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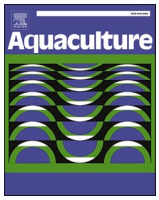

Economically optimal management of salmon louse requires adapting to their drug-resistance rather than attempting their eradication

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ABSTRACT

The growing global demand for seafood and concerns about overfishing have spurred the rapid expansion of aquaculture. In aquaculture, managing diseases and parasites presents a critical problem, with drug-based solutions being increasingly challenged by the evolution of drug resistance. In this study, we focus on managing salmon louse in the context of open-cage salmon mariculture with potential for the evolution of drug resistance. We devise a model combining parasite dynamics and fish dynamics in a system of fish farms connected to each other by dispersive stages of the parasite and then evaluate the system-wide economic performance of different management strategies involving three parasite-control measures: drug treatment (administering medicine through fish feed), mechanical treatment (pumping fish through a system of water jets and/or soft brushes), and depopulation (emptying a whole farm prematurely). Drug treatment controls drug-sensitive lice at low cost but becomes ineffective in the presence of drug-resistant lice. Mechanical treatment can clear both types of lice but at the cost of diminished fish growth and additional fish mortality. Depopulation removes both the fish and the parasites within the farm but results in prematurely harvested fish that fetch a lower price. Our results suggest that even when the drug is used only once per production cycle and mechanical treatment and depopulation provide the main control of the parasite, the spread of drug resistance is unavoidable in an open-cage system. Furthermore, it is often not economically optimal to drive resistance to the lowest possible level by minimizing drug use: because resistant lice are assumed to have a slightly reduced fecundity, slightly fewer non-drug treatments are needed for controlling drug-resistant parasites than drug-sensitive parasites. Building on these insights, our model predicts that economically optimal parasite management in the presence of drug resistance combines all three parasite-control measures: mechanical treatment is the main measure to reduce louse infestations, depopulation allows shorter production cycles that become optimal under reduced salmon growth and survival that result from frequent mechanical treatments, and the drug is used not only to provide some parasite control but also to keep the resistant parasites prevalent. Our results thus underscore the need for effective parasite management strategies in salmon aquaculture accounting for the unavoidable prevalence of drug resistance. Notably, the economically optimal approach does not involve combating resistance but rather adapting to it and capitalizing on its positive effects.

1. Introduction

Aquaculture is the fastest-growing sector in global food production, meeting increasing demands for food locally and globally (Subasinghe et al., 2009; FAO, 2024). In 2024, aquaculture accounted for 51 % of the total worldwide fishery production and for 57 % of fish used for human consumption (FAO, 2024). The commercialization and intensification of aquaculture have also brought challenges such as diseases and

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deterioration of the environment, which are resulting in substantial economic losses (Bondad-Reantaso et al., 2005; Martos-Sitcha et al., 2020).

Parasites and diseases are always a challenge in animal production systems (Paladini et al., 2017; Reverter et al., 2021). They pose a major threat not only to fish health and welfare but also to the economy of aquaculture enterprises (Subasinghe, 2005; Murray, 2009; Shinn et al., 2015). Open-cage mariculture systems are particularly vulnerable because the interaction of disease agents between farms is unavoidable and the parasites can easily spread (Salama and Rabe, 2013; Jones et al., 2015). Using drugs like antiparasitics has been a traditional strategy to prevent and control parasitic diseases in the last decades (Noga, 2010; Lefebvre et al., 2012; Cortez-Maya et al., 2020), which also benefits fish growth and improves feed conversion (Bondad-Reantaso et al., 2005). Drug treatments can be effective, but the problem is that resistant parasites almost inevitably evolve and spread (Aaen et al., 2015; Wunderlich et al., 2017; Preena et al., 2020; Coates, 2023). This situation is similar to human medicine where excessive use of antibiotics has been driving the spread of drug-resistant bacteria (WHO, 2022).

In marine finfish aquaculture, Atlantic salmon (*Salmo salar*) is the most important species in terms of total global production (FAO, 2024). Since the 1970s, the Atlantic-salmon farming industry has faced a significant challenge in the form of the salmon louse (*Lepeophtheirus salmonis*), a crustacean macroparasite (Brandal and Egidius, 1977; Costello, 2006; Overton et al., 2019; Sommerset et al., 2023; Boerlage et al., 2024), which is exerting a greater economic impact than any other parasite (Costello et al., 2004; Torrissen et al., 2013; Vollset et al., 2018; Cortez-Maya et al., 2020; Myhre Jensen et al., 2020; Sommerset et al., 2023). Despite the availability of antiparasitic drugs that have initially been effective, regular delousing operations create selection pressures favoring resistance evolution in the parasite, which renders the drugs less effective over time and leads to the recurrence of louse infestations (Torrissen et al., 2013; Aaen et al., 2015; Preena et al., 2020). While the introduction of new drug treatments can initially reduce lice loads, their long-term efficacy is often limited due to the rapid evolution of resistance, making new anti-parasite drugs valuable for only a short duration (Aaen et al., 2015; Overton et al., 2019; Mugimba et al., 2021; Coates, 2023). This situation underscores the urgent need for alternative strategies in managing parasites in aquaculture and in other animal production systems.

