Vol. 15: 35–43, 2023
https://doi.org/10.3354/aei00451

AQUACULTURE ENVIRONMENT INTERACTIONS
Aquacult Environ Interact

Published February 16

OPINION PIECE

Research pre-empting parasite adaptation is key to sustainable disease management in aquaculture

Andrew Coates*

School of BioSciences, University of Melbourne, Victoria 3010, Australia

ABSTRACT: As the aquaculture sector continues to expand, there is likely to be a growing need to combat infectious diseases. The desire for rapid and effective results means that any concerns about longer-term effects of disease controls are often sidelined. In particular, the well-documented capacity for parasites and pathogens to evolve treatment resistance must not be ignored in aquaculture. Outbreaks of resistant parasites pose significant threats to the environment, as well as to farm production. If an industry wishes to avoid treatment resistance, there must first be committed research into the evolutionary biology of the parasite species. Such research should be incorporated into the early phases of developing and implementing a treatment strategy — the sooner the risk of resistance is identified, the sooner its impacts on aquaculture can be mitigated. Here I discuss a research framework that can help guide this process. A combination of theoretical (reviewing the literature), empirical (testing for heritable resistance) and modelling (simulating evolutionary dynamics) studies is recommended. Armed with the knowledge from these studies, parasite management strategies can then be optimised at a regional scale (e.g. with refugia or treatment combinations) in ways that minimise the potential for adaptation. The interaction between salmonid aquaculture and parasitic sea lice is an ideal case study for this topic, and the insights gained from this system should be considered across aquaculture industries. Nevertheless, there is no one-size-fits-all solution to treatment resistance. For each system, dedicated research into parasite evolutionary biology — with a research framework as a guide — is required for aquaculture to home in on the most sustainable disease management strategies for the future.

KEY WORDS: Aquaculture · Disease · Resistance · Integrated pest management · Salmon lice

1. OVERVIEW

The aquaculture sector has grown extensively over the last 3 decades in both scale and the diversity of species cultured (Teletchea & Fontaine 2014, FAO 2020). A major challenge facing the 'Blue Revolution' is the need to manage a panoply of new parasites and pathogens (Blaylock & Bullard 2014, Lafferty et al. 2015, Krkošek 2017). Disease management practices such as quarantine of new stock, equipment decontamination and fallowing should be routine. These practices may be limited in their control of parasites and pathogens, however, especially in open-water farms exposed to the external environment. If outbreaks become too frequent and severe, there will be a demand for treatments that specifically target and remove the parasite species. As seen in the salmonid aquaculture industry, such demand can generate a wealth of diverse technologies for pest control (Coates et al. 2021a). During the

*Corresponding author: acoates@unimelb.edu.au

Publisher: Inter-Research · www.int-res.com

research and development stage of these technologies, the focus is invariably on maximising treatment efficacy. There are also usually human health, environmental or welfare considerations. What is usually absent is a long-term assessment of the risk that the parasite will eventually evolve resistance to the treatment being developed. Pesticide resistance has become such a common occurrence in terrestrial agriculture — as well as in sea lice infesting salmonid aquaculture (Aaen et al. 2015) — that it is naïve to assume that any new chemical treatment will retain its efficacy indefinitely. Non-chemical alternatives to pesticides are not necessarily immune to pest adaptation either. Evolutionary shifts in response to non-chemical selection pressures may have broad ecological ramifications (Coates et al. 2021a). Despite this, the desire for immediate results means that an industry is often quick to take up a new treatment and use it excessively, thus rapidly selecting for resistance and inadvertently shortening the lifespan of the treatment's usefulness. In addition to the direct consequences for farms, the evolution of resistant pests can also have environmental repercussions. Parasite spillover and spillback from aquaculture into wild host populations is a significant ecological issue (Goedknegt et al. 2016, Bouwmeester et al. 2021). Without the means to promptly and effectively control disease outbreaks on farms, the risk of transmission into the natural environment is increased. In addition, pesticides will need to be applied more frequently to keep tolerant/resistant pests in check, and this is problematic if the pesticide has adverse effects on the environment; e.g. chitin synthesis inhibitors used against sea lice risk disrupting the development of wild crustaceans (Moe et al. 2019).

Rather than simply waiting for pests to eventually adapt to a new technology, farms can incorporate evolutionary principles into their management strategies to better safeguard them against resistance. The relationship between farmed salmonids and parasitic sea lice (in particular the Atlantic salmon *Salmo salar*, and the louse *Lepeophtheirus salmonis*) dominates the literature on resistant pests in aquaculture. This underlines the economic value of the industry and the extent of investments made into developing new control technologies. Salmon lice are the ideal case study, but knowledge gained from this system can be applied more broadly: there is growing awareness throughout aquaculture of the challenges posed by parasite adaptation (Mennerat et al. 2010, Kennedy et al. 2016, Sundberg et al. 2016).

