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# Evolution of salmon lice in response to management strategies: a review

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## Abstract

Ectoparasitic salmon lice (*Lepeophtheirus salmonis*) present a major challenge to Atlantic salmon (*Salmo salar*) aquaculture. The demand for effective louse control has produced diverse management strategies. These strategies essentially impose novel selection pressures on parasite populations, driving the evolution of resistance. Here we assess the potential for salmon lice to adapt to current prevention and control methods. Lice have evolved resistance to at least four of five chemical therapeutants, and use of these chemicals has declined significantly in recent years. The industry has shifted to alternative non-chemical approaches, yet lice may adapt to these as well. Early research suggests that phenotypic variation exists in the louse population upon which non-chemical selection pressures could act and that this variation may have a genetic basis. From the existing evidence, as well as an examination of evolutionary processes in other relevant parasite and pest systems, we conclude that the evolution of non-chemical resistance is an emergent concern that must be considered by the industry. We recommend areas for focused research to better assess this risk. It is also important to determine whether phenotypic shifts in response to non-chemical selection may shift the ecological niche of the parasite, as this may have cascading effects on wild salmon populations. We also recommend further research to identify strategy combinations that have antagonistic selective effects that slow louse evolution and those with synergistic effects that should be avoided. Greater understanding of evolutionary processes can inform aquaculture policies that counteract the rise of resistant parasite populations.

**Key words:** Atlantic salmon, Lepeophtheirus salmonis, parasite, resistance, Salmo salar.

## Introduction

Agricultural pests are inherently adaptable, and this capacity to adapt provides an ongoing challenge to pest management. These parasites, pathogens and micropredators evolved for millennia under natural selection before exploiting farmed environments (Glass 1976), and they continue to evolve as we attempt to control them. Each agricultural species carries with it a diverse array of parasites and pathogens which can inflict significant damage to the industry (Blaylock & Bullard 2014; Lafferty *et al.* 2015). As these parasites transition from wild to farmed environments, they evolve and interact with hosts in new ways (Nowak 2007; Mennerat *et al.* 2010; Sundberg *et al.* 2016).

Aquaculture systems are typically younger than terrestrial agriculture systems, yet many more animal species are farmed in aquaculture than on land (Duarte *et al.* 2007). The early age and diversity of aquaculture systems mean that we are still very much learning how to make them resilient and productive. Atlantic salmon (*Salmo salar*) is one of the most valuable commodities in aquaculture (FAO 2019) and as such is one of the industries furthest along the learning curve. Despite being well advanced, the industry is heavily impacted by the salmon louse (*Lepeophtheirus salmonis*). Salmon lice (hereafter 'lice') are ectoparasitic copepods (Caligidae) that feed on blood, skin tissue and mucous (Costello 2006; Heggland *et al.* 2020). Severe infestations can lead to chronic stress, anaemia, reduced osmoregulation and death (Wagner *et al.* 2008; Fjelldal *et al.* 2019), which creates salmon welfare concerns and inflicts significant economic costs (Liu & Bjelland, 2014). Although lice occur naturally on wild salmonids, farms act as reservoirs that amplify parasite abundance above normal levels (Daszak 2000; Krkošek *et al.* 2005; Johansen *et al.* 2011). Outbreaks can then be transmitted from farms to wild populations, impacting their survival, productivity and migration (Bjørn *et al.* 2001; Krkošek & Hilborn 2011; Krkošek *et al.* 2013).

To minimise the environmental impact of lice, most jurisdictions require farms to maintain infestations below certain levels. In Norway, which is the leading producer of salmon (FAO 2018), regions with unacceptable levels are penalised with reduced production limits (Vollset *et al.* 2018). There is thus high demand for effective methods of louse control, and salmon aquaculture has become a lead innovator in aquatic pest management. A diverse array of controls and preventions has been developed to combat lice (Overton *et al.* 2019a; Bui *et al.* 2020c; Barrett *et al.* 2020a). The high demand encourages rapid deployment of new technologies, often before extensive research into their long-term effects is done (Groner *et al.* 2016; Brakstad *et al.* 2019).

Of particular concern is the ability of lice to adapt to the pressures of the farmed environment. Frequent parasite treatment on a farm selects for individuals that mature and reproduce rapidly (i.e. within the interval between treatments), driving the evolution of faster parasite life history (Mennerat *et al.* 2010). Indeed, salmon lice from areas of intensive farming invest more into early reproduction than those from wild host populations (Mennerat *et al.* 2017), with evidence that lice with earlier maturity and higher fecundity are also more virulent (Mennerat *et al.* 2012). High virulence can be costly to parasites in the wild; parasites that kill or incapacitate a host before transmission to a new host are selected against (Anderson & May 1979; Ewald 1994). The high host density of salmon farms, however, reduces this trade-off to virulence, since lice can jump between hosts (Nowak 2007; Mennerat *et al.* 2010). Supporting this, lice strains infesting salmon farms are more damaging to their host than those from wild populations (Ugelvik *et al.* 2017a).

The evolution of life history and virulence are generalised adaptations of parasites to management strategies. Additionally, each strategy can impose specific selective pressures that drive populations to evolve 'resistance'. This is well-documented in terrestrial agriculture, with many species having evolved resistance to pesticides applied to crops (Georghiou & Saito 1983; Brattsten *et al.* 1986) and parasiticides used to treat livestock (Kaplan & Vidyashankar 2012; Knolhoff & Onstad 2014). Pests can also adapt to non-chemical methods, such as biological control (Kerr 2012; Tomasetto *et al.* 2017) and crop rotation (Krysan *et al.* 1986; Levine *et al.* 2002). Resistance can quickly render new methods obsolete, which severely undermines efforts for sustainable pest control. This evolution-driven obsolescence can be curtailed with appropriate management strategies, but developing these requires an evolutionary understanding of the system (Mennerat *et al.* 2010; Kaplan & Vidyashankar 2012; Groner *et al.* 2016). Two major questions form the backbone of any evolution-aware management strategy: (i) is a trait under selection by a strategy and (ii) is there sufficient genetic variation in this trait? If both criteria are fulfilled, then there is the risk that the population can adapt to the strategy over time. We ask these questions for the strategies currently deployed by the Atlantic salmon industry.

Seven main louse management strategies are currently used on farms: chemotherapeutants, depth-based preventions, cleaner fish, mechanical delousing, thermal delousing, freshwater bathing and enhanced host resistance. These target different stages of the salmon louse lifecycle (which comprises eight instars; Hamre *et al.*, 2013) After mating, female lice carry their eggs until they hatch into the water column. The first three instars – two un-infective nauplius stages and the infective copepodid stage – are free-living and can drift in the plankton for several weeks and tens of kilometres (Salama *et al.* 2013; Serra-Llinares *et al.* 2014). Copepodids must locate and attach to a host before their yolk reserve is depleted; the length of this time window is dependent on temperature. They will then complete the lifecycle as a parasite, moulting through two chalimus and two pre-adult instars before becoming a sexually mature adult (Hamre *et al.* 2019). Chalimi are sessile, whereas the later motile stages can move on and between hosts (Ritchie 1997).

Louse management strategies can be categorised as either 'immediate', 'continuous' or 'preventative' (Table 1, Brakstad *et al.*, 2019). Prevention should be the first and foremost step in pest management (Barzman *et al.* 2015; Barrett *et al.* 2020a). Preventative strategies target copepodid larvae, reducing their chances of either attaching to a host or establishing shortly after attachment. Immediate strategies only remove lice during an acute treatment process; this is a common strategy employed in response to high infestations. Continuous strategies remove lice over a longer period and for some time after the treatment is administered (i.e. medicated feed administered, cleaner fish stocked). This approach places a chronic pressure on the louse population; it reduces infestations more slowly, but provides extended protection from new outbreaks.

Here, we analyse the available evidence for the adaptation of lice to each strategy, beginning with chemotherapeutants before examining six non-chemical methods in turn. Where resistance has already been described, we examine features of the louse population and of the aquaculture industry that may have facilitated this evolution. Where resistance has not yet been documented, we analyse the possibility of it arising in the future. To do so, we identify possible phenotypes that are selected for, assess the strength of this selection pressure, compare genetic and environmental factors that might influence variation in the trait under selection and describe trade-offs that may limit the spread of resistance. How louse adaptations might impact the wild parasite–host system is also explored. Finally, we detail how these strategies might interact to have synergistic or antagonistic effects on louse evolution.

## Chemotherapeutants

Through most of its history, salmon aquaculture has relied primarily on chemical therapeutants (chemotherapeutants) to manage louse infestations (Roth *et al.* 1993; Burka *et al.* 1997; Aaen *et al.* 2015). Five main types of chemotherapeutant have been used (Table 1): azamethiphos, pyrethroids (cypermethrin and deltamethrin), emamectin benzoate, hydrogen peroxide and benzoylphenyl ureas (diflubenzuron, teflubenzuron and lufenuron).