As parasites have an immense ability to adapt to their environment, one single approach to control parasites is rarely effective enough (McEwan et al., 2016; Buchmann, 2022). Effective control programs therefore utilize multiple approaches, with drug treatment often being the initial and convenient choice, and alternative solutions such as mechanical and biological control methods also being used, at least for ectoparasites (Buchmann, 2022). Mechanical treatment involves pumping fish through a system of water jets and/or soft brushes to remove ectoparasites but is stressful for the fish (Overton et al., 2019). Biological treatment involves using cleaner fish, which can be efficient if present at sufficiently high density but suffer from low survival and need to be frequently renewed (Overton et al., 2020). Because of resistance evolution, these alternative methods have gained importance despite increased costs and animal-welfare challenges. In some land-based animal production systems, depopulation, i.e., the premature emptying of a production unit, has been used in response to emergencies caused by disease or environmental disasters (Krushinskie et al., 2009; Arruda et al., 2020). In aquaculture, depopulation has been used to control viral and microbial diseases (Fofana and Baulcomb, 2012; Pettersen et al., 2016). Although current regulations in Norway can mandate depopulation in response to a persistent salmon-louse infestation (Nærings- og fiskeridepartementet, 2012), the efficacy of this measure in controlling a macroparasite with long-lived dispersive stage is unknown. A further challenge with depopulation is that it can be economically very costly (Fofana and Baulcomb, 2012; Pettersen et al., 2015). Lastly, exposure to parasites could be reduced by shortening the time that the fish spend in the sea by using larger smolts (Ytrestøyl et al., 2023) and lower slaughter weight (Barrett et al., 2022).

In this study, we investigate parasite-management strategies utilizing multiple control measures in the presence of drug resistance. Specifically, we want to understand which kind of strategies can be economically viable solutions, as seen from a social planner's perspective, when considering the costs and benefits that accrue over the production cycles on fish farms. We approach this question by developing a bioeconomic model combining parasite dynamics and fish dynamics in a system of fish farms connected to each other by the dispersive stages of the parasite.

Table 1
Model variables.

Type	Variable	Symbol*	Equation	Unit
State variables	Time in weeks	t, τ	1	–
	Number of fish	$N_i(t)$	1	–
	Number of drug-sensitive and drug-resistant eggs	$E_S(t), E_R(t)$	4a, 4b	–
	Number of drug-sensitive and drug-resistant juvenile lice	$J_{S,i}(t), J_{R,i}(t)$	4c, 4d	–
	Number of drug-sensitive and resistant adult lice	$A_{S,i}(t), A_{R,i}(t)$	4e, 4f	–
	Farm index	$i = 1, \ldots, n$		–
Structural variables	Indicator of drug use during a production cycle	$I^*_{\text{drug},i} = 0, 1$	5a	–
	Indicator of termination of a production cycle	$I_{\text{term},i}(t) = 0, 1$	1	–
	Indicators of drug treatments, mechanical treatments, and depopulation	$I_{\text{drug},i}(t) = 0, 1,$ $I_{\text{mech},i}(t) = 0, 1,$ $I_{\text{depop},i}(t) = 0, 1$	1, 5a, 5b	–
Emergent variables	Parasite effect on fish growth	$E_{\text{gr},i}(t)$	2a, 2d	–
	Total number of adult parasites	$A_i(t)$	2e	–
	Parasite load per unit surface area of fish	$P_i(t)$	2d	cm^{-2}
	Surface area of fish	$S_i(t)$	2e	cm^2
	Parasite effect on fish survival	$E_{\text{surv},i}(t)$	3a, 3b	–
	Probability of parasites to enter farm	$g_i(t)$	4 g	–
	Resistant proportion in adult parasite	$\rho_i(t)$	5a, 5b	–
	Realized death probability of parasites in case of drug treatment	$\epsilon_i(t)$	5a, 5b	–
	Total biomass gain of fish over one time step	$B_i(t)$	6d	kg
	Revenue	$R_i(t)$	6a, 6f	NOK
	Cost	$C_i(t)$	6d, 6f	NOK
	Profit	$\Pi_i(t)$	6f	NOK

* Subscripts S and R refer to drug-sensitive and drug-resistant parasites, respectively.

Table 2
Model parameters.