The first steps towards managing resistant parasites requires a research framework that combines theoretical, empirical and modelling approaches. This research framework can be summarised as follows:

(1) Review the literature and apply evolutionary theory to assess the risk of resistance to any given treatment.

(2) Identify and explore any heritable variation in treatment resistance within the pest population through experimental and monitoring methods.

(3) Use numerical models to simulate how resistance might evolve in the pest population.

(4) Combine models with knowledge on resistance mechanisms to determine how treatments can be coordinated across farms to delay pest adaptation (e.g. with refugia or treatment combinations).

This basic approach can be adapted to fit the particular aquaculture/parasite system of interest. Such research should be undertaken as early as possible in the development of a treatment so that evolutionarily durable management regimes can be identified and implemented. The industrialisation of aquaculture is associated with farms becoming larger, more numerous and having higher stocking densities, and this facilitates the rapid evolution of treatment resistance, as well as of various life history traits such as virulence (Kennedy et al. 2016, Sundberg et al. 2016, Ugelvik et al. 2017). Therefore, the larger and more connected an aquaculture industry becomes, the earlier that resistance to a new technology must be caught before it becomes widespread. This framework represents an idealised research pathway. In reality, it might be logistically unfeasible or prohibitively costly to carry out all of these steps for some systems. Still, selecting even 1 or 2 of these steps — and generating within the industry a greater awareness of the risks of pest adaptation — is better than doing nothing at all.

Here I discuss the 4 points of the above framework with regards to pest management in aquaculture in general, drawing upon specific examples from salmon farming. For point number 4, I focus on the potential of refugia and treatment combinations, and also discuss options for regulating pest management across farms.

2. REVIEWING THE LITERATURE

The literature across a range of relevant agricultural and natural systems (not just the system being studied) is a valuable resource for managing pest resistance. Different organisms follow the same evolutionary rulebook, and so insights into resistance can be gained from very different environments. Chemical pesticides used in aquaculture are repurposed from terrestrial farm systems, and this can lead to different species adapting in the same way. For example, organophosphates are used against terrestrial arthropod pests as well as salmon lice, and the mechanisms of resistance that have since evolved are similar across groups (Hotelier et al. 2010, Kaur et al. 2015). If these similarities had been recognised sooner, then perhaps research into resistant lice (such as identifying the molecular markers for organophosphate resistance) may have advanced more rapidly. With an open mind and a grasp of evolutionary principles, useful parallels can be drawn from surprising sources: e.g. the potential for lice to adapt to depth-based barriers through a phenotypic shift in swimming depth (Coates et al. 2021b) bears a striking resemblance to the adaptation of non-parasitic crustaceans in response to predation (Gliwicz 1986, De Meester 1996, Cousyn et al. 2001).

3. IDENTIFYING HERITABLE RESISTANCE

For resistance to evolve in a pest population, there are 2 criteria that must be fulfilled: (1) the management strategy must impose selection on a trait, and (2) there must be heritable variation in this trait. Research into whether these criteria are satisfied should, ideally, be conducted during the initial trial phase of any new parasite control technology. The first step is to assess if and why any parasites survive (and can reproduce) after using the strategy. The pest cannot adapt if there are no survivors, but there are numerous reasons as to why a strategy may be less than 100% effective. There is little cause for concern if the surviving parasites are always a random subset of the population, but if the survivors consistently share a certain attribute, then selection may be occurring. However, such attributes may not be obvious in the survivors' phenotype (e.g. pesticide resistance can arise from minute changes to target molecules). It is more useful to ascertain whether resistance is itself a heritable trait.

Any surviving parasites should be collected and, where possible, be allowed to reproduce in a controlled environment to determine whether this survival ability is passed to the next generation (e.g. Helgesen et al. 2017, Hamre et al. 2021). If individuals are indeed more likely to survive a treatment if they come from resistant parents, then this is a red flag indicating the potential for rapid adaptation.

By performing bioassays and propagating resistant and susceptible strains in the laboratory, the extent to which treatment efficacy is influenced by genetics can be assessed (e.g. Igboeli et al. 2014, Carmona-Antoñanzas et al. 2017, Bakke et al. 2018). Alternatively, assaying individuals within 1 generation and comparing their relatedness with their treatment susceptibility provides an indication of possible genetic effects (e.g. Ljungfeldt et al. 2014, 2017, Coates et al. 2020). If information on parasite relatedness is sufficiently detailed, then quantitative genetics methods can be applied to estimate a useful parameter of heritability — i.e. the degree to which phenotypic variation in the population (in this case, a metric of resistance) is due to genetic factors (Wilson et al. 2010). The practicality of collecting survivors, propagating strains and estimating heritability will depend on the biology of the parasite. A short generation time means that multi-generational selection experiments are feasible for some parasites (*Lepeophtheirus salmonis* is now readily cultured in laboratories), but difficult for those with more complex life cycles. Likewise, controlled parent crosses in the laboratory (to create known family structures) allows for estimating trait heritability using pedigree analysis, but is only suited for certain species (such as external macroparasites like sea lice). Even if logistically possible, this laboratory work might be especially costly and laborious for some systems. What is important for researchers and funding bodies to consider is whether the costs incurred on the industry if resistance is allowed to evolve outweighs the initial costs of the experimental work.

