

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

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21 ABSTRACT

22 The Atlantic salmon aquaculture industry still struggles with ectoparasitic sea lice despite
23 decades of research and development invested into louse removal methods. In contrast,
24 methods to prevent infestations before they occur have received relatively little research
25 effort, yet may offer key benefits over treatment-focused methods. Here, we summarise the
26 range of potential and existing preventative methods, conduct a meta-analysis of studies
27 trialling the efficacy of existing preventative methods, and discuss the rationale for a shift to
28 the prevention-focused louse management paradigm. Barrier technologies that minimise host-
29 parasite encounter rates provide the greatest protection against lice, with a weighted median
30 76% reduction in infestation density in cages with plankton mesh ‘snorkels’ or ‘skirts’, and
31 up to a 100% reduction for fully enclosed cages. Other methods such as geographic
32 spatiotemporal management, manipulation of swimming depth, functional feeds, repellents,
33 and host cue masking can drive smaller reductions that may be additive when used in
34 combination with barrier technologies. Finally, ongoing development of louse-resistant
35 salmon lineages may lead to long term improvements if genetic gain is maintained, while the
36 development of an effective vaccine remains a key target. Preventative methods emphasise
37 host resistance traits while simultaneously reducing host-parasite encounters. Effective
38 implementation has the potential to dramatically reduce the need for delousing and thus
39 improve fish welfare, productivity and sustainability in louse-prone salmon farming regions.

40

41 INTRODUCTION

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

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

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

67 The discovery of treatment-resistance has prompted a rapid and recent shift to mechanical
68 and thermal delousing methods in the Norwegian salmon farming industry (Overton *et al.*
69 2018), with these methods also gaining traction elsewhere (e.g. Canada, Chile, Scotland).
70 Mechanical and thermal delousing are highly effective at removing mobile lice and have little
71 or no impact on non-target species. However, they are stressful for host fish and can lead to
72 elevated post-treatment mortality rates compared to the use of chemotherapeutants (Overton
73 *et al.* 2018). Low salinity or hydrogen peroxide baths are also effective in the right conditions
74 and do not accumulate, although the long-term prospects for these methods are uncertain
75 given the possibility of increasingly resistant lice (Treasurer *et al.* 2000, Helgesen *et al.* 2018,
76 Groner *et al.* 2019). Alternatively, around 50 million cleaner fish (lumpfish *Cyclopterus*
77 *lumpus* and several wrasse species) are deployed annually at Norwegian salmon farms to eat
78 lice directly off salmon (Norwegian Directorate of Fisheries 2018), with >1.5 million cleaner
79 fish also used in Scotland (Marine Scotland Directorate, 2017). However, it is unclear
80 whether their efficacy (Overton *et al.* 2020; Barrett *et al.* 2020a) is sufficient to justify their
81 poor welfare in commercial sea cages (Nilsen *et al.* 2014; Hvas *et al.* 2018; Mo and Poppe
82 2018; Yuen *et al.* 2019; Stien *et al.* 2020).

83 Decades of innovation in louse control have allowed the salmon farming industry to continue
84 functioning in louse-prone regions, but not without significant environmental and ethical
85 concerns. Most research and development efforts so far have focused on treating at the post-

86 infestation stage. This likely reflects the relatively rapid return on investment into new
87 delousing methods but may be a sub-optimal strategy if opportunities to invest in long term
88 solutions are missed (Brakstad *et al.* 2019). An alternative approach is to focus louse
89 management efforts on preventing infestation via proactive interventions (‘preventative
90 methods’ herein) that may significantly reduce the need for farms to delouse. Here, we
91 summarise the range of potential or existing preventative methods and conduct a meta-
92 analysis of empirical estimates of sea louse removal efficacy for each method. Finally, we
93 discuss the rationale for a paradigm shift from reactive louse control to a proactive approach
94 that focuses on predicting and preventing infestations, and outline some possible strategies to
95 promote long term efficacy of preventative methods.