There are abundant examples of parasites evolving chemical resistance in terrestrial agriculture (Kaplan & Vidyashankar 2012; Knolhoff & Onstad 2014; Junquera *et al.* 2019). Similarly, there is strong evidence for resistance evolving in salmon lice, for all of the chemotherapeutants except benzoylphenyl ureas (Aaen *et al.* 2015). In most cases, the first reports of resistance emerged only a few years after the chemotherapeutant was introduced (Fig. 1a). Only two years after its introduction, azamethiphos efficacy remained high at some sites (>85% of motile lice removed) but was as low as 7% at others (Roth *et al.* 1996). Hydrogen peroxide efficacy fell from 75% to 8% on the same farm after 8 years of use (Treasurer *et al.* 2000).

The $EC_{50}$ (the effective concentration of chemotherapeutant needed to remove 50% of lice) for resistant strains can be more than 3 (emamectin benzoate; Espedal *et al.*, 2013; Igboeli, Burka and Fast, 2014; Sutherland *et al.*, 2015), 8 (hydrogen peroxide; Helgesen *et al.*, 2017), 50 (azamethiphos; Myhre Jensen *et al.*, 2017) or 100 (deltamethrin; Carmona-Antoñanzas *et al.*, 2017; Myhre Jensen *et al.*, 2017) times higher than for sensitive strains. Resistant strains (derived from lice collected from farm sites with reported treatment failures) have been maintained in the laboratory over multiple generations, demonstrating that chemical resistance mechanisms in lice are heritable (Espedal *et al.*, 2013; Igboeli, Burka and Fast, 2014; Ljungfeldt *et al.*, 2014; Helgesen *et al.*, 2015; Kaur *et al.*, 2015; Carmona-Antoñanzas *et al.*, 2017; Myhre Jensen *et al.*, 2017).

There have been dramatic declines in chemotherapeutant efficacy on farms (Roth *et al.* 1996; Treasurer *et al.* 2000; Sevatdal & Horsberg 2003; Sevatdal *et al.* 2005; Lees *et al.* 2008; Jones *et al.* 2013). A combination of several factors has likely facilitated the widespread establishment of resistance: strong selection pressures, high louse gene flow, low fitness costs of resistance and the minimal effect of wild host refugia.

### Treatment selection pressure

For more than two decades, salmon farmers around the world have had a very limited selection of chemotherapeutants at their disposal (Grant 2002; Aaen *et al.* 2015). As a result, the same chemicals have been regularly applied over a substantial proportion of the louse population. This can result in a strong and homogenous selection pressure that facilitates the rapid evolution of resistance (Falconer & Mackay 1996; McEwan *et al.* 2016). Despite their declining efficacies, chemotherapeutants continued to be used in increasing quantities, with all five treatments peaking in 2014–16, long after initial reports of resistance (Fig. 1a, b). In a process reminiscent of the 'tragedy of the commons' (Hardin 1968), farmers maximise use of whichever treatments are most effective, despite this accelerating the evolution of resistance, which impacts the whole farm network (Orzech & Nichter 2008).

The spread of pyrethroid, emamectin benzoate and organophosphate resistance coincided with the introduction of these chemicals through the North Atlantic (Kaur *et al.* 2016; Fjørtoft *et al.* 2017, 2019). Resistance developed faster, and genes conferring resistance reached higher frequencies, in areas with intensive chemical treatments (Jones *et al.*, 2013; Kaur *et al.*, 2016; Fjørtoft *et al.*, 2019). The rapid emergence of emamectin resistance in the sea louse *Caligus rogercresseyi* in Chile was likely accelerated by the fact that this was the sole chemotherapeutant available in the country for seven years (Bravo *et al.* 2008b). On the other hand, the relatively low use of benzoylphenyl ureas may explain why there have not been any reports of resistance to this treatment in salmon lice, despite resistance occurring regularly in other pest species (Junquera *et al.* 2019).

### Louse gene flow

Salmon louse populations are characterised by high gene flow over a large geographic scale (Todd *et al.* 2004; Glover *et al.* 2011; Messmer *et al.* 2011). If mutations conferring resistance are initially rare, gene flow enables them to rapidly disperse through the population, provided selection for them is also widespread. In this way, resistance to pyrethroids, emamectin and azamethiphos each emerged at localised points, before spreading across the North Atlantic over the course of a decade (Besnier *et al.* 2014; Kaur *et al.* 2017; Fjørtoft *et al.* 2020).

## Fitness costs

Traits that confer pesticide resistance will be less likely to evolve and persist if they come with trade-offs on other aspects of louse fitness. No significant costs have been

**Table 1** Efficacy (% louse reduction) of chemical and non-chemical strategies on salmon louse (*Lepeophtheirus salmonis*) life stages. Table is not comprehensive and provides mean efficacies from those studies that report moderate to high effectiveness. For four of the five chemical treatments, there is evidence for widespread resistance – in these instances efficacy is highly variable across time and/or space, with significantly lower efficacies for resistant strains. Management strategies are categorised as being either preventative, continuous or immediate groups. Empty cells indicate that the strategy does not act upon that life stage.

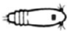
| | | | Estimated efficacy (% reduction) on louse life stage | | | |
|---|---|---|---|---|---|---|
| | | | Free-living  | Sessile  | Motile  | Adult female  |
| Chemical | Continuous | Emamectin benzoate | | Resistance common [abcd] | | |
| | | Benzoylphenyl ureas | | 79[e]<br>92[f] | Pre-adult<br>69[e]<br>74[f]<br>Sessile + Pre-adult<br>88[g]<br>73[h] | |
| | Immediate | Azamethiphos | | | Resistance common [ijk] | |
| | | Pyrethroids | | Resistance common [jkl] | | |
| | | Hydrogen peroxide | | | Resistance common [mn] | |
| Non-chemical | Preventative | Depth-based | Snorkel<br>75[a]<br>84[b]<br>93[c]<br>Skirt<br>82[d]<br>30[e] | | | |
| | | Host resistance | | Per generation of selective breeding†<br>5–28[fg]<br>Functional feeds<br>49[h]<br>31[i]<br>61[j] | | |
| | Continuous | Cleaner fish | | 20[k]<br>24[l]<br>30[m] | 55[k]<br>90[l]<br>34[m] | 78[k]<br>81[l]<br>44[n]<br>88[m] |
| | Immediate | Thermal | | | 90[o]<br>98[p] | 87[o] |
| | | Mechanical | | 79[q]<br>70[s] | 87[q]<br>94[r]<br>90[s]<br>95[t] | 75[q]<br>85[r]<br>95[s]<br>99[t] |
| | | Freshwater | | 100[uv]<br>Mechanical only<br>47[u]<br>77[v]<br>Copepodid (attached)<br>96[w] | 97[u]<br>77[v]<br>Mechanical only<br>59[u]<br>30[v] | 92[u]<br>88[v]<br>Mechanical only<br>31[u]<br>14[v] |

**Table 1** (continued)

References

Chemical

[a]Espedal et al. (2013)
[b]Igboeli et al. (2014)
[c]Ljungfeldt et al. (2014)
[d]Sutherland et al. (2015)
[e]Campbell et al. (2006a)
[f]Campbell et al. (2006b)
[g]Branson et al. (2000)
[h]Ritchie et al. (2002)
[i]Kaur et al. (2015)
[j]Grøntvedt et al. (2016)
[k]Myhre Jensen et al. (2017)
[l]Fjørtoft et al. (2020)
[m]Helgesen et al. (2015)
[n]Helgesen et al. (2018)

Non-chemical

[a]Geitung et al. (2019)
[b]Wright et al. (2017)
[c]Oppedal et al. (2017)
[d]Stien et al. (2018)
[e]Grøntvedt et al. (2018)
[f]AquaGen (n.d.)
[g]Hillestad et al. (2017)
[h]Purcell et al. (2013)
[i]Covello et al. (2012)
[j]Refstie et al. (2010)
[k]Imsland et al. (2018)
[l]Skiftesvik et al. (2013)
[m]Imsland et al. (2014)
[n]Barrett et al. (2020)
[o]Grøntvedt et al. (2015)
[p]Roth (2016)
[q]Erikson et al. (2018)
[r]Gismervik et al. (2017)
[s]Flatsetsund Engineering AS (2017)
[t]Moen Marin AS (2019)
[u]Reynolds (2013)
[v]Powell et al. (2015)
[w]Wright et al. (2016)

†The response to genetic improvement depends on the intensity and method of selection. The following studies were considered:
-28% louse reduction in homozygotes for a resistant QTL allele compared to homozygotes for a susceptible QTL allele would be possible using one generation of marker-assisted selection [f]
-49–54% (1 day post-infection) and 32–36% (18 days post-infection) louse reductions in high-resistance lines compared to low-resistance lines after 2 generations of genomic selection [f]
-10% reductions after 2.5 generations of traditional family-based selective breeding [g]

observed for resistant lice under laboratory conditions (Espedal *et al.*, 2013; Besnier *et al.*, 2014; Carmona-Antoñanzas *et al.*, 2017, 2019) and resistant strains persist under natural conditions in regions without chemotherapeutant use (Fallang *et al.* 2004; Fjørtoft *et al.* 2020). If mutations can provide chemical resistance by slightly altering target molecules (Besnier *et al.* 2014; Kaur *et al.* 2015) without having significant effects on broader louse biology, then this would allow resistance to diffuse and persist through areas where chemotherapeutants are used less frequently.