Parameter	Symbol	Equation	Value	Unit	Source
Parameters determining system structure					
Number of farms	n_{farm}		10	–	n.a.
Initial fish number per farm	N_0		1,600,000	–	Lybæk (2017)
Parameters related to fish growth and survival					
Target slaughter fish weight	W_{sell}	1	4.8	kg	Sjømat Norge, 2023
Maximum number of weeks in fish production cycle	t_{cycle}	1	105	–	See section "Model calibration"
Critical proportion of cumulatively surviving fish to trigger termination of production cycle	θ_{min}	1	0.1	–	See section "Model calibration"
Initial fish weight	W_0	2a	0.3	kg	Ytrestøyl et al. (2023)
Asymptotic maximum fish weight	W_{max}	2b	5.3658	kg	Thyholdt (2014)
Coefficient of fish growth curve	ω	2b	0.0706	–	Thyholdt (2014)
Sensitivity of fish growth to parasite load	δ_{gr}	2c	10.78	cm^2	Fjelldal et al. (2022)
Parasite load at which fish growth is halved	P_{gr50}	2c	0.41	cm^{-2}	Fjelldal et al. (2022)
Coefficient of fish surface area-weight relationship	b	2e	14.93	$cm^2 g^{-b}$	O'Shea et al. (2006)
Allometric exponent of fish surface area-weight relationship	β	2e	0.59	–	O'Shea et al. (2006)
Fish natural survival probability per week	s	3a	0.999	–	Oliveira et al. (2021)
Fish death probability caused by mechanical treatment	$d_{F,mech}$	3a	0.005	–	Iversen et al. (2017)
Sensitivity of fish survival probability per week to parasite load	δ_{surv}	3b	27.08	cm^2	Fjelldal et al. (2020)
Parasite load at which fish survival probability per week is halved	P_{surv50}	3b	0.22	cm^{-2}	Fjelldal et al. (2020)
Parameters related to parasite life history					
Fecundity of a drug-sensitive parasite per week	f	4a, 4b	190	–	Pike and Wadsworth (1999); Heuch et al. (2000)
Relative cost to parasite of drug resistance	q	4b	0.1	–	Espedal et al. (2013)
Parasite load at which parasite egg production is halved	P_{E50}	4a, 4b	0.089	cm^{-2}	Ugelvik et al. (2017)
Survival of parasite eggs per week	s_{egg}	4a, 4b	0.0652	–	Stien et al. (2005)
Survival of juvenile parasites per week	s_{juv}	4c, 4d	0.567	–	Stien et al. (2005)
Probability of juvenile parasite transitioning to adult stage per week	m	4c, 4d	0.12	–	Heuch et al. (2000)
Survival of adult parasites per week	s_{ad}	4e, 4f	0.769	–	Stien et al. (2005)
Baseline probability of parasites to enter a farm per week	g_0	4 g	0.02	–	Calibrated
Autocorrelation coefficient of probability of parasites to enter a farm per week	α	4 g	0.75	–	Calibrated
Standard deviation of probability of parasites to enter a farm per week	σ	4 g	0.03	–	Calibrated
Parameters related to parasite control					
Death probability of drug-sensitive parasites exposed to drug treatment	d_{dr}	4 h	0.9	–	Stone et al. (1999, 2000); Armstrong et al. (2000)
Strength of drug resistance in parasites	r	4 h	0.9	–	Aldrin et al. (2023)
Death probability of adult parasites exposed to mechanical treatment	$d_{A,mech}$	4 h	0.885	–	Calibrated
Death probability of juvenile parasites exposed to mechanical treatment	$d_{J,mech}$	4 h	0.7	–	Furberg (2022)
Sample size for estimating proportion of resistant parasites	n_{sample}		100, 500	–	Helgesen et al. (2023)
Threshold parasite density for triggering parasite-control measures	D_{crit}	5a	1	–	Nærings- og fiskeridepartementet (2012)
Threshold drug effectiveness for farmer to switch to non-drug treatments	ϵ_{switch}	5a, 5b	(0,1)	–	Decision variable
Threshold proportion of resistant parasites for farmer to switch to non-drug treatments	ρ_{switch}	5a, 5b	(0,1)	–	Decision variable
Minimum number of weeks between mechanical treatments	Δt_{min}	5b	2	–	Walde (2023)
Threshold density for triggering depopulation	D_{depop}	5a, 5b, 5c	$\geq D_{drug}$	–	Decision variable
Threshold weight for triggering depopulation	W_{depop}	5a, 5b, 5c	(W_0, W_{sell})	kg	Decision variable
Economic parameters					

(*continued on next page*)

Table 2 (*continued*)

Parameter	Symbol	Equation	Value	Unit	Source
Selling price of market-sized fish	p_{sell}	6b	48.7	NOK kg^{-1}	Directorate of Fisheries (2022)
Relative selling price of fish in price class j	$e_{sell,j}$	6b, 6c	0, 0.72, 0.89, 0.97, 1	–	NASDAQ Salmon Index
Conversion factor from gutted fish weight to live fish weight	e_g	6b	1.2	–	Directorate of Fisheries (2018)
Conversion factor from dry-feed weight to live-fish weight	e_{feed}	6d	1	–	Thorarensen and Farrell (2011); Torrissen et al. (2011)
Slaughter cost	$c_{slaughter}$	6d, 6e	3.26	NOK kg^{-1}	Iversen et al. (2017)
Unit price of stocking-size fish	p_0	6d	12.60	NOK	Directorate of Fisheries (2022)
Cost of fish feed	c_{feed}	6d	13.20	NOK kg^{-1}	Directorate of Fisheries (2022)
Cost of drug addition to fish feed	c_{drug}	6d	11.5	NOK kg^{-1}	Iversen et al. (2017)
Cost of mechanical treatment	c_{mech}	6d	0.22	NOK kg^{-1}	Iversen et al. (2017)
Relative magnitude of additional other costs	e_{other}	6d	0.18	–	Iversen et al. (2017)

2. Model description

Below, we start from a brief model overview, after which we detail all model equations. All model variables and parameters are listed in Tables 1 and 2, respectively.

