Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Fakulteten för veterinärmedicin och husdjursvetenskap
Institutionen för biomedicin och veterinär folkhälsovetenskap

Epidemiological aspects of infectious salmon anemia

Epidemiologiska aspekter av infektiös laxanemi

Karl Mård

Uppsala
2019

Veterinärprogrammet, examensarbete för kandidatexamen

Epidemiological aspects of infectious salmon anemia

Epidemiologiska aspekter av infektiös laxanemi

Karl Mård

Handledare: *Susanna Sternberg Lewerin, Sveriges lantbruksuniversitet, Institutionen för biomedicin och veterinär folkhälsovetenskap*

Examinator: *Maria Löfgren, Sveriges lantbruksuniversitet, Institutionen för biomedicin och veterinär folkhälsovetenskap*

Omfattning: *15 hp*
Nivå och fördjupning: *Grundnivå, G2E*
Kurstitel: *Självständigt arbete i veterinärmedicin*
Kurskod: *EX0862*
Program/utbildning: *Veterinärprogrammet*

Kursansvarig institution: *Institutionen för biomedicin och veterinär folkhälsovetenskap*

Utgivningsort: *Uppsala*
Utgivningsår: *2019*
Elektronisk publicering: *http://stud.epsilon.slu.se*

Nyckelord: *Infektiös laxanemi, ILA, Epidemiologi*
Key words: *Infectious salmon anemia, ISA, Epidemiology*

Sveriges lantbruksuniversitet
Swedish University of Agricultural Sciences

Fakulteten för veterinärmedicin och husdjursvetenskap
Institutionen för biomedicin och veterinär folkhälsovetenskap

CONTENT

SUMMARY

Infectious salmon anemia is an orthomyxyviral disease posing a serious challenge to the aquaculture of atlantic salmon (*Salmo salar*). The virus causes severe disease resulting in high moratlity and significant costs to the industry. Several factors, natural and human induced, have been studied as to their proposed role in the spread of the ISA-virus and its impact on salmon farming. Spread by equipment and fish movement is well substantiated. Equally substantial is the impact of geographical relations between farms, processing boat lanes, processing plants and other farms. However, the evidence for the proposed direct waterborne spread, that this often is attributed to, is inconclusive and perhaps even negligible in a natural setting. This is because the virion's ability to survive in biologically active and UV-radiated water might not allow waterborne spread over long distances. There is also evidence suggesting that the general health of a population of salmon affects the risk of outbreaks and that immunosuppression due to chronic stress induced by high stocking densities, routine vaccination via injection and major sea lice infestation might increase susceptibility to the disease. Much like mammalian and avian influenza (other orthomyxoviral agents) there is a substantial difference in the pathogenic potential between different strains, with some producing no clinical disease while others are deadly due to minor changes in the viral genome. The non-pathogenic strains, causing no clinical disease, was in one study found to be highly prevalent and have been shown to be potential ancestors to pathogenic strains, and as such might be central to the disease's epidemiology. Wild salmonids have been shown to be potential symptomless carriers of the virus and sea lice have under experimental conditions acted as mechanical vectors; suggesting a complex epidemiology that might be dependent on the combined prevalence of pathogenic and non-pathogenic strains as well as an unknown role of natural reservoirs and vectors in the spread of the disease.