### Wild refugia

In theory, the evolution of resistance might be slowed when there are large sympatric populations of wild salmonids, which act as refugia for sensitive lice (McEwan *et al.* 2015; Kreitzman *et al.* 2018). Immigration of sensitive genotypes from wild hosts dilutes the frequency of resistance; meanwhile, resistant genotypes moving from farmed to wild hosts are subsequently lost through fitness costs or genetic drift. In the Atlantic, however, farmed salmon greatly outnumber wild salmonids and are available to lice year-round along the coast. In Norway, comparisons of aquaculture production (Norwegian Directorate of Fisheries 2020) and estimated wild salmonid populations (Thorstad *et al.* 2020) suggest that farmed hosts outnumbered wild ones 257: 1 in coastal waters in 2017 (Dempster unpubl. data). This diminishes the effectiveness of refugia against louse adaptation ( McEwan *et al.* 2015; Kreitzman *et al.* 2018). Wild salmonids in the North Atlantic carry high proportions of pyrethroid- and azamethiphos-resistant lice (>80% of infestations in some areas, Fjørtoft *et al.* 2017, 2019). Rather than acting as refugia for sensitive lice, wild hosts can act as reservoirs of resistant lice and may even act as stepping stones that facilitate louse transmission to new areas. Since lice are most likely to encounter and infest farmed salmon, selection will favour traits that improve fitness in the farmed environment – even if these traits are maladaptive on wild hosts (Falconer & Mackay 1996).

### Chemical resistance in the Pacific

Atlantic salmon are also farmed on Canada's west coast, where emamectin benzoate has been the dominant louse control strategy since 1999 (Saksida *et al.* 2011; Messmer *et al.* 2018). Despite this, there has been minimal evidence of lice in the Pacific evolving resistance (Saksida *et al.* 2013), at least until very recently (Messmer *et al.* 2018). This may be due to a greater relative abundance of wild hosts than farmed in the Pacific than in the Atlantic; on the Canadian/US west coast, wild salmonid capture is approximately 5 times greater than the production from aquaculture (Kreitzman *et al.* 2018). Such a situation invokes the protective effect of wild refugia, slowing the adaptive response. Further, minimal genetic exchange between louse populations (Skern-Mauritzen *et al.* 2014) prevents resistant genotypes from arriving in the Pacific from the Atlantic.

## Non-chemical methods

Given the frequency with which pesticide resistance has evolved, there is renewed advocacy for the use of

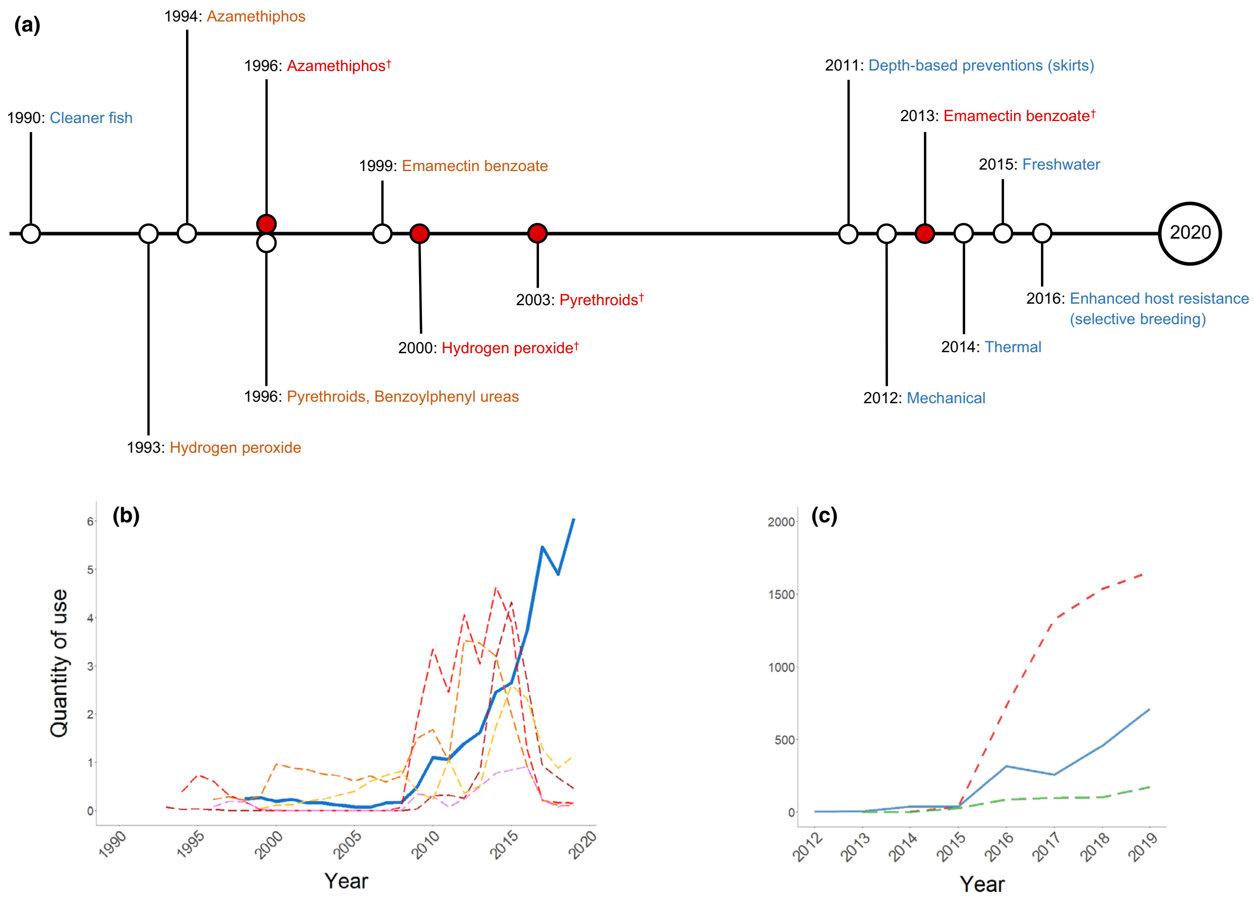


**Fig. 1** (a) The introduction of chemical (orange) and non-chemical (blue) louse management strategies on Norwegian salmon farms (1990–2020) and the first reports of resistance to chemotherapeutants (red†) from experimental studies. (b) Weight of active chemotherapeutant ingredients sold, and the number of cleaner fish stocked (from 1998), to combat salmon lice on Norwegian farms. Treatment type: 🟦, Cleaner fish (10 million individuals); 🟥, Hydrogen peroxide (10,000 t); 🟥, Azamethiphos (t); 🟧, Pyrethroids (100 kg); 🟪, Benzoylphenyl ureas (10 t); 🟨, Emamectin benzoate (100 kg). (c) Number of immediate non-chemical treatments reported by Norwegian salmon farms (2012–2019). Treatment type: 🟥, Thermal; 🟦, Mechanical; 🟩, Freshwater. From: Denholm et al. (2002), Norwegian Directorate of Fisheries (2019), BarentsWatch (2020), Norwegian Institute of Public Health (2020), Sommerset et al. (2020), Stien et al. (2020).

alternative, non-chemical approaches to pest management in agriculture (Barzman *et al.* 2015). No new families of pesticide have been introduced to salmon farms for over 20 years (Fig. 1a). Instead, a diverse array of non-chemical strategies has emerged on a commercial scale since 2010 (Fig. 1a). Since 2015, the use of chemotherapeutants on Norwegian farms has declined dramatically, whereas non-chemical use has increased (Fig. 1a, b**;** Overton *et al.* 2019a, 2020; Barrett *et al.* 2020a). Nevertheless, pests have the potential to adapt to non-chemical methods as well, including biological control (Kerr 2012; Tomasetto *et al.* 2017) and crop rotation (Krysan *et al.* 1986; Levine *et al.* 2002). There are concerns that lice may evolve resistance to non-chemical management strategies as well (Ljungfeldt *et al.* 2017; Groner *et al.* 2019; Hamre *et al.* 2020; Coates *et al.* 2020). If suitable genetic variation exists, adaptation to non-chemical pressures would be facilitated by the same factors that permitted chemical resistance to rapidly emerge: widespread use of a limited number of strategies, which imposes strong, homogeneous selection; high gene flow, which disseminates advantageous mutations; and a high relative abundance of farmed salmon, which minimises the opportunity for wild hosts to act as refugia for susceptible lice.

Adaptation to non-chemical methods, however, faces different pressures and constraints compared with adaptation to chemical treatments. Chemical resistance can arise through mutations to a small number of genes, whereas non-chemical resistance might require more complex changes to physiology, anatomy or behaviour (Table 2). These are likely to take longer to arise in the population and come with greater trade-offs.

