Bacterial kidney disease, infection and pathways in freshwater systems for wild and reared fish

A synthesis

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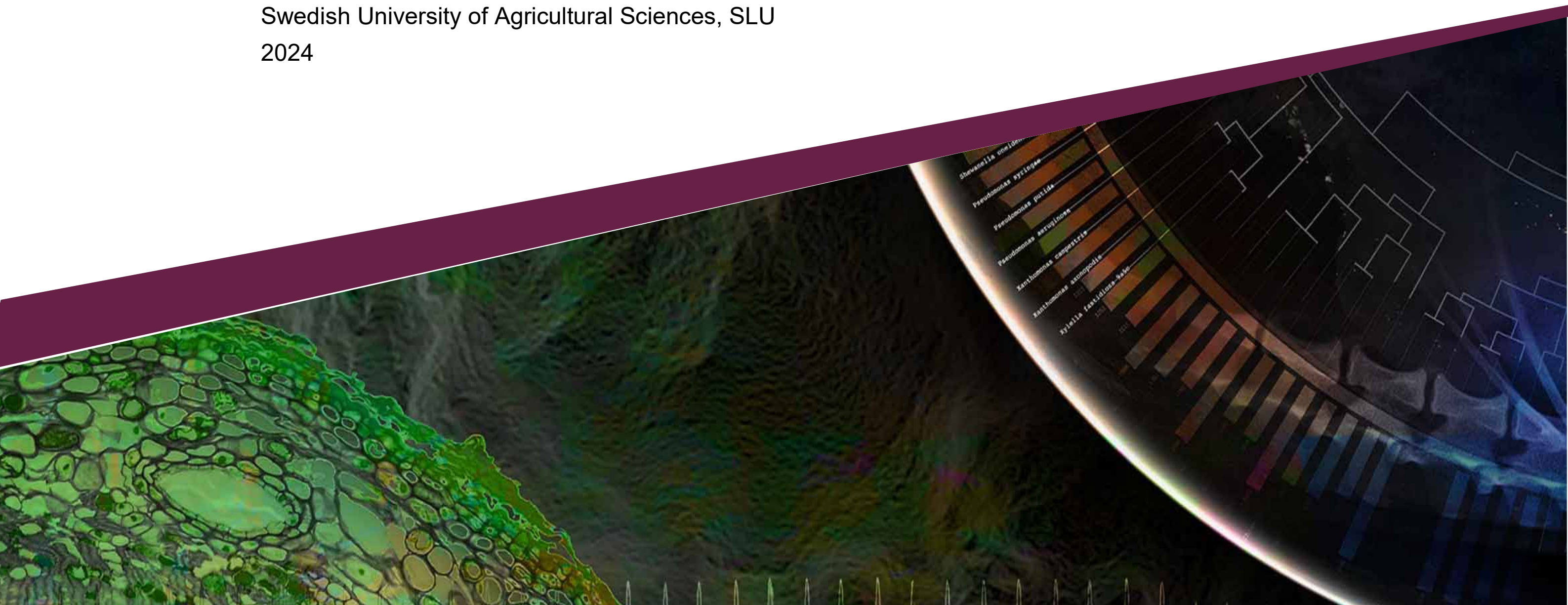

Bacterial kidney disease, infection and pathways in freshwater systems for wild and reared fish – A synthesis

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Executive summary

This document review bacterial kidney disease (BKD) caused by the bacterium *Renibacterium salmoninarum* (Rs). The disease is globally present in both wild and farmed salmonids. Below is an executive summary of the work regarding the disease's transmission routes and its effects on wild and farmed fish. More detailed information is available in the main text of this report.

Disease Overview

- BKD primarily affects salmonids but is also found in non-salmonids and bivalves.
- Clinical signs range from external blisters to internal organ swelling, affecting fish health and behaviour.

Transmission Pathways

- Vertical (parent to offspring) transmission dominates but horizontal (between fish) transmission is possible.
- Environmental factors and human activities are of importance for transmission.

Susceptibility

- Pacific salmon (e.g., Chinook, Coho) are highly susceptible while Atlantic salmon and rainbow trout are less affected.
- Non-salmonids may act as reservoirs without showing disease progression.

Environmental Survival

- Rs survives up to seven days in natural waters but persists longer in sediments and sterile environments.
- Detection of Rs DNA in sediments highlights monitoring potential.