SAMMANFATTNING

Infektiös laxanemi (ILA) är ett orthomyxovirus som representerar en betydande utmaning för kommersiell laxodling. Viruset orsakar allvarlig sjukdom hos atlantisk lax (*Salmo salar*) som ofta resulterar i hög dödlighet och stora kostnader för industrin. Flera faktorer, både naturliga och relaterade till mänsklig aktivitet, har studerats utefter deras roll i sjukdomens epidemiologi. Spridning via utrustning och fisktransporter är väldokumenterat och har stort stöd i litteraturen. Ett liknande stöd finns även för den geografiska relationen mellan odlingar, processeringsbåtar, processeringsstationer och andra odlingar. Stödet för den direkta spridningen via vatten som detta ofta associeras med är mindre entydigt, möjligen till och med negligerbart under naturliga förhållande. Det finns evidens som tyder på att den generella hälsostatusen i en odling påverkar risken för ILA-utbrott och att immunosuppression orsakat av kronisk stress till följd av hög beläggningsgrad, rutinmässig vaccination via injektion och betydande infestation av laxlus ökar mottagligheten för sjukdomen. I stil med influensa hos däggdjur och fåglar (andra orthomyxovirala agens) finns stora skillnader i virulens mellan olika stammar av viruset till följd av mindre skillnader i det virala genomet; vissa producerar ingen klinisk sjukdom medan andra leder till hög mortalitet. De lågpatogena stammarna visades i en studie ha en hög prevalens och anses vara en potentiell föregångare till högpatogena varianter, vilket kan tyda på att de har en viktig roll i sjukdomens spridning. Vilda laxfiskar har visats vara potentiella symptomfria bärare av viruset och likaså har laxlus under experimentella förhållanden agerat som mekaniska vektorer. Detta tyder på en komplex epidemiologi med inverkan av den kombinerade prevalensen av hög- och lågpatogena stammar tillsammans med en okänd roll av naturliga reservoarer och vektor.

INTRODUCTION

Infectious salmon anemia virus (ISAV) is an orthomyxoviral agent primarily affecting salmonid fish. The virus produces severe clinical disease, termed infectious salmon anemia (ISA), in the commercially valuable farmed atlantic salmon (*Salmo salar*), characterized by a slowly developing anemia, lethargy and hemorrhage; sometimes resulting in a mortality approaching 100% (SVA 2019). The virus is listed by the World Organisation For Animal Health (OIE 2019) as well as in the Swedish law of epizootic diseases (SFS 1999:657). After being described for the first time in Norway during the 1980-ies the disease now occur in most major salmon aquaculture sites around the world with documented outbreaks in Scotland, Canada, Chile and Ireland (SVA 2019). The literature concerning the epidemiology of the disease paint a picture of a multifactorial spread with several diverse variables implicated. This text aims to review currently available research and evaluate its content.

MATERIAL AND METHOD

The articles this work is based on was gathered from online databases and found by searching for combinations of the terms "infectious salmon anemia", "ISA", "risk factors" and "biosecurity". Several articles used where found in the lists of references of the articles found by the means stated above.

LITERATURE

Transportation of feed, fish and equipment and site placement.

Geographical spread of ISA is not completely understood but several human activities appear in the literature as being linked with an increased risk of outbreaks. McClure *et al*., 2005 performed a 6 months study following 83 aquaculture sites in New Brunswick, Canada. The study accounted for dozens of factors perceived to have a potential relation to the risk of ISA-outbreaks. Seven variables remained statistically significant in their final model. Of these the risk factor with strongest correlation with ISA-outbreaks was shown to be at which distance fish processing boats travel past a site. Sites having processing boats passing in close proximity had a higher risk for outbreaks. Their models attributed sites where processing boats passed within 1km with an OR of 9.43 and HR of 7.57 as opposed to sites where boats passed at a further distance.

Similarly, this study and another from New Brunswick (Hammell and Dohoo, 2005) also showed that sites that had their feed delivered by a boat operated by a feed company had an increased risk (OR 4.03 and 2.69, HR 2.66 (McClure *et al.*, 2005)) (HR 1.69 (Hammell & Dohoo, 2005)) compared with those with feed delivered by other means. The first OR (McClure *et al*.) was given by a model using variables accounted for by all participating sites while the later used a smaller sample of sites having a more complete record of variables. A Norwegian study (Lyngstad *et al*., 2018) modeled the impact of the length of a site's stocking period (a procedure requiring boat trafficking) on the risk of contracting ISA. Their study showed that when this period exceeded two months the risk for ISA-outbreaks increased (OR=3.88). An related issue appear to be receiving fish from more than one freshwater hatchery, which have been shown to increase the risk of ISA (Vagsholm *et al.*, 1994; Jarp & Karlsen, 1997).