96

97 **WHAT PREVENTATIVE METHODS ARE AVAILABLE?**

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

107 **1. Reducing encounters**

108 ***1.1 Barrier technologies***

109 A growing understanding of louse physiology and host-finding behaviour has led to several
110 important advances in louse prevention, and by using data on preferred swimming depths of
111 infective copepodids in relation to environmental parameters (Heuch 1995; Heuch *et al.*
112 1995; Crosbie *et al.* 2019), farmers can now separate hosts from parasites using depth-
113 specific louse barriers.

114 Barriers made from fluid-permeable plankton mesh or impermeable membranes can
115 dramatically reduce infestation rates by preventing infective copepodids from entering the
116 cage environment. ‘Skirt’ or ‘snorkel’ barriers prevent particles in the surface layers—where
117 most copepodids reside—from entering the cage while still allowing full water exchange

118 below the level of the barrier (Oppedal *et al.* 2017; Wright *et al.* 2017; Stien *et al.* 2018).
119 Salmon often choose to reside below the level of the skirt or snorkel, meaning that the barrier
120 functions by simultaneously (i) encouraging salmon to swim below the depth at which
121 infestation risk is highest, and (ii) protecting any individuals that use the surface layers, for
122 example, while feeding or refilling the swim bladder. In the most complete use of barrier
123 technologies, fully-enclosed cages are supplied with louse-free water either filtered or
124 pumped from depths below the typical depth range of copepodids (e.g. 25 m: Nilsen *et al.*
125 2017).

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

136 ***1.2 Manipulation of swimming depth***

137 Salmon behaviour, primarily swimming depth, can also be manipulated in the absence of
138 barrier technology to reduce spatial overlap (and therefore encounter rates) between hosts and
139 parasites, especially salmon lice. Typically, the aim is to reduce encounter rates by causing
140 salmon to swim below the depths at which lice are most abundant. Deep swimming
141 behaviour can be promoted through the use of deep feeding and/or lighting (Hevrøy *et al.*
142 2003; Frenzl *et al.* 2014; Bui *et al.* 2020). Where surface feeding is conducted, reducing the
143 frequency or regularity of feeding (e.g. twice daily at varying times) can reduce the amount
144 of time spent in the surface layers (Lyndon and Toovey 2000). Deep swimming can also be
145 forced by submerging cages to the desired depth (Dempster *et al.* 2008; Dempster *et al.*
146 2009), and there is evidence for reduced louse levels on salmon in submerged cages (Osland
147 *et al.* 2001; Hevrøy *et al.* 2003; Sievers *et al.* 2018; Glaropoulos *et al.* 2019). Long term
148 submergence can affect fish welfare as salmon lose buoyancy over time (Korsøyen *et al.* 2009;
149 Macaulay *et al.* 2020), however recent research indicates most welfare concerns can be

150 addressed by allowing periodic surface access or fitting a submerged air-filled dome for swim
151 bladder refilling (Korsøen *et al.* 2012; Glaropoulos *et al.* 2019; Oppedal *et al.* In Press).

152 ***1.3 Geographic spatiotemporal management***

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

161 ***1.4 Filtering and trapping***

162 Filters and traps may be deployed in or around cages to remove infective copepodids from
163 the water column before they encounter salmon. Filter-feeding shellfish racks hung around
164 sea cages may reduce louse abundance if deployed at sufficient scale (Byrne *et al.* 2018;
165 Montory *et al.* 2020), while powered filters are effective in the context of preventing lice and
166 eggs from entering the environment during delousing (O'Donohoe and Mcdermott 2014). In
167 other fish farming systems, cleaner shrimp have been used to remove parasites or parasite
168 eggs from fish and nets and reduce infestation or reinfestation risk (Vaughan *et al.* 2018a;
169 Vaughan *et al.* 2018b). However, this method may have limited application against sea lice
170 because of the planktonic mode of dispersal and infestation (i.e. larvae do not develop within
171 the cage structure). Light traps have been tested in the field with mixed results (Pahl *et al.*
172 1999; Novales Flamarique *et al.* 2009), and increasing knowledge of host-locating behaviour
173 in lice may present new possibilities for baiting traps with attractive chemosensory cues
174 (Devine *et al.* 2000; Ingvarsdóttir *et al.* 2002; Bailey *et al.* 2006; Mordue and Birkett 2009;
175 Fields *et al.* 2018). No preventative filtering or trapping methods have been widely deployed
176 in the industry, but some systems have recently become commercially available (e.g.
177 'Strømmen-rør', Fjord Miljø; 'NS Collector', Vard Aqua).