Impacts on fish

- BKD outbreaks cause variable mortality rates; subclinical infections can affect feed conversion but not always growth or mortality.
- Impacts on wild fish populations vary and are methodologically difficult to monitor.

Biosecurity and Management

- Improved hatchery practices and genetic resistance have reduced BKD prevalence in some regions.
- Swedish practices require culling of infected stocks, leading to economic losses.

Knowledge Gaps

- Limited understanding of strain-specific virulence, host susceptibility, and environmental transmission dynamics.
- Inadequate data on disease interactions between wild and farmed fish.

- Stakeholders also request risk assessment tools

Future Directions

- A PhD project has been initiated at SLU and aims to address key gaps, focusing on:
- Horizontal transmission pathways and Rs strain diversity in Sweden.
- Host susceptibility testing in rainbow trout and Arctic charr.
- Advanced molecular techniques for disease tracking and management.

Conclusion

BKD remains a significant challenge within Swedish aquaculture, necessitating scientific evidence to inform on transmission paths and effects. New research will advance understanding and support effective disease control.

Exekutiv sammanfattning

Detta dokument sammanställer publicerad litteratur om bakteriell njurinflammation (BKD) orsakad av bakterien *Renibacterium salmoninarum* (Rs). Sjukdomen förekommer globalt och påverkar både vilda och odlade laxfiskar. Här sammanfattas sjukdomens smittvägar och dess effekter på vild och odlad fisk i korthet. För mer utförlig information hänvisas till huvudtexten i detta dokument.

Sjukdomsöversikt

- BKD påverkar främst laxfiskar men förekommer även hos andra sorters fiskar och blötdjur.
- Kliniska tecken varierar men kan innefatta yttre blåsor samt svullnad i inre organ, vilket påverkar fiskens hälsa och beteende.

Smittvägar

- Vertikal överföring (från förälder till avkomma) dominerar, men horisontell överföring (mellan fiskar) är också möjlig.
- Miljöfaktorer och mänskliga aktiviteter påverkar smittspridning.

Mottaglighet

- Stilla havslax (t.ex. Chinook, Coho) är mycket känsliga, medan atlantlax och regnbågslax uppvisar en lägre grad av påverkan.
- Icke laxartade fiskarter kan utgöra reservoarer utan att visa sjukdomsprogression.

Överlevnad i miljön

- Rs överlever upp till sju dagar i naturliga vatten men längre, upp till 21 dagar i sediment och än längre i sterila miljöer.

Effekter på fisk

- Utbrott av BKD orsakar varierande dödlighet bland odlad fisk; subkliniska infektioner kan påverka foderomvandlingsförmågan men inte alltid tillväxt eller dödlighet.
- Effekter på vilda bestånd varierar och är metodologiskt svåra att övervaka.

Biosäkerhet och hantering

- Förbättrade avelsmetoder och genetisk motståndskraft har minskat förekomsten av BKD i vissa regioner.
- Enligt svenskt regelverk krävs avlivning av infekterade bestånd i vattenbruk, vilket leder till betydande ekonomiska förluster.

Kunskapsluckor

- Begränsad förståelse för stamspecifik virulens, värdkänslighet hos olika arter och överföringsdynamik i miljön.
- Otillräckliga data om sjukdomsinteraktioner mellan vilda och odlade fiskar.
- Intressenter efterfrågar även verktyg för riskanalys

Framtida perspektiv

Ett doktorandprojekt har inletts vid SLU och syftar till att belysa viktiga kunskapsluckor, med fokus på:

- Horisontella överföringsvägar och Rs-bakteriens stamdiversitet i Sverige.
- Värdkänslighetstester hos regnbågslax och Röding.
- Avancerade molekylära tekniker för sjukdomsspårning och hantering.

Slutsats

BKD utgör en betydande utmaning inom det svenska vattenbruket och vetenskapligt underlag behövs för att informera om smittvägar och påverkan. Ny forskning kommer att öka förståelsen och stödja effektiv sjukdomskontroll.

1. Bacterial kidney disease, infection and pathways in freshwater systems for wild and reared fish

Bacterial kidney disease (BKD) is caused by infection with *Renibacterium salmoninarum* (Rs), a slow-growing bacterium primarily affecting salmonids. Infected fish may exhibit a range of clinical signs that can alter behaviour, and result in mortality. Rs has been detected in both freshwater and marine environments worldwide, wherever salmonids are found. Outbreaks are most frequently reported in cultured fish populations (Bruno 2004, Johansen et al 2011, Wiens 2011). Rs has also been recorded in non-salmonid species and freshwater bivalves (Byford et al 2020, Eissa et al 2006, Polinski et al 2010, Starliper & Morrison 2000).