McClure *et al*. (2005) also showed the distance to neighboring ISA-positive sites was associated with the probability of a site contracting ISA. Farms having an infected neighboring site within 0.5 km had an OR of 2.27 over those where the closest ISA-neighbor where further off. This is supported by two Norwegian studies (Vagsholm *et al.*, 1994; Jarp & Karlsen, 1997) producing similar findings. The former showed increased risk related to the number of adjacent infected sites (OR 8.3) and processing plants (OR 5.2). In (Jarp & Karlsen, 1997) there was a significantly heightened risk (OR 14.6) for sites situated within 5km of a slaughterhouse without a system of disinfection.

In Norway (Lyngstad *et al.*, 2018) the risk of infection seems to increase with latitude. Of the 4471 sites in their study, 33 were identified as outbreaks, of which only one occurred between 58ºN and 62ºN while there were 32 cases evenly distributed between 62ºN and 71ºN

Survival in seawater of the ISAV is of interest regarding the epidemiology of the disease as it is related to several described risk factors. Therefor it has also been studied. Since salmonid fish appear to be the main host of the virus the temperature range in which it can replicate corresponds to the temperature of the water where salmonids are found. Usually around 5-15 ºC. (Rimstad & Mjaaland, 2002). However, reports differ regarding the virion's stability under different environmental conditions. Tapia *et al*., (2013) found that water temperature and salinity was significant determinants. In their study survivability in temperatures ranging from 5 º C to 20 ºC was tested, peaking at 10 ºC (55.5 days) and lowest at 20 ºC (25.5 days). Water salinity had an inversed relation to survivability with natural seawater having the lowest time of survival (8 days) and natural freshwater the highest (59 days). According to another study (Rimstad & Mjaaland, 2002) ISAV kept in 4 ºC seawater can be detected for at least 4 months. Nylund *et al*. (1994) states that ISAV remains infective for at least 20 hours when maintained in seawater but did not study it further.

In a more resent study (Vike *et al*., 2014) the authors argue that the previously mentioned studies regarding ISAV's survival in seawater fail to address several significant variables present in a natural setting, chiefly the impact of biological activity in seawater and the exposure of ultraviolet radiation (UVR). Vike *et al*., (2014) showed that ISA-virions were no longer able to infect smolt after 3 hours being maintained in non-sterilized seawater or seawater exposed to UVR in levels corresponding to what could be expected in a natural setting.

Replication of the virus reaches a maximum at about 15 ºC and drops to about 1% at 20 ºC, halting completely at 25 ºC (Falk *et al.*, 1997).

Smolt bathed in, or intraperitoneally (I.P) injected with seawater containing the ISAV did in one study not contract the disease unless biological matter from infected fish was present (Nylund *et al.*, 1994). Skin mucus, blood, urine and faeces taken from infected fish results in consequent infection if I.P injected in smolt (Totland *et al.*, 1996).

General stock health and non-ISA disease burden.

The general health status of fish on aquaculture sites has been shown to affect the risk of ISA-outbreaks. Sites with a post seawater transfer (from freshwater hatchery to marine grow-out residence) mortality of more than 5% during the first 30 days or subjected to 2 or less lice treatments during the timespan of the study was, by McClure *et al*. (2005) attributed with an OR of 4.52 and 3.31 respectively. The association between general mortalities, sea lice treatment and the risk of ISA-outbreaks is also supported by a study by Hammell and Dohoo. In the case of mortalities, they showed that sites with a cumulative mortality rate (CMR) during the years 1996/97 above 0.007 had on OR of 10.06 compared with those with a CMR less than 0.003. Regarding sea lice treatment the HR was reduced to 0.39 for those treated twice by bath compared to those never treated. Nor the cause of deaths or the presence of sea lice was specified in either study.

