, under laboratory conditions, succumb only after intraperitoneal infection [137]. Laboratory infections by bath immersion have shown that a number of other species including Macquarie perch (*Macquaria australasica*), silver perch (*Bidyanus bidyanus*), mosquito fish (*Gambusia affinis*) and mountain galaxias (*Galaxias olidus*) are susceptible to infection and associated mortality. Other host species including Murray cod (*Maccullochella peeli*), golden perch (*Macquaria ambigua*), Australian bass (*Macquaria novemaculeata*), Macquarie perch, silver perch and Atlantic salmon (*Salmo salar*) were also shown to be susceptible following intraperitoneal injection with varying degrees of mortality [138].

The disease associated with EHNV is termed epizootic hematopoietic necrosis (EHN). The name implies the pathology of the disease includes necrosis of hematopoietic tissues. Specifically, EHNV causes multifocal necrosis of the spleen and renal hematopoietic tissue as well as the liver. Microscopically, there is a distinctive feature of infected cells—basophilic intracytoplasmic inclusion bodies—these structures are assembly sites of the virus where, by electron microscopy, paracrystalline arrays can be observed. Other lesions include hyperplasia and multifocal necrosis of gill epithelial cells, necrosis of atrial trabeculae and gastrointestinal epithelial cells, focal pancreatic necrosis, necrotic circulating hematopoietic cells and degenerate vascular endothelial cells in many organs

[135,136,139–141]. Pathology such as ulcerative dermatitis and swim bladder oedema and necrosis has only been described in EHNV-infected rainbow trout [140]. EHNV infection is not associated with either enlarged/giant cells or erythrocytes.

Within Australia the geographical range is limited to south-east Australia (South Australia, New South Wales and Victoria). EHNV is endemic in these areas and is now only infrequently reported. Early work by Langdon [138] demonstrated that EHNV is extremely resistant to drying, can survive for months in water, can persist in frozen fish tissues and carcasses for at least a year [138,142]. To date, no vaccines exist for the control of EHN and so on-farm control relies on bio-security measures, health surveillance schemes and good husbandry practices that reduce physiological stressors. For infected properties, de-stocking and disinfection as per OIE protocols [4] assist in preventing re-infection.

## 7. Viral Hemorrhagic Septicemia Virus

Viral hemorrhagic septicemia virus (VHSV) is a rhabdovirus of the genus *Novirhabdovirus* (Family: *Rhabdoviridae*) and is the causative agent of viral hemorrhagic septicemia—the most serious disease of farmed rainbow trout in Europe [1]. Well-recognized since the early 1900s, VHS had been considered a disease more or less restricted to rainbow trout in Europe [1,143] until, in 1988, a VHS virus was isolated from Pacific salmon returning from the sea to two Washington State hatcheries. Subsequent genetic analyses demonstrated that this virus had not in fact been imported from Europe but was a distinct strain presumably emanating from reservoir fish species in the Pacific Ocean [144,145]. Since then, through systematic surveillance programs, the known host range for VHSV has expanded enormously to include species from several fish families including *Salmonidae*, *Esocidae*, *Clupidae*, *Gadidae*, *Pleuronectidae*, to name just a few [4]. It is likely that the true host range for this virus is so large that it will never be entirely known.

Currently, four genotypes (I-IV) and several sub-genotypes of VHSV have been identified using modern molecular tools [4]. Basically, genotype I includes the European freshwater isolates as well as some marine isolates. Genotype II consists of marine isolates from the Baltic Sea. Genotype III comprises marine isolates from the North Atlantic Ocean, and genotype IV consists of the North American (IVb) and Japanese/Korean (IVa) isolates. A separate paper in this special edition of *Viruses* is devoted to the emergence of the North American genotype IVb which has caused recent significant mortality episodes in a range of fish species inhabiting the Great Lakes of North America [146]. Therefore, the section on VHSV in this paper is only brief, understanding that there are some excellent reviews available [1,143,147,148]. Current knowledge indicates that VHSV is limited to the Northern Hemisphere, although there have been no extensive surveys of wild fish populations in the Southern Hemisphere.

It is recognized that the existence of various strains of VHSV, the large host range, and the differences in pathogenicity of these strains in the various host species presents difficulties for disease control programs. Nevertheless, it is significant that eradication of VHS post-disease outbreaks in the UK [149] and Norway [150] have been successful. Indeed, Denmark, through a persistent surveillance and control program, has been declared VHS-free, after decades with endemic VHS [151].

It was recognized early on that survivors of VHS outbreaks developed resistance to re-infection [152] and so research on vaccines against VHS has a long history [153]. Currently, while there is no available commercial vaccine, use of DNA vaccines appears promising [154].

### Conflict of Interest

The authors declare no conflict of interest.