2.1. Model overview

We use a model structure and parameter values tailored to salmon louse infesting farmed Atlantic salmon in Norway. We use a mean-field approach in which the effects of this parasite on a farm can be described by the mean parasite load per fish. There is no explicit spatial structure. The model dynamics are implemented using a time step of one week. We do not consider temperature effects on biological processes nor seasonal changes in the markets.

2.1.1. Fish production cycle

The modeled system consists of a number of fish farms. Farmers grow fish until they reach slaughter size, after which the production cycle starts anew. Each farm has its own production cycle, but the farms are connected to each other by the dispersive stage of the parasite. If not properly controlled, parasites can reduce the growth and survival of farmed fish and their wild conspecifics. Managers can obligate the farmers to combat the parasites with drugs, mechanical treatment, or depopulation if parasite levels exceed mandatory limits. The farmers may also end a production cycle when reaching the maximum length of a production cycle or when the number of fish declines below a certain proportion of their initial number.

2.1.2. Parasite life cycle

Adult parasites on each fish farm produce eggs that enter the common egg pool. Larvae from this egg pool have a similar likelihood of infesting fish on each of the farms. Larvae that successfully infest a fish develop into juvenile parasites. These juveniles have a constant probability per time step of becoming adult parasites. We assume an even primary sex ratio and model only female parasites.

2.1.3. Drug resistance

Drug-sensitive parasites and drug-resistant parasites are modeled as two competing populations of parasites. Drug-resistant parasites suffer less mortality when exposed to the drug treatment, but they are assumed to have a lower fecundity than drug-sensitive parasites.

2.1.4. Production economics

Farmers buy stocking-size smolts. At each time step, fish grow, but some die naturally. Fish growth requires fish feed, the amount and cost of which are proportional to the fish population's total biomass gain during each time step. When the fish reach a certain target weight, farmers sell them. A production cycle also incurs an overhead cost and slaughtering cost. Drug and mechanical treatments incur a cost each time they are applied, and the mechanical treatment incurs extra mortality on the treated fish. The cost of drug treatment is proportional to the total weight gain of the treated fish because the drug is administered as an additive to the feed, while the cost of mechanical treatment is proportional to the total weight of the treated fish because larger fish require larger treatment facilities. The overall treatment cost is higher for the mechanical treatment than for the drug treatment. Depopulation does not incur a direct cost, but if premature depopulation is triggered, the fish are still below their target weight and thus fetch a reduced price per fish.

2.1.5. Parasite control

When parasites are present, they negatively affect the growth and survival of the fish, but this effect becomes significant only at high parasite loads. If the maximum allowed parasite density, measured in terms of lice per fish, set by the authorities is exceeded, the farmers will have to combat the parasites by using drug treatment, mechanical treatment, or depopulation. Their choice of measure against the parasites is specified by the decision tree shown in Fig. 1 and explained in the next section.

2.2. Parasite-control strategy

We consider two alternative scenarios regarding the information available on the proportion of resistant lice on a farm for choosing the most appropriate management action. In the first scenario, the farmers can estimate the proportion of resistant lice on their farm only indirectly, by using the drug and observing its effectiveness. In the second scenario, the farmers can estimate the resistant proportion directly, e.g., by applying a molecular probe to a sample of parasites, as already is possible for resistance to some drugs. These scenarios correspond to two different decision trees (Fig. 1).

2.2.1. Decision tree based on drug effectiveness (Fig. 1A)

Farmers use the drug and assess its effectiveness, defined as the average death probability across all parasites in a farm when the drug is used, to decide whether to continue using it. In the beginning of a production cycle, the drug effectiveness is unknown; hence, the farmers must use the drug at least once per production cycle. If the drug is less effective than a set threshold, the farmer will switch to a non-drug