The presence of adult sea lice may induce chronic stress, resulting in elevated plasma corticosteroid levels of infested fish (Bowers *et al.*, 2000), which has been shown to increase susceptibility to microbial infections (Pickering & Pottinger, 1989). Routine vaccination intraperitoneal injection, as opposed to less invasive means, was shown by (Vagsholm *et al.*, 1994) to increase the risk of contracting ISA.

Lyngstad *et al*., (2018) showed that sites having a history of infectious pancreatic necrosis were about three times more likely to experience an ISA-outbreak.

Vaccination

Currently several commercial vaccines against ISA are available. Most of these are administered by injection, a procedure that might increase susceptibility to other microbial infections. This has led to an interest in developing orally administered versions, which has proven to be effective. (Caruffo *et al.*, 2016)

Pens and hydrography

A shallow pen design might increase risk of the resident salmon contracting ISA, as was shown by McClure *et al*. (2005) Their study compared pens 9 meter or less in depth with deeper ones, resulting in an OR of 3.34 for the former.

In Hammell and Dohoo's (2005), larger amounts of fish in a pen and high stocking density proved significant risk factors. Pens stocked with 5000-12000 fish had an OR of 4.42, increasing to 15.60 for those stocked with 12000 or more compared to those with fewer than 5000 fish. When comparing stocking density their model gave an OR of 7.27 for pens stocked with 2.5-5 fish per cubic meter over pens with a lesser density. The model showed no statistically significant increase in risk when comparing pens stocked with more than 5 fish per cubic meter and pens stocked with less than 2.5. The study by Lyngstad *et al*. (2018) supports these findings, having also shown that risk increases with maximum stocking density.

In Hammell and Dohoo, (2005) the number of months where the fish were given moist feed decrease risk of contracting ISA, having an HR of 0.08 when fish were fed moist feed for 5-7 months between January and July opposed as to those receiving none. Weight of smolt at time

of recruitment appear to affect risk. Pens stocked with larger fish are more susceptible (McClure *et al*., 2005).

Natural reservoirs

Natural reservoirs have been hypothesized as an important factor in the spread of ISA. Sampling of salmon farms have yielded several different strains of ISAV, some highly pathogenic, some causing no apparent clinical infection and some somewhere in between (Mjaaland *et al.*, 2002). This diversity in pathology have been attributed to the deletions, or lack of deletions, of a highly polymorphic region (HPR) in the hemagglutinin gene (Christiansen *et al.*, 2017). The highly pathogenic HPR-deleted strains are able to infect endothelial cells throughout a host body (Aamelfot *et al.*, 2012) while the HPR0 strains seem to only affect epithelial cells in the gills (Christiansen *et al.*, 2011). HPR0 (non-deleted) ISA may the ancestral form of the pathogenic strains (Mjaaland *et al.*, 2002). This have led to the theory that pathogenic strains may arise independently as a mutation of circulating strains that do not produce clinical symptoms (Mjaaland *et al*., 2002; Christiansen *et al*., 2011).

In the Faroe Islands HPR0-ISA infections have been found to appear as a prevalent and self-limiting infection of sea-stocked salmon, most prominent during winter months. HPR0-ISAV spread and cleared rapidly within a farm, suggesting that the virus originated in a natural reservoir. (Christiansen *et al.*, 2011).