Once a genetic basis to resistance has been identified, the next step is to unpack its various components. By quantifying the relative fitness of resistant vs. susceptible genotypes, the type and strength of selection imposed by treatments can be estimated. Resistance is predicted to evolve more rapidly under stronger selection gradients (Kingsolver & Pfennig 2007). It is important to compare other aspects of pest biology in addition to treatment survival. There may be pleiotropic effects associated with resistance (such as slower growth rate or reduced fecundity) that counter-balance selection for a trait. If strong trade-offs are identified, researchers may conclude that a resistant phenotype is in fact unlikely to persist for long in the population. An indication of the mode of inheritance to resistance helps to predict how advantageous traits will spread though the pest population. For example, traits that are maternally inherited, such as pyrethroid resistance in salmon lice (Carmona-Antoñanzas et al. 2017), can respond to selection in very different ways compared to traits with Mendelian inheritance (Kirkpatrick & Lande 1989). When a single locus has a major effect, as is often the case for pesticide resistance, knowing the underlying genetic architecture (such as the dominance of resistant alleles) is valuable. If marker genes corresponding to resistance can be identified, then large swathes of the parasite population can be tested without the need for bioassays (Fjørtoft et al. 2021). However, in most cases, traits will be affected by many loci of weak effect, which makes understanding resistance on a molecular level very difficult.

Early trials might not find any evidence for genetic resistance, but this doesn't mean it cannot arise eventually. There are sampling limitations in the methods outlined above: the cohort of parasites studied is not likely to be representative of the entire parasite population, especially for parasites with large geographic ranges or that occur on multiple host species. Genes conferring resistance may be harboured in untested pockets of the parasite population or, more rarely, arise later through de novo mutations (Besnier et al. 2014). Regular surveillance programs are therefore needed as an early warning system for resistance (Downes et al. 2010, Grøntvedt et al. 2016).

Monitoring programs coordinated across large geographic areas and long timeframes are also critical for tracking the real-time spread and severity of resistance after it has been identified. Monitoring can be conducted using a system of bioassays (Jansen et al. 2016), testing for marker genes (Fjørtoft et al. 2021), or with population genomics. Recent advances in population genomics means it is becoming increasingly cheap to screen populations across multiple loci in the genome (Hupalo et al. 2015). Spikes in gene frequency at certain loci not only warn of possible emerging resistance, but can also provide information on the genetic architecture, heritability and selection involved (Schmidt et al. 2021). Farmers themselves are also an important component of surveillance: a farm that experiences a significant drop in treatment efficacy should report this immediately to an appropriate body for further assessment.

4. MODELLING

Numerical models can be powerful tools for predicting patterns of pest adaptation to different management strategies (MacKenzie & Bishop 2001, Kemper et al. 2013, Onstad et al. 2013). A number of models have been constructed that simulate either the metapopulation dynamics of salmon lice across a network of salmon farms (e.g. Aldrin et al. 2019, Kragesteen et al. 2019, Toorians & Adams 2020) or the evolutionary dynamics of treatment resistance within a single louse population (e.g. McEwan et al. 2016, Kreitzman et al. 2018, Bateman et al. 2020). If these 2 types of models can be integrated into one that captures both metapopulation and evolutionary dynamics (e.g. Coates et al. 2022), then the options for exploring louse adaptation at a regional scale are vast. The underlying machinery of such a model could also be adapted for a range of other parasite and/or aquaculture systems. Building a strong knowledge base of resistance as discussed in the previous section — on its mode of inheritance, the strength of selection by treatments, and any fitness costs, for example — is crucial for accurately parameterising these models. Still, at their base level, evolution models can be run assuming current farming conditions to predict how rapidly advantageous genes might spread and to pinpoint any evolutionary hotspots. Armed with these predictions, those trying to prevent resistance have an indication of how much time there is to act and which regions should be prioritised for action.