Further, lice only encounter a chemotherapeutant if they are infesting a farmed host that is treated with that compound. In contrast, non-chemical strategies harness environmental pressures (such as temperature, salinity or physical stress) similar to those naturally experienced by lice throughout their life. Thus, shifts in how lice respond to these pressures can lead to shifts in their niche, inside and outside of farms (Groner *et al.* 2019). Non-chemical resistance may come with strong fitness trade-offs, and lice may interact with the ecosystem in new ways, in particular with wild salmonid populations.

A major goal of louse management is to reduce the infestation pressure on wild salmonids (Myksvoll *et al.* 2020), yet it may have unintended consequences for natural populations by pushing lice to evolve in unforeseen directions. There are six main non-chemical strategies currently used on commercial farms: depth-based preventions, enhanced host resistance, cleaner fish, mechanical delousing, thermal delousing and freshwater bathing. We discuss the possibility of lice adapting to each of these, and its potential implications, in turn.

## Depth-based preventions

Copepodids aggregate at shallow depths in the water column (McKibben & Hay 2004; Penston *et al.* 2008; Samsing *et al.* 2016a). This is likely an adaptation to improve host encounter rates (Johannessen 1978; Heuch *et al.* 1995), since wild salmonids usually swim at shallow depths, especially during migration (Rikardsen *et al.* 2007; Plantalech Manel-La *et al.* 2009; Einarsson *et al.* 2018; Strøm *et al.* 2018). Depth-based preventions segregate salmon from incoming copepodids at the surface, whilst leaving deeper sections of the cage open for water circulation (Barrett *et al.* 2020a). Lice skirts are the most common approach, first trialled in 2011–2012 (Fig. 1a; Lien & Høy 2011; Næs *et al.* 2012). Skirts are barriers of fine mesh or an impermeable material that encircle the upper several metres of a cage, preventing the access of louse larvae at this depth (Grøntvedt *et al.* 2018; Bui *et al.* 2020c). 'Snorkel' cages are also used commercially (Geitung *et al.* 2019; Olsen 2020). Snorkel cages create a mismatch in parasite and host distributions by submerging salmon beneath the lice layer (with access to the surface, so salmon can refill their swim bladders, provided by a skirt-enclosed tube; Geitung *et al.*, 2019). Both technologies can exclude a large proportion of copepodids from cages (Table 1), although their efficacy is affected by environmental conditions and salmon behaviour (Samsing *et al.* 2016a; Bui *et al.* 2020c). In addition to physical barriers, using submerged lights and feeders to entice salmon below the 'lice layer' can also reduce infestations (Frenzl *et al.* 2014; Bui *et al.* 2020c), although how widespread and successful this method is remains unknown.

### Selection for deeper copepodid distributions

Depth-based preventions impose selection on individual copepodid swimming depth, since larvae occurring deeper in the water column can pass beneath these barriers and infest a cage. Hydrodynamics play a role in pushing larvae deeper under certain conditions (Frank *et al.* 2015; Samsing *et al.* 2016a; Crosbie *et al.* 2019; Bui *et al.* 2020c), but copepodid depth may also be influenced by variation in behaviour, morphology or physiology. Free-living copepods (Calanoida), for example, vary in depth according to individual variation in lipid content (Zarubin *et al.* 2014).

Salmon louse copepodids from different families exhibit significant variation in their vertical swimming behaviour across the range of water pressures experienced from 0 to 10 m depth (Coates *et al.* 2020). Some genetic families have reduced rates of upwards migration, which likely translates to being distributed, on average, deeper in the water column. A family's tendency to either ascend or descend could mean the difference between passing around a 10 m skirt or snorkel (bypassing the cage) or passing underneath it (and infesting the cage), even when other hydrodynamic factors are involved. The strong patterns across related groups, and the absence of observed environmental or maternal effects, suggests a genetically inherited element to the vertical distribution of copepodids (Coates *et al.* 2020). Such genetic variation has been observed in other planktonic crustaceans: *Daphnia* are stratified in the water according to genotype (Dumont *et al.* 1985; De Meester 1993; King & Miracle 1995).

If copepodid depth is influenced by heritable traits, then selection acting on these traits by depth-based preventions could lead to an evolutionary shift in the vertical distribution of copepodids. This is a form of spatial sorting, whereby individuals are sorted into mating populations on the basis of dispersal traits (Phillips & Perkins 2019). For example, if depth-based preventions select for deep-dispersing phenotypes, then the louse population within these cages will predominantly be of these phenotypes, which mate and release a high proportion of deep offspring.

### Implications of a shifting depth distribution

The vertical position of larvae in the water column determines horizontal dispersal, since currents that drive plankton transport vary with depth in their direction and strength (Johnsen *et al.* 2014; Samsing *et al.* 2016a). An evolutionary shift in the depth distribution of copepodids would affect how the parasite is dispersed, with flow-on effects to the

**Table 2** Possible directions through which salmon lice (*Lepeophtheirus salmonis*) could evolve resistance to non-chemical management strategies used in salmon aquaculture. Included are possible louse traits selected for by each strategy, the underlying genetic and environmental factors that influence these traits, the implications of evolution for louse ecology and the potential for synergistic or antagonist interactions with other strategies.

| Management strategy | Louse traits under possible selection | Possible genetic factors influencing trait | Possible environmental factors influencing trait | Implications of evolution | Synergistic/ antagonistic with |
|---|---|---|---|---|---|
| Depth-based preventions | Deeper distribution of copepodids in water column | Copepodid vertical swimming behaviour | Hydrodynamic mixing and turbulence<br>Salinity stratification<br>Temperature | Different larval dispersal<br>Reduced encounter rate with wild salmonids | Cleaner fish (snorkels; synergistic) |
| Cleaner fish | Pale coloration (crypsis) | Louse pigmentation (fixed or plastic) | Light level<br>Microhabitat | Increased sensitivity to ultraviolet radiation | Depth-based preventions (snorkels; synergistic) |
| | Attachment to host head | Microhabitat choice | Intra-specific louse competition | Increased virulence | Mechanical delousing (antagonistic) |
| | Small body size | | Development temperature | | Mechanical delousing (antagonistic) |
| Thermal delousing | Heat tolerance | Physiological mechanisms for knockdown resistance | Ambient water temperature | Thermal niche shifted to warmer environments | Mechanical delousing (synergistic) |
| Mechanical delousing | Improved attachment ability | Morphologies of carapace, hooked appendages, frontal filament<br>Attachment behaviours | Microhabitat | Reduced success of salmon anti-parasite behaviours (leaping, rolling)<br>Increased virulence | Cleaner fish (antagonistic)<br>Thermal and freshwater delousing (synergistic) |
| Freshwater delousing | Freshwater tolerance | Physiological mechanisms for improved osmoregulation | | Reduced success of salmon anti-parasite behaviours (freshwater self-treatment)<br>Improved fitness in low salinity environments | Mechanical delousing (synergistic) |
| Enhanced host resistance | Tolerance to host defences | Immunomodulatory secretions, physiological mechanisms for evading/ tolerating host defences | Host strain and immune response | Different infectivity on wild hosts | |

connectivity (and so gene flow) among farmed sites and wild populations (Johnsen *et al.* 2016; Crosbie *et al.* 2019).

Aggregation of copepodids at shallow depths is likely an adaptation to improve wild host encounter rates. Selection for traits linked to a deeper distribution would therefore represent a major change to the parasite's evolutionary trajectory. This shift draws parallels with one of the few known cases of a pest adapting to a non-chemical prevention: the evolved resistance of the corn rootworm beetle (*Diabrotica virgifera*) to crop rotation (Levine *et al.* 2002). In both cases, migration to naturally suboptimal host environments (deeper water for lice, non-host plants for beetles) becomes beneficial when preventative strategies are deployed. If copepodids with a deeper distribution have fewer encounters with shallow-swimming wild salmonids, this could transform natural parasite–host dynamics. Hypothetically, as lice adapt to depth-based preventions, the transmission rate to wild salmonid populations would be reduced. The possibility that resistance to a preventative method could reduce the environmental impact of a pest is a tantalising prospect worth further investigation.

## Cleaner fish

Cleaner fish species are commonly stocked in cages alongside salmon as a form of biological control (Barrett *et al.* 2020b). The most common species used are the lumpfish (*Cyclopterus lumpus*) and multiple species of wrasse (family Labridae) which prey upon parasitic lice attached to the salmon (Skiftesvik *et al.* 2013; Imsland *et al.* 2014; Leclercq *et al.* 2014). Cleaner fish use first emerged in the late 1980s to early 1990s but increased dramatically from 2009, with approximately 60 million fish now stocked on farms worldwide (Fig. 1a, b**;** Treasurer, 2002; Norwegian Directorate of Fisheries, 2018; Overton *et al*., 2020). Although cleaner fish have been a potential selective pressure on lice for some time, the strength of this pressure is likely to have increased significantly over the last decade. Whilst lumpfish can reduce infestations in some commercial settings (Imsland *et al.* 2018), the degree to which lice are removed on farms across environmental conditions and for other cleaner fish species is poorly known (Overton *et al.* 2020; Barrett *et al.* 2020b). A recent analysis of more than 500 farms in Norway suggested that the louse removal effects of cleaner fish are patchy in space and time (Barrett *et al.* 2020b). Whether cleaner fish efficacy has declined over three decades of use is unknown, due to a shortage of data collected on efficacy across this period.