Devold *et al*. (2000) managed to experimentally infect sea trout (*Salmo trutta*) by challenging them via intraperitoneal injection of ISAV acquired from the blood of infected Atlantic salmon. Blood and kidney tissue taken from the challenged trout was introduced to susceptible cell cultures. These proved infective 135 days after the trout was injected with the virus (previous attempts were unsuccessful) and only after the trout were given corticosteroids prior to the taking of blood and tissue. The study also attempted to use blood from the trout to infect Atlantic salmon in an experimental environment. Here, blood taken 25 days post challenge and injected intra peritoneally in a group of salmon resulted in clinical ISA-infection. This occurred without any immunomodulation of either group of fish. Injecting blood taken from the trout on later dates did not result in clinical disease, however, after 25 days the injected salmon were tested positive for the ISA-virus by RT-PCR.

Sea lice have under experimental conditions been able to transmit ISAV to naïve salmon, as in a study by Oelckers *et al*. (2014) where ISA-positive *Caligus rogercresseyi* managed to transfer the infection to salmon up to 48 hours after the lice had been in contact with infected fish. The presence of viral particles on or in the ISA-positive lice decreased dramatically after spending more than 48 hours in seawater without an infected host, suggesting that they are not true biological vectors but rather act as mechanical transmitters. This is supported by another study (Nylund *et al.*, 1994) that showed that groups of salmon that were infested with lice taken from ISA-positive fish were more susceptible to ISA-infection.

McClure *et al*. (2005) inquired about the presence of wild pollock (*Pollachius virens*) in farms attending the study, asking whether the farmers perceived that there were more than 1000 in any individual pen. When put in a logistic regression model that only used what they considered "Cage-level" factors, (variables directly concerning the pens used in the study) pens with that

amount of resident pollock had a higher risk of contracting ISA. It is, however, unlikely that pollock have a direct role as vectors or reservoirs of the virus. Snow *et al*. (2002) challenged pollock originating from the wild via co-inhabitation with infected salmon and i.p. injection with isolated ISAV. Neither case provided PCR-detectable establishment of ISAV in the pollock and nor where the challenged fish able to transmit the virus to healthy naïve salmon. Similarly McClure *et al*. (2004) found no ISAV in tissue samples (by RT-PCR) taken from pollock originating from pens stocked with salmon carrying the ISA-infection. McClure *et al*. (2005) concluded that the increased risk seen in the presence of large numbers of pollock was likely linked to the stress their presence might induce on the salmon and the increase in stocking density.

DISCUSSION

The support for spatial relations and transport connections as risk factors is substantial, representing a common significant variable in several studies. Both ISA-positive sites and processing boats spread the infection within a reasonable proximity. Interestingly, boat trafficking seems to do this more effectively than actual outbreaks. Why this is the case cannot be convincingly decided from the literature reviewed here. This conundrum is probably linked to the role that direct spread by seawater holds in the epidemiology of the disease. The literature used here is contradictory on the subject of the virion's survivability in the environment, with the study using what most closely resembles natural conditions (Vike *et al.*, 2014) reporting the shortest time of survival (3 hours). More precise knowledge regarding a given area's hydrology would be needed to draw any substantial conclusions. Still, the decreased survival they showed in biologically active and radiated seawater might in part explain the increased prevalence of HPR0-ISAV seen during winter months in the Faroe Islands (Christiansen *et al.*, 2011) when the cold and cloudy North Atlantic winter might limit the amount of UVR reaching sea level and the overall biological activity in surface seawater.

McClure et al., (2005) originally investigated another variable describing trafficking in relation to a site, namely the frequency of which processing boats travelled past a site. However, they argued that since a site located close to a processing plant would invariably have boats passing both closer and more frequently they discontinued the study of passing frequency and did not integrate it in their final models due to confounding issues. Based on this, one could assume that the distance to processing boats is also highly related to the proximity of processing plants. Also assuming that one processing boat passing within 1km of a site could not possibly prove a more significant source of viral contamination than an infected farm within 0.5km of a site (as their model indicated) it would seem likely that the proximity to processing plants or the frequency of boat passage would have proven to be the significant risk factor if these had been accounted for. This is supported by the short time of survival in naturally situated seawater shown by Vike et al., (2014) and the increased risk for sites located close to slaughterhouses shown by Jarp and Karlsen, (1997) supports this. These findings might show that direct waterborne spread is not the major factor in the epidemiology of the disease, suggesting that the location of, rather than the amount of contaminated water is of importance. This is based on that boat routes tend to lie further off shore than farming locations where, perhaps, hydrology and potential presence of wild reservoirs are more favorable. This is possibly supported by the increased risk when boats deliver fish or feed directly to a site, which, would likely be the

location where any potential contamination would pose the greatest risk. However, this idea is perhaps contradicted by the decreased risk seen when boats travel further off.