An early step might be implementing restrictions on where new farm sites can be established. The extent of restrictions needed to have an appreciable effect on parasite evolution can be determined with the help of model simulations. For systems like salmonid aquaculture, where parasite transmission is a direct function of the physical placement of farm sites, models can identify areas that could be established as farm-free 'fire breaks' that reduce parasite gene flow, as well as the severity of outbreaks (Samsing et al. 2019). For parasites with different routes of transmission (e.g. through direct host contact, vectors or via intermediate hosts), or for more contained farm systems (e.g. tank or pond aquaculture), the geographic location of farms may be less relevant for disease connectivity than other factors (such as quarantining new stock, deep-cleaning facilities, or coordinated fallowing). The frequency and effect sizes of such farm practices that are needed to appreciably limit parasite gene flow, and hence evolution, can also be incorporated into metapopulation models (Werkman et al. 2011, Jeong et al. 2021).

5. REFUGIA

Establishing treatment refugia can be highly effective at delaying or preventing the evolution of resistance (Downes et al. 2010, Tabashnik & Carrière 2017). Refugia are most successful when (1) they support a relatively large parasite population, (2) there is strong gene flow between refugia and treated sites and (3) resistant parasites have reduced fitness when in refugia (Crowder & Carrière 2009, McEwan et al. 2015). In some instances, parasites regularly jump between farmed and wild host populations (indeed, all species of parasites occurring in aquaculture have made at least one jump from their original wild host population). In such cases, wild populations can act as refugia for susceptible parasite strains. This is exemplified by the large wild salmon populations in the North American Pacific, which have likely buffered against lice evolving pesticide resistance within the smaller farmed salmon population (Kreitzman et al. 2018). This effect may be more common in generalist parasites that have a range of host species available. When farmed hosts vastly outnumber wild ones (e.g. Atlantic salmon in the Norwegian Atlantic; Dempster et al. 2021), however, wild host stocks are unlikely to have an appreciable effect on parasite evolution. Furthermore, whilst relatively strong gene flow between farm and refugia hosts is desired to slow the evolution of resistance, excessive parasite spillover into wild populations can have adverse ecological impacts (Krkošek 2017). Evolution models can be valuable tools for evaluating the relative sizes of farmed and wild populations — and rates of parasite transmission between them — that are needed to have a refugia effect (e.g. McEwan et al. 2015, Kreitzman et al. 2018, Bateman et al. 2020).

Rather than relying on wild populations, it may be more effective if some farmed host populations are established as refugia, with those farms abstaining from the treatment in question. Deciding which farms must forego a new, effective treatment for the 'greater good' is a difficult decision, however, especially if there are only a limited number of controls available in the first place. This is where numerical modelling is useful. Metapopulation models can predict which farms (and when) could be established as refugia to have the greatest effect in halting resistance, whilst still ensuring infections do not get out of control (Sisterson et al. 2005, Pan et al. 2011). Models can also help to navigate the risks associated with relying on treatment-free refugia: in particular, refugia acting as parasite reservoirs that spill over into wild host populations (Bouwmeester et al. 2021). Severe outbreaks within refugia (and transmission to wild hosts) can be minimised if there are alternative management strategies available within refugia.

6. COMBINING TREATMENTS

Combining multiple treatments makes it far more difficult for pests to adapt, since a larger suite of traits are needed for complete resistance. This concept is well established in the medical field, with combination antiviral therapy highly effective at suppressing HIV (Soriano et al. 2017). In agriculture, a number of evolutionary models have shown that combining treatments on the same farm has the greatest effect at slowing pest adaptation, although it also runs the risk of rapidly producing multi-resistant strains (REX Consortium 2013, McEwan et al. 2016). Perhaps one of the most promising pathways for slowing adaptation is by enhancing parasite resistance in the host species through genomic selection or gene editing. If each gene coding for resistance in the host can be considered an individual pressure that the parasite must overcome, then multiple improvements in the host genome make counter-adaptation in the parasite increasingly difficult (REX Consortium 2016, Rimbaud et al. 2018, Robinson et al. 2022).

Treatments can also be applied in a mosaic pattern, so that each farm site receives at least one treatment, but still acts as a refugium from another treatment. With many treatment types, locations and times available, the total number of possible treatment regimes — and their outcomes — becomes vast. When searching for a deployment strategy that optimises production and welfare, it is very clear that modelling will be required. By simulating a range of scenarios, numerical models and optimisation techniques can, in principle, identify the spatial and temporal distribution of treatments that provide maximum protection from development of resistance.

Special attention should be paid to any 'weak points' that can be exploited in the adaptive capacity of a parasite. For example, 2 different management strategies might work antagonistically to impose stabilising selection on the pest (Coates et al. 2021a). Usually, when multiple treatments are combined (e.g. pesticide rotation, pyramiding of host resistant genes), they each select for completely unrelated traits. Antagonistic combinations, on the other hand, impose selection on the same trait, but in opposite directions. Such selection can be used to effectively pin the pest population's phenotype in place, preventing it from shifting in either direction towards resistance. Finding and developing complementary pairs of treatments means a higher initial workload, but this will pay off in the long run if it means ensuring treatment longevity. The research framework provided above can guide the process of conceiving, testing and deploying effective antagonistic combinations at the industry scale.