Rs causes a slow-progressing systemic infection that is chronic in nature (Banner et al 1986). Infected fish may develop blebs, exhibit exophthalmia, and display erratic swimming behavior (Grayson et al 2002). External signs can include skin blisters and hemorrhages, while internal signs often involve swelling of the kidneys, spleen, heart, and liver (Fryer & Sanders 1981, Smith 1964).

Transmission of Rs can occur vertically (from parent to progeny) (Evelyn et al 1986, Pascho et al 1991) or horizontally (between fish) (Balfry et al 1996, Bell et al 1984, Mitchum & Sherman 1981). The routes of transmission, together with salmonids natural migration patterns, human interference in fish movements through compensatory releases, transfer of fish and eggs etc. enable transmission routes between wild and farmed fish and vice versa (Johansen et al 2011). Experimental studies have indicated a survival time of the bacterium of up to seven days outside the host (Balfry et al 1996).

Outbreaks of BKD in farmed, feral, and wild salmonids have historically been associated with high levels of infection, as documented in regions such as Colorado, USA (Fetherman et al 2020, Kingswood 1996) and Iceland (Jónsdóttir et al 1998). More recent studies spanning extensive geographical areas have detected Rs in fish populations often with no clinical disease or only mild clinical signs, with bacterial remnants commonly observed in wild and feral fish (Faisal et al 2012, Kowalski et al 2022). Studies of infection in aquaculture operations presents conflicting findings regarding the effects of outbreaks on fish health, growth, and mortality rates (Boerlage et al 2019). Furthermore, natural and methodological challenges hinder comprehensive assessments of the impact of BKD on wild fish populations, leading to significant knowledge gaps.

Biosecurity measures implemented within the aquaculture industry, including in hatcheries producing fry for release into the wild, have been shown to reduce the prevalence of infected fish (Faisal et al 2012, Sigurjónsdóttir et al 2000). Further, an increased genetic resistance over time has also been suggested to be a reason for a lower occurrence of the disease in studied wild populations (Faisal et al 2012).

BKD was first reported in Sweden in 1985, and since then, cases of infected fish have been sporadically confirmed in geographically dispersed fish farms at irregular intervals. A national screening program has been ongoing since the early 1990s. In Sweden, positive identification of Rs in fish farms results in culling of the entire stock, causing significant economic losses for the farmers. Current practice commonly allows farmers to keep fish on the farm during one farming season if fish show no clinical signs of disease. The site thereafter needs to be fallowed for 30 days before new fish can be stocked in the facility.

This literature review aims to summarize the current knowledge on bacterial kidney disease's (BKD) impacts and horizontal transmission pathways, identify existing knowledge gaps, and highlight priority areas for future research, specifically focusing on the Swedish context.

1.1 Susceptibility within and among species

Salmonids are the primary target for Rs infections, but the bacterium has also been recorded in other fish species and aquatic organisms. Chinook salmon (*Oncorhynchus tshawytscha*), Atlantic salmon (*Salmo salar*), and Coho salmon (*Oncorhynchus kisutch*) are recognized as the most susceptible species (Delghandi et al 2020, Guðmundsdóttir et al 2017, Pfeil-Putzien et al 1985, Wiens 2011). Atlantic salmon has lower susceptibility than the Pacific salmonids (Delghandi et al 2020). According to Persson et al (2022) Arctic charr (*Salvelinus Alpinus*) is a susceptible species based on observations from unpublished Swedish data from the 1980’s, also shown by Gudmundsdottir et al (2017). Rainbow trout (*Oncorhynchus mykiss*) is relatively resistant, though infection still occurs (Sanders et al 1978). This is in line with several other studies that have concluded that rainbow trout displays the lowest occurrence of BKD among the Oncorhynchus *spp*. (Mitchum & Sherman 1981, Starliper et al 1997). Brown trout (*Salmo trutta*) is, according to Chambers and co-workers (2008), among the less susceptible, and grayling (*Thymallus thymallus*) and white fish (*Coregonus laveretus*) are more poorly studied though infection has been recorded (Faisal et al 2010, Persson et al 2022, Rimaila-Parnanen 2002, Kettler et al 1986).