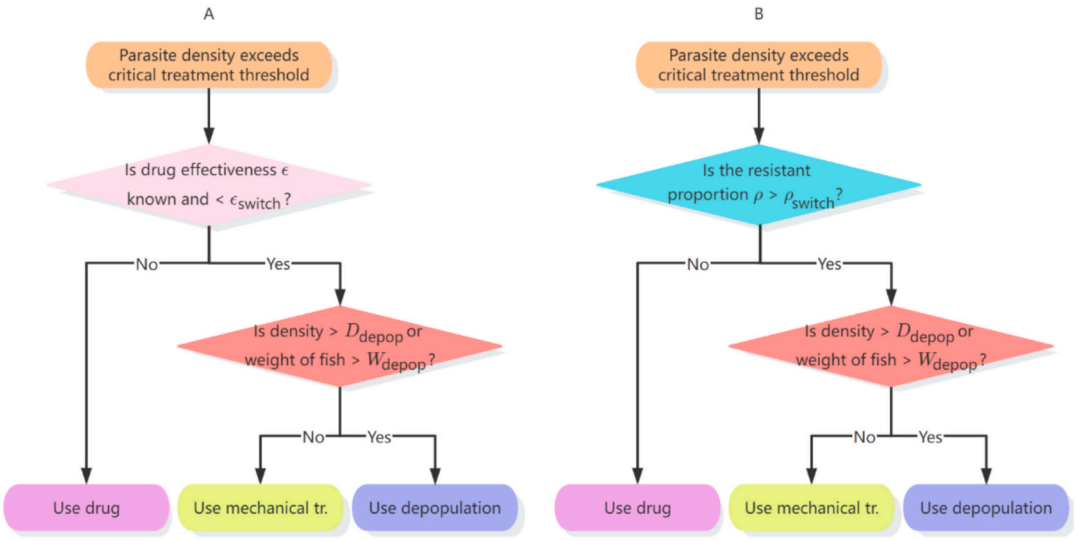

Fig. 1. Decision trees used to select management action when the parasite density exceeds the threshold level D_{crit} requiring action. Both decision trees have three control parameters. In A, the first decision establishes whether the drug effectiveness ϵ is high enough to warrant drug use, i.e., it is known and exceeds the switching threshold ϵ_{switch}. In B, the first decision establishes whether the resistant proportion ρ of parasite is low enough to warrant drug use, i.e., it is below the threshold ρ_{switch} for a farmer to switch to non-drug measures. The final decision is the same for both trees and establishes whether depopulation should take place, i.e., the lice density D exceeds the threshold density D_{depop} or the weight W of fish exceeds the threshold weight W_{depop}.

treatment. If the parasite density reaches a set threshold or if the fish weight reaches a set threshold, the farmer will depopulate the farm. If depopulation conditions are not met, the farmer will use mechanical treatment.

2.2.2. Decision tree based on direct information (Fig. 1B)

Farmers can directly estimate the resistant proportion among the parasites on their farm through sampling. If the estimated proportion is lower than a set threshold, the farmer will use the drug. Otherwise, the farmer will switch to a non-drug treatment, similarly as in the first decision tree.

2.3. Production cycle

A production cycle on farm i starts with N_0 fish of initial weight W_0 each and with the drug-use indicator $I^*_{drug,i}$ set to zero. During the production cycle, the fish grow and die as detailed in the next two sections. The production cycle is terminated (1) when the fish reach the target slaughter fish weight W_{sell}, (2) when the proportion of surviving fish falls below the critical proportion θ_{min}, (3) when the maximum duration t_{cycle} in fish production cycle is reached, or (4) when depopulation is triggered,

$$I_{term,i}\left(t\right) = \begin{cases} 1 & \text{if } W_i(t) \geq W_{sell} \text{ or } N_i(t)/N_0 \leq \theta_{min} \text{ or} \\ & \tau_i = t_{cycle} \text{ or } I_{depop,i}(t) = 1, \\ 0 & \text{otherwise,} \end{cases} \tag{1}$$

where $I_{term,i}(t)$ is the indicator variable for the termination of the production cycle on farm i at time t, $W_i(t)$ is the mean weight of fish on farm i at time t, $N_i(t)$ is the total number of fish on farm i at time t, τ_i is the time within the production cycle on farm i, and $I_{depop,i}(t)$ is the indicator variable for depopulation on farm i at time t.

2.4. Fish growth

Fish growth is affected by both mechanical treatments and parasites. The parasite effect $E_{gr,i}(t) \leq 1$ on growth is modeled as a multiplicative effect. Following a mechanical treatment, fish stop growing for one week. Hence, the fish weight on farm i is given by

$$W_i(t+1) = \begin{cases} W_0 & \text{if } I_{term,i}(t) = 1, \\ W_i(t) + E_{gr,i}(t)\Delta W(W_i(t)) & \text{if } I_{mech,i}(t) = 0, \\ W_i(t) & \text{if } I_{mech,i}(t) = 1, \end{cases} \tag{2a}$$

where $\Delta W(W_i(t))$ is the maximum weight gain over one time step on farm i at time t as a function of the current fish weight $W_i(t)$. We derive this weight gain from the growth model by Thyholdt (2014, see the supplementary methods), which yields

$$\Delta W(W_i(t)) = \frac{W_{max}}{1 + \omega(W_{max}/W_i(t) - 1)} - W_i(t), \tag{2b}$$

where W_{max} and ω are parameters of the weight growth of fish.

