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**Author(s):** Klemme, Ines; Hendrikx, Lysanne; Ashrafi, Roghaieh; Sundberg, Lotta-Riina; Rähä, Ville; Piironen, Jorma; Hyvärinen, Pekka; Karvonen, Anssi

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# Opposing health effects of hybridization for conservation

Ines Klemme<sup>1</sup>  | Lysanne Hendrikx<sup>1</sup> | Roghaieh Ashrafi<sup>1</sup> |  
Lotta-Riina Sundberg<sup>1</sup> | Ville Rähkä<sup>1</sup> | Jorma Piironen<sup>2</sup> | Pekka Hyvärinen<sup>2</sup> |  
Anssi Karvonen<sup>1</sup>

<sup>1</sup>Department of Biological and Environmental Science, University of Jyväskylä, Jyväskylä, Finland

<sup>2</sup>Aquatic Population Dynamics, Natural Resources Institute, Paltamo, Finland

## Correspondence

Ines Klemme, Department of Biological and Environmental Science, University of Jyväskylä, P.O. Box 35, 40014 University of Jyväskylä, Finland.

Email: ines.klemme@jyu.fi

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## Abstract

The continuing decline of many natural plant and animal populations emphasizes the importance of conservation strategies. Hybridization as a management tool has proven successful in introducing gene flow to small, inbred populations, but can be also associated with health risks. For example, hybridization can change susceptibility to infection in either direction due to heterosis (hybrid vigor) and outbreeding depression, but such health effects have rarely been considered in the genetic management of populations. Here, we investigated the effects of experimental outcrossing between the critically endangered Saimaa landlocked salmon (*Salmo salar* m. *sebago*) and the genetically more diverse Atlantic salmon (*S. salar*) on infection susceptibility. We exposed the parent populations and their hybrids to two parasites that commonly infect these species, the bacterium *Flavobacterium columnare* and the macroparasitic fluke *Diplostomum pseudospathaceum*. We found that landlocked salmon had lower survival during the bacterial epidemic, but higher resistance against the fluke, compared with Atlantic salmon. Hybrids showed intermediate survival and resistance, suggesting that hybridization decreased susceptibility to one parasite, but concurrently increased it to another. Our results emphasize the importance of considering health effects of different types of infections when employing hybridization for conservation.

## KEYWORDS

disease, gene flow, heterosis, hybridization, inbreeding, outbreeding depression, parasite, salmonid

## 1 | INTRODUCTION

The ongoing habitat loss and associated population declines generate a growing need for conservation actions that restore and maintain viable populations. To combat negative effects of inbreeding, wildlife managers increasingly employ assisted gene flow to small populations by

introducing individuals from divergent populations or related species (Chan, Hoffmann, & van Oppen, 2019; Frankham, 2015; Ralls et al., 2018). Such strategies have proven successful in the past, with the Florida panther (*Puma concolor coryi*) representing a well-known and documented example of population recovery following translocations (Johnson et al., 2010).

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Despite the documented benefits, there is also a number of risks involved in wildlife translocations, including those that can compromise population health. For example, introducing immigrants could expose both translocated and resident individuals to new diseases (Hess, 1996; Kock, Woodford, & Rossiter, 2010; McCallum & Dobson, 2002), elevate stress levels and thereby increase susceptibility to infection (Dickens, Delehanty, & Michael Romero, 2010; Hing et al., 2017), or increase disease transmission rates due to enlarged populations (Aiello et al., 2014). In addition to these non-genetic effects, hybridization itself could also have substantial impact on disease susceptibility. However, such effects have received little attention in conservation management actions.