178 ***1.5 Repellents and host cue masking***

179 Interventions may be used to repel lice or mask host cues, potentially reducing host-parasite
180 encounters even when parasites enter the sea cage. Repellents or masking compounds can
181 either be released into the water column or included in feed to alter the host's semiochemical

182 profile (Hastie *et al.* 2013; O’Shea *et al.* 2017). Indeed, some existing commercially available
183 functional feeds are claimed to reduce attraction of lice toward fish (e.g. Shield, Skretting;
184 Robust, EWOS/Cargill). Visual cues may also be important, and the effect of modified light
185 conditions on infestation rates have been trialled with mixed results. Browman *et al.* (2004)
186 concluded that ultraviolet-A and polarisation were not important for host detection at small
187 spatial scales. Light intensity interacted with salinity and host velocity to influence
188 distribution of louse attachment in another study (Genna *et al.* 2005), while Hamoutene *et al.*
189 (2016) reported that 24-hour darkness affected the attachment location but not abundance of
190 salmon lice.

191 ***1.6 Incapacitation***

192 Several methods have been proposed for disabling or killing lice—from egg to adult stages—
193 in or around sea cages. These include ultrasonic cavitation (Alevy 2017; Skjelvareid *et al.*
194 2018; Svendsen *et al.* 2018), direct current electricity (Bredahl 2014) and irradiation with
195 short wavelength light (Barrett *et al.* 2020b, Barrett *et al.* 2020c). Some have demonstrated
196 efficacy at close range (Skjelvareid *et al.* 2018, Barrett *et al.* 2020b, Barrett *et al.* 2020c), but
197 it is currently unclear whether any such methods can be effective at commercial scale.

198 ***1.7 Louse population control***

199 Interventions to suppress louse populations outside the cage environment would require
200 careful consideration before deployment and must be specific to targeted louse species. Very
201 little work has been done in this area, but possible avenues may include the release of
202 parasites and pathogens that are specific to sea lice (Økland *et al.* 2014; Økland *et al.* 2018;
203 Øvergård *et al.* 2018), or CRISPR-based ‘gene drives’ (McFarlane *et al.* 2018; Noble *et al.*
204 2019).

205 **2. Reducing post-encounter infestation success**

206 ***2.1 Functional feeds***

207 Feeds that provide physiological benefits beyond basic nutritional requirements are termed
208 functional feeds and are increasingly prevalent in industrial fish farming (Tacchi *et al.* 2011).
209 Feed ingredients that modify the mucus layer or modulate skin immune responses may
210 reduce initial attachment success or facilitate effective immune responses against newly-
211 attached lice (Martin and Krol 2017). Functional feeds may also include ingredients that are
212 toxic or repellent to attached lice – these are not necessarily distinct from in-feed
213 chemotherapeutants, except that they tend to be derived from ‘natural’ sources (e.g. plant-

214 derived essential oils: Jensen *et al.* 2015). Functional feeds aimed at improving salmon louse
215 resistance are already commercially available (e.g. Shield, Skretting; Robust, EWOS/Cargill).
216 It will be important to test for any adverse effects of new functional feeds. For instance,
217 glucosinolates and beta-glucans have been shown to be effective for reducing louse
218 infestation (Refstie *et al.* 2010; Holm *et al.* 2016), but glucosinolates also have a range of
219 effects on liver, muscle and kidney function that would need to be investigated (Skugor *et al.*
220 2016). Hormonal treatments may also be effective at reducing louse infestation (Krasnov *et*
221 *al.* 2015), but preventative hormone treatments are likely to be perceived negatively by
222 consumers.