We use a sigmoid function to describe the parasite effect $E_{gr,i}(t)$ on fish growth, such that the effect is practically absent when there are few parasites but becomes strong for sufficiently heavy parasite loads:

$$E_{gr,i}(t) = \frac{1}{1 + exp\left(\delta_{gr}\left(P_i(t) - P_{gr50}\right)\right)}, \tag{2c}$$

where δ_{gr} is the sensitivity of fish growth to parasite load, $P_i(t)$ is the parasite load per unit surface area of the fish on farm i at time t, and P_{gr50} is the parasite load where fish growth is halved. The parasite load $P_i(t)$ per unit surface area of fish is defined as

$$P_i(t) = \frac{A_i(t)}{N_i(t)S_i(t)}, \tag{2d}$$

where $A_i(t)$ is the total number of adult parasites on farm i at time t and $S_i(t)$ is the mean surface area of fish on farm i at time t, defined by the allometric relationship

$$S_i(t) = bW_i(t)^{\beta}, \tag{2e}$$

where b and β are the parameters of this fish surface area-weight relationship.

2.5. Fish population dynamics

In absence of parasites, the fish have a constant survival probability s over a time step. The mechanical treatment will cause an additional

death probability $d_{\mathrm{F,mech}}$ to fish. The parasite effect $E_{\mathrm{surv},i}(t) \leq 1$ on survival is modeled as a multiplicative effect. Fish population dynamics on farm i follows then

$$N_i(t+1) = \begin{cases} N_0 & \text{if } I_{\mathrm{term},i}(t) = 1, \\ sN_i(t)E_{\mathrm{surv},i}(t) & \text{if } I_{\mathrm{mech},i}(t) = 0, \\ sN_i(t)E_{\mathrm{surv},i}(t)\left(1 - d_{\mathrm{F,mech}}\right) & \text{if } I_{\mathrm{mech},i}(t) = 1. \end{cases} \tag{3a}$$

We use a sigmoid function to describe the parasite effect $E_{\mathrm{surv},i}(t)$ on fish survival, such that the effect is practically absent when there are few parasites but becomes strong for sufficiently heavy parasite loads:

$$E_{\mathrm{surv}}(t) = \frac{1}{1 + exp(\delta_{\mathrm{surv}}(P_i(t) - P_{\mathrm{surv50}}))}, \tag{3b}$$

where δ_{surv} is the sensitivity of fish survival to parasite load and P_{surv50} is the parasite load where fish survival is halved.

2.6. Parasite population dynamics

The parasite life cycle consists of three stages: eggs (with density E), juveniles (with density J), and adults (with density A). There are two types of parasites, drug-sensitive and drug-resistant, indicated by the subscripts S and R, which reproduce independently but whose population dynamics are linked through jointly regulated egg production and jointly determined management measures. Parasite population dynamics are defined by the following equations:

$$E_{\mathrm{S}}(t+1) = f\sum\nolimits_i A_{\mathrm{S},i}(t)\, 2^{-\frac{P_i(t)}{P_{\mathrm{E50}}}} + s_{\mathrm{egg}}E_{\mathrm{S}}(t)\left(1 - \sum\nolimits_i g_i(t)\right), \tag{4a}$$

$$E_{\mathrm{R}}(t+1) = f(1-q)\sum\nolimits_i A_{\mathrm{R},i}(t)\, 2^{-\frac{P_i(t)}{P_{\mathrm{E50}}}} + s_{\mathrm{egg}}E_{\mathrm{R}}(t)\left(1 - \sum\nolimits_i g_i(t)\right), \tag{4b}$$

$$J_{\mathrm{S},i}(t+1) = \left(1 - d_{\mathrm{SJ},i}(t)\right)\left(s_{\mathrm{egg}}E_{\mathrm{S}}(t)g_i(t) + \left[s_{\mathrm{juv}}J_{\mathrm{S},i}(t)(1-m)\right]\right), \tag{4c}$$

$$J_{\mathrm{R},i}(t+1) = \left(1 - d_{\mathrm{RJ},i}(t)\right)\left(s_{\mathrm{egg}}E_{\mathrm{R}}(t)g_i(t) + \left[s_{\mathrm{juv}}J_{\mathrm{R},i}(t)(1-m)\right]\right), \tag{4d}$$

$$A_{\mathrm{S},i}(t+1) = \left(1 - d_{\mathrm{SA},i}(t)\right)\left(ms_{\mathrm{juv}}J_{\mathrm{S},i}(t) + s_{\mathrm{ad}}A_{\mathrm{S},i}(t)\right), \tag{4e}$$

$$A_{\mathrm{R},i}(t+1) = \left(1 - d_{\mathrm{RA},i}(t)\right)\left(ms_{\mathrm{juv}}J_{\mathrm{R},i}(t) + s_{\mathrm{ad}}A_{\mathrm{R},i}(t)\right), \tag{4f}$$

where f is the fecundity of the drug-sensitive parasite, q is the cost of resistance in terms of relative fecundity loss ($0 < q < 1$), P_{E50} is the parasite load at which parasite egg production is halved, $g_i(t)$ is the time-varying probability of parasites to enter farm i, s_{egg} is the survival of parasite eggs, s_{juv} is the survival of juvenile parasites, m is the maturation probability of juvenile parasites transitioning to adult stage, s_{ad} is the survival of adult parasites, and $d_{\mathrm{SJ},i}(t)$, $d_{\mathrm{RJ},i}(t)$, $d_{\mathrm{SA},i}(t)$, and $d_{\mathrm{RA},i}(t)$ are the death probabilities of drug-sensitive and drug-resistant juvenile and adult parasites exposed to the parasite-control treatments on farm i at time t.

