Prevention not cure: a review of methods to avoid sea lice infestations in salmon aquaculture

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Prevention not cure: a review of methods to avoid sea lice infestations in salmon aquaculture

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ABSTRACT

The Atlantic salmon aquaculture industry still struggles with ectoparasitic sea lice despite decades of research and development invested into louse removal methods. In contrast, methods to prevent infestations before they occur have received relatively little research effort, yet may offer key benefits over treatment-focused methods. Here, we summarise the range of potential and existing preventative methods, conduct a meta-analysis of studies trialling the efficacy of existing preventative methods, and discuss the rationale for a shift to the prevention-focused louse management paradigm. Barrier technologies that minimise host-parasite encounter rates provide the greatest protection against lice, with a weighted median 76% reduction in infestation density in cages with plankton mesh 'snorkels' or 'skirts', and up to a 100% reduction for fully enclosed cages. Other methods such as geographic spatiotemporal management, manipulation of swimming depth, functional feeds, repellents, and host cue masking can drive smaller reductions that may be additive when used in combination with barrier technologies. Finally, ongoing development of louse-resistant salmon lineages may lead to long term improvements if genetic gain is maintained, while the development of an effective vaccine remains a key target. Preventative methods emphasise host resistance traits while simultaneously reducing host-parasite encounters. Effective implementation has the potential to dramatically reduce the need for delousing and thus improve fish welfare, productivity and sustainability in louse-prone salmon farming regions.

INTRODUCTION

The global expansion of sea cage fish farming has driven considerable shifts in the population dynamics of marine pathogens. For 40 years, ectoparasitic lice have been an intractable problem for Atlantic salmon (*Salmo salar*) farming industries in Europe and the Americas (Torrissen *et al.* 2013; Iversen *et al.* 2015). Louse infestations are almost ubiquitous on salmon farms in these regions – primarily the salmon louse *Lepeophtheirus salmonis* but also *Caligus elongatus* in the northern hemisphere, and *Caligus rogercresseyi* in South America (Hemmingsen *et al.* 2020). Lice are natural parasites of fish, but intensive salmon farming amplifies louse densities, resulting in unnaturally high infestation pressure for both farmed and wild salmonids. Lice feed on the skin, blood and mucus of host fish, and severe infestations can cause ulceration leading to stress, osmotic imbalance, anaemia and bacterial infection (Grimnes and Jakobsen 1996; Øverli *et al.* 2014; González *et al.* 2016).

Accordingly, management of louse infestations on farmed fish is crucial to maintain acceptable stock welfare, limit production losses and reduce impacts on adjacent wild salmonid populations (Krkošek *et al.* 2013; Thorstad *et al.* 2015).

In most jurisdictions, the primary management approach is to monitor louse densities on farmed fish, with mandatory delousing or other sanctions implemented when louse levels exceed allowable limits. Regulations also cap the number of active sites or total biomass in each management zone according to estimated infestation pressure on wild salmonids, and may mandate coordinated fallowing or other measures (e.g. Norway: Ministry of Trade and Fisheries, 2012). The introduction of chemotherapeutants in the 1970s allowed farms to treat sea louse infestations without substantially reducing production (Aaen *et al.* 2015). However, most chemotherapeutants are not environmentally benign, leading to concerns about bioaccumulation and effects on non-target invertebrate species (Burridge *et al.* 2010). More recently, treatment-resistant lice have emerged on farms in Europe and the Americas (Aaen *et al.* 2015) rendering many chemotherapeutants less effective.

The discovery of treatment-resistance has prompted a rapid and recent shift to mechanical and thermal delousing methods in the Norwegian salmon farming industry (Overton *et al.* 2018), with these methods also gaining traction elsewhere (e.g. Canada, Chile, Scotland). Mechanical and thermal delousing are highly effective at removing mobile lice and have little or no impact on non-target species. However, they are stressful for host fish and can lead to elevated post-treatment mortality rates compared to the use of chemotherapeutants (Overton *et al.* 2018). Low salinity or hydrogen peroxide baths are also effective in the right conditions and do not accumulate, although the long-term prospects for these methods are uncertain given the possibility of increasingly resistant lice (Treasurer *et al.* 2000, Helgesen *et al.* 2018, Groner *et al.* 2019). Alternatively, around 50 million cleaner fish (lumpfish *Cyclopterus lumpus* and several wrasse species) are deployed annually at Norwegian salmon farms to eat lice directly off salmon (Norwegian Directorate of Fisheries 2018), with >1.5 million cleaner fish also used in Scotland (Marine Scotland Directorate, 2017). However, it is unclear whether their efficacy (Overton *et al.* 2020; Barrett *et al.* 2020a) is sufficient to justify their poor welfare in commercial sea cages (Nilsen *et al.* 2014; Hvas *et al.* 2018; Mo and Poppe 2018; Yuen *et al.* 2019; Stien *et al.* 2020).

Decades of innovation in louse control have allowed the salmon farming industry to continue functioning in louse-prone regions, but not without significant environmental and ethical concerns. Most research and development efforts so far have focused on treating at the postinfestation stage. This likely reflects the relatively rapid return on investment into new delousing methods but may be a sub-optimal strategy if opportunities to invest in long term solutions are missed (Brakstad *et al.* 2019). An alternative approach is to focus louse management efforts on preventing infestation via proactive interventions ('preventative methods' herein) that may significantly reduce the need for farms to delouse. Here, we summarise the range of potential or existing preventative methods and conduct a meta-analysis of empirical estimates of sea louse removal efficacy for each method. Finally, we discuss the rationale for a paradigm shift from reactive louse control to a proactive approach that focuses on predicting and preventing infestations, and outline some possible strategies to promote long term efficacy of preventative methods.

WHAT PREVENTATIVE METHODS ARE AVAILABLE?

Preventative methods are deployed pre-emptively to reduce the rate of new infestations. Within this classification, we include approaches that either: (1) reduce encounter rates between salmon and infective copepodid stage lice; or (2) reduce the attachment success and/or early post-settlement survival of copepodids via interventions that begin to act at the moment of attachment or first feeding (Fig. 1). These approaches are distinct from control via delousing treatments, which are generally implemented as a reaction to an existing infestation (i.e. 'immediate' control), or via cleaner fish, which may be deployed prior to infestation and function on an ongoing basis (i.e. 'continuous' control) but are not typically effective against newly attached lice (e.g. Imsland *et al.* 2015).

1. Reducing encounters

1.1 Barrier technologies

A growing understanding of louse physiology and host-finding behaviour has led to several important advances in louse prevention, and by using data on preferred swimming depths of infective copepodids in relation to environmental parameters (Heuch 1995; Heuch *et al.* 1995; Crosbie *et al.* 2019), farmers can now separate hosts from parasites using depth-specific louse barriers.