Variations in disease severity and clinical signs between fish species may relate to differences in virulence between strains. One potential factor is the p57 protein, located on the bacterial surface (O'Farrell & Strom 1999), and studies of mutated strains (lower expression of p57) indicate that the level of expression of p57 is linked to virulence (Bruno 1988). A method using single nucleotide typing (SNP) has been established (Brynildsrud et al 2014) enabling tracking of differences between isolates by farms. This method can be used as a molecular epidemiology tool to show transmission between different species and potentially link mortality to genetic fingerprints. However, no such link has so far been established.

Apart from salmonids, studies show that other fish species can carry the bacterium, along with mussels (e.g. Starliper & Morrison 2000). Experimental infection and mortality have been induced in a couple of cases on non-salmonids (see, e.g. Bell et al 1990, Polinski et al 2010) but unsuccessful in other studies (Bell & Traxler 1986, Sakai et al 1989). Lumpfish (*Cyclopterus lumpus*), used as cleaner fish in salmon farms, were susceptible to Rs. In a controlled experiment, the bacterium caused mortality and chronic infection for surviving individuals (Gnanagobal et al 2021). A recent study by Byford et al (2020) showed that ten non-salmonid species hosted the bacterium in The Great Lakes, USA. The sampled fish with Rs present did not show any progression to disease and thereby more possibly act as a reservoir for infection (Byford et al 2020).

1.1.1 Susceptibility within a population

Species susceptibility depends on the host and environmental factors, but as mentioned, little is known about the importance of virulence traits between Rs strains. Host genetic components may add to differences in phenotype (Mesa et al 1999). Infection prevalence in the progeny will depend on the infection status of the broodstock, and vertical transmission facilitates early-stage infection of the off-spring when they are at a susceptible physiological state.

Studies and surveys made in the 1980s and 1990s showed high rates of infected fish in populations of Brown trout (Jónsdóttir et al 1998), and Arctic charr (Jónsdóttir et al 1998). Later studies display lower infection rates in the same study systems. Faisal et al. (2012) reported infection levels (prevalence and intensity) in broodstock and pre-stocking fingerlings of three Oncorhynchus spp. decreased substantially over time. The authors conclude that combining broodstock culling and better measures for biosecurity in the hatcheries has minimized both vertical and horizontal transmission risks. Genetic selection is also suggested to contribute to decreased disease prevalence in the investigated populations (Faisal et al 2012, Purcell et al 2008).

Faisal et al (2010) focused on whitefish in northern US lakes and found 62 % (n=1284) positive samples by ELISA. Studies of the occurrence of Rs infection in three Oncorhynchus spp. were carried out in the same northern US lakes (n=3530).

Broodstock was monitored over 10 years, and systemic biosecurity measures substantially reduced the prevalence in broodstock from all studied species (Faisal et al 2012). A more recent study by Richards and co-workers on feral Oncorhynchus *spp*. Showed that about 80% of feral fish had measurable Rs antibodies (Richards et al 2021). The results presented by Faisal et al (2012) provide documentation that the level of Rs-infected fish may decrease over time, at least for feral fish, if measures are taken. Further, studies show that fish may recover from BKD or become latent carriers showing no clinical symptoms (Richards et al 2021).

1.2 Clinical signs

Fish may experience a chronic infection that can be carried over extended periods (Banner et al 1986). Infected fish show various signs such as blebs, erratic swimming patterns and exophthalmia (Grayson et al 2002). Skin blisters, haemorrhages, and eye ulcers are signs of an ongoing active infection. Internal signs comprise swollen kidney, liver, and spleen (Fryer & Sanders 1981, Smith 1964). Granulomatous changes are typically seen in the kidney, spleen, and liver; especially at lower temperatures, fluid accumulation in the abdomen (ascites) is also a known sign of chronic infection (Evenden et al 1993).

In experimental studies, fish with medium or high infection levels have displayed lowered feed intake (Pirhonen et al 2000) and reduced ability to saltwater adaptation (Mesa et al 1999, Moles 1997). The disease is chronic, but studies show that high antibodies can be detected in wild populations, indicating that fish respond immunologically to the bacterium. For example, Richards et al. (2021) found that of 160 feral fish from the Oncorhynchus spp. 129 fish carried antibodies, while only three showed Rs antigen in the kidney, spleen, or reproductive fluids. To what extent this is linked to protective immune responses is not known. Studies show that antigens are found in wild fish, e.g., in Iceland (Jónsdóttir et al 1998) and the US (Faisal et al 2012) indicating that components from the bacterium are present over extended periods.