Assuming that the duration of an outbreak at an aquaculture site is comparatively limited compared with the time during which a farm has a geographical connection to processing plants or processing boat lanes one could theorize that the temporal span of viral contamination is of importance. A continuous release of ISAV in an area might favor the establishment of the virus in the possible resident population of wild reservoirs and vectors. These might in turn eventually be central actors in the subsequent spread of the disease to adjacent farms. Perhaps more so than direct spread by seawater. The role of sea lice in the overall epidemiology of ISA is not entirely certain but the literature indicates that long-term infestation might induce immunosuppressive levels of stress and, at least mechanically, transmit the virus between fish. Both factors probably increase severity and the speed at which ISA moves through a farm and is significant in the acquisition of the disease. This could be a result of immunosuppression in conjunction to waterborne spread but since the knowledge about the spread by seawater is inconclusive, it is conceivable that vector borne spread by sea lice originating from infected wild reservoirs attracted by feed to, or casually passing, a farm. It seems likely that this is the case when outbreaks emerge without an epidemiological connection with other outbreaks. As shown by Christiansen et al., (2011) subclinical infection with HPR0-ISAV is prevalent in the Faroe Islands (and probably elsewhere), and as is suggested by their study, is spread by a natural reservoir. These subclinical strains might then occasionally evolve into the HPR-deleted type and cause severe disease (Mjaaland *et al.*, 2002; Christiansen *et al.*, 2017).

Based on this it is possible that wild fish play a role in the spread of pathogenic strains as well. Once a strain of HPR0-ISAV present in a farm has mutated into the pathogenic type, it might be able be transmitted back to the reservoir (as indicated by Devold et al., (2000)). Judging by the findings of Devold et al., (2000) this might require immunosuppression of the reservoir, which, as shown by Bowers et al., (2000) could be induced by lice infestation. This could create a scenario in which the sea lice weaken the immune system of both wild and farmed fish which in turn facilitate the transmission of non-pathogenic strains between them. These strains might then become pathogenic and return to the reservoir that is free to travel to other farms, resulting in the spread of the disease; possibly over long distances.

Interestingly, wild or escaped Atlantic salmon are scarcely mentioned in literature concerning the spread of the ISAV(Christiansen *et al.*, 2011), being mostly reserved for other salmonids (Devold *et al.*, 2000) and the occasional gladiform (McClure *et al.*, 2005). Since they are considered the primary host of the disease they should be able to spread it between farms, perhaps more so than other fish. Even if the strains producing severe disease would prove self-limiting in the wild the less pathogenic ones might be sustainable. No literature used here explains why they appear to be excluded from study. Perhaps the more prevalent migratory pattern of Atlantic salmon, who more rarely venture close to the coastline, (where most farms are situated) prevents them from having a significant impact on the spread of ISA. The low population density that is probably associated with an oceanic lifestyle should also limit the overall burden of sea lice, and with that possibly also the ability to transmit the virus. The speed in which Atlantic salmon clear the subclinical form of ISA (Christiansen *et al.*, 2011), as

opposed to trout (Devold *et al.*, 2000), might also hold the prevalence of the virus in wild populations of salmon at a low level. However, there is no research showing that this would not be the case with any given reservoir.