Barriers made from fluid-permeable plankton mesh or impermeable membranes can dramatically reduce infestation rates by preventing infective copepodids from entering the cage environment. 'Skirt' or 'snorkel' barriers prevent particles in the surface layers—where most copepodids reside—from entering the cage while still allowing full water exchange below the level of the barrier (Oppedal *et al.* 2017; Wright *et al.* 2017; Stien *et al.* 2018). Salmon often choose to reside below the level of the skirt or snorkel, meaning that the barrier functions by simultaneously (i) encouraging salmon to swim below the depth at which infestation risk is highest, and (ii) protecting any individuals that use the surface layers, for example, while feeding or refilling the swim bladder. In the most complete use of barrier technologies, fully-enclosed cages are supplied with louse-free water either filtered or pumped from depths below the typical depth range of copepodids (e.g. 25 m: Nilsen *et al.* 2017).

Barrier technologies (particularly skirts) are already widely used by the industry, but specific designs should be matched to local environmental conditions to avoid problems with low dissolved oxygen or net deformation (Stien *et al.* 2012; Frank *et al.* 2015; Nilsen *et al.* 2017). For example, Nilsen *et al.* (2017) prevented deformation of impermeable tarpaulin barriers at relatively sheltered sites by creating slight positive pressure within the cage (i.e. inside water level 2-3 cm above sea level). At more exposed sites, it is preferable to use fluid-permeable plankton mesh barriers (e.g. Grøntvedt *et al.* 2018). Brackish surface water can also reduce the efficacy of skirts and snorkels by causing both lice and salmon to reside below the level of the barrier (Oppedal *et al.* 2019), while there is evidence that barrier technology may reduce the performance of cleaner fish when used in combination (Gentry *et al*. 2020).

1.2 Manipulation of swimming depth

Salmon behaviour, primarily swimming depth, can also be manipulated in the absence of barrier technology to reduce spatial overlap (and therefore encounter rates) between hosts and parasites, especially salmon lice. Typically, the aim is to reduce encounter rates by causing salmon to swim below the depths at which lice are most abundant. Deep swimming behaviour can be promoted through the use of deep feeding and/or lighting (Hevrøy *et al.* 2003; Frenzl *et al.* 2014; Bui *et al.* 2020). Where surface feeding is conducted, reducing the frequency or regularity of feeding (e.g. twice daily at varying times) can reduce the amount of time spent in the surface layers (Lyndon and Toovey 2000). Deep swimming can also be forced by submerging cages to the desired depth (Dempster *et al.* 2008; Dempster *et al.* 2009), and there is evidence for reduced louse levels on salmon in submerged cages (Osland *et al.* 2001; Hevrøy *et al.* 2003; Sievers *et al.* 2018; Glaropoulos *et al.* 2019). Long term submergence can affect fish welfare as salmon lose buoyancy over time (Korsøen *et al.* 2009; Macaulay *et al*. 2020), however recent research indicates most welfare concerns can be addressed by allowing periodic surface access or fitting a submerged air-filled dome for swim bladder refilling (Korsøen *et al.* 2012; Glaropoulos *et al.* 2019; Oppedal *et al*. In Press).

1.3 Geographic spatiotemporal management

A range of spatiotemporal management approaches are applied at the landscape scale to reduce infestation risk by controlling where and when salmon are farmed. Some farm sites have consistently low louse abundances and rarely require delousing (www.barentswatch.no). Locating farms to take advantage of beneficial oceanographic conditions and minimise connectivity with adjacent sites may reduce the number of host-parasite encounters over a grow-out cycle (Bron *et al.* 1993; Samsing *et al.* 2017; Samsing *et al.* 2019). Fallowing during periods of high propagule pressure may also delay first infestation after sea transfer of smolts (Bron *et al.* 1993).

1.4 Filtering and trapping

Filters and traps may be deployed in or around cages to remove infective copepodids from the water column before they encounter salmon. Filter-feeding shellfish racks hung around sea cages may reduce louse abundance if deployed at sufficient scale (Byrne *et al.* 2018; Montory *et al*. 2020), while powered filters are effective in the context of preventing lice and eggs from entering the environment during delousing (O'Donohoe and Mcdermott 2014). In other fish farming systems, cleaner shrimp have been used to remove parasites or parasite eggs from fish and nets and reduce infestation or reinfestation risk (Vaughan *et al.* 2018a; Vaughan *et al.* 2018b). However, this method may have limited application against sea lice because of the planktonic mode of dispersal and infestation (i.e. larvae do not develop within the cage structure). Light traps have been tested in the field with mixed results (Pahl *et al.* 1999; Novales Flamarique *et al.* 2009), and increasing knowledge of host-locating behaviour in lice may present new possibilities for baiting traps with attractive chemosensory cues (Devine *et al.* 2000; Ingvarsdóttir *et al.* 2002; Bailey *et al.* 2006; Mordue and Birkett 2009; Fields *et al.* 2018). No preventative filtering or trapping methods have been widely deployed in the industry, but some systems have recently become commercially available (e.g. 'Strømmen-rør', Fjord Miljø; 'NS Collector', Vard Aqua).

1.5 Repellents and host cue masking

Interventions may be used to repel lice or mask host cues, potentially reducing host-parasite encounters even when parasites enter the sea cage. Repellents or masking compounds can either be released into the water column or included in feed to alter the host's semiochemical profile (Hastie *et al.* 2013; O'Shea *et al.* 2017). Indeed, some existing commercially available functional feeds are claimed to reduce attraction of lice toward fish (e.g. Shield, Skretting; Robust, EWOS/Cargill). Visual cues may also be important, and the effect of modified light conditions on infestation rates have been trialled with mixed results. Browman *et al*. (2004) concluded that ultraviolet-A and polarisation were not important for host detection at small spatial scales. Light intensity interacted with salinity and host velocity to influence distribution of louse attachment in another study (Genna et al. 2005), while Hamoutene *et al.* (2016) reported that 24-hour darkness affected the attachment location but not abundance of salmon lice.

1.6 Incapacitation

Several methods have been proposed for disabling or killing lice—from egg to adult stages—in or around sea cages. These include ultrasonic cavitation (Alevy 2017; Skjelvareid *et al.* 2018; Svendsen *et al.* 2018), direct current electricity (Bredahl 2014) and irradiation with short wavelength light (Barrett *et al.* 2020b, Barrett *et al.* 2020c). Some have demonstrated efficacy at close range (Skjelvareid *et al.* 2018, Barrett *et al.* 2020b, Barrett *et al.* 2020c), but it is currently unclear whether any such methods can be effective at commercial scale.

1.7 Louse population control

Interventions to suppress louse populations outside the cage environment would require careful consideration before deployment and must be specific to targeted louse species. Very little work has been done in this area, but possible avenues may include the release of parasites and pathogens that are specific to sea lice (Økland *et al.* 2014; Økland *et al.* 2018; Øvergård *et al.* 2018), or CRISPR-based 'gene drives' (McFarlane *et al.* 2018; Noble *et al.* 2019).