### Arms races in biological controls and cleaning symbioses

Biological control is unique among pest management strategies in that the control agent can co-evolve with the pest population. For every adaptation the pest might acquire, the control population might evolve a counter-adaptation, and the net efficacy of the control stays the same (Holt & Hochberg 1997). This may explain why examples of pests evolving ‘resistance’ to biological controls are relatively rare (Holt & Hochberg 1997; Hufbauer & Roderick 2005). Nonetheless, in some instances a pest species can evolve more rapidly and outpace its enemies, for example, if the standing genetic variation or recombination rate is higher in the pest population (Tomasetto *et al.* 2017). Asymmetrical arms races are a common attribute in wild predator–prey systems (Dawkins & Krebs 1979; Humphreys & Ruxton 2020) and are likely in salmon aquaculture also. Perhaps the clearest reason for this is that individual cleaner fish are not reused in the next production cycle and rarely transferred to other sites. As such, they do not establish self-sustaining populations in salmon cages, and so, any selection occurring in that environment does not affect the next generation. There is evidence that cleaning efficacy is a heritable trait in lumpfish and as such could be improved through selective breeding (Imsland *et al.* 2016). If cleaner fish efficacy can be improved at the same pace that lice adapt, then resistance could be mitigated. Selective breeding programs are, however, still in their early stages (Brooker *et al.* 2018).

The arms race between cleaner and parasite is an important but often overlooked aspect of the evolution of cleaning symbioses found in nature (Grutter 2002). Cleaning behaviour has been observed in the wild for two of the wrasse species used in aquaculture: the goldsinny (*Ctenolabrus rupestris*) and rock cook (*Centrolabrus exoletus*) wrasse, both observed apparently cleaning ballan wrasse (*Labrus bergylta*; Potts 1973; Hilldén 1983). However, there is no evidence of salmonids being cleaned in the wild (Vaughan *et al.* 2016). As such, salmon lice are unlikely to already be equipped with adaptations against cleaner fish. Nevertheless, in emulating the cleaning mutualisms found in the wild, farms also risk driving parasite evolution similar to that found in nature. For lice to become resistant, cleaner fish must carry out selective predation, such that certain louse phenotypes have a higher chance than others of being eaten. Selective predation (e.g. for colour variants) is a well-known driver of evolutionary change (Cook *et al.* 2012).

### Colour selection

There are anecdotal reports of translucent salmon lice emerging on farms in response to cleaner fish use (Soltveit 2018). Leclercq, Davie and Migaud (2014) also noted that lice were generally lighter in colour following exposure to cleaner fish than before. Other fish parasite species that are preyed upon by cleaner organisms have evolved to be cryptically pigmented or almost transparent, possibly to camouflage them against their host (Kearn 1979, 1994; Roubal & Quartararo 1992; Whittington 1996). In free-living copepod species, less pigmented individuals have lower rates of predation (Hairston 1979; Luecke & O’Brien 1981; Utne-Palm 1999). It seems likely then that cleaner fish selectively prey upon darkly pigmented lice, whereas paler individuals avoid detection (Hamre *et al.* 2020).

There is also early evidence that the high variation in louse pigmentation may have a genetic component (Hamre *et al.* 2020). Lice could therefore become resistant to cleaner fish through an evolutionary shift towards lower pigmentation. Further research is needed to assess this possibility, testing (i) whether cleaner fish predation does impose a selection on louse colour and (ii) whether colour has the heritability sufficient for an adaptive response.

Although the function of louse coloration has not been studied, pigments in other copepods provide protection from harmful ultraviolet (UV) radiation (Ringelberg *et al.* 1984; Hansson *et al.* 2007). Whilst attached to a host, lice have a limited degree of habitat selection and may be exposed to harmful UV levels when the salmon swims close to the surface. The costs of photodamage under certain conditions may therefore limit the extent to which lice can evolve translucence. Certainly, such trade-offs between predation and photodamage are known to occur in free-living copepods (Luecke & O'Brien 1981; Hansson 2004). For lice infesting wild hosts, especially, the costs are likely to outweigh the benefits, since wild salmonids are not exposed to cleaner fish and swim close to the surface, where UV levels are higher (LaBar *et al.* 1978; Rikardsen *et al.* 2007; Plantalech Manel-La *et al.* 2009).

### Colour plasticity

In free-living crustaceans (copepods and *Daphnia*), pigmentation is a highly plastic trait that can be adjusted in response to UV levels and predator cues (Hansson 2000, 2004; Scoville & Pfrender 2010; Brüsin *et al.* 2016). Similarly, there appears to be a strong environmental effect on louse pigmentation. Lice from the same strain were lighter in colour when reared on salmon in outdoor tanks than those kept indoors (Hamre *et al.* 2020). Exposure to natural daylight (UV radiation in particular) is one explanation for this plastic response. Supporting this, it has also been observed that lice attached to the shaded ventral surface of salmon are lighter than those on the dorsal surface (Hamre *et al.* 2020). Pigment production is energetically costly and slows growth in *Daphnia* (Scoville & Pfrender 2010). As there is high louse gene flow across different environments (Todd *et al.* 2004; Glover *et al.* 2011; Messmer *et al.* 2011), it might be advantageous to reduce pigment production when the risk of UV damage is low (e.g. at high latitudes and during winter). A plastic component to coloration does not exclude the possibility of adaptation, since phenotypic plasticity is itself regulated by genes which can be selected for. For example, in predator-free populations of *Daphnia melanica*, pigmentation is a highly plastic trait that changes with UV levels. In populations with introduced visual predators, predation of dark individuals has selected for low levels of plasticity, so that *Daphnia* remain pale across UV conditions (Scoville & Pfrender 2010). Similarly, selection by cleaner fish could result in lice with a stable, translucent phenotype (Pfennig *et al.* 2010; Ehrenreich & Pfennig 2016).

### Size selection

In addition to colour, louse size may be under selection. Small parasites can be more difficult for cleaner organisms to detect (Grutter 2002), resulting in selective removal of larger parasites (Grutter 1997; Grutter *et al.* 2002). Cleaner fish preferentially prey upon adult females over the smaller pre-adults and males (Treasurer 1994; Losos *et al.* 2010; Leclercq *et al.* 2014), and both are removed far more frequently than the chalimus stages (Tully *et al.* 1996; Skiftesvik *et al.* 2013; Imsland *et al.* 2018). Louse size is predominantly determined by life stage and sex, and the removal of specific age and sex classes would alter population demographics. The selective removal of larger individuals can lead to an evolutionary shift towards earlier maturation and smaller body sizes (Conover & Munch 2002; Fisk *et al.* 2007). For salmon lice, however, the variation in size attained by adults is determined predominantly by temperature (Samsing *et al.* 2016b) and is uncorrelated with fecundity or age at maturity (Mennerat *et al.* 2012). Adult body size is also strongly correlated with pigmentation, with larger individuals being darker in colour (Hamre *et al.* 2020). As co-selection for size and colour may occur, the individual effects of these traits on cleaner fish efficacy need to be teased apart.

### Host microhabitat selection

Certain attachment locations (microhabitats) of lice on their host may also be selected for when cleaner fish are present. Leclercq, Davie and Migaud (2014) noted that after exposure to cleaner fish, remaining motile lice were mostly located on the head of salmon, where before they were distributed across the dorsal surface with a preference for the posterior end of the fish. Lice that attach to the head may have improved survival if this area is less frequently or successfully cleaned.

Salmon lice move on and between hosts to find mates and avoid intra-specific competition (Hull *et al.* 1998; Todd *et al.* 2005). Motile louse stages are distributed differently on wild and farmed hosts, with farmed salmon having greater concentrations on the head (Jaworski & Holm 1992; Bjørn & Finstad 1998; Todd *et al.* 2000; Bui *et al.* 2020b). This may be due to lice choosing microhabitats based on environmental conditions, such as host density or host swimming behaviour. Alternatively, selective pressures such as cleaner fish may be driving an observable shift in attachment sites.

Increased infestations on the head would be expected to come with density-dependent effects. Salmon have thinner skin and fewer scales on the head and concentrated feeding in this area can cause severe lesions (Jónsdóttir *et al.* 1992; Bjørn & Finstad 1998; Fast 2014). The extent to which lice could aggregate on the head to avoid cleaner fish might be limited by intra-specific competition for these sites. Smaller lice may be displaced by larger ones from optimal sites and suffer reduced fitness (Todd *et al.* 2000; Ugelvik *et al.* 2017b). Research is needed to determine the heritability of microhabitat choice and to assess whether selection for attachment sites could lead to an adaptive response.