### References and Notes

1. Wolf, K. 1988. *Fish Viruses and Fish Viral Diseases*; Cornell University Press: Ithaca, NY, USA, 1988; p. 476.
2. Wolf, K.; Quimby, M.C. Established eurythermic line of fish cells *in vitro*. *Science* **1962**, *135*, 1065–1066.
3. Gravell, M.; Malsberger, R.G. A permanent cell line from Fathead Minnow (*Pimephales promelas*). *Ann. NY Acad. Sci.* **1965**, *126*, 555–565.
4. OIE. *Manual of Diagnostic Tests for Aquatic Animals*, 6th ed.; World Organisation for Animal Health: Paris, France, 2009; p. 383.
5. Wolf, K.; Sniesko, S.F.; Dunbar, C.E.; Pyle, E. Virus nature of infectious pancreatic necrosis in trout. *Proc. Soc. Exp. Med. Biol.* **1960**, *104*, 105–108.
6. Wood, E.M.; Snieszko, S.F.; Yasutake, W.T. Infectious pancreatic necrosis in brook trout. *Am. Med. Assoc. Arch. Pathol.* **1955**, *60*, 26–28.
7. Hill, B.J.; Way, K. Serological classification of infectious pancreatic necrosis (IPN) virus and other aquatic birnaviruses. *Ann. Rev. Fish Dis.* **1995**, *5*, 55–77.
8. Reno, P.W. Infectious pancreatic necrosis and associated aquatic birnaviruses. In *Fish Diseases and Disorders. Volume 3: Viral, Bacterial and Fungal Infections*; Woo, P.T.K., Bruno, D.W., Eds.; CABI Publishing: Wallingford, UK, 1999; pp. 1–56.
9. Sorimachi, M.; Hara, T. Characteristics and pathogenicity of a virus isolated from yellowtail fingerlings showing ascites. *Fish Pathol.* **1985**, *19*, 231–238.
10. Isshiki, T.; Nagano, T.; Kanehira, K.; Suzuki, S. Distribution of marine birnavirus in cultured marine fish species from Kagawa prefecture, Japan. *J. Fish Dis.* **2004**, *27*, 89–98.
11. Christie, K.E.; Håvarstein, L.S.; Djuvik, H.O.; Ness, S.; Endresen, C. Characterisation of a new serotype of infectious pancreatic necrosis virus isolated from Atlantic salmon. *Arch. Virol.* **1988**, *103*, 167–177.
12. Roberts, R.J.; Pearson, M.D. Infectious pancreatic necrosis in Atlantic salmon, *Salmo salar* L. *J. Fish Dis.* **2005**, *28*, 383–390.
13. John, K.R.; Richards R.H. Characteristics of a new birnavirus associated with a warm-water fish cell line. *J. Gen. Virol.* **1999**, *80*, 2061–2065.
14. Dixon, P.F.; Ngoh, G.H.; Stone, D.M.; Chang, S.F.; Way, K.; Kueh, S.L.F. Proposal for a fourth aquabirnavirus serogroup. *Arch. Virol.* **2008**, *153*, 1937–1941.
15. Zhang, C.X.; Suzuki, S. Aquabirnaviruses isolated from marine organisms form a distinct genogroup from othe aquabirnaviruses. *J. Fish Dis.* **2004**, *27*, 633–43.

16. Nishizawa, T.; Kinoshita, S.; Yoshimizu, M. An approach for genogrouping of Japanese isolates of aquabirnaviruses in a new genogroup, VII, based on the VP2/NS junction region. *J. Gen. Virol.* **2005**, *86*, 1973–1978.
17. Davies, K.R.; McColl, K.A.; Wang, L.-F.; Yu, M.; Williams, L.M.; Crane, M.St.J. Molecular characterisation of Australasian isolates of aquabirnavirus. *Dis. Aquat. Org.* **2010**, *93*, 1–15.
18. Dobos, P. The molecular biology of infectious pancreatic necrosis virus (IPNV). *Ann. Rev. Fish Dis.* **1995**, *5*, 25–54.
19. Dobos, P.; Hill, B.J.; Hallet, R.; Kells, D.T.; Becht, H.; Teninges, D. Biophysical and biochemical characterisation of five animal viruses with bisegmented double-stranded RNA genomes. *J. Virol.* **1979**, *32*, 593–605.
20. Snieszko, S.F. Your fishes' health: Diseases of fishes. *Trop. Fish Hobbyist.* **1981**, *3*, 78.
21. Sano, M.; Okamoto, N.; Fukuda, H.; Saneyoshi, M.; Sano, T. 1992. Virulence of infectious pancreatic necrosis virus is associated with the larger RNA segment (RNA segment A). *J. Fish Dis.* **1998**, *15*, 283–293.
22. Santi, N.; Vakharia, V.N.; Evensen, Ø. Identification of putative motifs involved in the virulence of infectious pancreatic necrosis virus. *Virology* **2004**, *322*, 31–40.
23. Santi, N.; Sandtrø, A.; Sindre, H.; Song, H.; Hong, J.-R.; Thu, B.; Wu, J.-L.; Vakharia, V.N.; Evensen, Ø. Infectious pancreatic necrosis virus induces apoptosis *in vitro* and *in vivo* independent of VP5 expression. *Virology* **2005**, *342*, 13–25.
24. Bowden, T.J.; Smail, D.A.; Ellis, A.E. Development of a reproducible infectious pancreatic necrosis virus challenge model for Atlantic salmon, *Salmo salar* L. *J. Fish Dis.* **2002**, *25*, 555–563.
25. Ramstad, A.; Romstad, A.B.; Knappskog, D.H.; Midtlyng, P.J. Field validation of experimental challenge models for IPN vaccines. *J. Fish Dis.* **2007**, *30*, 723–731.
26. Ramstad, A.; Midtlyng, P.J. Strong genetic influence on IPN vaccination-and-challenge trials in Atlantic salmon *Salmo salar* L. *J. Fish Dis.* **2008**, *31*, 567–578.
27. Evensen, Ø.; Santi, N. Infectious pancreatic necrosis virus. In *Encyclopaedia of Virology*; Mahy, B.W.J., Van Regenmortel, M.H.V., Eds; Elsevier: Oxford, UK, 2008; pp. 83–89.
28. Ball, L.A.; Hendry, D.A.; Johnson, J.E.; Ruekert, R.R.; Scotti, P.D. Family Nodaviridae. In *Virus Taxonomy Seventh Report of the International Committee on Taxonomy of Viruses*; Regenmortel, M.H.V., Fauquet, C.M., Bishop, D.H.L., Carstens, E.B., Estes, M.K., Lemon, S.D.M., Maniloff, J., Mayo, M.A., McGeoch, D.J., Pringle, C.R., Wickner R.B., Eds.; Academic Press: San Diego, CA, USA, 2000; pp. 747–755.
29. Glazebrook, J.S.; Heasman, M.P.; de Beer, S.W. Picorna-like viral particles associated with mass mortalities in larval barramundi, *Lates calcarifer* (Bloch). *J. Fish Dis.* **1990**, *13*, 245–249.
30. Munday, B.L.; Kwang, J.; Moody, N. Betanodavirus infections of teleost fish: A review. *J. Fish Dis.* **2002**, *25*, 127–142.
31. Yoshikoshi, K.; Inoue, K. Viral nervous necrosis in hatchery-reared larvae and juveniles of Japanese parrotfish, *Oplegnathus fasciatus* (Temminck & Schlegel). *J. Fish Dis.* **1990**, *13*, 69–77.
32. Bloch, B.; Gravningen, K.; Larsen, J.L. Encephalomyelitis among turbot associated with a picornavirus-like agent. *Dis. Aquat. Org.* **1991**, *10*, 65–70.