2. Reducing post-encounter infestation success

2.1 Functional feeds

Feeds that provide physiological benefits beyond basic nutritional requirements are termed functional feeds and are increasingly prevalent in industrial fish farming (Tacchi *et al.* 2011). Feed ingredients that modify the mucus layer or modulate skin immune responses may reduce initial attachment success or facilitate effective immune responses against newly-attached lice (Martin and Krol 2017). Functional feeds may also include ingredients that are toxic or repellent to attached lice – these are not necessarily distinct from in-feed chemotherapeutants, except that they tend to be derived from 'natural' sources (e.g. plantderived essential oils: Jensen *et al.* 2015). Functional feeds aimed at improving salmon louse resistance are already commercially available (e.g. Shield, Skretting; Robust, EWOS/Cargill). It will be important to test for any adverse effects of new functional feeds. For instance, glucosinolates and beta-glucans have been shown to be effective for reducing louse infestation (Refstie *et al.* 2010; Holm *et al.* 2016), but glucosinolates also have a range of effects on liver, muscle and kidney function that would need to be investigated (Skugor *et al.* 2016). Hormonal treatments may also be effective at reducing louse infestation (Krasnov *et al.* 2015), but preventative hormone treatments are likely to be perceived negatively by consumers.

2.2 Vaccines

Vaccines against bacteria and viruses are increasingly widespread in fish farming. In Norway, antibiotics have been almost entirely replaced by injectable multi-component oil-based vaccines (Brudeseth *et al.* 2013), and there is increasing use of injected or orally administered vaccines in North America and Chile (Brudeseth *et al.* 2013). However, to our knowledge there is currently only one (partially effective) vaccine available for sea lice (*C. rogercresseyi*: Providean Aquatec Sea Lice, Tecnovax). While there are no in-principle barriers, the development of vaccines for ectoparasites is technically challenging; despite the identification of numerous vaccine targets in a range of ectoparasites, the cattle tick (*Rhipicephalus microplus*) remains the only ectoparasite with a highly effective vaccine (Stutzer *et al.* 2018).

Successful development of a recombinant or DNA vaccine would allow cost-effective production and delivery (Raynard *et al.* 2002; Sommerset *et al.* 2005; Brudeseth *et al.* 2013). Potential vaccines exist at various stages of development, from localisation of candidate antigens in lice (Roper *et al.* 1995), demonstration of antibody production in response to inoculation with louse extracts (Reilly and Mulcahy 1993), and use of recombinant proteins to vaccinate salmon in tank trials (Carpio *et al.* 2011; Carpio *et al.* 2013; Basabe *et al.* 2014; Contreras et al. 2020). Recently, RNA interference has been used to knock down candidate vaccine targets and assess potential efficacy through challenge experiments (Eichner *et al.* 2014; Eichner *et al.* 2015; Komisarczuk *et al.* 2017).

2.3 Breeding for louse resistance

Variation in louse resistance is considerable among Atlantic salmon and has a heritable component (Glover *et al.* 2005; Kolstad *et al.* 2005; Gjerde *et al.* 2011; Tsai *et al.* 2016;

Holborn *et al*. 2019), indicating that there is sufficient additive genetic variation for selective breeding. Observed variation in louse resistance is probably due to differences in expression of both host cues and immune responses (Holm *et al.* 2015). Decades of selective breeding has resulted in much higher growth rates for farmed salmonid strains (Gjedrem *et al.* 2012) and increased resistance to some diseases (Leeds *et al.* 2010; Ødegård *et al.* 2018; Storset *et al.* 2007; reviewed by Robinson *et al.* 2017). More recently, the development of high-throughput single nucleotide polymorphism (SNP) genotyping technology has enabled relatively rapid and affordable genomic selection and fine mapping of quantitative trait loci associated with disease resistance.

Quantitative trait loci explaining between 6-13% of the genetic variation in sea louse resistance (louse density on fish) have been detected in North American and Chilean populations of Atlantic salmon (Rochus *et al.* 2018; Robledo *et al.* 2019). Salmon families with greater resistance to sea lice show upregulation of several immune pathway and pattern recognition genes compared to more susceptible families (Robledo *et al.* 2018), and the two major breeding companies in Norway (AquaGen and SalmoBreed) offer salmon lines that have been selected using marker assisted section or genomic selection for sea louse resistance. Use of genomic selection has been shown to increase the accuracy of selection for sea louse resistance by up to 22% (Tsai *et al.* 2016; Correa *et al.* 2017), and two generations of genomic selection focused on just sea louse resistance led to a 40-45% reduced sea louse infestation compared to unselected fish (Ødegård *et al.* 2018).

Other possible approaches for improving sea louse resistance in Atlantic salmon include hybridisation of Atlantic salmon with more louse-resistant salmonid species (Fleming *et al.* 2014), genetic modification of Atlantic salmon with immune genes from other salmonids, or use of gene editing to modify protein function or regulate the expression of genes affecting resistance. In the case of hybridisation or any genetic modification, the effect on other production traits would need to be assessed before hybrids or edited fish are used by the industry. Gene editing approaches have high potential (Gratacap *et al.* 2019), but successful implementation depends on knowing which genes to modify to have the desired effect, on developing effective methods for implementing and spreading the gene edits through the breeding population, and on the acceptability of the use of the technology by the general public and government.

EFFICACY OF PREVENTATIVE METHODS

To assess the state of knowledge on the efficacy of preventative methods, we conducted a systematic review and meta-analysis of published studies pertaining to preventative methods. To find relevant studies, we searched ISI Web of Science, Scopus and Google Scholar in February 2020 using the following search string: *(aquacult* OR farm*) AND (salmon* or Salmo) AND (lice OR louse OR salmonis OR Caligus)*. We also discovered additional studies referenced within articles returned by the search string. Together, our searches returned >1200 peer-reviewed articles, technical reports and patents relevant to lice and salmon aquaculture, of which 141 provided evidence on the efficacy of preventative methods and were included in the review.

Studies that provided relevant response variables were included in a meta-analysis, allowing the comparison of effect sizes across the range of preventative approaches. For inclusion, studies were required to provide empirical measures of relative louse infestation densities for treatment groups (preventative methods used) and control groups (no preventative methods used). Studies that applied treatments to lice but did not directly test for effects on infestation were not included. Effect sizes were standardised using the natural log of the response ratio: $ln\text{RR} = ln(\mu_T/\mu_C)$, where μ_T is the treatment group response and μ_C is the control group response. In most cases, response variables were either mean or median attached lice per fish. Where a study tested multiple qualitatively different treatments, each treatment was considered a replicate comparison in the meta-analysis. Where there were several qualitatively similar treatments (e.g. a range of doses of the same substance) the strongest treatment was included in the meta-analysis. Epidemiological studies typically did not have clear control or treatment groups; in such cases, the area or condition with the highest louse density was designated as the control group for the purposes of calculating a response ratio; this practice may inflate average effect sizes.