Hybridization can change infection susceptibility relative to the parent taxa, with hybrids showing either lower, intermediate or higher infection levels (Fritz, Mouliia, & Newcombe, 1999; Mouliia, 1999; Theodosopoulos, Hund, & Taylor, 2019). Low genetic diversity is often associated with increased susceptibility to infection (King & Lively, 2012) due to homogeneity at loci associated with immunity (e.g., MHC, Spurgin & Richardson, 2010) or negative effects of inbreeding, such as the expression of deleterious recessive alleles (King & Lively, 2012; O'Brien & Evermann, 1988). Assisted gene-flow to inbred populations could therefore improve population health, as demonstrated in an epidemiological study following translocations to an inbred lion (*Panthera leo*) population (Trinkel, Cooper, Packer, & Slotow, 2011). However, outbreeding depression, a reduction in hybrid fitness due to genetic incompatibility or reduced local adaptation (Edmands, 2007), could also increase disease susceptibility. For example, natural hybridization between two subspecies of house mice (*Mus musculus musculus* and *M. m. domesticus*) is known to disrupt co-adapted gene complexes, resulting in hybrids carrying higher parasite loads than either parent species (reviewed in Mouliia, 1999). Moreover, host adaptation to local parasite fauna, a common consequence of evolutionary arms-race in host-parasite interactions, could be lost as consequence of introgression (Garant, Forde, & Hendry, 2007). Such complex hybridization effects could result in varying infection outcomes, depending on the parasite and host genotypes involved. Because hosts typically encounter a multitude of different parasites, it is important to study the effects of multiple parasites in hybrids of multiple genetic backgrounds to understand the overall effect of assisted hybridization on disease susceptibility.

Here, we explored how experimental outcrossing of the critically endangered Saimaa landlocked salmon (*Salmo salar* m. *sebago*) with two populations of the

genetically more diverse Atlantic salmon (*S. salar*) affects susceptibility to two taxonomically different parasites. The Saimaa landlocked salmon (hereafter LS) is an endemic ecological form of the sea-migrating Atlantic salmon (hereafter AS), which became isolated within the Lake Saimaa area in Finland after the last glacial period about 10,000 years ago (Berg, 1985; Lumme, Ozerov, Veselov, & Primmer, 2016). Since the 1950s, the population has declined significantly due to damming of natural spawning rivers for hydropower production (Pursiainen, Makkonen, & Piironen, 1998). Consequently, the effective population size has become critically small (Koljonen, Tähtinen, Säisä, & Koskiniemi, 2002) and the level of genetic diversity has decreased, now being the lowest among the salmon populations in the Baltic Sea area (Koljonen et al., 2002; Primmer, Koskinen, & Piironen, 2000; Säisä et al., 2005; Vuorinen, 1982). Low genetic diversity in LS is associated with impaired foraging success (Primmer et al., 2003) and developmental malformations (Tiira, Piironen, & Primmer, 2006), which are suggestive of inbreeding depression. The remaining wild LS population is currently heavily supported by stocking of hatchery-reared offspring (Pursiainen et al., 1998). Although such practices are often associated with domestication effects (Christie, Marine, French, & Blouin, 2012), they could also provide opportunities for targeted genetic management.

We exposed the parental populations and their respective hybrid crosses to infection with the pathogenic bacterium *Flavobacterium columnare* and the macroparasitic eye fluke *Diplostomum pseudospathaceum*, in two separate experiments. Both parasites are generalists and commonly found in lakes and rivers throughout the northern hemisphere (Laanto, Sundberg, & Bamford, 2011; Louhi, Karvonen, Rellstab, & Jokela, 2010; Valtonen & Gibson, 1997). The bacterium infects the skin and gills of fish, causing epidermal lesions and gill necrosis, known as columnaris disease, which can result in high mortality (Declercq, Haesebrouck, Van den Broeck, Bossier, & Decostere, 2013; Pulkkinen et al., 2010). Flukes are among the most common parasites of fresh water fish, with *D. pseudospathaceum* infecting the eye lenses, where they induce cataracts that reduce growth (Karvonen & Seppälä, 2008) and increase susceptibility to predation (Seppälä, Karvonen, & Valtonen, 2004, 2005). We asked whether hybridization of LS with AS increases survival following exposure to *Flavobacterium* and decreases parasite load following exposure to the eye fluke, relative to LS. Such experimentally assessed health effects of multiple parasite infections could be used in conservation decision-making regarding assisted gene-flow to endangered populations.