1.2.1 Wild fish

It is often suggested that BKD is associated with high mortality rates among wild fish populations (Elliott et al 1989, Pascho et al 2002, Persson et al 2022). Observations indicate that juvenile salmonids (6-12 months old) and adults approaching spawning exhibit the highest mortality rates (Evelyn 1993). However, accurately estimating disease prevalence and fish losses due to BKD in the wild remains methodologically challenging (Johansen et al 2011). A common notion is that fish affected by BKD are prone to die from secondary infections (see, e.g., Kotob et al (2017)) or predation. Mesa et al (1999) showed that juvenile chinook salmon with high or medium infection levels showed an increased vulnerability to predation. The experiments were conducted in a controlled environment, but these results highlight that BKD may have ecological impacts beyond direct deaths caused by the disease. The authors address the need for further studies to understand how BKD affects fish in the wild. Results from a different, large-scale investigation of wild fish in Colorado, U.S., showed that active infections in wild fish were rare but that the presence of Rs antigens was relatively common. Kowalski et al conclude that resident trout often are silent carriers of Rs (Kowalski et al 2022). Similar results were obtained in Iceland as Jonsdottir et al. (1998) demonstrated a high prevalence of Rs antigens in 9 brown trout and 22 Arctic charr populations. Antigens were found in all studied populations, and 46% and 35% of the Arctic charr and brown trout, respectively, carried antigens. Of the total 961 fish in the study, no fish showed pathological signs of BKD. The authors concluded that most likely Rs had been endemic in the studied populations for an extended period and that low-density infections likely occurred in the studied area.

1.2.2 Farmed fish

Impacts of BKD outbreaks on farmed fish have been documented and reported. Mortality rates vary (Bruno et al 1986), and some studies report high mortalities from BKD outbreaks while others point in the opposite direction (Boerlage et al 2019, Murray et al 2012).

An overview of outbreaks in Scottish fish farms during 1967-1985 reports mortalities ranging from 0-2% to 15-20% in rainbow trout farms (Bruno 1986). Murray et al. (2012) also describe varying mortalities from BKD outbreaks ranging from 0-ca 80% in Scottish salmon farms from 2003 to 2007.

Boerlage and co-workers performed a study to quantify the effect of subclinical BKD on mortality, growth, and feed conversion ratio (FCR) for Atlantic salmon marine farms (Boerlage et al 2019). The study showed no effect on growth or mortality but a slight negative impact (increase) in FCR could be seen.

1.3 Routes of transmission

R. salmoninarum can be transferred vertically (from mother to progeny) or horizontally (between individuals) (Wiens 2011). The vertical transmission path is the most frequent (Evenden et al 1993). For natural reasons, horizontal transfer in the wild is more difficult to study (Johansen et al 2011). Many factors may affect the spread of Rs, such as geographic location, ecosystem variations, age and size of the fish and its condition, along with factors in a farming environment, if applicable, such as feed, transport, fish densities, and welfare (Delghandi et al 2020).

For transmission to occur horizontally, cohabiting fish must be exposed to a sufficient dose of infectious bacteria shed from infected fish. Survival time of Rs outside the host is of interest in understanding transmission. Transmission paths can be studied using whole-genome sequencing to understand better isolates, introduction events, and the spread of the disease (Bayliss et al 2018, Brynildsrud et al 2014). Using such methods increases understanding of the disease ecology.

1.3.1 Survival in the environment

Survival of the bacteria in the environment is central to understand horizontal transmission. The survival of Rs in the environment is influenced by substrate type, with longer persistence in sediments, faecal matter, and sterile water compared to the free water column.

In the free water column, Rs bacteria have a limited survival time. Austin and Rayment (1985) showed that Rs bacteria were dead after four days kept under experimental conditions. Balfry et al (1996) found that the bacteria could survive up to seven days outside a host in saline ocean water. These two studies also showed more prolonged survival in sterile and filtrated water, so survival in natural waters has been suggested to be limited by competition with aquatic microflora (Austin & Rayment 1985, Balfry et al 1996, Elliott 2017). A study by Hirvelä-Koski (2004) showed survival in autoclaved lake water for 20 weeks. The author discuss whether the results are relevant for natural waters considering the pre-treatment of the water.

In faecal matter/sediments, Rs can survive up to 21 days (Austin & Rayment 1985). Transmission through faeces and sediments has been stated to be a more credible transmission path than free bacteria in the water (Murray et al 2012).