A total of 41 articles provided 98 comparisons that met the criteria for inclusion in the meta-analysis. For each preventative approach, we calculated a median effect size. When calculating a median effect, weighting studies according to their sample size can reduce bias. However, this was difficult in practice due to inconsistent definition of units of replication and therefore sample size across studies. Given this, we applied weightings to studies within each preventative approach (except vaccination, breeding and functional feed approaches, which are usually challenge tested in tanks) according to the scale or level of evidence of the experiment (in descending order of relative weights, level A: multiple farm experiment – 1.0;

level B: experiment in full size sea cages at a single site – 0.8; level C: experiment in small sea cages at a single site – 0.6, level D: observational/epidemiology – 0.4; level E: experiment in tanks – 0.2).

To allow a visual assessment of potential publication bias, we produced a 'funnel plot' in which study effect sizes are fitted against the precision (1/SE) of the effect. This is based on sample size as defined by the study authors, or else the best available approximation. Precision is typically increased by sample size and/or experimental power, and typically, in a field without publication bias, the average direction and size of effect should not vary systematically with study precision (Hedges *et al.* 1999; Nakagawa *et al.* 2017).

Which preventative methods are most effective against sea lice?

Comparison of response ratios revealed high variability in effect sizes among trials of preventative methods (Fig. 2), but evidence from sea cage trials indicates that barrier technologies can drive the largest and most consistent reductions in louse infestation levels (weighted median 78% reduction, range 8% increase to 99% reduction, n = 13 ; Fig. 2). Efficacy of specific barrier technologies appeared to be related to the extent of coverage: skirts were moderately effective (median 55% reduction, range 30-81%, n = 2), snorkels were highly effective (median 76% reduction, range 8% increase to 95% reduction, n = 9), and in the sole closed containment study (Nilsen *et al.* 2017), infestations were almost entirely avoided (98–99.7% reduction).

Approaches utilising manipulation of salmon swimming depth offered variable outcomes, but with strong effects in certain situations (weighted median 26% reduction, range 72% increase to 93% reduction, n = 11; Fig. 2). Geographic spatiotemporal management of farming effort (or related variables such as simulated current speed: Samsing *et al.* 2015) had similarly variable effects (weighted median 13% reduction, range 81% increase to 73% reduction, n = 14; Fig. 2). Functional feeds tended to have small but beneficial effects on sea louse infestations (median 24% reduction, range 108% increase to 67% reduction, n = 32: Fig. 2), as do published vaccine trial results (median 4% reduction, range 20% increase to 57% reduction). Notably, deployment of multiple preventative methods in combination with cleaner fish had highly variable effects in three published studies using replicated modern commercial sea cages (weighted median 9% reduction, range 143% increase to 49% reduction, n = 5: Bui *et al*. 2019b; Bui *et al*. 2020; Gentry *et al*. 2020).

Several potential preventative approaches have seen little effort to test their effects on infestation rates. The use of repelling non-host cues was effective in one small-scale cage study (53-74% reduction, n = 3: Hastie *et al.* 2013), as was filtering of copepodids using oyster racks ((32% reduction: Byrne *et al*. 2018) or light traps (12% reduction: Pahl *et al*. 1999), and the incapacitation of lice using electric fences (78% reduction: Bredahl 2014) and ultrasonic cavitation (37% increase to 39% decrease: Skjelvareid *et al*. 2018).

Efficacy of selective breeding for louse resistance should be interpreted with a long-term view. Iterative improvements tend to be small-moderate but can lead to large genetic gain over generations (Yanez *et al.* 2014; Gjedrem 2015), especially if genomic or marker assisted selection for sea louse resistance is given a high weighting in the overall breeding index (Ødegård *et al.* 2018). Estimates of heritability in louse resistance are moderate to high depending on the method used (range 0.07-0.35: e.g. Gjerde *et al.* 2011; Glover *et al.* 2005; Houston *et al.* 2014; Holborn *et al*. 2019), indicating that there is sufficient heritable variation available for genetic improvement.

Is the evidence base representative and robust?

Most preventative approaches have only been assessed a few times. Among the 41 articles that met the criteria for inclusion in the meta-analysis, 7 provided data on efficacy of barrier technologies, 6 on manipulation of swimming depth, 1 on breeding, 13 on functional feeds, 2 on incapacitation, 2 on repellents or cue-masking, 5 on geographic spatiotemporal management, 2 on trapping and filtering, and 3 on candidate vaccines. Most articles (n = 38) were primarily concerned with salmon lice *L. salmonis* (i.e. those in Europe and North America), while the remaining 3 articles targeted prevention of sea lice *C. rogercresseyi* (i.e. those in Central or South America). All tested efficacy using Atlantic salmon.

Levels of evidence ranged widely: Barrier technologies had the most rigorous evidence base, with multiple studies with evidence levels from A-C (Fig. 2). Evidence levels should be considered when interpreting estimated efficacy, as preventative approaches may vary in their scalability to commercial sea cages (e.g. viability of methods to filter or trap copepodids are likely to be highly dependent on water volume).

Units of replication also varied widely between studies, from individual fish to tanks, sea cages or farms. 51 out of 98 comparisons treated individual fish as replicates, in most cases resulting in a pseudoreplicated design as individuals were kept within a comparatively small number of tanks or cages (often <3 tanks or cages per group). We recommend that where fish are treated as replicates, the number of tanks or cages should also be reported, and mixed effects statistical methods employed to account for non-independence between fish held within the same tank or cage (Harrison *et al.* 2018).

Finally, the meta-analysis revealed possible evidence for publication bias, with fewer studies than expected present in the area of the plot corresponding to low precision and negative findings (Fig. 3). In other words, the funnel plot indicates that among studies with small sample sizes and/or highly variable data, those with positive results regarding efficacy of a preventative method were more likely to be published. Not publishing negative findings can (a) artificially inflate estimates of efficacy when averaging across studies, and (b) lead researchers to waste resources testing methods that have already been found to be ineffective, perhaps multiple times. Accordingly, it is important that researchers and managers are aware of the potential for publication bias when considering the evidence for novel louse management strategies (whether preventative or otherwise). The prevalence of publication bias is likely to be influenced by the type of study and preventative method. For example, tests of barrier technologies and swimming depth manipulation are generally conducted in sea cages, and given the effort and cost involved, results are perhaps more likely to be published in full. Other approaches may be inherently more susceptible to publication bias, for example when a large range of substances or doses are tested in the early stages of a study and only those that are reasonably successful are reported.

THE NEW PARADIGM: A FOCUS ON PREVENTATIVE METHODS AGAINST SEA LICE

The evidence base demonstrates that effective implementation of preventative methods can reduce infestation pressure within sea cages and therefore reduce the need for louse control. A prevention-focused louse management paradigm may lead to several key benefits:

(1) Most preventative methods have small if any impacts on non-target organisms (like mechanical and thermal delousing methods, but unlike some common chemotherapeutants: Burridge *et al.* 2010; Taranger *et al.* 2015).