### Optical delousing

The Stingray™ laser delouser (Stingray Marine Solutions AS, Norway, stingray.no) functions as an abiotic analogue to cleaner fish. The system deploys underwater 'nodes' in cages which automatically detect lice using cameras and machine learning software. Once a target is acquired, nodes fire a laser pulse that kills the parasite but leaves the host unharmed. An independent study on laser efficacy that compared multiple commercial cages with and without lasers found no significant effect on infestations after 50 days of operation (Bui *et al.* 2020a). Given their market penetration at present (5%; ~200 out of ~4000 cages in Norway) and limited scientific evidence of efficacy, the Stingray™ system does not at present exert a strong selective pressure on the lice population.

## Thermal delousing

Automated thermal delousing systems (the Optilice, optimar.no; the Thermolicer, steinsvik.no) detach lice by bathing salmon in warm water for a short period of time (up to 36°C for approximately 30 s). Thermal treatments began in 2016 but by 2019 already comprised >60% of all immediate delousing strategies in Norway (Fig. 1c; Stien *et al.*, 2020) Given its frequent use and high efficacy (Table 1), thermal stress has rapidly emerged as a potentially powerful selection pressure. Lice may also be physically dislodged as salmon are crowded in the net, exposed to air in water separators and pumped through the treatment chamber. How these physical stresses might interact with thermal stress, individually and synergistically, has not yet been clarified.

### Selection for thermal tolerance

Lice exhibit significant variation in their ability to maintain attachment to a substrate during heat challenge experiments (Ljungfeldt *et al.* 2017). Attachment success was strongly influenced by family, with within-family success ranging from 58% to 81% (Ljungfeldt *et al.* 2017). This suggests that the host attachment during thermal delousing may have a heritable basis. Selection for lice with higher heat tolerance could lead to an evolutionary upwards shift in this parasite's thermal threshold. Alternatively, these effects might reflect variation in attachment strength, independent of thermal physiology.

Further research is needed to determine the degree to which this evolution can occur, although studies on other taxa, most using *Drosophila* (Hangartner & Hoffmann 2016), provide insight. Both *Drosophila* and salmon lice are forced to detach from their substrate under a critical high temperature, without this exposure necessarily having lethal effects (Huey *et al.* 1992; Ljungfeldt *et al.* 2017). This 'knockdown' temperature is a popular measure of thermal sensitivity in *Drosophila* (Huey *et al.* 1992). Artificial selection has improved knockdown resistance (increased exposure times and/or temperatures) in *Drosophila* multiple times in the laboratory (Huey *et al.* 1992; McColl *et al.* 1996; Hoffmann *et al.* 1997; Bubli *et al.* 1998; Gilchrist & Huey 1999). Similarly, in crustaceans (*Daphnia*) the thermal limit at which individuals lose motor function cease movement can be increased by 3.6 °C under natural selection (Geerts *et al.* 2015). There are limits to this evolution, however. Mean knockdown temperatures in one selected *Drosophila* population increased by a few degrees but the maximum upper limit could not be shifted higher, even after 32 generations of selection (Gilchrist & Huey 1999). Raising temperatures to match the evolving louse population is probably not an option, however, since the treatment temperatures currently used appear to be approaching the upper limit for salmon welfare (Gismervik *et al.* 2019; Nilsson *et al.* 2019).

### Costs of thermal tolerance

Shifts in the thermal tolerance window of an organism can shift its ecological niche (Huey & Kingsolver 1993). Tolerance to extreme heat stress (+30°C) is unlikely to confer direct advantages to lice under natural conditions. However, heat-resistant individuals can be more sensitive to low temperatures (Gilchrist *et al.* 1997; Portner 2002; Willett 2010) or have reduced plasticity in response to thermal variation (Stillman & Somero 2000; Hoffmann *et al.* 2003; van Heerwaarden *et al.* 2016), which could be trade-offs to adapting to thermal treatments.

Salmon lice develop normally within a relatively large temperature window (6–21°C, Hamre *et al.*, 2019), which is advantageous for a species that is transported through a range of thermal environments by forces outside their control (currents as larvae and host movement as parasites). Relatively high gene flow between cooler and warmer climates (Glover *et al.* 2011; Messmer *et al.* 2011; Besnier *et al.* 2014; Jacobs *et al.* 2018) could limit the spread of thermal resistance if it is costly in certain environments. That said, knockdown resistance is not necessarily correlated with other measures of heat tolerance (Gilchrist *et al.* 1997; Hoffmann *et al.* 1997; Bubli *et al.* 1998).

### Thermal plasticity

Short-term and long-term exposure to warmer temperatures (hardening and acclimatisation, respectively) can induce a plastic response that improves tolerance to a subsequent heat shock. The nauplius stages are more likely to survive a 31°C heat shock when hardened with a 26°C shock an hour earlier (Borchel *et al.* 2018). This is linked to the production of heat shock proteins (HSPs). The expression of HSP genes differs between genetic lines of nauplii (Borchel *et al.* 2018), suggesting that certain genotypes are better suited to periods of fluctuating temperatures. The experiment used in Ljungfeldt *et al.* (2017) to describe variation in thermal tolerance may have highlighted variation in thermal plasticity. The heat challenge had two stages, and the first (at 22°C) may have hardened lice before the subsequent stage (at 24–26°C). Families with a higher upregulation of HSPs during hardening are expected to have had improved survival. Future bioassays for thermal tolerance should closely replicate the conditions of delousing by exposing lice to sudden heat shocks instead of gradually warming conditions. Hardening is not likely to be a common issue on salmon farms, but longer-term acclimatisation does affect thermal delousing. In warm summer waters, treatments must be 5 °C higher than in early spring to achieve the same efficacy (Roth 2016). As with louse pigmentation in response to cleaner fish (see above), the degree to which lice respond plastically to heat stress could itself be a genetic trait that evolves under selection (Scoville & Pfrender 2010; Sgrò *et al.* 2010; Williams *et al.* 2012). Further research is needed to understand how thermally resistant lice interact with their wider environment.

## Mechanical delousing

In mechanical delousing, salmon are pumped through automated systems in which lice are physically removed using jets of pressurised water, turbulence and/or brushes (the Hydrolicer, smir.no; the FLS delouser, fls.no; the Ska-Mik, moenmarin.no). In Norway, mechanical delousing came into general use in 2016 and now comprises approximately 25% of all immediate strategies (Fig. 1c; Stien *et al.*, 2020). Chalimi and adult female lice appear to be more resistant to these technologies than other life stages (Table 1). This is also the case during the incidental mechanical delousing that occurs when salmon are transferred between pens or handled during sampling (Reynolds 2013; Powell *et al.* 2015; Bui *et al.* 2020b). This selective removal of certain age and sex classes would alter the demographics of louse populations. Further, mechanical delousing could impose selection within classes.

### Selection for improved attachment

Mechanical removal of parasites commonly occurs in nature through grooming behaviours (Hart 1990, 2011) which can lead to parasite adaptations (Murray 1987). In addition to enlisting the help of cleaner organisms, aquatic animals can also dislodge parasites with deliberate changes in swimming behaviour or by chafing against a substrate (Wyman & Walters-Wyman 1985; Daly & Johnson 2011). The characteristic leaping behaviour of salmonids may be a form of self-treatment for infestations. Atlantic and pink (*Oncorhynchus gorbuscha*) salmon increase their leaping and rolling activity when exposed to louse copepodids (Grimnes & Jakobsen 1996; Webster *et al.* 2007), and this behaviour can reduce new infestations by up to 31% (Bui *et al.* 2018c). Motile lice are also removed in this way by sockeye salmon (*O. nerka*; Atkinson *et al.* 2018). As salmonids evolved new ‘mechanical delousing’ behaviours, lice may in turn have evolved improved attachment ability. The introduction of mechanical treatments on farms could therefore be an extension of this evolutionary arms race. Although farm treatments are more effective than leaping behaviours at removing lice (Atkinson *et al.* 2018), they may also accelerate selection for traits already present in the louse population.

Chalimi are secured to the host with their frontal filament, which likely makes them harder to detach than motile stages. This filament is inserted through the host’s epidermis and anchored with an adhesive basal plate that is secreted between the epidermis and the underlying basement membrane (Bron *et al.* 1991). The chalimi that remain following delousing (~30%, Gismervik *et al.*, 2017; Erikson *et al.*, 2018) may be those with thicker filaments or larger basal plates, although variation in filament morphology has not yet been studied. In fact, reports have not specified whether mechanical delousing kills chalimi without detaching them.

The motile stages attach by using their cephalothorax as a suction cup (Kabata 1982). The size and shape of the cephalothorax likely reflect suction strength, which may explain why adult females are harder to remove than smaller stages. Lice also grasp onto the epidermis with hooked antennae and post-antennary processes (Jónsdóttir *et al.* 1992). Selection may occur for individuals with improved suction ability and/or more powerful gripping appendages. Morphological traits tend to evolve in response to selection more rapidly than other traits (Kingsolver *et al.* 2001), and so, a genetic basis to these traits may lead to a rise in ‘grippier’ motile lice.

Certain attachment behaviours may also be selected for, although how and why these vary in the population is also unknown. Lice sometimes burrow the anterior part of their carapace beneath the scales of the host (Jónsdóttir *et al.* 1992) which may make them more difficult to dislodge. As with cleaner fish (see above), behaviours related to microhabitat selection may be selected for. Lice that prefer sheltered locations (such as behind the fins) may be protected from water turbulence (Jónsdóttir *et al.* 1992) used in mechanical delousing.