223 **2.2 Vaccines**

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

234 Successful development of a recombinant or DNA vaccine would allow cost-effective
235 production and delivery (Raynard *et al.* 2002; Sommerset *et al.* 2005; Brudeseth *et al.* 2013).
236 Potential vaccines exist at various stages of development, from localisation of candidate
237 antigens in lice (Roper *et al.* 1995), demonstration of antibody production in response to
238 inoculation with louse extracts (Reilly and Mulcahy 1993), and use of recombinant proteins
239 to vaccinate salmon in tank trials (Carpio *et al.* 2011; Carpio *et al.* 2013; Basabe *et al.* 2014;
240 Contreras *et al.* 2020). Recently, RNA interference has been used to knock down candidate
241 vaccine targets and assess potential efficacy through challenge experiments (Eichner *et al.*
242 2014; Eichner *et al.* 2015; Komisarczuk *et al.* 2017).

243 **2.3 Breeding for louse resistance**

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

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

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

266 Other possible approaches for improving sea louse resistance in Atlantic salmon include
267 hybridisation of Atlantic salmon with more louse-resistant salmonid species (Fleming *et al.*
268 2014), genetic modification of Atlantic salmon with immune genes from other salmonids, or
269 use of gene editing to modify protein function or regulate the expression of genes affecting
270 resistance. In the case of hybridisation or any genetic modification, the effect on other
271 production traits would need to be assessed before hybrids or edited fish are used by the
272 industry. Gene editing approaches have high potential (Gratacap *et al.* 2019), but successful
273 implementation depends on knowing which genes to modify to have the desired effect, on
274 developing effective methods for implementing and spreading the gene edits through the
275 breeding population, and on the acceptability of the use of the technology by the general
276 public and government.

277

278 EFFICACY OF PREVENTATIVE METHODS

279 To assess the state of knowledge on the efficacy of preventative methods, we conducted a
280 systematic review and meta-analysis of published studies pertaining to preventative methods.
281 To find relevant studies, we searched ISI Web of Science, Scopus and Google Scholar in
282 February 2020 using the following search string: (*aquacult* OR farm**) AND (*salmon* or*
283 *Salmo*) AND (*lice OR louse OR salmonis OR Caligus*). We also discovered additional studies
284 referenced within articles returned by the search string. Together, our searches returned
285 >1200 peer-reviewed articles, technical reports and patents relevant to lice and salmon
286 aquaculture, of which 141 provided evidence on the efficacy of preventative methods and
287 were included in the review.

288 Studies that provided relevant response variables were included in a meta-analysis, allowing
289 the comparison of effect sizes across the range of preventative approaches. For inclusion,
290 studies were required to provide empirical measures of relative louse infestation densities for
291 treatment groups (preventative methods used) and control groups (no preventative methods
292 used). Studies that applied treatments to lice but did not directly test for effects on infestation
293 were not included. Effect sizes were standardised using the natural log of the response ratio:
294 $lnRR = ln(\mu_T/\mu_C)$, where μ_T is the treatment group response and μ_C is the control group
295 response. In most cases, response variables were either mean or median attached lice per fish.
296 Where a study tested multiple qualitatively different treatments, each treatment was
297 considered a replicate comparison in the meta-analysis. Where there were several
298 qualitatively similar treatments (e.g. a range of doses of the same substance) the strongest
299 treatment was included in the meta-analysis. Epidemiological studies typically did not have
300 clear control or treatment groups; in such cases, the area or condition with the highest louse
301 density was designated as the control group for the purposes of calculating a response ratio;
302 this practice may inflate average effect sizes.

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

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

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

320 **Which preventative methods are most effective against sea lice?**

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

330 Approaches utilising manipulation of salmon swimming depth offered variable outcomes, but
331 with strong effects in certain situations (weighted median 26% reduction, range 72% increase
332 to 93% reduction, n = 11; Fig. 2). Geographic spatiotemporal management of farming effort
333 (or related variables such as simulated current speed: Samsing *et al.* 2015) had similarly
334 variable effects (weighted median 13% reduction, range 81% increase to 73% reduction, n =
335 14; Fig. 2). Functional feeds tended to have small but beneficial effects on sea louse
336 infestations (median 24% reduction, range 108% increase to 67% reduction, n = 32: Fig. 2),
337 as do published vaccine trial results (median 4% reduction, range 20% increase to 57%
338 reduction). Notably, deployment of multiple preventative methods in combination with
339 cleaner fish had highly variable effects in three published studies using replicated modern
340 commercial sea cages (weighted median 9% reduction, range 143% increase to 49%
341 reduction, n = 5: Bui *et al.* 2019b; Bui *et al.* 2020; Gentry *et al.* 2020).