(2) Delousing treatments cause stress and injury to stock, leading to welfare concerns and production losses from reduced growth, higher mortality and a lower quality product (Overton *et al.* 2018). By focusing on avoiding encounters and reducing initial infestation success, preventative methods may be targeted at infective louse stages without also

impacting host fish (Fig. 4). Conversely, some preventative methods can selectively target host traits to improve innate resistance (Fig. 4), such as promoting parasite avoidance behaviour via behavioural manipulation or immune function via functional feeds and selective breeding.

(3) Multiple preventative methods can be deployed together and on a continuous basis, although specific combinations should be trialled first (Bui *et al*. 2020; Gentry *et al*. 2020). This contrasts with current louse control methods, which are less amenable to being used in combination (for example, cleaner fish should not be subjected to mechanical delousing along with the salmon). The technical ability already exists to place farms strategically to minimise connectivity (Samsing *et al.* 2019), and salmon with higher louse resistance are already being stocked by some farms in combination with barrier technologies (primarily skirts) and/or functional feeds for louse resistance. Effective use of multiple preventative methods in combination could reduce louse densities by orders of magnitude without negative effects on fish welfare, although as with any control strategy, potential welfare concerns (e.g. those arising from holding salmon at depth) should be tested and mitigated prior to widespread deployment. Vaccines may eventually result in even greater additive reductions in louse densities.

MAINTAINING LONG-TERM EFFICACY

Host-parasite interactions are subject to a coevolutionary arms race in which organisms must constantly evolve to keep up with the coevolution occurring in opposing organisms (i.e. the Red Queen hypothesis: Hamilton *et al.* 1990). Most lice never encounter a potential host, and those that do will likely only have one opportunity to attach. This could precipitate strong selective pressures, and because farmed salmon represent the majority of available hosts for lice in some regions (especially in the north-east Atlantic), louse control interventions on farms are likely to exert directional selection pressure on louse populations wherever certain genotypes are favoured over others. Evolution of resistance occurred relatively quickly in response to chemical delousing (global reviews: Aaen *et al.* 2015; Gallardo-Escárate *et al.* 2019) and presently remains high (Helgesen *et al.* 2018), although in areas where wild salmonids are abundant, flow of susceptible genes from lice on wild hosts may help to maintain treatment efficacy (Kreitzman *et al.* 2017).

It is currently unclear whether preventative methods will be similarly vulnerable to the evolution of resistance in lice, but some methods will likely create suitable conditions. For example, barrier technologies that span the surface layers (e.g. 0-10 m) may select for lice that preferentially swim deeper. Potential for evolution will depend on many factors including the heritability of the resistance to the preventative treatment in lice, the levels of genetic variation existing in the louse population, the intensity of selection, treatment season, frequency and geographic locations, prevailing currents and tides (louse dispersal) and the biological complexity of the preventative mechanism. Nonetheless, the preventative paradigm does have the advantage of a diversity of methods that may disrupt directional selection for resistance to a given method. Research is needed to outline the best way forward, but management strategies to slow the evolution of resistance to preventative methods should heed lessons from other systems (e.g. antibiotic resistance in human medicine: Raymond 2019). Potential strategies to slow the evolution of resistance to preventative methods may include:

(1) Continuing to delouse when necessary. Effective use of preventative methods will greatly reduce the required frequency of delousing, but periodic delousing will hamper the genetic proliferation of any lice that successfully infest stock.

(2) Deployment of multiple methods in combination to counteract directional selection. For example, combining skirts or snorkels with non-depth-specific methods such as functional feeds or spatial management may reduce directional selection for louse swimming depth.

(3) Planning of spatial ‘firebreaks’ whereby farms are removed or fallowed at strategic areas to minimise louse population connectivity, thus reducing reinfestation rates and potentially slowing the spread of resistant genotypes between farming areas (Besnier *et al.* 2014; Samsing *et al.* 2017; Samsing *et al.* 2019).

(4) Ongoing selective breeding for louse-resistant salmon lineages to ensure that genetic gains are not lost through random genetic drift. Using current cohorts of wild sea lice when calibrating breeding value predictions for each generation will help to ensure that genetic gains continue to be relevant and account for any evolutionary developments in the louse population. Like other vertebrates, salmon have a complex immune system and biology, which should provide a range of potential defence options against parasites. Genomic selection probably affects a number of biological processes in the fish, and sea lice would therefore need to have sufficient genetic variability to be able to successfully adapt and

counter the genomic selection. Development of multiple louse-resistant salmon strains may dampen directional selection for corresponding adaptation in louse populations.

Conversely, preventative methods could be utilised in a way that promotes evolution of certain resistant traits (such as deeper swimming) in order to increase specificity of louse populations to salmon in farming environments, and therefore reduce infestation pressure on wild salmon. Modelling is needed to determine whether such an approach could prove beneficial in decoupling encounters between farm-derived lice and wild salmonids.

CONCLUSIONS

Effective use of barrier technologies such as skirts, snorkels, or closed containment, coupled with supplementary preventative methods may make delousing treatments unnecessary at many sites, while high-risk locations may require additional management and regulation. Breeding of louse-resistant salmon has begun; heritable variation exists, and cumulative improvements are reducing susceptibility to lice in some salmon lineages. The successful development of an effective vaccine would also be an important advance. In general, preventative methods are preferable to reactive delousing, and moving towards a prevention-focused paradigm on Atlantic salmon farms may yield significant improvements in fish welfare and productivity, while avoiding significant environmental impacts.

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TABLES

Table 1. Studies that assessed efficacy of preventative methods against louse infestation in Atlantic salmon. Effect sizes given are raw response ratios (treatment/control group) for louse infestation densities. Smaller values indicate more effective prevention. Where a study includes multiple treatment levels, the effect size range is given.