7. REGULATING EVOLUTIONARILY DURABLE PEST MANAGEMENT

Once enough knowledge of the parasite–host system has been accumulated, bespoke management regimes can be designed that ensure diseases are kept in check whilst also preventing development of resistance; however, for these management regimes to have an effect, they must be adopted by the aquaculture industry. Today, the concept of pesticide resistance is understood by the general public, and an understanding of the drivers of resistance is growing in the aquaculture sector, particularly in the salmonid industry, where the adaptive capacity of sea lice has become apparent. Nevertheless, some of the more complex aspects of evolutionary theory underpinning durable pest management might be difficult for non-scientists to understand. Strategies such as establishing treatment-free refugia appear, on the surface, counter-productive to pest control, and farmers may, understandably, be hesitant to adopt these approaches. More education is needed to make the understanding of evolutionary processes accessible to a wider audience and to instil a greater appreciation of their importance in farming.

Farms acting individually will invariably use whichever pest control method is most effective, despite this accelerating the evolution of resistance to the detriment of all farms in the region (à la 'the tragedy of the commons'; Kragesteen et al. 2019). Therefore, it is better if management strategies are coordinated across a network of farms (the size and shape of the network will be determined by how parasites are transmitted between farms). Top-down regulation from the government can help to enforce sustainable pest management practices. Salmon aquaculture, especially in Norway, is subject to a range of regulations intended to minimise the ecological impact of the growing industry (Jackson et al. 2018, Afewerki et al. 2022). Mandates such as louse limits and production caps under Norway's 'Traffic Light System' are directly aimed at reducing parasite spillover into wild salmonid populations (Johnsen et al. 2021). Approval is already required for salmon farms to use chemical therapeutants — individually and in combination — and there are strict guidelines as to how they are used (Jackson et al. 2018). It is not outlandish, therefore, to imagine additional regulations that restrict the use of different treatments to certain locations and times — selected according to the evolutionary principles described above. To assist this process, it might be appropriate to establish a 'Treatment Commission' — an independent body that works alongside farms and regulates how management strategies are deployed in an area. Commissions have previously been established for other important issues in aquaculture (such as the Norwegian Aquaculture Escapes Commission). A Treatment Commission or other regulatory authority will require dedicated research and development that looks at the industry as a whole and juggles the many other factors involved in farming. To start, each aquaculture system is not necessarily restricted to 1 parasite species. Atlantic salmon farms in Norway are beset by a range of parasites, including 2 species of sea lice, gill disease-causing amoeba, tapeworms and various viruses. Different parasites may interact on a host and shape one another's evolutionary trajectory, and attempts to treat one parasite species could inadvertently impose a selection pressure on another. On top of this are the myriad economic, environmental, human health and animal welfare factors surrounding pest management, in addition to the politics associated with the placement and production of individual farm sites. Risk assessments can assist with navigating these various concerns to settle on the most suitable strategy (Taranger et al. 2015, Rico et al. 2017, Jackson et al. 2018, Andersen et al. 2022). As with the research framework described above, establishing long-term monitoring and management protocols at a regional level is a costly endeavour. The rewards of this labour may not be visible, and in some cases, resistance might never have evolved in the first place. On the other hand, if significant economic or environmental impacts might arise from resistance, then the future benefits of pre-emptive action can be vast. Each system needs to be examined on a case-by-case basis to find the appropriate cost–reward balance — the important thing is the early consideration of the potential for pest resistance.

8. CLOSING REMARKS

Many aspects of pest control are derived from practices in terrestrial agriculture. These range from general farming practices such as fallowing to the use of specific chemical compounds as pesticides. In the last few decades, the aquaculture sector has become a powerhouse of global food production (FAO 2020). Industries such as salmon aquaculture are pioneering innovative new technologies for pest management that do not have clear analogues on land (e.g. cleaner fish, mechanical delousing, lice skirts). These technologies may inadvertently impose whole new types of selection pressures, to which we do not yet know how pest populations may respond. Active research in this area is crucial for identifying and preparing for resistance early on rather than attempting to mitigate its impacts later. The application of evolutionary principles should be a key component to ensuring sustainable disease management in aquaculture.

Acknowledgements. Funding for this work was provided by the project 'CrispResist: Harnessing cross-species variation in sea lice resistance', by the Norwegian Seafood Research Fund (FHF, project 901631).