A study by Persson et al (2022) could detect Rs by tracking eDNA in sediments close to an open cage fish farm where the disease had been confirmed. Initial samples were taken between one week and one month after fish were removed from the cages. After three months, Rs could not be detected in the sediments. The method cannot provide information regarding whether the bacteria found in the sediments are alive; only that DNA is present. This pilot indicates that sediments may be of interest for monitoring.

1.3.2 Horizontal transmission

Horizontal transmission between fish occurs through ingesting enough bacteria shedded from infected fish, carcasses, or feces (Balfry et al 1996) Horizontal transmission has been displayed through laboratory studies. Bacteria in the range of 10^6 bacteria/ml have been confirmed to be able to induce transmission through experimental studies (Watson et al 2023).

In a Swedish study from 2022 four rivers with net pen farming is present where Rs had been detected during the last seven years were sampled. Infected fish were mainly detected in one of the rivers. Based on these results, the authors suggest that the spread of the disease among wild fish possibly depends on water flow and water volume that affect the concentration of the bacterium (Persson et al 2022).

Anthropogenic activities such as transport of fish, fish stocking, and transport of water or materials such as boats or fishing gear have been pointed out as possible sources of transmission (Murray et al 2012). Activities within aquaculture production, such as the relocation of eggs, broodstock, or fingerlings, may also be a source of the spread of disease (Kristmundsson et al 2016, Murray et al 2012). Nevertheless, confirmed events of such direct events have been challenging to prove with the available methods.

In a doctoral thesis from 2022 transmission of Rs in cutthroat trout (*Oncorhynchus clarkia*) was investigated (Riepe 2022). Fish were placed in cages near fish diagnosed with BKD. Water temperature was optimal for Rs, and the cages were placed in raceways with infected fish, in sedimentation dams, and at the outlet of a flow-through facility. Fish in cages had no possibility of direct interaction with contaminated fish. One out of 360 fish displayed BKD infection after 30 days, and the conclusion was made that horizontal transfer was low but possible within 30 days. The author suggests that the lack of direct contact between the groups of fish and a low degree of exposure to faecal matter could have contributed to the low number of infected fish in the study (Riepe 2022). A drawback of the study was the lack of possibility of sampling fish that died during the experiment.

The importance of other species acting as reservoirs for horizontal transfer in lakes, streams, and the ocean is unknown. Byford et al. (2020) found several non-salmonid fish species carrying Rs Bottom-dwelling fish species were common in their study, this finding supports the theory that sediments may be a possible path of transmission and that non-salmonid species may function as reservoirs for infection (Byford et al 2020). However, bacteria show low genetic variation over a geographic area, indicating host-restricted lineage, meaning that a transfer between species may likely be smaller than first believed (Bayliss et al 2018). Nevertheless, it is stated that organisms are more likely to be a source of horizontal transmission than, for example, sediments (Rhodes & Mimeault 2019).

1.4 Conclusions and gap statements

Rs is a well-studied bacterium in many ways, but there are knowledge gaps. Different salmonid species show varying susceptibility towards infection. An increased understanding of various bacterial strains and their effects on different salmonid species would be of great interest and contribute to increasing knowledge of how BKD affects wild fish. It would allow for a more nuanced approach to understanding BKD, its transmission, and its implications in Swedish waters. The importance of horizontal transmission and its paths also needs more attention, especially on interactions between wild and farmed fish and transmission through the environment. Increased knowledge could also contribute to enabling risk assessments and developing relevant protective measures.

To address some of the knowledge gaps identified within the frames of this work, a PhD project has been initiated by SLU, NMBU, and SVA during this project's time. The main topics that will be investigated are:

- Exploring the main routes for horizontal transfer of BKD. This can be done by sequencing Rs isolates and in-depth analysis of variations and differences in single nucleotides. This to better understand if a Rs infection has transferred between wild and farmed fish. An increased understanding of genetic epidemiology could be an essential piece in the puzzle to understand transmission paths better and identify risks.
- The diversity of Swedish Rs strains. Isolates will be investigated to increase understanding regarding introducing Rs and different strains of the bacterium in Sweden.
- The susceptibility of different strains of Rs to our most commonly farmed species in Sweden, rainbow trout and Arctic charr is to be investigated by conducting challenge tests.

Using new DNA techniques and the fact that these methods have become less expensive over time open great possibilities for increased understanding.

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