METHOD	*EFFECT SIZE (T/C)*	*STUDY TYPE*	*STUDY ENVIRONMENT*	*STUDY LOCATION*	*FOCAL LOUSE*	*NOTES*	*REFERENCE*
1.1 Barrier technologies							
Snorkel cages	0.57	Sea cage trial	Small cage	Norway	*L. salmonis*		Stien *et al.* 2016
	0.05–0.37	Sea cage trial	Small cage	Norway	*L. salmonis*		Oppedal *et al.* 2017
	0.17	Sea cage trial	Large cage	Norway	*L. salmonis*		Wright *et al.* 2017
	0.24	Sea cage trial	Large cage	Norway	*L. salmonis*		Geitung *et al.* 2019
	0.36–1.08	Sea cage trial	Small cage	Norway	*L. salmonis*		Oppedal *et al.* 2019
Skirts	0.70	Sea cage trial	Multi farm	Norway	*L. salmonis*		Grøntvedt *et al.* 2018
	0.19	Sea cage trial	Large cage	Norway	*L. salmonis*		Stien *et al.* 2018
Closed containment	0.00–0.02	Sea cage trial	Multi farm	Norway	*L. salmonis*		Nilsen *et al.* 2017
1.2 Manipulation of swimming depth							
Forced submergence	0.08–1.72	Sea cage trial	Small cage	Norway	*L. salmonis*		Hevrøy *et al.* 2003
	0.31–0.45	Sea cage trial	Large cage	UK	*L. salmonis*		Frenzl *et al.* 2014
	1.09	Sea cage trial	Large cage	Norway	*L. salmonis*		Nilsson *et al.* 2017
	0.28	Sea cage trial	Small cage	Norway	*L. salmonis*		Sievers *et al.* 2018
	0.70	Sea cage trial	Small cage	Norway	*L. salmonis*		Glaropoulos *et al.* 2019
Deep lights/feeding	0.74	Sea cage trial	Large cage	UK	*L. salmonis*		Lyndon and Toovey 2000
1.3 Geographic spatiotemporal management							
Location	NA	Challenge trial	Tank	UK	*L. salmonis*	Salinity	Genna *et al.* 2005)
	0.45–0.93	Epidemiology	Multi farm	Chile	*C. rogercresseyi*	Various risk factors	Zagmutt-Vergara *et al.* 2005
	0.27–0.88	Epidemiology	Multi farm	Canada	*L. salmonis*	Spatial risk factors	Saksida *et al.* 2007
	0.48–0.58	Epidemiology	Multi farm	Chile	*C. rogercresseyi*	Spatial risk factors	Kristoffersen *et al.* 2013

Current speed	NA	Challenge trial	Tank	UK	*L. salmonis*		Genna *et al.* 2005
	0.40–1.00	Challenge trial	Tank	Norway	*L. salmonis*		Samsing *et al.* 2015
Fallowing	NA	Epidemiology	Multi farm	UK	*L. salmonis*	Louse accumulation	Bron *et al.* 1993
	1.05–1.81	Epidemiology	Multi farm	Norway	*L. salmonis*	Louse accumulation	Guarracino *et al.* 2018
Firebreaks	NA	Modelling	Multi farm	Norway	*L. salmonis*	Dispersal modelling	Samsing *et al.* 2019
1.4 Filtering and trapping							
Light traps	0.88	Sea cage trial	Small cage	USA	*L. salmonis*		Pahl *et al.* 1999
Filtering	0.68	Sea cage trial	Large cage	Canada	*L. salmonis*	Oyster racks	Byrne *et al.* 2018
1.5 Repellents and host cue masking							
In-water compounds	0.26–0.47	Sea cage trial	Small cage	UK	*L. salmonis*		Hastie *et al.* 2013
In-feed compounds	*None*	-	-	-	-		*No published studies*
Light modification	0.93–1.08	Challenge trial	Tank	Norway	*L. salmonis*		Browman *et al.* 2004
	NA	Challenge trial	Tank	UK	*L. salmonis*		Genna *et al.* 2005
	NA	Challenge trial	Tank	Canada	*L. salmonis*		Hamoutene *et al.* 2016
1.6 Incapacitation							
Electricity	0.22	Sea cage trial	Small cage	Norway	*L. salmonis*	DC electric fence	Bredahl 2014
Ultrasound	0.61–1.37	Challenge trial	Tank	Norway	*L. salmonis*		Skjelvareid *et al.* 2018
Irradiation	*None*	-	-	-	-		*No published studies*
1.7 Louse population control							
Pathogens	*None*	-	-	-	-		*No published studies*
Gene drives	*None*	-	-	-	-		*No published studies*
2.1 Functional feeds							
Immunomodulation	0.56	Challenge trial	Tank	UK	*L. salmonis*	Nucleotides	Burrells *et al.* 2001
	0.61–1.09	Challenge trial	Tank	Canada	*L. salmonis*	Various additives	Covello *et al.* 2012
	0.48–1.31	Challenge trial	Small cage	Norway	*L. salmonis*	Various additives	Refstie *et al.* 2010
	0.70–0.81	Challenge trial	Tank	Canada	*L. salmonis*	Aquate, CpG	Poley *et al.* 2013
	0.73–0.85	Challenge trial	Tank	Norway	*L. salmonis*	Various additives	Provan *et al.* 2013
	0.84	Challenge trial	Tank	Canada	*L. salmonis*	CpG	Purcell *et al.* 2013
	0.80	Challenge trial	Tank	UK	*L. salmonis*	Various additives	Jensen *et al.* 2015
	0.48–0.67	Cage trial	Small cage	Norway	*L. salmonis*	Sex hormones	Krasnov *et al.* 2015
	0.78	Challenge trial	Tank	Chile	*C. rogercresseyi*	Various additives	Nunez-Acuna *et al.* 2015
	0.33–0.67	Challenge trial	Tank	Canada	*L. salmonis*	Peptidoglycan extract	Sutherland *et al.* 2017
	1.22	Sea cage trial	Large cage	Norway	*L. salmonis*	Skretting Shield (all cages had cleaner fish)	Bui *et al.* 2020
	2.08	Sea cage trial	Large cage	Norway	*L. salmonis*	Skretting Shield (all cages	Gentry *et al.* 2020

						had cleaner fish)	
Repellents/toxins	0.83	Challenge trial	Tank	Norway	*L. salmonis*	Phytochemicals	Holm *et al.* 2016
2.2 Vaccination							
Recombinant protein	0.43	Challenge trial	Tank	Chile	*C. rogercresseyi*	my32 protein	Carpio *et al.* 2011
	0.45–0.47	Challenge trial	Tank	Norway	*L. salmonis*	my32 protein	Kumari Swain *et al.* 2018
	0.65–1	Challenge trial	Tank	Norway	*L. salmonis*	P33 protein offered strongest effect	Contreras *et al.* 2020
2.3 Breeding for louse resistance							
Various	0.65	Sea cage trial	Small cages	Norway	*L. salmonis*	Comparison of most resistant and susceptible families	Holm *et al.* 2015
Multiple methods	0.91	Sea cage trial	Multi farm	Norway	*L. salmonis*	All cages had cleaner fish	Bui *et al.* 2019b
	0.51	Sea cage trial	Large cage	Norway	*L. salmonis*	Functional feed + deep feeding and lighting (all cages had cleaner fish)	Bui *et al.* 2020
	0.79	Sea cage trial	Large cage	Norway	*L. salmonis*	Functional feed + deep feeding and lighting + skirt (all cages had cleaner fish)	Bui *et al.* 2020
	1.91	Sea cage trial	Large cage	Norway	*L. salmonis*	Functional feed + deep feeding and lighting (all cages had cleaner fish)	Gentry *et al.* 2020
	2.43	Sea cage trial	Large cage	Norway	*L. salmonis*	Functional feed + deep feeding and lighting + skirt (all cages had cleaner fish)	Gentry *et al.* 2020