LITERATURE CITED

Aaen SM, Helgesen KO, Bakke MJ, Kaur K, Horsberg TE (2015) Drug resistance in sea lice: a threat to salmonid aquaculture. Trends Parasitol 31:72–81

Afewerki S, Asche F, Misund B, Thorvaldsen T, Tveteras R (2022) Innovation in the Norwegian aquaculture industry. Rev Aquacult, doi:10.1111/raq.12755

Aldrin M, Jansen PA, Stryhn H (2019) A partly stage-structured model for the abundance of salmon lice in salmonid farms. Epidemics 26:9–22

Andersen LB, Grefsrud ES, Svåsand T, Sandlund N (2022) Risk understanding and risk acknowledgement: a new approach to environmental risk assessment in marine aquaculture. ICES J Mar Sci 79:987–996

Bakke MJ, Agusti C, Bruusgaard JC, Sundaram AYM, Horsberg TE (2018) Deltamethrin resistance in the salmon louse, *Lepeophtheirus salmonis* (Krøyer): maternal inheritance and reduced apoptosis. Sci Rep 8:8450

Bateman AW, Peacock SJ, Krkošek M, Lewis MA (2020) Migratory hosts can maintain the high-dose/refuge effect in a structured host-parasite system: the case of sea lice and salmon. Evol Appl 13:2521–2535

Besnier F, Kent M, Skern-Mauritzen R, Lien S and others (2014) Human-induced evolution caught in action: SNP-array reveals rapid amphi-atlantic spread of pesticide resistance in the salmon ecotoparasite *Lepeophtheirus salmonis.* BMC Genomics 15:937

Blaylock RB, Bullard SA (2014) Counter-insurgents of the Blue Revolution? Parasites and diseases affecting aquaculture and science. J Parasitol 100:743–755

Bouwmeester MM, Goedknegt MA, Poulin R, Thieltges DW (2021) Collateral diseases: aquaculture impacts on wildlife infections. J Appl Ecol 58:453–464

Carmona-Antoñanzas G, Bekaert M, Humble JL, Boyd S and others (2017) Maternal inheritance of deltamethrin resistance in the salmon louse *Lepeophtheirus salmonis* (Krøyer) is associated with unique mtDNA haplotypes. PLOS ONE 12:e0180625

Coates A, Phillips BL, Oppedal F, Bui S, Overton K, Dempster T (2020) Parasites under pressure: Salmon lice have the capacity to adapt to depth-based preventions in aquaculture. Int J Parasitol 50:865–872

Coates A, Phillips BL, Bui S, Oppedal F, Robinson NA, Dempster T (2021a) Evolution of salmon lice in response to management strategies: a review. Rev Aquacult 13:1397–1422

Coates A, Johnsen IA, Dempster T, Phillips BL (2021b) Parasite management in aquaculture exerts selection on salmon louse behaviour. Evol Appl 14:2025–2038

Coates A, Robinson N, Dempster T, Samsing F, Johnsen IA, Phillips BL (2022) A metapopulation model reveals connectivity-driven hotspots in treatment resistance evolution in a marine parasite. ICES J Mar Sci 79:2682–2696

Cousyn C, De Meester L, Colbourne JK, Brendonck L, Verschuren D, Volckaert F (2001) Rapid, local adaptation of zooplankton behavior to changes in predation pressure in the absence of neutral genetic changes. Proc Natl Acad Sci USA 98:6256–6260

Crowder DW, Carrière Y (2009) Comparing the refuge strategy for managing the evolution of insect resistance under different reproductive strategies. J Theor Biol 261: 423–430

De Meester L (1996) Evolutionary potential and local genetic differentiation in a phenotypically plastic trait of a cyclical parthenogen, *Daphnia magna.* Evolution 50:1293–1298

Dempster T, Overton K, Bui S, Stien LH and others (2021) Farmed salmonids drive the abundance, ecology and evolution of parasitic salmon lice in Norway. Aquacult Environ Interact 13:237–248

Downes S, Mahon RJ, Rossiter L, Kauter G, Leven T, Fitt G, Baker G (2010) Adaptive management of pest resistance by *Helicoverpa* species (Noctuidae) in Australia to the Cry2Ab Bt toxin in Bollgard II® cotton. Evol Appl 3: 574–584

FAO (2020) The state of world fisheries and aquaculture 2020: sustainability in action. FAO, Rome

Fjørtoft HB, Nilsen F, Besnier F, Stene A and others (2021) Losing the 'arms race': Multiresistant salmon lice are dispersed throughout the North Atlantic Ocean. R Soc Open Sci 8:210265

Gliwicz MZ (1986) Predation and the evolution of vertical migration in zooplankton. Nature 320:746–748

Goedknegt MA, Feis ME, Wegner KM, Luttikhuizen PC and others (2016) Parasites and marine invasions: ecological and evolutionary perspectives. J Sea Res 113:11–27