## 2 | MATERIAL AND METHODS

### 2.1 | Origin of fish

We conducted two experiments at Kainuu Fisheries Research Station in Finland (KFRS, [www.kfrs.fi](http://www.kfrs.fi)), a flow-through facility supplied with lake water. Crosses were produced at KFRS in November 2017 using brood fish of Saimaa landlocked salmon (origin River Pielisjoki, basin at Saimaa watercourse, 62°N, 29°E) and Atlantic salmon originating from two geographically isolated populations, River Neva (hereafter NS, basin at Eastern Baltic sea, 59°N, 30°E) and River Tornio (hereafter TS, basin at Northern Baltic sea 65°N, 24°E). Eggs and sperm were retrieved from hatchery parent fish, using 12 females and 12 males of LS, NS and TS for Experiment 1 and 30 females and 30 males of LS, NS and TS for Experiment 2 (one male per female). For both experiments, we created seven cross types: three pure lineages of LS, NS and TS, and two hybrid lineages with reciprocal maternity, that is, LS females crossed with TS and NS males, and TS and NS females crossed with LS males. The eggs were incubated using standard methods (Eronen et al., 2021) and maintained in replicated units either at the family level (Experiment 1) or at the cross level (Experiment 2).

### 2.2 | Experiment 1: Exposure to *F. columnare*

The aim of the first experiment was to investigate the susceptibility of LS, AS and their hybrids to infection with the bacterium *F. columnare*. We examined seven crosses, each represented by 12 full-sibling families (see above). For the purpose of another experiment, the newly hatched fish were first reared in family-specific rearing boxes (60 × 40 × 32 cm) placed within semi-natural outdoor flow-through channels (Eronen et al., in press). Each box contained 20 full siblings and we had three replicate boxes for each family, totalling 252 boxes randomly distributed across 8 channels with respect to cross and family. After 35–36 days, we collected all surviving fish, pooled them according to cross and randomly sampled 260 individuals per cross for the exposures.

The fish were exposed in July 2018 to *F. columnare* strain B351, which was originally isolated from the outlet water of a fish farm in Finland (Sundberg et al., 2016) and subsequently stored at –80°C in Shieh medium containing 10% glycerol and 10% fetal calf serum. For this experiment, bacteria were revived and inoculated in 3 ml of modified Shieh medium (Song, Fryer, & Rohovec, 1988) and kept at 25°C for 24 hr under constant

shaking. These overnight cultures were enriched into a larger volume of Shieh medium (1:10), kept in the same conditions for another 24 hr and used for the exposures.

The exposures were conducted in 91 flow-through containers, 11 exposed and 2 sham-exposed control containers per cross. Each container was filled with 2 L of water (mean temperature  $\pm SE = 16.7 \pm 0.1^\circ\text{C}$ ), and 20 fish, totaling 1820 fish. For the exposure, the incoming water was turned off for 1 hr and 20 ml of *F. columnare* culture ( $2 \times 10^6$  colony forming units per ml) was added to each container. Control containers received 20 ml of Shieh medium without bacteria. We monitored fish mortality every 6 hr until the first signs of the disease (morbidity) occurred, and every 4 hr afterwards. Morbid fish with no response to external stimuli were removed from the container and the time of death as well as body length were recorded. In addition, bacterial cultures were taken from the gills and skin of the first five moribund fish per container. Cultivations were spread on Shieh agar plates supplemented with tobramycin and checked for *F. columnare* colonies after 48 hr of incubation. Bacterial cultivations showed signs of *F. columnare* in 195/384 (50.8%) samples. The relatively low percentage was most likely due to low ambient temperature at bacterial sampling; similar exposures in laboratory conditions typically resulted in >95% prevalence (Louhi, Sundberg, Jokela, & Karvonen, 2015). However, we found positive samples in the majority of containers exposed to *F. columnare* (75/77) and most deceased fish (including those with negative cultivation results) showed visible symptoms of *F. columnare* infection, such as gill necrosis and bleaching of the dorsal skin. All samples from the control fish were negative for *F. columnare* and no symptoms of the infection were detected. We terminated the experiment 137 hr post exposure, at which time mortality had reached 21–33%, depending on the cross (2% in the control fish). All surviving fish were euthanized with an overdose of Benzocaine and measured for length; the mean  $\pm SE$  of all fish in the experiment was  $31.8 \pm 0.1$  mm.