342 Several potential preventative approaches have seen little effort to test their effects on
343 infestation rates. The use of repelling non-host cues was effective in one small-scale cage
344 study (53-74% reduction, n = 3: Hastie *et al.* 2013), as was filtering of copepodids using
345 oyster racks ((32% reduction: Byrne *et al.* 2018) or light traps (12% reduction: Pahl *et al.*
346 1999), and the incapacitation of lice using electric fences (78% reduction: Bredahl 2014) and
347 ultrasonic cavitation (37% increase to 39% decrease: Skjelvareid *et al.* 2018).

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

356 **Is the evidence base representative and robust?**

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

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

370 Units of replication also varied widely between studies, from individual fish to tanks, sea
371 cages or farms. 51 out of 98 comparisons treated individual fish as replicates, in most cases
372 resulting in a pseudoreplicated design as individuals were kept within a comparatively small
373 number of tanks or cages (often <3 tanks or cages per group). We recommend that where

374 fish are treated as replicates, the number of tanks or cages should also be reported, and mixed
375 effects statistical methods employed to account for non-independence between fish held
376 within the same tank or cage (Harrison *et al.* 2018).

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

393

394 **THE NEW PARADIGM: A FOCUS ON PREVENTATIVE METHODS AGAINST** 395 **SEA LICE**

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

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

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

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

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

423

424 **MAINTAINING LONG-TERM EFFICACY**

425 Host-parasite interactions are subject to a coevolutionary arms race in which organisms must
426 constantly evolve to keep up with the coevolution occurring in opposing organisms (i.e. the
427 Red Queen hypothesis: Hamilton *et al.* 1990). Most lice never encounter a potential host, and
428 those that do will likely only have one opportunity to attach. This could precipitate strong
429 selective pressures, and because farmed salmon represent the majority of available hosts for
430 lice in some regions (especially in the north-east Atlantic), louse control interventions on
431 farms are likely to exert directional selection pressure on louse populations wherever certain
432 genotypes are favoured over others. Evolution of resistance occurred relatively quickly in
433 response to chemical delousing (global reviews: Aaen *et al.* 2015; Gallardo-Escárate *et al.*
434 2019) and presently remains high (Helgesen *et al.* 2018), although in areas where wild
435 salmonids are abundant, flow of susceptible genes from lice on wild hosts may help to
436 maintain treatment efficacy (Kreitzman *et al.* 2017).

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

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

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

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

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

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

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

476

477 **CONCLUSIONS**

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

487

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493

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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.