33. Breuil, G.; Bonami, J.R.; Pepin, J.F.; Pichot Y. Viral infection (picorna-like virus) associated with mass mortalities in hatchery-reared sea bass (*Dicentrarchus labrax*) larvae and juveniles. *Aquaculture* **1991**, *97*, 109–116.
34. Mori, K.; Nakai, T.; Nagahara, M.; Muroga, K.; Mekuchi, T.; Kanno, T. A viral disease in hatchery-reared larvae and juveniles of redspotted grouper. *Fish Pathol.* **1991**, *26*, 209–210.
35. Mori, K.; Nakai, T.; Muroga, K.; Arimoto, M.; Mushiake, K.; Furusawa, I. Properties of a new virus belonging to *Nodaviridae* found in larval striped jack (*Pseudocaranx dentex*) with nervous necrosis. *Virology* **1992**, *187*, 368–371.
36. Tanaka, S.; Takagi, M.; Miyazaki, T. Histopathological studies on viral nervous necrosis of sevenband grouper, *Epinephelus septemfasciatus* Thunberg, at the grow-out stage. *J. Fish Dis.* **2004**, *27*, 385–399.
37. Frerichs, G.N.; Roger, H.D.; Peric, Z. Cell culture isolation of piscine neuropathy nodavirus from juvenile sea bass, *Dicentrarchus labrax*. *J. Gen. Virol.* **1996**, *77*, 2067–2071.
38. Furusawa, R.; Okinaka, Y.; Uematsu, K.; Nakai, T. Screening of freshwater fish species for their susceptibility to a betanodavirus. *Dis. Aquat. Org.* **2007**, *77*, 119–125.
39. Moody, N.J.G.; Horwood, P.F.; Reynolds, A.; Mahony, T.J.; Anderson, I.G.; Oakey, H.J. Phylogenetic analysis of betanodavirus isolates from Australian finfish. *Dis. Aquat. Org.* **2009**, *87*, 151–160.
40. Gomez, D.K.; Mori, K.-I.; Okinaka, Y.; Nakai, T.; Park, S.C. Trash fish can be a source of betanodavirus for cultured marine fish. *Aquaculture* **2010**, *302*, 158–163.
41. Tan, C.; Huang, B.; Chang, S.F.; Ngoh, G.H.; Munday, B.; Chen, S.C.; Kwang, J. Determination of the complete nucleotide sequences of RNA1 and RNA2 from greasy grouper (*Epinephelus tauvina*) nervous necrosis virus, Singapore strain. *J. Gen. Virol.* **2001**, *82*, 647–653.
42. Nagai, T.; Nishizawa, T. Sequence of the non-structural protein gene encoded by RNA1 of striped jack nervous necrosis virus. *J. Gen. Virol.* **1999**, *80*, 3019–3022.
43. Skliris, G.P.; Krondiris, J.V.; Sieris, D.C.; Shinn, A.P.; Starkey, W.G.; Richards, R.H. Phylogenetic and antigenic characterisation of new fish nodavirus isolates from Europe and Asia. *Virus Res.* **2001**, *75*, 59–67.
44. Nishizawa, T.; Furuhashi, M.; Nagai, T.; Nakai, T.; Muroga, K. Genomic classification of fish nodaviruses by phylogenetic analysis of the coat protein gene. *Appl. Environ. Microbiol.* **1997**, *63*, 1633–1636.
45. Gagné, N.; Johnson, S.C.; Cook-Versloot, M.; MacKinnon, A.M.; Olivier, G. Molecular detection and characterization of nodavirus in several marine fish species from the northeastern Atlantic. *Dis. Aquat. Org.* **2004**, *62*, 181–189.
46. Johansen, R.; Sommerset, I.; Tørud, B.; Korsnes, K.; Hjortaas, M.J.; Nilsen, F.; Nerland, A.H.; Dannevig, B.H. Characterization of nodavirus and viral encephalopathy and retinopathy in farmed turbot, *Scophthalmus maximus* (L.). *J. Fish Dis.* **2004**, *27*, 591–601.
47. Nakai, T.; Mori, K.; Sugaya, T.; Nishioka, T.; Mushiake, K.; Yamashita, H. Current knowledge on viral nervous necrosis (VNN) and its causative betanodaviruses. *Isr. J. Aquaculture* **2009**, *61*, 198–207.