FIGURES

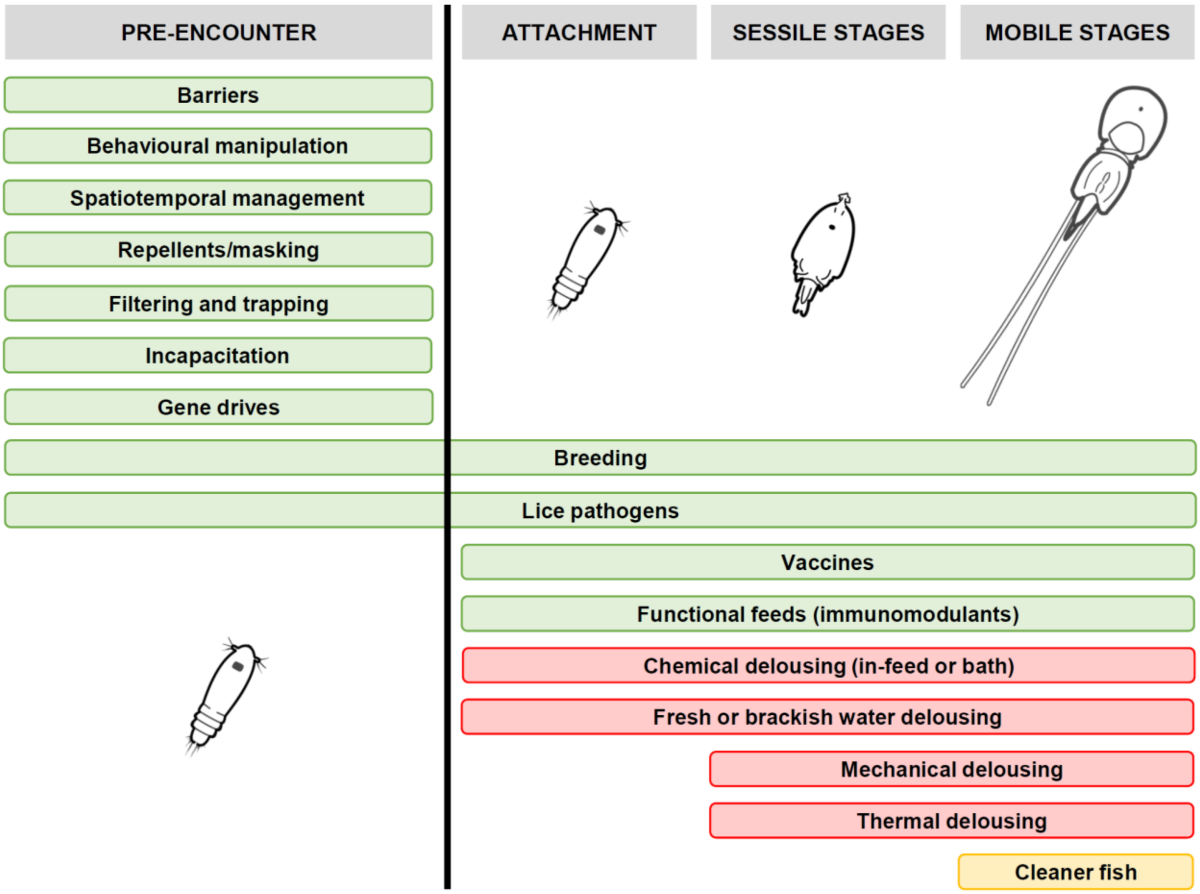

Figure 1. Sea louse infestation timepoints targeted by preventative methods and delousing treatments. Colours denote on-demand delousing (**red**), continuous delousing (**orange**) and preventative methods (**green**). Line drawings indicate the stage of louse predominantly affected by each method, L-R: larvae (nauplii and copepodids), sessile stages (chalimus I and II), and mobile stages (pre-adults and adults).

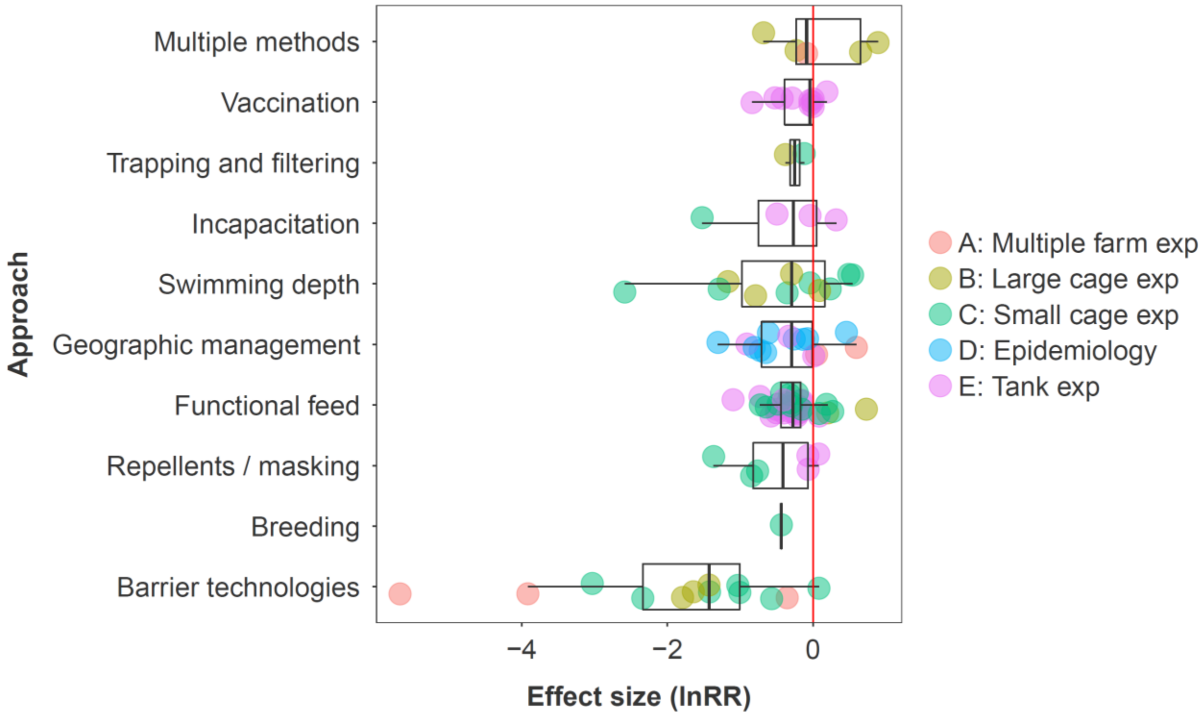

Figure 2. Distribution of effect sizes (natural log of the response ratio: lnRR) across studies testing preventive methods. Studies are grouped by the type of preventative method tested (Approach). Points denote the effect size of each study, coloured by the level of evidence provided. Negative values for lnRR indicate an effective approach. lnRR = 0 corresponds to no difference between control and treatment groups. Boxes indicate the median and 25-75% interquartile range of effect sizes from studies testing each approach.