We analyzed survival using a mixed effects Cox-regression in SAS v. 9.4 including all fish exposed to *F. columnare* that died or survived the experiment. We conducted two separate analyses for comparisons of LS with each of the two Atlantic salmon populations (NS and TS) and included cross (AS, LS and their hybrids) as categorical factor, fish length as covariate and exposure container as random effect. For post hoc comparisons between crosses, we calculated hazard ratios (HR) and their 95% confidence intervals (CI). If the CIs were outside 1, the HR was significantly different from 1 at the  $\alpha = .05$  level, indicating statistically significant difference in survival.

## 2.3 | Experiment 2: Exposure to *D. pseudospathaceum*

The aim of the second experiment was to investigate resistance of the seven fish crosses to *D. pseudospathaceum* infection. Due to technical reasons, we lost the pure LS cross before the experiment and replaced it by another pure LS cross, originating from sibling fish (32 females crossed with 32 males, one male per female) of the original parent fish. Note that the effective population size of LS is critically low (Koljonen et al., 2002; Primmer et al., 2000; Säisä et al., 2005; Vuorinen, 1982), which suggests close overall relatedness in LS. The replacement cross had been fertilized at the same time as the original cross and was maintained in identical conditions. After hatching, we reared the crosses in two replicated fiberglass tanks each. For the exposures, we randomly collected 15 individuals from each tank, totalling 30 individuals per cross and 210 exposed fish.

Parasite larvae (cercariae) used in the exposures originated from seven naturally infected *Lymnaea stagnalis* snails, the first intermediate host of *D. pseudospathaceum*. We collected the snails 4 weeks before the experiment in Central Finland. However, the origin of the parasites was unlikely to affect the results as *D. pseudospathaceum* does not show a detectable population genetic structure across a large geographic scale in Finland (Louhi et al., 2010). We stored the snails in 1 L of lake water at 4°C with food ad libitum. Three hours before the exposures, they were each transferred to 100 ml of lake water at room temperature to induce cercarial shedding. We then combined the solutions from all snails and estimated cercarial density from ten 1 ml samples.

Exposures were conducted in July 2018 in individual containers with 250 ml of lake water (16.5°C) and 50 cercariae. The exposure lasted for 30 min. Upon encounter of a fish, cercariae penetrate the host's epithelium and migrate through host tissues to the eye lenses (Chappell, Hardie, & Secombes, 1994). Thus, we maintained the exposed fish for 24 hr post exposure to allow parasite establishment, after which we euthanized them with an overdose of benzocaine. Each fish was measured for length (mean  $\pm$  SE = 43.1  $\pm$  0.3 mm) and dissected for parasite counts in both eye lenses.

Parasite load (left and right eye combined) was analyzed using generalized linear models (GLM) with negative binomial error distribution and a log link function in SAS v. 9.4. We conducted two separate analyses to compare the effects of hybridization between LS and NS, and between LS and TS. In both models, we entered cross as categorical factor and fish length as covariate. To verify

that our data fit the assumptions of the negative binomial error distribution, we run chi-square tests that evaluated the model residual deviances and degrees of freedom (LS versus NS:  $p = .234$ , LS versus TS:  $p = .316$ ). Significance values of post hoc comparisons were *Bonferroni*-corrected.