The amount of fish in a pen and the density of stocking appear to increase the risk of contracting ISA but since these factors likely are highly correlated it is unclear if one has a higher impact than the other. Hammell and Dohoo (2005) showed a clear relation between the total population at risk and the risk of a site becoming ISA-positive but when converted to stocking density the correlation was to a certain degree lost, showing the highest risk in pens with a medium density of fish. The model made by Lyngstad et al. (2018) showed a clearer relation with stocking density and risk but did not account for the total population at risk. Similarly, McClure et al. (2005) concluded that the increased stocking density caused by high numbers of resident pollock accounted for the increased risk seen in their models. If each fish in a population is regarded as a potential viral entry-point it would be natural for farms with a high population of fish to have a higher risk of outbreak. It is also conceivable that a larger population is correlated to an extended stocking period and the amount of freshwater hatcheries that the fish has been supplied from, which has been shown to increase risk (Vagsholm *et al.*, 1994; Jarp & Karlsen, 1997; McClure *et al.*, 2005). High stocking density probably increases stress and perhaps ease the transmission of the virus between fish.

REFERENCES

Aamelfot, M., Dale, O.B., Weli, S.C., Koppang, E.O. & Falk, K. (2012). Expression of the Infectious Salmon Anemia Virus Receptor on Atlantic Salmon Endothelial Cells Correlates with the Cell Tropism of the Virus. *Journal of Virology*, vol. 86 (19), ss. 10571–10578.

Bowers, J.M., Mustafa, A., Speare, D.J., Conboy, G.A., Brimacombe, M., Sims, D.E. & Burka, J.F. (2000). The physiological response of Atlantic salmon, Salmo salar L., to a single experimental challenge with sea lice, Lepeophtheirus salmonis. *Journal of Fish Diseases*, vol. 23 (3), ss. 165–172.

Caruffo, M., Maturana, C., Kambalapally, S., Larenas, J. & Tobar, J.A. (2016). Protective oral vaccination against infectious salmon anaemia virus in Salmo salar. *Fish & Shellfish Immunology*, vol. 54, ss. 54–59.

Christiansen, D.H., McBeath, A.J.A., Aamelfot, M., Matejusova, I., Fourrier, M., White, P., Petersen, P.E. & Falk, K. (2017). First field evidence of the evolution from a non-virulent HPR0 to a virulent HPR-deleted infectious salmon anaemia virus. *Journal of General Virology*, vol. 98 (4), ss. 595–606.

Christiansen, D.H., Østergaard, P.S., Snow, M., Dale, O.B. & Falk, K. (2011). 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. *Journal of General Virology*, vol. 92 (4), ss. 909–918.

Devold, M., Krossøy, B., Aspehaug, V. & Nylund, A. (2000). Use of RT-PCR for diagnosis of infectious salmon anaemia virus (ISAV) in carrier sea trout Salmo trutta after experimental infection. *Diseases of Aquatic Organisms*, vol. 40 (1), ss. 9–18.

Falk, K., Namork, E., Rimstad, E., Mjaaland, S. & Dannevig, B.H. (1997). Characterization of infectious salmon anemia virus, an orthomyxo-like virus isolated from Atlantic salmon (Salmo salar L.). *Journal of Virology*, vol. 71 (12), ss. 9016–9023.

Hammell, K.L. & Dohoo, I.R. (2005). Risk factors associated with mortalities attributed to infectious salmon anaemia virus in New Brunswick, Canada. *Journal of Fish Diseases*, vol. 28 (11), ss. 651–661.

Jarp, J. & Karlsen, E. (1997). Infectious salmon anaemia (ISA) risk factors in sea-cultured Atlantic salmon Salmo salar. *Diseases of Aquatic Organisms*, vol. 28 (2), ss. 79–86.

Lyngstad, T.M., Qviller, L., Sindre, H., Brun, E. & Kristoffersen, A.B. (2018). Risk Factors Associated With Outbreaks of Infectious Salmon Anemia (ISA) With Unknown Source of Infection in Norway. *Frontiers in Veterinary Science*, vol. 5. DOI: https://doi.org/10.3389/fvets.2018.00308.