48. Sommerset, I.; Skern, R.; Biering, E.; Bleie, H.; Fiksdal, I.U.; Grove, S.; Nerland, A.H. Protection against Atlantic halibut nodavirus in turbot is induced by recombinant capsid protein vaccination but not following DNA vaccination. *Fish Shellfish Immunol.* **2005**, *18*, 13–29.
49. Thiéry, R.; Cozien, J.; Cabon, J.; Lamour, F.; Baud, M.; Scheemann, A. Induction of protective immune response against viral nervous necrosis in the European sea bass *Dicentrarchus labrax* by using betanodavirus virus-like particles. *J. Virol.* **2006**, *80*, 10201–10207.
50. Kai, Y.-H.; Chi, S.-C. Efficacies of inactivated vaccines against betanodavirus in grouper larvae (*Epinephelus coioides*) by bath immunization. *Vaccine* **2008**, *26*, 1450–1457.
51. Yamashita, H.; Mori, K.; Kuroda, A.; Nakai, T. Neutralizing antibody levels for protection against betanodavirus infection in sevenband grouper, *Epinephelus septemfasciatus* (Thunberg), immunized with an inactivated virus vaccine. *J. Fish Dis.* **2009**, *32*, 767–775.
52. Pakingking, R.; Bautista, N.B.; de Jesus-Ayson, E.G.; Reyes, O. Protective immunity against viral nervous necrosis (VNN) in brown-marbled grouper (*Epinephelus fuscogutattus*) following vaccination with inactivated betanodavirus. *Fish Shellfish Immunol.* **2010**, *28*, 525–533.
53. Pakingking, R.; Seron, R.; dela Pena, L.; Mori, K.; Yamashita, H.; Nakai, T. Immune responses of Asian sea bass, *Lates calcarifer* Bloch, against inactivated betanodavirus vaccine. *J. Fish Dis.* **2009**, *32*, 457–463.
54. Thorud, K.E.; Djupvik, H.O. Infectious salmon anaemia in Atlantic salmon (*Salmo salar* L.). *Bull. Eur. Assoc. Fish Pathol.* **1988**, *8*, 109–111.
55. Dannevig, B.H.; Falk, K.; Namork, E. Isolation of the causal virus of infectious salmon anaemia (ISA) in a long-term cell line from Atlantic salmon head kidney. *J. Gen. Virol.* **1995**, *76*, 1353–1359.
56. Dannevig, B.H.; Mjaaland, S.; Rimstad, E. Infectious salmon anemia virus. In *Encyclopaedia of Virology*; Mahy, B.W.J.; Van Regenmortel, M.H.V., Eds; Elsevier: Oxford, UK, 2008; pp. 89–95.
57. Mullins, J.E.; Groman, D.; Wadowska, D. Infectious salmon anaemia in salt water Atlantic salmon (*Salmo salar* L.) in New Brunswick, Canada. *Bull. Eur. Assoc. Fish Pathol.* **1998**, *18*, 110–114.
58. Bouchard, D.; Keleher, W.; Opitz, H.M.; Blake, S.; Edwards, K.C.; Nicholson, B.L. Isolation of infectious salmon anemia virus (ISAV) from Atlantic salmon in New Brunswick, Canada. *Dis. Aquat. Org.* **1999**, *35*, 131–137.
59. Lovely, J.E.; Dannevig, B.H.; Falk, K.; Hutchin, L.; Mackinnon, A.M.; Melville, K.J.; Rimstad, E.; Griffiths, S.G. First identification of infectious salmon anaemia virus in North America with haemorrhagic kidney syndrome. *Dis. Aquat. Org.* **1999**, *35*, 145–148.
60. Rodger, H.D.; Turnbull, T.; Muir, F.; Millar, S.; Richards, R.H. Infectious salmon anaemia (ISA) in the United Kingdom. *Bull. Eur. Assoc. Fish Pathol.* **1998**, *18*, 115–116.
61. Rowley, H.M.; Campbell, S.J.; Curran, W.L.; Turnbull, T.; Bryson, D.G. Isolation of infectious salmon anaemia virus (ISAV) from Scottish farmed Atlantic salmon, *Salmo salar* L. *J. Fish Dis.* **1999**, *22*, 483–487.

62. Christiansen, D.H.; Østergaard, P.S.; Snow, M.; Dale, O.B.; Falk, K. A low-pathogenic variant of infectious salmon anemia virus (ISAV-HPR0) is highly prevalent and causes a non-clinical transient infection in farmed Atlantic salmon (*Salmo salar* L.) in the Faroe Islands. *J. Gen. Virol.* **2011**, *92*, 909–18.
63. Bouchard, D.A.; Brockway, K.; Giray, C.; Keleher, W.; Merrill, P.L. First report of infectious salmon anaemia (ISA) in the United States. *Bull. Eur. Assoc. Fish Pathol.* **2001**, *21*, 86–88.
64. Godoy, M.G.; Aedo, A.; Kibenge, M.J.T.; Groman, D.B.; Yason, C.V.; Grothusen, H.; Lisperguer, A.; Calbucura, M.; Avendaño, F.; Imilán, M.; Jarpa, M.; Kibenge, F.S.B. First detection, isolation and molecular characterization of infectious salmon anaemia virus associated with clinical disease in farmed Atlantic salmon (*Salmo salar*) in Chile. *BMC Vet. Res.* **2008**, *4*, 28.
65. Geoghegan, F. First isolation and identification of ISAV in Ireland. In Proceedings of the 6th Annual Meeting of EU National Reference Laboratories for Fish Diseases, Brussels, Belgium, 23–24 September 2002.
66. Kibenge, F.S.B.; Gárate, O.N.; Johnson, G.; Arriagada, R.; Kibenge, M.J.T.; Wadowska, D. Isolation and identification of infectious salmon anaemia virus (ISAV) from Coho salmon in Chile. *Dis. Aquat. Org.* **2001**, *45*, 9–18.
67. Krossøy, B.; Hordvik, I.; Nilsen, F.; Nylund, A.; Endresen, C. The putative polymerase sequence of infectious salmon anemia virus suggests a new genus within the *Orthomyxoviridae*. *J. Virol.* **1999**, *73*, 2136–2142.
68. Kawaoka, Y.; Cox, N.J.; Haller, O.; Hongo, S.; Kaverin, N.; Klenk, H.D.; Lamb, R.A.; McCauley, J.; Palese, P.; Rimstad, E.; Webster, R.G. Infectious Salmon Anaemia Virus. In *Virus Taxonomy—Eight Report of the International Committee on Taxonomy Viruses*; Fauquet, C.M., Mayo, M.A., Maniloff, J., Desselberger, U., Ball, L.A., Eds.; Academic Press: New York, NY, USA, 2005; pp. 681–693.
69. Clouthier, S.C.; Rector, T.; Brown, N.E.C.; Anderson, E.D. Genomic organization of infectious salmon anaemia. *J. Gen. Virol.* **2002**, *83*, 421–428.
70. Cunningham, C.O.; Snow, M. Genetic analysis of infectious salmon anaemia virus (ISAV) from Scotland. *Dis. Aquat. Org.* **2000**, *41*, 1–8.
71. Inglis, J.A.; Bruce, J.; Cunningham, C.O. Nucleotide sequence variation in isolates of infectious salmon anaemia virus (ISAV) from Atlantic salmon *Salmo salar* in Scotland and Norway. *Dis. Aquat. Org.* **2001**, *43*, 71–76.
72. Ritchie, R.J.; Cook, M.; Melville, K.; Simard, N.; Cusack, R.; Griffiths, S. Identification of infectious salmon anaemia virus in Atlantic salmon from Nova Scotia (Canada): Evidence for functional strain differences. *Dis. Aquat. Org.* **2001**, *44*, 171–178.
73. Devold, M.; Falk, K.; Dale, O.B.; Krossøy, B.; Biering, E.; Aspehaug, V.; Nilsen, F.; Nylund, A. Strain variation, based on the hemagglutinin gene, in Norwegian ISA virus isolates collected from 1987 to 2001: Indications of recombination. *Dis. Aquat. Org.* **2001**, *47*, 119–128.
74. Kibenge, F.S.B.; Kibenge, M.J.T.; McKenna, P.K.; Stothard, P.; Marshall, R.; Cusack, R.R.; McGeachy, S. Antigenic variation among isolates of infectious salmon anaemia virus correlates with genetic variation of the viral haemagglutinin gene. *J. Gen. Virol.* **2001**, *82*, 2869–2879.



