Infectious Salmon Anaemia

Summary

Introduction

1. This note provides a summary of the Disease and Product analysis prepared by a DISCONTOOLS group of experts on Infectious Salmon Anaemia (ISA). They reviewed the current knowledge on the disease, considered the existing disease control tools, identified current gaps in the availability and quality of the control tools and finally determined the research necessary to develop new or improved tools. Full details are available on the website at http://www.discontools.eu/ while the full gap analyses matrices can be found on the website and downloaded here

Disease profile

2. Atlantic salmon (*Salmo salar*) is the only species reported to develop clinical Infectious Salmon Anaemia. In addition, WOAH considers rainbow trout (*Oncorynchus mykiss*) and brown trout (*Salmo trutta*) susceptible species to the virus causing ISA. The virus has been detected in wild susceptible species probably due to horizontal transmission from farms with an on-going disease outbreak.

3. Although outbreaks in commercial fresh-water farms have been reported, the disease is regarded to predominantly affect fish in the sea water phase of production, most often several months after sea transfer. This may be due to slow development of the infection (latent infection or mutation from HPR0 to HPRdel – see below). Outbreaks may also occur just a few weeks after sea transfer, probably due to an infection started in the hatchery.

4.Infectious salmon anaemia is caused by *Isavirus salaris* (ISAV), an orthomyxovirus structurally resembling the influenza virus in terrestrial animals. This virus appears in two main forms; a non-virulent form denoted ISAV HPR0 and a virulent form denoted ISAV HPR. The HPR0 form is regarded as the wild-type (original form) that under certain conditions (drivers not known) changes genetically in multiple independent transitions to the virulent form. The transition to virulence is characterized by a deletion in the highly polymorphic region (HPR) of the genomic segment encoding haemagglutinin esterase, and a change in the genomic region encoding the activating cleavage site. Together, these changes increase the efficiency of ISAV fusion and cellular entry. The mutations create a variety of virulent forms commonly denoted as ISAV HPRdel (deleted). These variants vary in their ability to cause disease, some causing a cumulative mortality of 10-15 % in a month while others causing almost no mortality. HPR0 primarily replicates superficially in gill epithelial cells, with no detectable cellular damage (low cytopathogenicity). The virus sheds apically from the cells, meaning that HPR0 ends up in the water and then appears to spread rapidly to other fish. The HPRdel variants are all able to invade and infect vascular endothelial cells. HPRdel is shed to the blood vessel lumen and may then cause severe anaemia and circulatory disturbances leading to high mortality. Shedding of HPRdel to the environment could be relatively low until severe disease and mortality ensue. The early removal of net pens harbouring infected fish appears to substantially slow disease progression in neighbouring net pens.

5.Historically, field outbreaks often resulted in extreme anaemia with high mortality and devasting economic impact, both for the individual farmer and the industry in general. However, current management regimes are designed to detect disease early, and mortality in infected net pens is often low, in the range of 0.5-1‰. In contrast, experimental bath challenge with strains of suspected high virulence can give 100% mortality after approximately 3-4 weeks. Different countries have different procedures for controlling ISA. Some countries stamp out and fallow the whole site when outbreaks occur, others take out the affected pens only.

Risk

6. ISA has been diagnosed and caused devastating mortalities in all Atlantic salmon farming countries except Tasmania. An ISA-infection may start slowly without clinical disease. The virus is transmitted horizontally within a cage and often with some delay to other cages on a site. ISAV from infected fish or dead fish may be transmitted through water to neighbouring farms. A radius of 5 km is often established as a protection zone, despite limited knowledge about the survival of the virus (protected or non-protected) in surface sea water. Virus transmission between farms is also known to occur due to movement of live fish, sharing of farming equipment, and service boats. There is no

strong evidence for true vertical transmission, but poor surface disinfection of fertilized eggs from infected broodstock could result in virus transmission.
7. ISA does not have zoonotic potential.

Diagnostics
8. Clinical signs of reduced appetite, slow movements, general circulatory problems with pale gills, low haematocrit, bleeding, pin-point bleeds in the skin, together with autopsy findings (most typical lesions in the liver and congestion of internal organs) can be indicative of ISA.
9. A verification of the diagnosis is done by two independent methods, commonly PCR analysis and histopathological/ immunohistochemical examination, alternatively PCR and virus isolation. Sequencing is required to differentiate between the different ISA virus variants.

Vaccines
10. Vaccines (intraperitoneal injection) against ISA are commercially available in countries where the disease is a problem, and mandatory in Chile and the Faroe Islands. Most vaccines are multivalent water-in-oil formulations where the ISAV component is mixed with bacterial and other viral components. The ISAV antigen is either inactivated whole virus particles or recombinant ISAV proteins. The antigens used are based on European and North American- genotypes, depending on manufacturer.
11. Whether vaccination can reduce the risk of emerging variants evading the host immunity response and replicate and shed from endothelial tissues, is not known. There is a lack of randomised field trials for effectiveness of the vaccine over the production cycle. The relatively low frequency of field transitions from HPR0 to HPRdel makes it difficult to establish whether vaccination affects this risk.

Pharmaceuticals
12. No pharmaceuticals are available for ISA treatment, and treating populations infected with HPRdel is not a viable option. Future strategies developed for viruses with similarity to ISAV such as avian influenza, could, however, offer promising avenues for adaptation or further research.

Knowledge
13. Little is known about the dynamics of potentially mixed HPR0 and HPRdel infections and their interactions. There is a need for reliable, validated, and practical diagnostic methods; non-lethal testing and other methods to detect the early emergence of HPRdel, as well as segment reassortments. There is also a need to understand fish and environmental factors that affect the ability of ISAV to infect endothelium, which appears to be central to disease progression. Cell lines that allow ISAV HPR0 replication are not available, but would help increase the understanding of the pathogenesis, evolution, disease dynamic, and potentially develop better vaccines. In the meantime, studies using reverse genetics could expand our knowledge on the emergence of virulent ISAV. Epidemiological and modelling studies are vital to support the design of policies and regulatory measures, as well as identifying new host and environmental risk factors created by the very dynamic industry of fish farming since the ground-breaking studies of ISA decades ago.

Conclusions
14. Effective control of ISAV requires an integrated approach combining improved biosecurity, epidemiological understanding, enhanced diagnostics, and effective vaccines. The expert group has identified the endemic presence of HPR0 as a key challenge for the control of infectious salmon anaemia, because it represents an unclear relevance and a source of new pathogenic HPRdel viruses. Better model systems are needed to understand the infection dynamics and persistence/maintenance of HPR0. Moreover, information is needed about environmental, management and host factors that influence the potential of emerging HPRdel variants to cause ISA outbreaks, including the impact of vaccination. There is also a need for better understanding how the genomic variations among different HPRdel viruses influence vaccine efficiency, virulence, and the potential for transmission. Moreover, it is central to identify host, management, and environmental drivers that direct the susceptibility to both HPR0 and HPRdel infection, as well as the emergence of new pathogenic strains.