## 3 | RESULTS

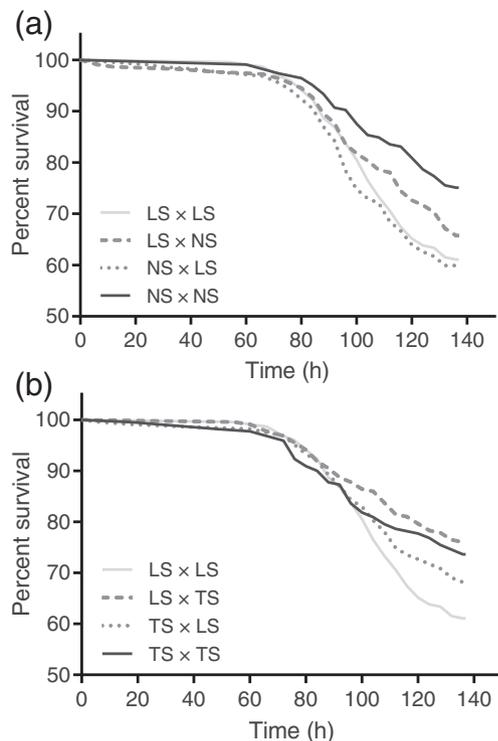
### 3.1 | Experiment 1: Susceptibility to *F. columnare*

Survival after exposure to *F. columnare* was significantly affected by cross in both comparisons of LS crossed with NS (Wald = 10.13, df = 2.41,  $p = .010$ ) and LS crossed with TS (Wald = 13.85, df = 2.82,  $p = .003$ ). Pure NS and TS showed higher survival than pure LS (Table 1, Figure 1a,b). Average hybrid survival was intermediate, suggesting that hybridization improved survival of LS (Figure 1a,b). However, hybrid performance depended on the specific cross. In crosses with NS, the survival of both hybrids (dam/sire reciprocal) did not differ significantly from pure LS, but in crosses with TS, hybrids survived significantly better than pure LS (Table 1, Figure 1a,b). In crosses with both AS populations, hybrids with a LS dam and an AS sire survived better than those with an AS dam and a LS sire (Figure 1a,b), but these differences were not significant (NS: HR = 0.83, CI 0.59–1.17; TS: HR = 0.82, CI 0.56–1.18). Cross-specific survival in

**TABLE 1** Post hoc analyses of the significant “cross” effect in a mixed effects Cox-regression on survival following exposure to *Flavobacterium columnare* (Experiment 1) and a GLM on parasite load following exposure to *Diplostomum pseudospathaceum* (Experiment 2)

LS $\times$ LS versus	Experiment 1		Experiment 2		
	HR	CI	z	p	CI
NS $\times$ NS	1.64	1.13–2.39	–3.67	.001	0.17–0.81
LS $\times$ NS	1.11	0.79–1.58	–2.46	.042	0.01–0.64
NS $\times$ LS	0.93	0.66–1.29	–2.44	.044	0.01–0.63
TS $\times$ TS	1.77	1.25–2.50	–4.10	<.001	0.23–0.88
LS $\times$ TS	1.71	1.20–2.44	–1.68	.278	–0.11–0.62
TS $\times$ LS	1.40	1.01–1.94	–1.84	.195	–0.07–0.58

Note: All crosses are presented as dam  $\times$  sire and all pairwise comparisons were calculated against the pure landlocked salmon cross (LS  $\times$  LS; NS = Atlantic salmon from population Neva, TS = Atlantic salmon from population Tornio). For cox regressions, hazard ratios (HR) and their 95% confidence intervals (CI) are displayed (CI outside 1 indicates significant effect) and for GLMs, z-values and p-values together with their 95% confidence intervals (CI) are shown.



**FIGURE 1** Survival curves of different salmon crosses exposed to the bacterium *Flavobacterium columnare*. Panel (a) displays the curves for all crosses (dam  $\times$  sire) between the endangered landlocked salmon (LS) and Atlantic salmon from population Neva (NS). Panel (b) displays curves for all crosses between LS and Atlantic salmon from population Tornio (TS)