75. Nylund, A.; Devold, M.; Plarre, H.; Isdal, E.; Aarseth, M. Emergence and maintenance of infectious salmon anaemia virus (ISAV) in Europe: a new hypothesis. *Dis. Aquat. Org.* **2003**, *56*, 11–24.
76. Cook-Versloot, M.; Griffiths, S.; Cusack, R.; McGeachy, S.; Ritchie, R. Identification and characterisation of infectious salmon anaemia virus (ISAV) haemagglutinin gene highly polymorphic region (HPR) type 0 in North America. *Bull. Eur. Assoc. Fish Pathol.* **2004**, *24*, 203–208.
77. Cunningham, C.O.; Gregory, A.; Black, J.; Simpson, I.; Raynard, R.S. A novel variant of the infectious salmon anaemia virus (ISAV) haemagglutinin gene suggests mechanisms for virus diversity. *Bull. Eur. Assoc. Fish Pathol.* **2002**, *22*, 366–373.
78. Devold, M.; Karlsen, M.; Nylund, A. Sequence analysis of the fusion protein gene from infectious salmon anemia virus isolates: evidence of recombination and reassortment. *J. Gen. Virol.* **2006**, *87*, 2031–2040.
79. Markussen, T.; Jonassen, C.M.; Numanovic, S.; Braaen, S.; Hjortaa, M.; Nilsen, H.; Mjaaland, S. Evolutionary mechanisms involved in the virulence of infectious salmon anaemia virus (ISAV), a piscine orthomyxovirus. *Virology* **2008**, *374*, 515–527.
80. McBeath, A.J.; Bain, N.; Snow, M. Surveillance for infectious salmon anaemia virus HPR0 in marine Atlantic salmon farms across Scotland. *Dis. Aquat. Org.* **2009**, *87*, 161–169.
81. Nylund, A.; Devold, M.; Mullins, J.; Plarre, H. Herring (*Clupea harengus*): A host for infectious salmon anaemia virus (ISAV). *Bull. Eur. Assoc. Fish Pathol.* **2002**, *22*, 311–318.
82. Snow, M.; Raynard, R.S.; Inglis, J.; Bruno, D.W. Investigation into the potential for seawater rainbow trout (*Oncorhynchus mykiss*) to act as vectors of infectious salmon anaemia virus (ISAV). *Bull. Eur. Assoc. Fish Pathol.* **2001**, *21*, 252–262.
83. Snow, M.; Raynard, R.S.; Bruno, D.W. Comparative susceptibility of Arctic char (*Salvelinus alpinus*), rainbow trout (*Oncorhynchus mykiss*) and brown trout (*Salmo trutta*) to the Scottish isolate of infectious salmon anaemia virus. *Aquaculture* **2001**, *196*, 47–54.
84. Nylund, A.; Jakobsen, P. Sea trout as a carrier of infectious salmon anaemia virus. *J. Fish Biol.* **1995**, *47*, 174–176.
85. Rolland, J.B.; Winton, J.R. Relative resistance of Pacific salmon to infectious salmon anaemia virus. *J. Fish Dis.* **2003**, *26*, 511–520.
86. Dannevig, B.H.; Thorud, K.E. Other viral diseases and agents of cold-water fish: Infectious salmon anaemia, pancreas disease and viral erythrocytic necrosis. In *Fish Diseases and Disorders. Volume 3: Viral, Bacterial and Fungal Infections*; Woo, P.T.K., Bruno, D.W., Eds.; CABI Publishing: Wallingford, UK, 1999; pp. 149–175.
87. Jarp, J.; Karlsen, E. Infectious salmon anaemia (ISA) risk factors in sea-cultured Atlantic salmon *Salmo salar*. *Dis. Aquat. Org.* **1997**, *28*, 79–86.
88. Gustafson, L.L.; Ellis, S.K.; Bartlett, C.A. Using expert opinion to identify risk factors important to infectious salmon-anemia (ISA) outbreaks on salmon farms in Maine, USA and New Brunswick, Canada. *Prev. Vet. Med.* **2005**, *70*, 17–28.