McClure, C., Hammell, K., Dohoo, I. & Gagné, N. (2004). Lack of evidence of infectious salmon anemia virus in pollock Pollachius virens cohabitating with infected farmed Atlantic salmon Salmo salar. *Diseases of Aquatic Organisms*, vol. 61, ss. 149–152.

McClure, C.A., Hammell, K.L. & Dohoo, I.R. (2005). Risk factors for outbreaks of infectious salmon anemia in farmed Atlantic salmon, Salmo salar. *Preventive Veterinary Medicine*, vol. 72 (3–4), ss. 263–280.

Mjaaland, S., Hungnes, O., Teig, A., Dannevig, B.H., Thorud, K. & Rimstad, E. (2002). Polymorphism in the Infectious Salmon Anemia Virus Hemagglutinin Gene: Importance and Possible Implications for Evolution and Ecology of Infectious Salmon Anemia Disease. *Virology*, vol. 304 (2), ss. 379–391.

Nylund, A., Hovland, T., Hodneland, K., Nilsen, F. & Lovik, P. (1994). Mechanisms for transmission of infectious salmon anaemia (ISA). *Diseases of Aquatic Organisms*, vol. 19, ss. 95–100.

Oelckers, K., Vike, S., Duesund, H., Gonzalez, J., Wadsworth, S. & Nylund, A. (2014). Caligus rogercresseyi as a potential vector for transmission of Infectious Salmon Anaemia (ISA) virus in Chile. *Aquaculture*, vol. 420, ss. 126–132.

Pickering, A.D. & Pottinger, T.G. (1989). Stress responses and disease resistance in salmonid fish: Effects of chronic elevation of plasma cortisol. *Fish Physiology and Biochemistry*, vol. 7 (1–6), ss. 253–258.

Rimstad, E. & Mjaaland, S. (2002). Infectious salmon anaemia virus. *APMIS*, vol. 110 (4), ss. 273–282.

Snow, M., Raynard, R., Bruno, D., van Nieuwstadt, A., Olesen, N., Løvold, T. & Wallace, C. (2002). Investigation into the susceptibility of saithe Pollachius virens to infectious salmon anaemia virus (ISAV) and their potential role as a vector for viral transmission. *Diseases of Aquatic Organisms*, vol. 50, ss. 13–18.

Statens veterinärmedicinska anstalt (SVA) (2017). *Infektiös laxanemi (ILA)/Infectious salmon anemia (ISA)*. https://www.sva.se/djurhalsa/epizootier/infektios-lax-anemi-infectious-salmon-anemia-ila-isa [2019-04-23]

Totland, G., Hjeltnes, B. & Flood, P. (1996). Transmission of infectious salmon anaemia (ISA) through natural secretions and excretions from infected smolts of Atlantic salmon Salmo salar during their presymptomatic phase. *Diseases of Aquatic Organisms*, vol. 26, ss. 25–31.

Vagsholm, I., Djupvik, H., Willumsen, F., Tveit, A. & Tangen, K. (1994). Infectious Salmon Anemia (isa) Epidemiology in Norway. *Preventive Veterinary Medicine*, vol. 19 (3–4), ss. 277–290.

Vike, S., Oelckers, K., Duesund, H., Erga, S.R., Gonzalez, J., Hamre, B., Frette, O. & Nylund, A. (2014). Infectious Salmon Anemia (ISA) Virus: Infectivity in Seawater under Different Physical Conditions. *Journal of Aquatic Animal Health*, vol. 26 (1), ss. 33–42.

World organistation for animal health (OIE) (2019). *OIE-listed diseases, infections and infestations in force in 2019.* http://www.oie.int/animal-health-in-the-world/oie-listed-diseases-2019/ [2019-04-23]