The time-varying probability $g_i(t)$ of parasites to enter farm i at time t is defined by

$$g_i(t) = g_0 + \alpha g_i(t-1) + \sigma \mathrm{N}(01), \tag{4g}$$

where g_0 is the baseline probability of parasites to enter a farm, α and σ are parameters determining the temporal autocorrelation and standard deviation of the probabilities $g_i(t)$, and $\mathrm{N}(0,1)$ is a random variable drawn from the standard normal distribution.

The death probabilities $d_{\mathrm{SJ},i}(t)$, $d_{\mathrm{RJ},i}(t)$, $d_{\mathrm{SA},i}(t)$, and $d_{\mathrm{RA},i}(t)$ of drug-sensitive and drug-resistant juvenile and adult parasites exposed to the parasite-control measures are defined by

$$d_{\mathrm{SJ},i}(t) = \begin{cases} d_{\mathrm{dr}} & \text{if } I_{\mathrm{drug},i}(t) = 1, \\ d_{\mathrm{J,mech}} & \text{if } I_{\mathrm{mech},i}(t) = 1, \\ 1 & \text{if } I_{\mathrm{term},i}(t) = 1, \\ 0 & \text{otherwise}, \end{cases}$$

$$d_{\mathrm{RJ},i}(t) = \begin{cases} d_{\mathrm{dr}}(1-r) & \text{if } I_{\mathrm{drug},i}(t) = 1, \\ d_{\mathrm{J,mech}} & \text{if } I_{\mathrm{mech},i}(t) = 1, \\ 1 & \text{if } I_{\mathrm{term},i}(t) = 1, \\ 0 & \text{otherwise}, \end{cases} \tag{4h}$$

$$d_{\mathrm{SA},i}(t) = \begin{cases} d_{\mathrm{dr}} & \text{if } I_{\mathrm{drug},i}(t) = 1, \\ d_{\mathrm{A,mech}} & \text{if } I_{\mathrm{mech},i}(t) = 1, \\ 1 & \text{if } I_{\mathrm{term},i}(t) = 1, \\ 0 & \text{otherwise}, \end{cases}$$

$$d_{\mathrm{RA},i}(t) = \begin{cases} d_{\mathrm{dr}}(1-r) & \text{if } I_{\mathrm{drug},i}(t) = 1, \\ d_{\mathrm{A,mech}} & \text{if } I_{\mathrm{mech},i}(t) = 1, \\ 1 & \text{if } I_{\mathrm{term},i}(t) = 1, \\ 0 & \text{otherwise}, \end{cases}$$

where d_{dr} is the death probability of drug-sensitive parasites exposed to the drug treatment, r is the strength of drug resistance in parasites, $d_{\mathrm{J,mech}}$ is the death probability of juvenile parasites exposed to the mechanical treatment, $d_{\mathrm{A,mech}}$ is the death probability of adult parasites exposed to the mechanical treatment, and $I_{\mathrm{drug},i}(t)$ and $I_{\mathrm{mech},i}(t)$ are indicator variables for the drug treatment and the mechanical treatment defined in the next subsection.

2.7. Parasite control

Parasite-control measures are triggered whenever the parasite density $D_i(t)$ on farm i at time t, defined as the number of adult parasites per fish, $D_i(t) = A_i(t)/N_i(t)$, exceeds the critical parasite density, $D_i(t) \geq D_{\mathrm{crit}}$. We consider three types of parasite-control measures: drug treatment, mechanical treatment, and depopulation. The choice of the specific parasite-control measure depends on a number of additional criteria outlined in Fig. 1 and described in detail below. We differentiate between the decision trees based on either drug effectiveness ϵ (Fig. 1A) or resistant proportion ρ among adult parasites (Fig. 1B) by setting the decision thresholds $\epsilon_{\mathrm{switch}}$ and ρ_{switch} as follows: if drug effectiveness is used, $0 < \epsilon_{\mathrm{switch}} < 1$ and $\rho_{\mathrm{switch}} = 0$, whereas if resistant proportion is used, $0 < \rho_{\mathrm{switch}} < 1$ and $\epsilon_{\mathrm{switch}} = \infty$. The resistant proportion ρ is estimated based on a sample n_{sample} of randomly chosen parasites.