89. Mjaaland, S.; Markussen, T.; Sindre, H.; Kjøglum, S.; Dannevig, B.H.; Larsen, S.; Grimholt, U. Susceptibility and immune responses following experimental infection of MHC compatible Atlantic salmon (*Salmo salar* L.) with different infectious salmon anaemia virus isolates. *Arch. Virol.* **2005**, *150*, 2195–2216.
90. Falk, K.; Dannevig, B.H. Demonstration of a protective immune response in infectious salmon anaemia (ISA)-infected Atlantic salmon *Salmo salar*. *Dis. Aquat. Org.* **1995**, *21*, 1–5.
91. Jones, S.R.M.; MacKinnon, A.M.; Salonijs, K. Vaccination of freshwater-reared Atlantic salmon reduces mortality associated with infectious salmon anaemia virus. *Bull. Eur. Assoc. Fish Pathol.* **1999**, *19*, 98–101.
92. Kibenge, F.S.B.; Kibenge, M.J.T.; Joseph, T.; McDougall, J. The development of infectious salmon anaemia vaccines in Canada. In *Technical Bulletin 1902, International Response to Infectious Salmon Anemia: Prevention, Control and Eradication*; Miller, O., Cipriano, R.C., Eds.; USDA, APHIS; US Dept Interior, US Geological Survey: US Dept Commerce, National Marine Fisheries Service, Washington DC, USA, 2003; pp. 39–49.
93. Mikalsen, A.B.; Sindre, H.; Torgersen, J.; Rimstad, E. Protective effects of a DNA vaccine expressing the infectious salmon anemia virus hemagglutinin-esterase in Atlantic salmon. *Vaccine* **2005**, *23*, 4895–4905.
94. Nelson, R.T.; McLoughlin, M.F.; Rowley, H.M.; Platten, M.A.; McCormick, J.I. Isolation of a toga-like virus from farmed Atlantic salmon *Salmon salar* with pancreas disease. *Dis. Aquat. Org.* **1995**, *22*, 25–32.
95. Christie, K.E.; Fyrand, K.; Holtet, L.; Rowley, H.M. Isolation of pancreas disease virus from farmed Atlantic salmon, *Salmo salar* L., in Norway. *J. Fish Dis.* **1998**, *21*, 391–394.
96. Rowley, H.M.; Doherty, C.E.; McLoughlin, M.F.; Welsh, M.D. Isolation of salmon pancreas disease virus (SPDV) from farmed Atlantic salmon, *Salmo salar* L., in Scotland. *J. Fish Dis.* **1998**, *21*, 469–471.
97. Weston, J.; Welsh, M.D.; McLoughlin, M.F.; Todd, D. Salmon pancreas disease virus, an alphavirus infecting farmed Atlantic salmon, *Salmo salar* L. *Virology* **1999**, *256*, 188–195.
98. Fringuelli, E.; Rowley, H.M.; Wilson, J.C.; Hunter, R.; Rodger, H.; Graham, D.A. Phylogenetic analyses and molecular epidemiology of European salmonid alphaviruses (SAV) based on partial E2 and nsP3 gene nucleotide sequences. *J. Fish Dis.* **2008**, *31*, 811–823.
99. McLoughlin, M.F.; Graham, D.A. Alphavirus infections in salmonids—A review. *J. Fish Dis.* **2007**, *30*, 511–531.
100. Hodneland, K.; Bratland, A.; Christie, K.E.; Endresen, C.; Nylund, A. New subtype of salmonid alphavirus (SAV), *Togaviridae*, from Atlantic salmon *Salmo salar* and rainbow trout *Oncorhynchus mykiss* in Norway. *Dis. Aquat. Org.* **2005**, *66*, 113–120.
101. Chamberlain R.W. Epidemiology of arthropod-borne togaviruses: The role of arthropods as hosts and vectors and of vertebrate hosts in natural transmission cycles. In *The Togaviruses*; Schlesinger, R.W., Ed.; Academic Press: New York, NY, USA, 1980; pp. 175–227.
102. McLoughlin, M.F.; Nelson, R.T.; Rowley, H.M.; Cox, D.I.; Grant, A.N. Experimental pancreas disease virus in Atlantic salmon *Salmo salar* post-smolts induced by salmon pancreas disease virus (SPDV). *Dis. Aquat. Org.* **1996**, *26*, 117–124.

103. Karlsen, M.; Villoing, S.; Rimstad, E.; Nylund, A. Characterisation of untranslated regions of the salmonid alphavirus 3 (SAV3) genome and construction of a SAV3 based replicon. *Virol. J.* **2009**, *6*, 173.
104. Weston, J.; Villoing, S.; Bremont, M.; Castric, J.; Pfeffer, M.; Jewhurst, V.; McLoughlin, M.; Rødseth, O.; Christie, K.E.; Koumans, J.; Todd, D. Comparison of two aquatic alphaviruses, salmon pancreas disease virus and sleeping disease virus, by using genome sequence analysis, monoclonal reactivity, and cross-infection. *J. Virol.* **2002**, *76*, 6155–6163.
105. Boucher, P.; Baudin Laurencin, F. Sleeping disease and pancreas disease; comparative histopathology and acquired cross-protection. *J. Fish Dis.* **1996**, *19*, 303–310.
106. Houghton, G. Acquired protection in Atlantic salmon *Salmo salar* parr and post-smolts against pancreas disease. *Dis. Aquat. Org.* **1994**, *18*, 109–118.
107. Lopez-Doriga, M.V.; Smail, D.A.; Smith, R.J.; Domenech, A.; Castric, J.; Smith, P.D.; Ellis, A.E. Isolation of salmon pancreas disease virus (SPDV) in cell culture and its ability to protect against infection by the ‘wild type’ agent. *Fish Shellfish Immunol.* **2001**, *11*, 505–522.
108. Moriette, C.; LeBerre, M.; Lamoureux, A.; Thanh-Lan, L.; Bremont, M. Recovery of a recombinant salmonid alphavirus fully attenuated and protective for rainbow trout. *J. Virol.* **2005**, *80*, 4088–4098.
109. Bootland, L.M.; Leong, J.C. Infectious haematopoietic necrosis virus. In *Fish Diseases and Disorders. Volume 3: Viral, Bacterial and Fungal Infections*; Woo, P.T.K., Bruno, D.W., Eds.; CABI Publishing: Wallingford, UK, 1999; pp. 57–122.
110. Rohovec, J.S.; Fryer, J.L. Dispersal of microbial pathogens through introductions and transfer of finfish. *J. Shellfish Res.* **1988**, *7*, 555.
111. Enzmann, P.-J.; Castric, J.; Bovo, G.; Thiery, R.; Fichtner, D.; Schütze, H.; Wahli T. Evolution of infectious hematopoietic necrosis virus (IHNV), a fish rhabdovirus, in Europe over 20 years: Implications for control. *Dis. Aquat. Org.* **2010**, *89*, 9–15.
112. Nishizawa, T.; Kinoshita, S.; Kim, W.-S.; Higashi, S.; Yoshimizu, M. Nucleotide diversity of Japanese isolates of infectious hematopoietic necrosis virus (IHNV) based on the glycoprotein gene. *Dis. Aquat. Org.* **2006**, *71*, 267–272.
113. Schütze, H.; Enzmann, P.J.; Kuchling, R.; Mundt, E.; Niemann, H.; Mettenleiter, T.C. Complete genomic sequence of the fish rhabdovirus infectious haematopoietic necrosis virus. *J. Gen. Virol.* **1995**, *76*, 2519–2527.
114. Morzunov, S.P.; Winton, J.R.; Nichol, S.T. The complete genome structure and phylogenetic relationship of infectious hematopoietic necrosis virus. *Virus Res.* **1995**, *38*, 175–192.
115. Mulcahy, D.; Wood, J. A natural epizootic of infectious haematopoietic necrosis in imported Atlantic salmon, *Salmo salar* L., reared in the enzootic region. *J. Fish Dis.* **1986**, *9*, 173–175.
116. LaPatra, S.E.; Jones, G.R.; Lauda, K.A.; McDowell, T.S.; Schneider, R.; Hedrick, R.P. White sturgeon as a potential vector of infectious hematopoietic necrosis virus. *J. Aquat. Anim. Health* **1995**, *7*, 225–230.
117. Kimura, T.; Yoshimizu, M.; Gorie, S. A new rhabdovirus isolated in Japan from cultured hirame (Japanese flounder) *Paralichthys olivaceus* and ayu *Plecoglossus altivelis*. *Dis. Aquat. Org.* **1986**, *1*, 209–217.