### Implications of improved attachment

If lice evolved resistance to mechanical delousing, it is likely they would also be more difficult for salmonids to naturally remove with anti-parasite behaviours. With infestations harder to shake off, louse loads could increase, especially for wild salmon which exhibit these behaviours less frequently than domesticated strains (Bui *et al.* 2018a). Leaping and rolling are likely energetically costly and increases predation risk (Webster *et al.* 2007; Atkinson *et al.* 2018). These trade-offs may limit the extent to which wild salmonids can use these behaviours as a counteradaptation to improved louse attachment.

The mechanisms for improving attachment could also increase virulence. For example, the chalimus filament can cause lesions and inflammation, especially when left embedded in the epidermis after the louse moults (Jones *et al.* 1990). The hooked appendages used to grip the host can also cause damage (Jones *et al.* 1990; Jónsdóttir *et al.* 1992). Lice wedging beneath scales can increase the risk of scale loss, which makes a fish vulnerable to osmotic stress and secondary infections (Jónsdóttir *et al.* 1992). These costs might only be small individually, but could accumulate under high louse intensity, especially with the evolution of more aggressive attachment mechanisms (more invasive filaments, gripping appendages or burrowing behaviours). Selection for mechanical resistance could exacerbate the evolution of increased virulence already observed on farms (Ugelvik *et al.* 2017a) and is therefore an important area for future research.

## Freshwater delousing

Bathing salmon in freshwater for a few hours is another approach for removing lice, which are sensitive to low salinities. There are concerns that this strategy may impose a selection pressure strong enough for lice to evolve freshwater resistance (Groner *et al.* 2019). However, only ~5% of immediate delousing treatments are freshwater bathing (Fig. 1c; Stien *et al.*, 2020; Sommerset *et al.*, 2020), and since only a small portion of the louse population are exposed, this currently constitutes a relatively weak selection pressure (Falconer & Mackay 1996; McEwan *et al.* 2015).

Wild salmonids return to freshwater to breed and also self-treat against infestations by choosing brackish environments (Bjørn *et al.* 2001; Webster *et al.* 2007; Halttunen *et al.* 2018), and this is expected to have selected for freshwater tolerance in lice over the millennia. Indeed, lice can survive attached to hosts in freshwater for hours or even days as chalimi (Stone *et al.* 2002; Wright *et al.* 2016) and over a week as adults (Finstad *et al.* 1995; Wright *et al.* 2016).

Lice appear to be more susceptible to freshwater when used as a control strategy on farms, perhaps because the drop in salinity is more sudden and acute than occurs naturally. At least half of the efficacy of freshwater bathing may also be attributed to the mechanical removal of lice as salmon are crowded and pumped, rather than the freshwater itself (Table 1; Reynolds 2013; Powell *et al.* 2015). Synergism between freshwater and mechanical effects would also explain the higher efficacy on farms than in the laboratory. For example, lice that are physically dislodged in freshwater may have compromised osmoregulation and a lower chance of reattaching. It is possible, then, that selection for freshwater tolerance is different on farms than during natural processes, either in intensity or in the underlying traits selected for.

Recent studies have noted lice to be more tolerant to freshwater than in earlier work (Sievers *et al.* 2019; Andrews & Horsberg 2020), which might indicate an evolutionary shift (but might also reflect different methods used; Sievers *et al.*, 2019). Ljungfeldt *et al.* (2017) found survival in brackish water to range from <1 to 42% for different families of lice, suggesting a heritable component to this variation. The conditions in this study (exposure to ~15 ppt for 12 days) were quite different to those experienced by lice during delousing (exposure to ~0 ppt for a few hours), so results should be taken with caution. The authors also note that the variation between families may reflect background mortality rates, rather than salinity tolerance *per se* (Ljungfeldt *et al.* 2017). Free-living copepodids collected from geographically separated populations also vary significantly in freshwater tolerance, although this variation disappears for pre-adult and adult lice (Andrews & Horsberg 2020). It is unclear how large a genetic pool these copepodids were sourced from. If the lice from each population were collected from a small number of families, the variation could be attributed to any number of environmental or maternal effects. Indeed, in the same study the survival of adult lice in full salinity seawater varied between 60 and 90%, suggesting factors other than salinity at play. Population differences may also have been accentuated by inbreeding, since these groups were reared in the laboratory for 3+ years prior.

Populations of the sea louse *Caligus rogercresseyi*, which affects salmon aquaculture in Chile, also vary in tolerance to brackish water (Bravo *et al.* 2008a). Individuals collected from regions with high levels of brackish water runoff were more tolerant in salinity assays, although this study lacked statistical analyses to support this. This variation could reflect local adaptation but may also be due to phenotypic plasticity – lice were assayed immediately after collection and those from brackish regions may have acclimatised to lower salinities. The opportunity for local adaptations in *L. salmonis* is limited by relatively high panmixia.

### Implications of freshwater resistance

Lice that are attached to a host and more tolerant to low salinities (particularly the vulnerable copepodid and chalimus stages) would be more difficult for wild salmonids to remove by swimming through brackish water. Wild populations occupying coastal waters with high infestation pressures could suffer increased and sustained infestations as a result. The extent to which salmon and sea trout could adapt their migration and return earlier to freshwater is likely limited by the fewer food resources available in freshwater environments (Serra-Llinares *et al.* 2020). Low salinities presently provide an obstacle to initial infestation in certain areas, but this could be diminished by improved freshwater tolerance. More research is needed to determine whether freshwater tolerance is correlated for attached and free-living copepodids. Different salinity preferences for free-living copepodids would influence how larvae are dispersed in the water column (Johnsen *et al.* 2014; Samsing *et al.* 2016a; Crosbie *et al.* 2019).

## Enhanced host resistance

Another management approach is to focus on salmon and improve their natural resistance to lice. A number of immune responses are triggered in salmonids following sea louse infestation, including inflammation, leucocyte proliferation and changes in mucous composition (Fast 2014). Salmonids with heightened immunological defences against lice (such as coho, *Oncorhynchus kisutch*, and pink, *O. gorbuscha*, salmon) can reject large numbers of the parasite shortly after attachment (Johnson & Albright 1992; Jones *et al.* 2007; Braden *et al.* 2015). Augmentation of the immune response is an option for preventing infestation of Atlantic salmon (Barrett *et al.* 2020a), which is a comparatively susceptible host species (Fast *et al.* 2002).

### Functional feeds and selective breeding

One approach for enhancing host resistance is to provision salmon with ‘functional feeds’ that contain immunostimulatory additives. By inducing a heightened immune response, some functional feeds can reduce infestations by ~50% (Refstie *et al.* 2010; Covello *et al.* 2012; Purcell *et al.* 2013) although others have little effect (Refstie *et al.* 2010; Covello *et al.* 2012; Poley *et al.* 2013; Jensen *et al.* 2015). This strategy provides only temporary protection from infestation (Covello *et al.* 2012). Long-term disease resistance can be obtained in aquaculture through selective breeding (Houston 2017; Gjedrem & Rye 2018). Sufficient genetic variation exists in the susceptibility of Atlantic salmon to lice for selective breeding to be a feasible management strategy (Kolstad *et al.* 2005; Ødegård *et al.* 2014; Gharbi *et al.* 2015; Tsai *et al.* 2016; Holborn *et al.* 2019). Resistant strains have been offered by major salmon breeding companies since 2016 (e.g. AquaGen, aquagen.no; SalmoBreed, salmobreed.no; Fig. 1a). Over generations of selective breeding, genetic differences could accumulate to provide lasting protection from lice throughout the production cycle. Ten generations of family-based selective breeding have been predicted to reduce the frequency of chemical delousing by 60% (Gharbi *et al.* 2015), assuming lice do not adapt to the changing host population over this time.

### Adaptation to resistant hosts

Parasites can evolve a variety of counteradaptations for evading or suppressing the immune response of resistant hosts (Damian 1997; Wilfert & Jiggins 2010; Kerr *et al.* 2017). In agriculture, resistant plant cultivars are increasingly susceptible to disease as pathogens adapt to the new genotypes (Kiyosawa 1982; Cowger *et al.* 2000; Rouxel *et al.* 2003; Allen 2004). Resistance appears to be more robust against parasite evolution in livestock (Stear *et al.* 2001). For example, two species of parasitic nematode showed no indication of adapting to resistant hosts after 30 generations (Kemper *et al.* 2009). The more host genes that are selected for, the more complex the mechanisms of resistance and the harder it is for parasites to adapt (Bishop *et al.* 2002). This may be the case for louse resistance, which is a polygenic trait in Atlantic salmon (Tsai *et al.* 2016; Holborn *et al.* 2019).