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

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

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

FIGURES

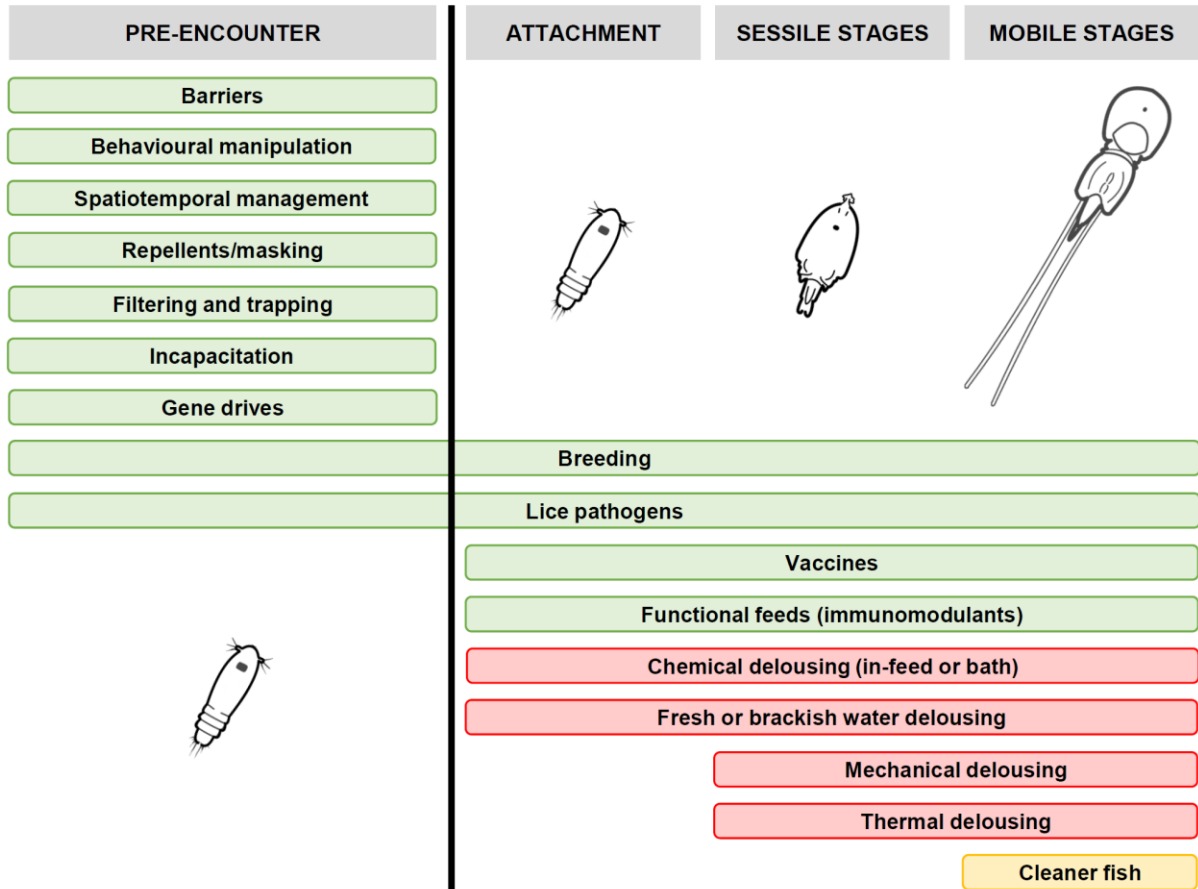


Figure 1. Sea louse infestation timepoints targeted by preventative methods and delousing treatments. Colours denote on-demand delousing (**red**), continuous delousing (**orange**) and preventative methods (**green**). Line drawings indicate the stage of louse predominantly affected by each method,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