118. Kurath, G.; Higman, K.H.; Björklund, H.V. Distribution and variation of NV genes in fish rhabdoviruses. *J. Gen. Virol.* **1997**, *78*, 113–117.
119. LaPatra, S.E. Factors affecting pathogenicity of infectious hematopoietic necrosis virus (IHNV) for salmonid fish. *J. Aquat. Anim. Health* **1998**, *10*, 121–131.
120. Kurath, G.; Garver, K.A.; Troyer, R.M.; Emmenegger, E.J.; Einer-Jensen, K.; Anderson, E.D. Phylogeography of infectious hematopoietic necrosis virus. *J. Gen. Virol.* **2003**, *84*, 803–814.
121. Garver, K.A.; Troyer, R.M.; Kurath, G. Two distinct phylogenetic clades of infectious hematopoietic necrosis virus overlap within the Columbia River basin. *Dis. Aquat. Org.* **2003**, *55*, 187–203.
122. Garver, K.A.; Batts, W.N.; Kurath, G. Virulence comparisons of infectious hematopoietic necrosis virus U and M genogroups in sockeye salmon and rainbow trout. *J. Aquat. Anim. Health* **2006**, *18*, 232–243.
123. Peñaranda, M.M.D.; Purcell, M.K.; Kurath, G. Differential virulence mechanisms of infectious hematopoietic necrosis virus in rainbow trout (*Oncorhynchus mykiss*) include host entry and virus replication kinetics. *J. Gen. Virol.* **2009**, *90*, 2172–2182.
124. Engelking, H.M.; Leong, J.C. Glycoprotein from infectious hematopoietic necrosis virus (IHNV) induces protective immunity against five IHNV types. *J. Aquat. Anim. Health* **1989**, *1*, 291–300.
125. Hedrick, R.P.; LaPatra, S.E.; Yun, S.; Lauda, K.A.; Jones, G.R.; Congleton, J.L.; De Kinkelin, P. Induction of protection from infectious hematopoietic necrosis virus in rainbow trout *Oncorhynchus mykiss* by pre-exposure to the avirulent cutthroat trout virus (CTV). *Dis. Aquat. Org.* **1994**, *20*, 111–118.
126. LaPatra, S.E.; Lauda, K.A.; Jones, G.R. Antigenic variants of infectious hematopoietic necrosis virus and implications for vaccine development. *Dis. Aquat. Org.* **1994**, *20*, 119–126.
127. Anderson, E.; Clouthier, S.; Shewmaker, W.; Weighall, A.; LaPatra, S. Inactivated infectious haematopoietic necrosis virus (IHNV) vaccines. *J. Fish Dis.* **2008**, *31*, 729–745.
128. Noonan, B.; Enzmann, P.J.; Trust, T.J. Recombinant infectious hematopoietic necrosis virus and viral hemorrhagic septicemia virus glycoprotein epitopes expressed in *Aeromonas salmonicida* induce protective immunity in rainbow trout (*Oncorhynchus mykiss*). *Appl. Environ. Microbiol.* **1995**, *61*, 3586–3591.
129. Corbeil, S.; LaPatra, S.E.; Anderson, E.D.; Kurath, G. Nanogram quantities of a DNA vaccine protect rainbow trout fry against heterologous strains of infectious hematopoietic necrosis virus. *Vaccine* **2000**, *18*, 2817–2824.
130. Kurath, G.; Garver, K.A.; Corbeil, S.; Elliott, D.G.; Anderson, E.D.; LaPatra, S.E. Protective immunity and lack of histopathological damage two years after DNA vaccination against infectious hematopoietic necrosis virus in trout. *Vaccine* **2006**, *24*, 345–354.
131. Peñaranda, M.M.D.; LaPatra, S.; Kurath, G. Specificity of DNA vaccines against the U and M genogroups of infectious hematopoietic necrosis virus (IHNV) in rainbow trout (*Oncorhynchus mykiss*). *Fish Shellfish Immunol.* **2011**, *31*, 43–51.
132. Alonso, M.; Chiou, P.P.; Leong, J.-A. Development of a suicidal DNA vaccine for infectious hematopoietic necrosis virus. *Fish Shellfish Immunol.* **2011**, *30*, 815–823.