Grøntvedt RN, Jansen PA, Horsberg TA, Helgesen K, Tarpai A (2016) The surveillance programme for resistance to chemotherapeutants in salmon lice (*Lepeophtheirus salmonis*) in Norway 2015. Surveillance programmes for terrestrial and aquatic animals in Norway. Annual report 2015. Norwegian Veterinary Institute, Oslo

Hamre LA, Oldham T, Oppedal F, Nilsen F, Glover KA (2021) The potential for cleaner fish-driven evolution in the salmon louse *Lepeophtheirus salmonis*: genetic or environmental control of pigmentation? Ecol Evol 11:7865–7878

Helgesen KO, Bakke MJ, Kaur K, Horsberg TE (2017) Increased catalase activity — a possible resistance mechanism in hydrogen peroxide resistant salmon lice (*Lepeophtheirus salmonis*). Aquaculture 468:135–140

Hotelier T, Nègre V, Marchot P, Chatonnet A (2010) Insecticide resistance through mutations in cholinesterases or carboxylesterases: data mining in the ESTHER database. J Pestic Sci 35:315–320

Hupalo DN, Bradic M, Carlton JM (2015) The impact of genomics on population genetics of parasitic diseases. Curr Opin Microbiol 23:49–54

Igboeli OO, Burka JF, Fast MD (2014) Sea lice population and sex differences in P-glycoprotein expression and emamectin benzoate resistance on salmon farms in the Bay of Fundy, New Brunswick, Canada. Pest Manag Sci 70:905–914

Jackson D, Moberg O, Stenevik Djupevåg EM, Kane F, Hareide H (2018) The drivers of sea lice management policies and how best to integrate them into a risk management strategy: an ecosystem approach to sea lice management. J Fish Dis 41:927–933

Jansen PA, Grøntvedt RN, Tarpai A, Helgesen KO, Horsberg TE (2016) Surveillance of the sensitivity towards antiparasitic bath-treatments in the salmon louse (*Lepeophtheirus salmonis*). PLOS ONE 11:e0149006

Jeong J, Stormoen M, McEwan GF, Thakur KK, Revie CW (2021) Salmon lice should be managed before they attach to salmon: exploring epidemiological factors affecting *Lepeophtheirus salmonis* abundance on salmon farms. Aquaculture 541:736792

Johnsen IA, Harvey A, Sævik PN, Sandvik AD and others (2021) Salmon lice-induced mortality of Atlantic salmon during post-smolt migration in Norway. ICES J Mar Sci 78:142–154

Kaur K, Helgesen KO, Bakke MJ, Horsberg TE (2015) Mechanism behind resistance against the organophosphate azamethiphos in salmon lice (*Lepeophtheirus salmonis*). PLOS ONE 10:e0124220

Kemper KE, Goddard ME, Bishop SC (2013) Adaptation of gastrointestinal nematode parasites to host genotype: single locus simulation models. Genet Sel Evol 45:14

Kennedy DA, Kurath G, Brito IL, Purcell MK, Read AF, Winton JR, Wargo AR (2016) Potential drivers of virulence evolution in aquaculture. Evol Appl 9:344–354

Kingsolver JG, Pfennig DW (2007) Patterns and power of phenotypic selection in nature. Bioscience 57:561–572

Kirkpatrick M, Lande R (1989) The evolution of maternal characters. Evolution 43:485–503

Kragesteen TJ, Simonsen K, Visser AW, Andersen KH (2019) Optimal salmon lice treatment threshold and tragedy of the commons in salmon farm networks. Aquaculture 512: 734329

Kreitzman M, Ashander J, Driscoll J, Bateman AW, Chan KMA, Lewis MA, Krkosek M (2018) Wild salmon sustain the effectiveness of parasite control on salmon farms: conservation implications from an evolutionary ecosystem service. Conserv Lett 11:e12395

Krkošek M (2017) Population biology of infectious diseases shared by wild and farmed fish. Can J Fish Aquat Sci 74: 620–628

Lafferty KD, Harvell CD, Conrad JM, Friedman CS and others (2015) Infectious diseases affect marine fisheries and aquaculture economics. Annu Rev Mar Sci 7: 471–496

Ljungfeldt LE, Espedal P, Nilsen F, Skern-Mauritzen M, Glover K (2014) A common-garden experiment to quantify evolutionary processes in copepods: the case of emamectin benzoate resistance in the parasitic sea louse *Lepeophtheirus salmonis.* BMC Evol Biol 14:108

Ljungfeldt LER, Quintela M, Besnier F, Nilsen F, Glover KA (2017) A pedigree-based experiment reveals variation in salinity and thermal tolerance in the salmon louse, *Lepeophtheirus salmonis.* Evol Appl 10:1007–1019

MacKenzie K, Bishop SC (2001) Utilizing stochastic genetic epidemiological models to quantify the impact of selection for resistance to infectious diseases in domestic livestock. J Anim Sci 79:2057