In other parasite–host systems, infestation success is determined by both the host and parasite genotypes (Ebert 2008). Infestation levels in cloned salmon are highly variable, indicating that factors other than host genotype influence louse establishment (Glover *et al.* 2017). Research is needed to assess whether some louse strains have a higher success of infestation on resistant salmon. Lice produce a number of compounds during feeding that are thought to suppress or alter the immune defences of salmon (Fast *et al.* 2004, 2007). The production of one of these compounds, prostaglandin $E_2$, varies between individual lice, although the source of this variation is unknown (Fast *et al.* 2004). Resistant hosts could drive natural selection for lice that secrete higher concentrations or different compositions of such compounds. Co-evolutionary arms races have resulted in the development of diverse strategies for modulation of the host immune system by other parasitic arthropods (Wikel 1999; Schoeler & Wikel 2001).

A potential alternative to traditional selective breeding is the use of gene editing technologies to modify immune pathways in Atlantic salmon to resemble those found in more resistant Pacific salmon species (Barrett *et al.* 2020). As this strategy is explored and developed for commercial use in the future (e.g. https://www.fhf.no/prosjekter/prosjektbasen/901631/), it will be important to consider the co-evolutionary relationship of lice with these different host species. Salmon lice occupying the Atlantic and Pacific

Oceans are allopatric subspecies (*L. salmonis salmonis* and *L. salmonis oncorhynchi*) with minimal genetic exchange between the two populations (Skern-Mauritzen *et al.* 2014). Each subspecies releases a greater quantity of enzymes – thought to assist in feeding and host immunomodulation – when exposed to the mucous of a sympatric host species, than for an allopatric host species (Fast *et al.* 2003). This suggests the two subspecies have locally adapted their hosts to some extent. Nevertheless, lice infesting Atlantic salmon have higher survival and develop faster than on Pacific salmon species, regardless of louse subspecies (Johnson & Albright 1992; Fast *et al.* 2002; Bui *et al.* 2018b). That Pacific lice have not overcome the resistance of sympatric hosts is used to support the argument that lice will also be slow to adapt to genetically modified Atlantic salmon (Gjerde 2018).

### Implications for wild populations

More research into the evolutionary response of lice to enhanced host resistance is important because if lice can adapt to new resistant salmon strains, they may interact with more susceptible salmon strains – wild salmonids in particular – in new ways. There is already evidence that wild and farmed salmon are diverging in their louse susceptibility, with farmed strains exhibiting heightened anti-parasite behaviours and greater louse rejection (Bui *et al.* 2018a). If the majority of hosts available to lice in the Atlantic are farmed salmon with enhanced immune systems, wild salmonids may become immunodeficient hosts by comparison. If lice adapt to resistant host genotypes, such specialisation might come with trade-offs that reduce their infectivity and/or fitness on the less abundant wild genotypes (Roth *et al.* 2012). Producing multiple host strains with different underlying resistance mechanisms, and alternating these strains across time and space, would help to slow any parasite counter-evolution (Ebert 1998).

## Co-ordinating louse management strategies

There is strong evidence that salmon lice have evolved resistance to at least four of the five groups of chemotherapeutants dominating salmon aquaculture (Table 1). In response, the industry has shifted to non-chemical management strategies, yet little attention has been given to the possibility that lice can adapt to these as well (but see Ljungfeldt *et al.*, 2017; Groner *et al.*, 2019; Coates *et al.*, 2020; Hamre *et al.*, 2020). Even the most efficacious non-chemical methods still leave a fraction of lice attached (Table 1), although the survival and reproductive output of these remaining lice needs to be assessed. In the short-term, any reduction in louse levels is desirable, as this mitigates the infestation pressure of outbreaks on farm networks and nearby wild populations (Myksvoll *et al.* 2020). The survival of small portions of lice following treatment, however, raises the concern that certain traits might be selected for. Over the long-term, selection for resistant traits could lead to these new methods becoming obsolete. Table 2 summarises possible directions through which non-chemical resistance could evolve, based on the limited evidence currently available. Rather than being an attempt at scaremongering, we hope the ideas presented here provide a starting point for further research. Directed studies are needed to determine the shape and strength of selection that occurs during louse management. Estimates of trait heritability are also crucial for evolutionary predictions; this involves determining the extent to which trait variation is explained by genetic variation, as opposed to being influenced by environmental variation (Table 2). More research is also needed into the trade-offs of adaptive phenotypes. The sooner that these are quantified, the sooner that precautionary actions can be taken against the evolution of resistance (Groner *et al.* 2016; McEwan *et al.* 2016).

### Synergism and antagonism between management strategies

It is important to recognise that the management strategies discussed here do not occur in isolation. Rather, the louse population is subject to multiple pressures at once. Multiple strategies can even be implemented together in the same cage (Bui *et al.* 2020c). Using a combination of different treatments across farms can effectively slow or halt the evolution of resistance to any one method (REX Consortium, 2013; Mcewan *et al.*, 2016), assuming that each treatment selects for resistant genotypes independently. In reality, different selection pressures might act on the same trait to have synergistic or antagonistic effects on louse evolution (Table 2).

A synergistic effect can occur when different management strategies impose directional selection on the same trait in the same direction, leading to the evolution of cross-resistance. Multiple chemotherapeutants belonging to the same chemical families have been used in salmon farming (Denholm *et al.* 2002). If different chemicals within a family select for the same mutations conferring resistance, then they may all rapidly become obsolete when used together (Jones *et al.* 1992; Roth *et al.* 1996; Bravo *et al.* 2008b). The chemotherapeutant emamectin benzoate is also less effective when combined with immunostimulatory functional feeds (Igboeli *et al.* 2013; Poley *et al.* 2013). This suggests that resistance to the two methods involve similar mechanisms, and selection for the same traits could lead to cross-resistance arising. Freshwater and thermal delousing likely involve some mechanical removal of lice as salmon are crowded and pumped through the treatment chamber.

Adaptation of lice to mechanical delousing may improve tolerance to thermal and freshwater methods, and vice versa.

Another type of synergistic effect can occur if one strategy facilitates the evolution of resistance to another by minimising the trade-offs to the resistant trait. For example, the evolution of reduced pigmentation in response to cleaner fish could be accelerated by the widespread use of submerged snorkels cages. Snorkels hold salmon at depths where UV levels are lower, reducing the possible fitness costs associated with low pigmentation. Conversely, an antagonistic effect can occur when different strategies impose selection on the same trait, but in opposite directions (stabilising selection). In this instance, the trait is pinioned between two conflicting pressures, restricting evolution in either direction. For example, cleaner fish are less effective against lice that are larger and attached to the head of the salmon; whereas mechanical delousing is less effective against smaller lice, and possibly those in more sheltered microhabitats. Together, these strategies may buffer each other against resistance by providing stabilising selection on traits related to body size or microhabitat choice. Cold-water delousing is a new method being trialled (Overton *et al.* 2019b) which might work antagonistically with warm water delousing, by pushing the thermal window of lice in the opposite direction. In addition, new countermeasures against resistance could be implemented on farms to impose stabilising selection on certain traits. For example, artificial UV lights on farms could counter selection by cleaner fish for reduced pigmentation. Cage barriers that only permit access to copepodids distributed in shallow waters could counter any selection imposed by depth-based preventions.

It must be noted that these interactions (as presented in Table 2) are purely speculative for the time being. Further research into the relative strength of each selective pressure, as well as the trade-offs of each of the phenotypes selected for, is needed to rigorously assess whether these effects are possible. Once more knowledge is available, farms within a region can then co-ordinate management strategies through space and time according to evolutionary principles. Farms in the same area should avoid concurrent use of strategies with synergistic effects, as this can accelerate louse adaptation and lead to the loss of multiple strategies through cross-resistance. Antagonistic combinations of strategies, on the other hand, hold immense value for the industry and should be imposed where possible to slow the evolution of resistance. As illustrated in Table 1, different strategies also target different stages of the louse life cycle. Whether treatments should be combined to target different life stages, or to overlap on the same stage, depends on how life cycle influences selection. Co-ordination between farms across the louse population is key to sustainable louse control, alongside other integrated approaches such as maintaining wild host populations as refugia (Kreitzman *et al.* 2018), fallowing (Werkman *et al.* 2011), epidemiological modelling (Groner *et al.* 2016) and focussing on preventative, rather than reactionary, techniques (Barrett *et al.*, 2020). More generally, an improved understanding of how human pressures can drive parasite evolution is vital.

## Conclusion

The salmon louse *L. salmonis* is one of the most significant hurdles to the sustainable growth of salmon aquaculture. The demand for effective louse management has led to a diverse range of anti-parasite technologies being implemented on farms. Parasites are highly adaptable organisms, however, and each new imposes selection that can lead to an evolutionary response. This is exemplified by the evolution of resistance to most of the chemotherapeutants historically used against lice. The salmon industry has shifted to alternative, non-chemicals approaches, yet research into whether lice can adapt to these as well is still in its infancy. The existing evidence suggests that the evolution of non-chemical resistance is theoretically possible, but rigorous experimental studies are needed to properly assess this risk. Focus should be on three key questions. First, does the strategy select for certain louse traits? Second, are these traits heritable? Third, can additional strategies be imposed that act to stabilise the overall effect of selection? By taking the adaptive capacity of lice into account, management strategies can be co-ordinated in ways that safeguard their efficacy from resistance.

## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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