133. Yan, X.; Yu, Z.; Zhang, P.; Battisti, A.J.; Holdaway, H.A.; Chipman, P.R.; Bajaj, C.; Bergoin, M.; Rossmann, M.G.; Baker, T.S. The capsid proteins of a large, icosahedral dsDNA virus. *J. Mol. Biol.* **2009**, *385*, 1287–1299.
134. Langdon, J.S.; Humphrey, J.D.; Williams, L.M.; Hyatt, A.D.; Westbury, H.A. First virus isolation from Australian fish: an iridovirus-like pathogen from redfin perch, *Perca fluviatilis* L. *J. Fish Dis.* **1986**, *9*, 263–268.
135. Langdon, J.S.; Humphrey, J.D. Epizootic haematopoietic necrosis a new viral disease in redfin perch, *Perca fluviatilis* L., in Australia. *J. Fish Dis.* **1987**, *10*, 289–298.
136. Langdon, J.S.; Humphrey, J.D.; Williams, L.M. Outbreaks of an EHNV-like iridovirus in cultured rainbow trout, *Salmo gairdneri* Richardson, in Australia. *J. Fish Dis.* **1988**, *11*, 93–96.
137. Whittington, R.J.; Reddacliff, G.L. Influence of environmental temperature on experimental infection of redfin perch (*Perca fluviatilis*) and rainbow trout (*Oncorhynchus mykiss*) with epizootic haematopoietic necrosis virus, an Australian iridovirus. *Aus. Vet. J.* **1995**, *72*, 421–424.
138. Langdon, J.S. Experimental transmission and pathogenicity of epizootic haematopoietic necrosis virus (EHNV) in redfin perch, *Perca fluviatilis* L., and 11 other teleosts. *J. Fish Dis.* **1989**, *12*, 295–310.
139. Whittington, R.J.; Philbey, A.; Reddacliff, G.L.; MacGown A.R. Epidemiology of epizootic haematopoietic necrosis virus (EHNV) infection in farmed rainbow trout, *Oncorhynchus mykiss* (Walbaum): Findings based on virus isolation, antigen capture ELISA and serology. *J. Fish Dis.* **1994**, *17*, 205–218.
140. Reddacliff, L.A.; Whittington, R.J. Pathology of epizootic haematopoietic necrosis virus (EHNV) infection in rainbow trout (*Oncorhynchus mykiss* Walbaum) and redfin perch (*Perca fluviatilis* L.). *J. Comp. Pathol.* **1996**, *115*, 103–115.
141. Whittington, R.J.; Becker, J.A.; Dennis, M.M. Iridovirus infections in finfish—A critical review with emphasis on ranaviruses. *J. Fish Dis.* **2010**, *33*, 95–122.
142. Whittington, R.J.; Kearns, C.; Hyatt, A.D.; Hengstberger, S.; Rutzou, T. Spread of epizootic haematopoietic necrosis virus (EHNV) in redfin perch (*Perca fluviatilis*) in southern Australia. *Aus. Vet. J.* **1996**, *73*, 112–114.
143. Meyers, T.R.; Winton, J.R. Viral hemorrhagic septicaemia virus in North America. *Ann. Rev. Fish Dis.* **1995**, *5*, 3–24.
144. Oshima, K.H.; Higman, K.H.; Arakawa, C.K.; de Kinkelin, P.; Jørgensen, P.E.V.; Meyers, T.R.; Winton, J.R. Genetic comparison of viral hemorrhagic septicaemia virus isolates from North America and Europe. *Dis. Aquat. Org.* **1993**, *17*, 73–80.
145. Batts, W.N.; Arakawa, C.K.; Bernard, J.; Winton, J.R. Isolates of viral hemorrhagic septicemia virus from North America and Europe can be detected and distinguished by DNA probes. *Dis. Aquat. Org.* **1993**, *17*, 67–71.
146. Faisal, M. Michigan State University, MI, USA. *Viruses* to be submitted for publication, 2011.
147. Smail, D.A. Viral haemorrhagic septicaemia. In *Fish Diseases and Disorders. Volume 3: Viral, Bacterial and Fungal Infections*; Woo, P.T.K., Bruno, D.W., Eds.; CABI Publishing: Wallingford, UK, **1999**; pp. 123–148.
148. Skall, H.F.; Olesen, N.J.; Møllergaard, S. Viral hemorrhagic septicaemia virus in marine fish and its implications for fish farming—A review. *J. Fish Dis.* **2005**, *28*, 509–529.

149. Stone, D.M.; Ferguson, H.W.; Tyson, P.A.; Savage, J.; Wood, G.; Dodge, M.J.; Woolford, G.; Dixon, P.F.; Feist, S.W.; Way, K. The first report of viral haemorrhagic septicaemia in farmed rainbow trout, *Oncorhynchus mykiss* (Walbaum), in the United Kingdom. *J. Fish Dis.* **2008**, *31*, 775–784.
150. Dale, O.B.; Ørpetveit, I.; Lyngstad, T.M.; Kahns, S.; Skall, H.F.; Olesen, N.J.; Dannevig, B.H. Outbreak of viral haemorrhagic septicaemia (VHS) in seawater-farmed rainbow trout in Norway caused by VHS virus Genotype III. *Dis. Aquat. Org.* **2009**, *85*, 93–103.
151. Mellergaard, S. Surveillance and eradication of VHS in Denmark. In Report on the 15th Annual Meeting of EU National Reference Laboratories for Fish Diseases, Copenhagen, Denmark, 26–27 May, 2011; p. 18.
152. Vestergard Jorgensen, P.E. Egtved virus: Temperature-dependent immune response of trout to infection with low-virulence virus. *J. Fish Dis.* **1982**, *5*, 47–55.
153. de Kinkelin, P.; Bearzotti, M.; Castric, J.; Nougayrede, P.; Lecocqxonneux, F.; Thiry, M. Eighteen years of vaccination against viral haemorrhagic septicaemia in France. *Vet. Res.* **1995**, *26*, 379–387.
154. Lorenzen, E.; Lorenzen, N.; Einer-Jensen, K.; Brudeseth, B.; Evensen, Ø. Time course study of *in situ* expression of antigens following DNA-vaccination against VHS in rainbow trout *Oncorhynchus mykiss* (Walbaum) fry. *Fish Shellfish Immunol.* **2005**, *19*, 27–41.

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