McEwan GF, Groner ML, Fast MD, Gettinby G, Revie CW (2015) Using agent-based modelling to predict the role of wild refugia in the evolution of resistance of sea lice to chemotherapeutants. PLOS ONE 10: e0139128

McEwan GF, Groner ML, Burnett DL, Fast MD, Revie CW (2016) Managing aquatic parasites for reduced drug resistance: lessons from the land. J R Soc Interface 13: 20160830

Mennerat A, Nilsen F, Ebert D, Skorping A (2010) Intensive farming: evolutionary implications for parasites and pathogens. Evol Biol 37:59–67

Moe SJ, Hjermann DØ, Ravagnan E, Bechmann RK (2019) Effects of an aquaculture pesticide (diflubenzuron) on non-target shrimp populations: extrapolation from laboratory experiments to the risk of population decline. Ecol Modell 413:108833

Onstad DW, Liu X, Chen M, Roush R, Shelton AM (2013) Modeling the integration of parasitoid, insecticide, and transgenic insecticidal crop for the long-term control of an insect pest. J Econ Entomol 106:1103–1111

Pan Z, Onstad DW, Nowatzki TM, Stanley BH, Meinke LJ, Flexner JL (2011) Western corn rootworm (Coleoptera: Chrysomelidae) dispersal and adaptation to single-toxin transgenic corn deployed with block or blended refuge. Environ Entomol 40:964–978

REX Consortium (2013) Heterogeneity of selection and the evolution of resistance. Trends Ecol Evol 28:110–118

REX Consortium (2016) Combining selective pressures to enhance the durability of disease resistance genes. Front Plant Sci 7:1916

Rico A, Jacobs R, Van den Brink PJ, Tello A (2017) A probabilistic approach to assess antibiotic resistance development risks in environmental compartments and its application to an intensive aquaculture production scenario. Environ Pollut 231:918–928

Rimbaud L, Papaïx J, Barrett LG, Burdon JJ, Thrall PH (2018) Mosaics, mixtures, rotations or pyramiding: What is the optimal strategy to deploy major gene resistance? Evol Appl 11:1791–1810

Robinson NA, Robledo D, Sveen L, Daniels RR and others (2022) Applying genetic technologies to combat infectious diseases in aquaculture. Rev Aquacult, doi:10.1111/raq.12733

Samsing F, Johnsen I, Treml EA, Dempster T (2019) Identifying ‘firebreaks’ to fragment dispersal networks of a marine parasite. Int J Parasitol 49:277–286

Schmidt TL, Endersby-Harshman NM, Hoffmann AA (2021) Improving mosquito control strategies with population genomics. Trends Parasitol 37:907–921

Sisterson MS, Carrière Y, Dennehy TJ, Tabashnik BE (2005) Evolution of resistance to transgenic crops: interactions between insect movement and field distribution. J Econ Entomol 98:1751–1762

Soriano V, Fernandez-Montero JV, Benitez-Gutierrez L, de Mendoza C and others (2017) Dual antiretroviral therapy for HIV infection. Expert Opin Drug Saf 16: 923–932

Sundberg LRR, Ketola T, Laanto E, Kinnula H, Bamford JKHH, Penttinen R, Mappes J (2016) Intensive aquaculture selects for increased virulence and interference competition in bacteria. Proc R Soc B 283:20153069

Tabashnik BE, Carrière Y (2017) Surge in insect resistance to transgenic crops and prospects for sustainability. Nat Biotechnol 35:926–935

Taranger GL, Karlsen Ø, Bannister RJ, Glover KA and others (2015) Risk assessment of the environmental impact of Norwegian Atlantic salmon farming. J Mar Sci 72: 997–1021

Teletchea F, Fontaine P (2014) Levels of domestication in fish: implications for the sustainable future of aquaculture. Fish Fish 15:181–195

Toorians MEM, Adams TP (2020) Critical connectivity thresholds and the role of temperature in parasite metapopulations. Ecol Modell 435:109258

Ugelvik MS, Skorping A, Moberg O, Mennerat A (2017) Evolution of virulence under intensive farming: Salmon lice increase skin lesions and reduce host growth in salmon farms. J Evol Biol 30:1136–1142

Werkman M, Green DMM, Murray AGG, Turnbull JFF (2011) The effectiveness of fallowing strategies in disease control in salmon aquaculture assessed with an SIS model. Prev Vet Med 98:64–73

Wilson AJ, Réale D, Clements MN, Morrissey MM and others (2010) An ecologist's guide to the animal model. J Anim Ecol 79:13–26

Editorial responsibility: Bengt Finstad, Trondheim, Norway
Reviewed by: M. Bakke and 2 anonymous referees

Submitted: July 12, 2022
Accepted: December 28, 2022
Proofs received from author(s): February 9, 2023