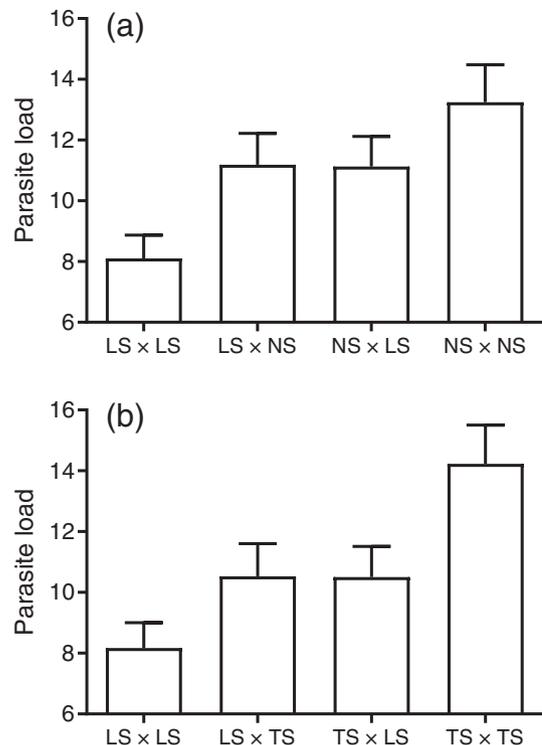
the bacterial exposure did not correlate with survival in the semi-natural channels before the experiment (Pearson correlation:  $r = .225$ ,  $p = .628$ ).

### 3.2 | Experiment 2: Susceptibility to *D. pseudospathaceum*

Parasite load was significantly affected by cross in both comparisons of LS crossed with NS ( $\chi^2 = 13.43$ ,  $df = 3$ ,  $p = .004$ ) and of LS crossed with TS ( $\chi^2 = 16.41$ ,  $df = 3$ ,  $p = .001$ ). Here, pure LS showed the lowest parasite load and both pure AS populations the highest (Table 1, Figure 2a,b). Hybrid parasite load was intermediate, suggesting that hybridization increased susceptibility of LS (Figure 2a,b). This increase was statistically significant in crosses with NS, but not in crosses with TS (Table 1).

## 4 | DISCUSSION

Assisted hybridization has been successfully used to mitigate inbreeding depression in endangered populations



**FIGURE 2** Parasite load of different salmon crosses exposed to the fluke *Diplostomum pseudospathaceum*. Panel (a) displays least square means  $\pm$  SE for all crosses (dam  $\times$  sire) between the endangered landlocked salmon (LS) and Atlantic salmon from population Neva (NS). Panel (b) for all crosses between LS and Atlantic salmon from population Tornio (TS)

(Chan et al., 2019), but not all aspects of this conservation management tool are well understood. While nongenetic health risks associated with wildlife translocations have been acknowledged and taken into account (Aiello et al., 2014; Frankham, 2015; Hess, 1996; McCallum & Dobson, 2002), empirical studies addressing explicitly the effects of genome mixing on infection susceptibility are scarce. We studied this question in the endangered Saimaa landlocked salmon whose genetic diversity decreased critically as a consequence of habitat destruction and associated population decline. We found that hybridization of landlocked salmon with Atlantic salmon decreased susceptibility to one parasite and concurrently increased it to another. This suggests that health effects of hybridization for conservation can be opposite, which calls for careful evaluation before implementing such measures.

Population-level heterogeneity in susceptibility to infection can arise through genetic differences, including the level of diversity at loci connected with immune functions or selection pressures that populations have experienced in the past. Mortality associated with exposure to *F. columnare* was higher in LS compared with AS, with

the hybrids, on average, falling in between and thus, surviving better than LS. This could be attributed to an increase of genetic diversity following hybridization. However, despite the low genetic polymorphism, LS was more resistant to infection with the eye fluke and therefore hybridization, which again resulted in intermediate resistance, increased susceptibility. Selection pressures for defenses against *D. pseudospathaceum* in fish are expected to be higher in lakes than in rivers, because the parasite's second intermediate snail hosts prefer stagnant over flowing water. It is therefore possible that LS, which migrates from its natal river to a lake for growth before reproduction, would be better adapted to this freshwater parasite than the sea-migrating AS. Such gene-environment interactions can become disrupted in hybrids, resulting in increased susceptibility (outbreeding depression). Similar findings have been shown in three-spined sticklebacks (*Gasterosteus aculeatus*), where individuals from a lake population were more resistant to *D. pseudospathaceum* than those from a river population, and their hybrids displayed intermediate resistance (Kalbe & Kurtz, 2006). Thus, our results emphasize the importance of considering the contribution from a range of different parasites when assessing the health effects of assisted hybridization.