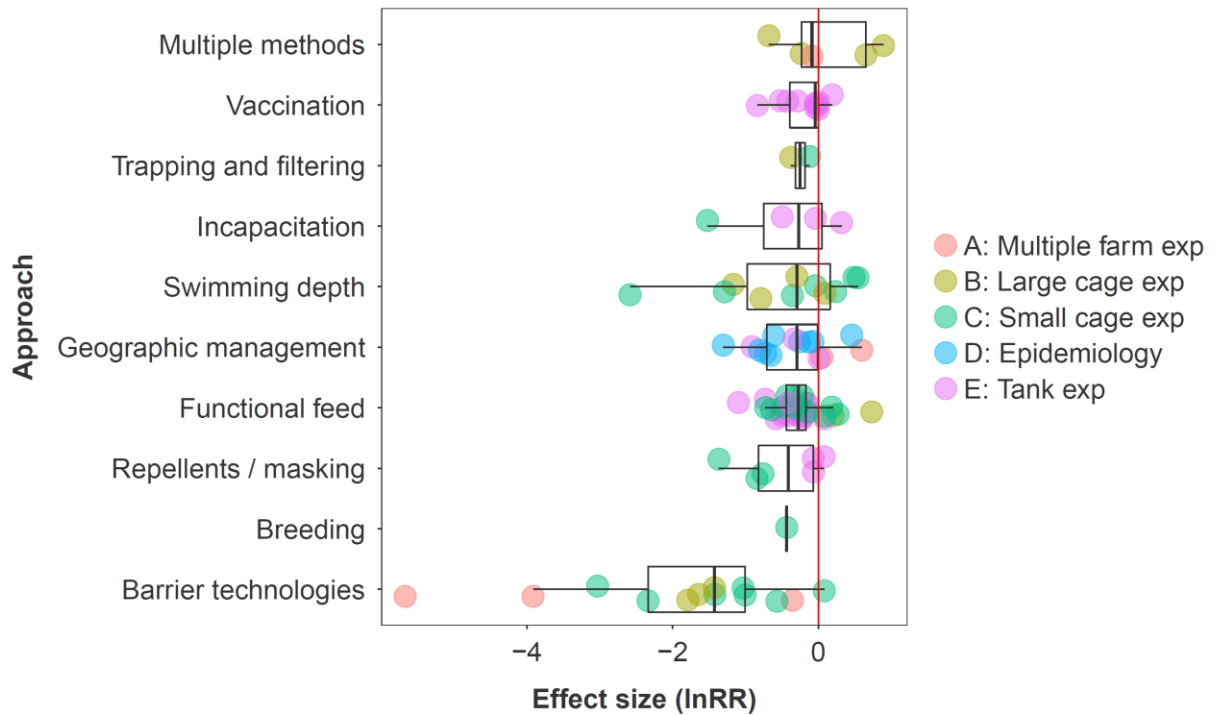


Figure 2. Distribution of effect sizes (natural log of the response ratio: lnRR) across studies testing preventive methods. Studies are grouped by the type of preventative method tested (Approach). Points denote the effect size of each study, coloured by the level of evidence provided. Negative values 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.