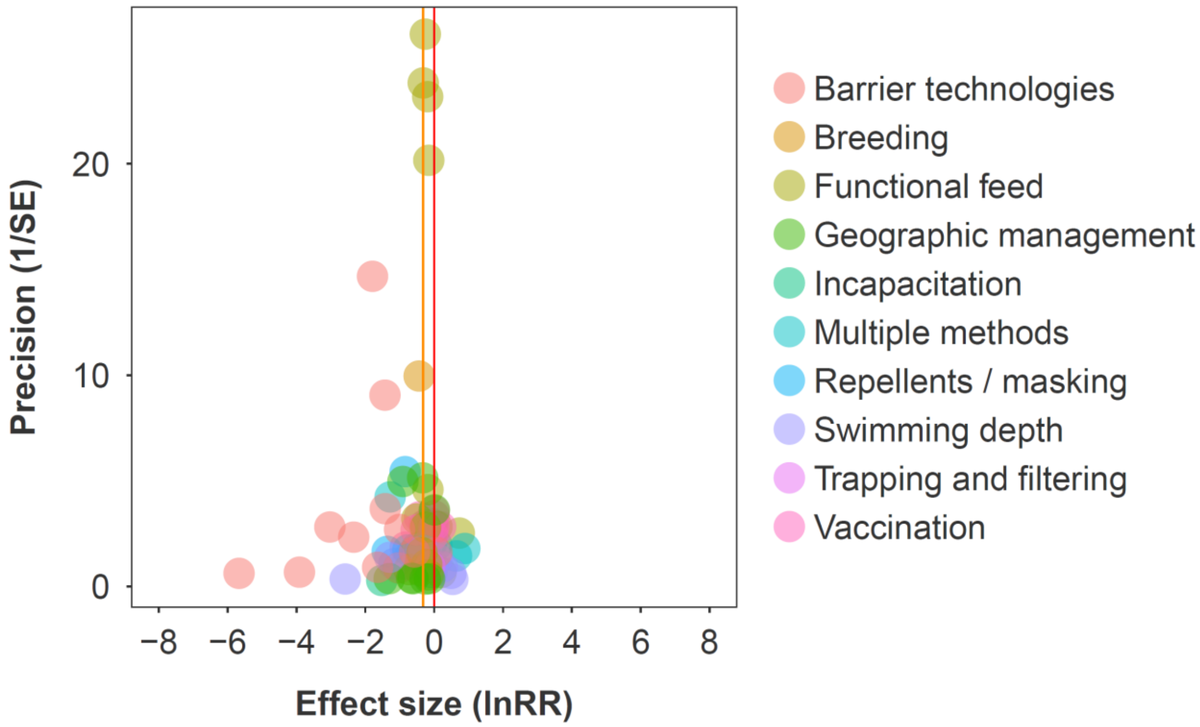

Figure 3. Funnel plot of published effect sizes (natural log of the response ratio) of preventative methods against sea louse infestations on Atlantic salmon. Effect sizes are plotted against the precision of the experiment (inverse of the standard error). The absence of studies on the right side of the plot is suggestive of publication bias against negative findings. **Red** line indicates zero effect (lnRR = 0), **orange** line indicates median effect size.

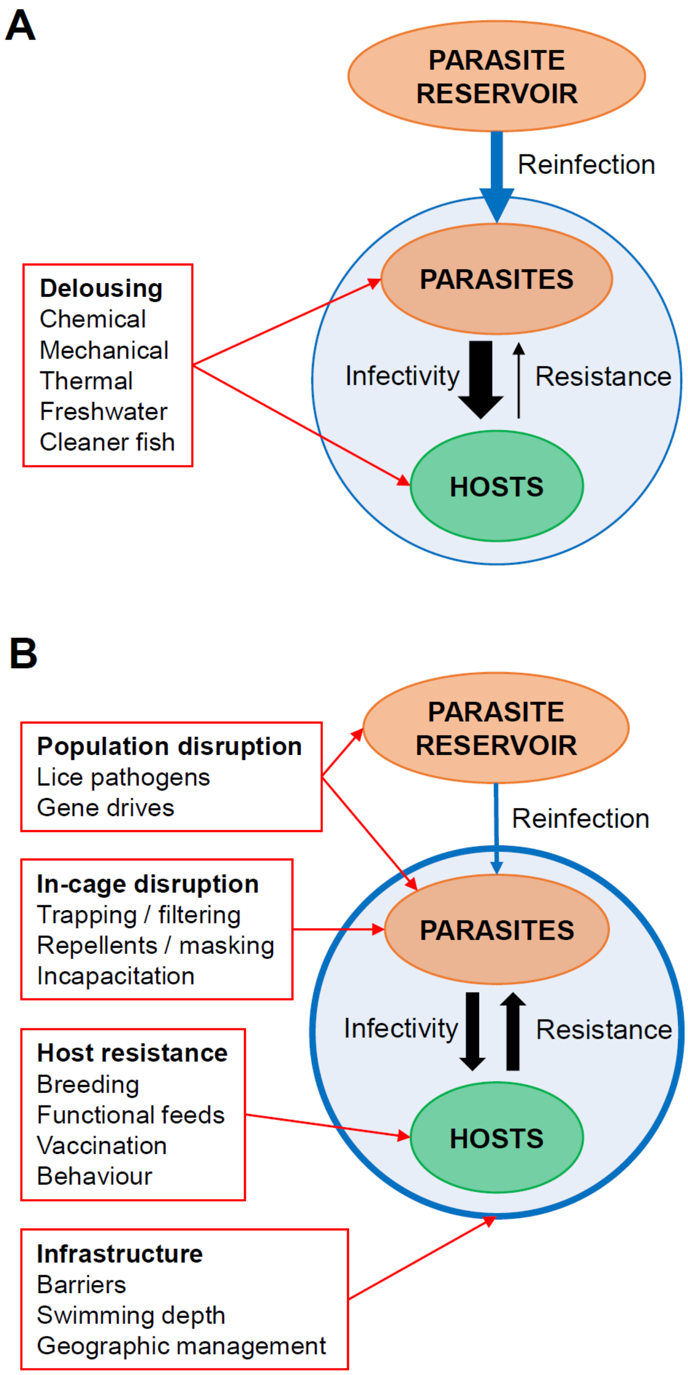

Figure 4. Conceptual diagram outlining: (**A**) the current delousing treatment-dominated paradigm for parasite control; (**B**) the new paradigm with a focus on prevention rather than treatment. **Red** arrows indicate management actions and how they are targeted (i.e. specificity, mediation). **Blue** arrows indicate supply of infective larvae (line thickness scales with number entering cages). **Black** arrows indicate host and parasite traits (line thickness scales with relative importance).