The threat of outbreeding depression in assisted gene flow has been much debated (Bell et al., 2019; Frankham et al., 2011; Ralls et al., 2018; Whiteley, Fitzpatrick, Funk, & Tallmon, 2015). To minimize the risk, guidelines recommend the use of donor populations that show low genetic divergence from the recipient population (isolated for less than 500 years) and inhabit similar environments (Frankham et al., 2011). However, for many populations requiring conservation efforts, including the Saimaa landlocked salmon, such donors are not available (Kronenberger et al., 2017). Although recent translocation studies suggest that longer periods of adaptive divergence do not inevitably lead to outbreeding depression (Fitzpatrick et al., 2020; Kronenberger et al., 2017), our results confirm that the risk needs to be carefully evaluated when donor populations do not meet the recommended guidelines (Frankham et al., 2011).

Future studies should also look into net consequences of hybridization effects. In the present system, acute *D. pseudospathaceum* infection is typically less detrimental than infection with *F. columnare*, but once fluke numbers increase and the infection becomes chronic, it can seriously reduce growth and survival (Karvonen & Seppälä, 2008; Seppälä et al., 2004, 2005). Thus, increased susceptibility to *D. pseudospathaceum* can compromise host fitness, possibly outweighing the otherwise positive effects of gene flow. A solution in the case of Saimaa

landlocked salmon could be to cross it with other landlocked salmon populations in the Baltic Sea area, if these showed similar habitat preferences and parasite exposure in the wild. Although all of these populations show low genetic diversity (Säisä et al., 2005), assisted gene flow between inbred populations can also alleviate inbreeding depression (Fredrickson, Siminski, Woolf, & Hedrick, 2007; Heber et al., 2013), for example through heterosis.

We also observed some degree of variation in hybridization effects with the parental AS population used. Specifically, the increased survival with *F. columnare* was more evident in crosses with TS, and the reduction in resistance to *D. pseudospathaceum* in crosses with NS. This suggests that TS could be more suitable for assisted hybridization from the overall health perspective of LS. It also suggests that the identity of the donor population can be vital, even if the level of genetic differentiation between recipient and different donor options is comparable, as in our system (Ryynänen, Tonteri, Vasemägi, & Primmer, 2007; Säisä et al., 2005). This emphasizes the importance of conducting experimental crosses with different source populations (if available) before implementing assisted gene flow.

Researchers are increasingly recommending the use of assisted gene flow in conservation efforts (Bell et al., 2019; Frankham, 2015; Ralls et al., 2018; Weeks, Stoklosa, & Hoffmann, 2016). Hybridization for conservation is relatively easy to implement in species that rely on stocking enhancement with hatchery-reared offspring. Our study revealed opposing health effects of such measures, but further research, including other fitness traits and multigenerational approaches, will help understanding the overall net effects. Ultimately, benefits of population management actions are often limited by persistent habitat constraints, which therefore need to be overcome to secure long-term conservation success.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

Ines Klemme, Lysanne Hendrikx, Roghaieh Ashrafi, Lotta-Riina Sundberg, and Anssi Karvonen conceived the study, all authors conducted the experiments. Ines

Klemme analyzed the data and wrote the article with substantial input from all authors.

## DATA AVAILABILITY STATEMENT

All data for this study are accessible as online supporting information.

## ETHICS STATEMENT

This study was carried out with permission from the Finnish Regional State Administrative Agency (license no. ESAVI/5184/04.10.07/2017 and ESAVI/8187/2018) and complied with the animal care legislation of Finland.

## ORCID

Ines Klemme  <https://orcid.org/0000-0001-9757-7356>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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