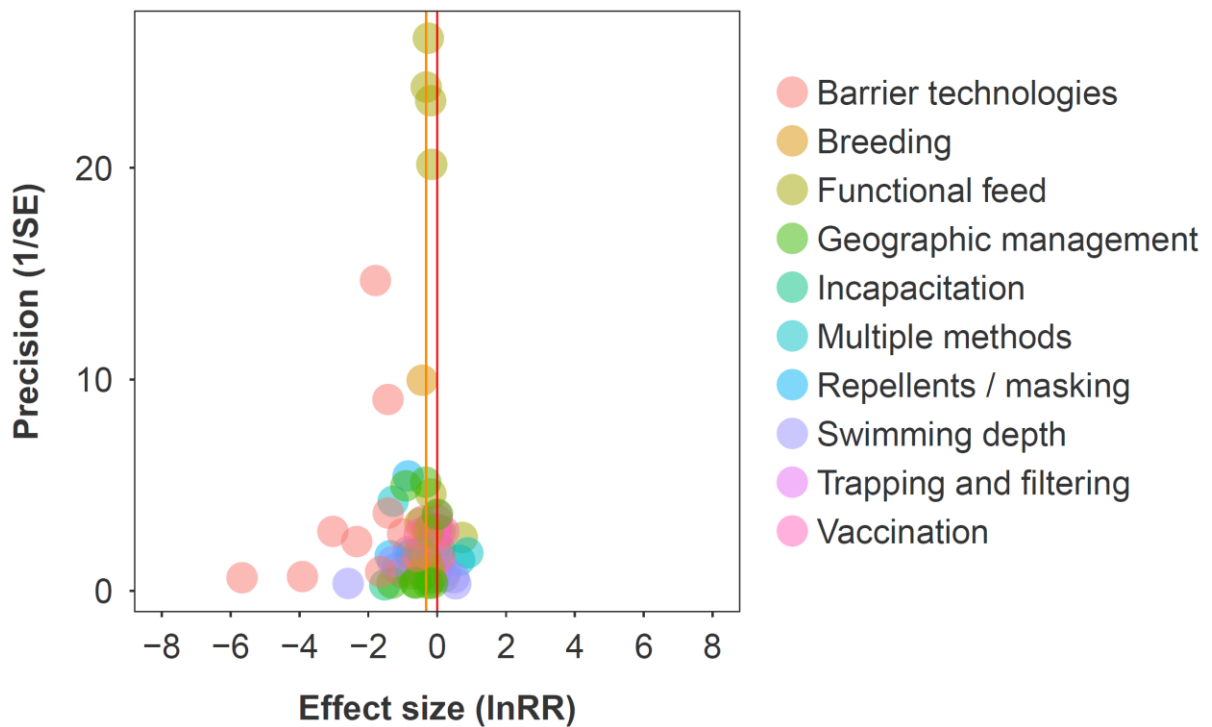


Figure 3. Funnel plot of published effect sizes (natural log of the response ratio) of preventative methods against sea louse infestations on Atlantic salmon. Effect sizes are plotted against the precision of the experiment (inverse of the standard error). The absence of studies on the right side of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

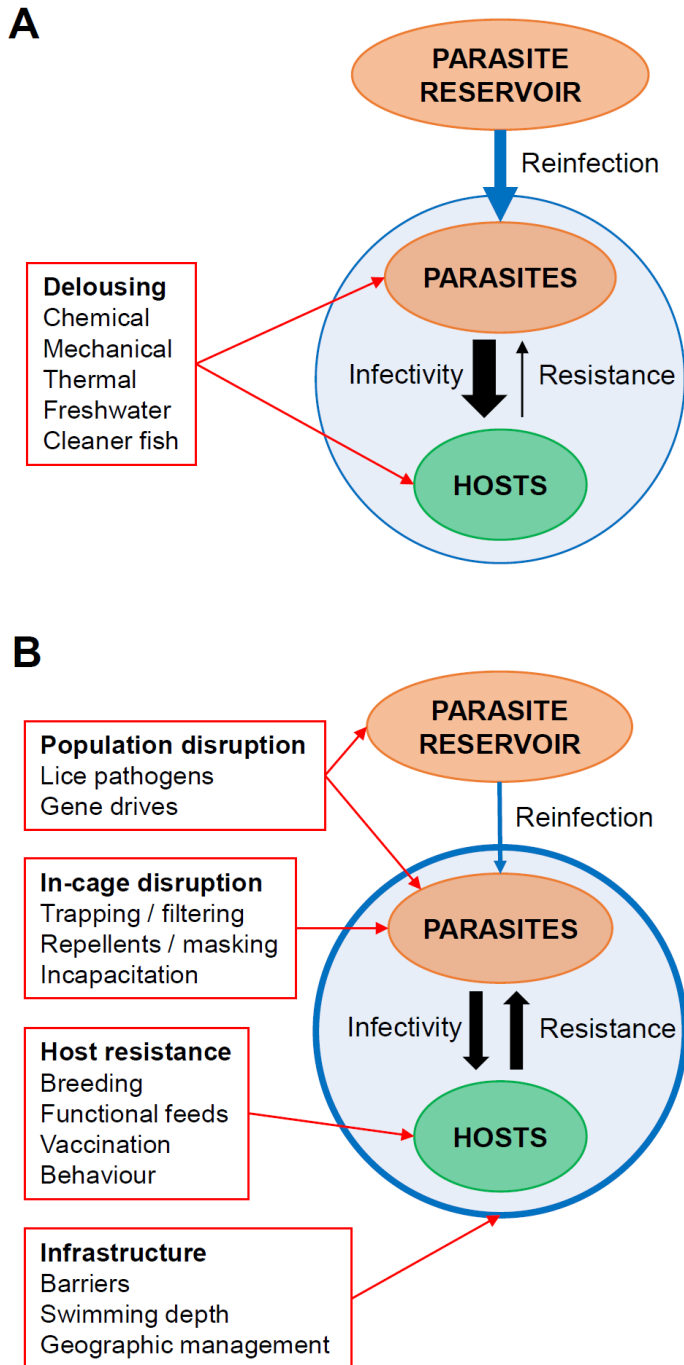


Figure 4. Conceptual diagram outlining: (A) the current delousing treatment-dominated paradigm for parasite control; (B) the new paradigm with a focus on prevention rather than treatment. **Red** arrows indicate management actions and how they are targeted (i.e. specificity, mediation). **Blue** arrows 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).