2.7.1. Drug treatment

Drug treatment is applied if $D_i(t-1) \geq D_{\mathrm{crit}}$ and either (1) the decisions are based on drug effectiveness $\epsilon_i(t)$ on farm i at time t, $\epsilon_{\mathrm{switch}} < \infty$, and (1a) $\epsilon_i(t)$ is unknown because the drug has not yet been used, $I^*_{\mathrm{drug},i} = 0$, or (1b) $\epsilon_i(t)$ is known because the drug has been used, $I^*_{\mathrm{drug},i} = 1$, and it exceeds the threshold $\epsilon_{\mathrm{switch}}$ for farmers to switch to non-drug treatments or (2) the decisions are based on the resistant proportion $\rho_i(t)$ among adult parasites on farm i at time t, $\rho_{\mathrm{switch}} > 0$, and $\rho_i(t)$ is below the threshold ρ_{switch} for farmers to switch to non-drug treatments,

$$I_{\mathrm{drug},i}\left(t\right) = \begin{cases} 1 & \text{if } D_i(t-1) \geq D_{\mathrm{crit}} \text{ and} \\ & \left\{\left[\epsilon_{\mathrm{switch}} < \infty \text{ and } \left(I^*_{\mathrm{drug},i} = 0 \text{ or } \epsilon_i(t) \geq \epsilon_{\mathrm{switch}}\right)\right] \text{ or} \right. \\ & \left. [\rho_{\mathrm{switch}} > 0 \text{ and } \rho_i(t) < \rho_{\mathrm{switch}}]\right\}, \\ 0 & \text{otherwise}. \end{cases} \tag{5a}$$

The drug-use indicator $I^*_{\mathrm{drug},i}$ is set to 0 at the beginning of each production cycle and to 1 once the drug has been used.

2.7.2. Depopulation

Depopulation is applied if $D_i(t-1) \geq D_{\text{crit}}$ but the conditions for triggering drug treatment (Eq. 5a) are not met and either (1) the parasite density $D_i(t)$ exceeds the threshold density D_{depop} for triggering depopulation or (2) the fish weight threshold W_{depop} for triggering depopulation is exceeded,

$$I_{\text{depop},i}(t) = \begin{cases} 1 & \text{if } I_{\text{drug},i}(t) = 0 \text{ and} \\ & \left[D_i(t-1) \geq D_{\text{depop}} \text{ or} \right. \\ & \left. \left(D_i(t-1) \geq D_{\text{crit}} \text{ and } W_i(t) \geq W_{\text{depop}}\right)\right], \\ 0 & \text{otherwise.} \end{cases} \tag{5b}$$

2.7.3. Mechanical treatment

Mechanical treatment is applied if $D_i(t-1) \geq D_{\text{crit}}$ but neither of the conditions for triggering drug treatment (Eq. 5a) or depopulation (Eq. 5b) are met and the minimum interval Δt_{min} between mechanical treatments has passed, $I^*_{\text{mech},i}(t) = \sum_{\tau=t-\Delta t_{\text{min}}}^{t-1} I_{\text{mech},i}(\tau) = 0$,

$$I_{\text{mech},i}(t) = \begin{cases} 1 & \text{if } D_i(t-1) \geq D_{\text{crit}} \text{ and} \\ & I_{\text{drug},i}(t) = 0 \text{ and } I_{\text{depop},i}(t) = 0 \text{ and} \\ & I^*_{\text{mech},i}(t) = 0, \\ 0 & \text{otherwise.} \end{cases} \tag{5c}$$

2.8. Economic dynamics

Revenue. The revenue $R_i(t_{\text{term}})$ of farm i over a single production cycle is based on the time t_{term} when the production cycle is terminated, the weight $W_i(t_{\text{term}})$ of all $N_i(t_{\text{term}})$ fish on farm i at that time, and the weight-specific price $p(W_i(t_{\text{term}}))$ of those fish,

$$R_i(t_{\text{term}}) = W_i(t_{\text{term}}) N_i(t_{\text{term}}) p(W_i(t_{\text{term}})). \tag{6a}$$

We express the weight-specific price $p(W_i(t))$ of fish as a product of the selling price p_{sell} in the target weight bracket of market-sized fish of 4–5 kg and the discounting factor $e_{\text{sell}} \leq 1$ depending on how much the gutted weight $W_{g,i}(t) = W_i(t)/e_g$ of fish, where $e_g > 1$ is the conversion factor from gutted fish weight to live fish weight, is below the target weight bracket,

$$p(W_i(t)) = p_{\text{sell}} e_{\text{sell}}\left(W_{g,i}(t)\right), \tag{6b}$$

$$e_{\text{sell}}\left(W_{g,i}(t)\right) = \begin{cases} e_{\text{sell},1} & \text{if } W_{g,i}(t) < 1 \text{ kg}, \\ e_{\text{sell},2} & \text{if } 1 \text{ kg} \leq W_{g,i}(t) < 2 \text{ kg}, \\ e_{\text{sell},3} & \text{if } 2 \text{ kg} \leq W_{g,i}(t) < 3 \text{ kg}, \\ e_{\text{sell},4} & \text{if } 3 \text{ kg} \leq W_{g,i}(t) < 4 \text{ kg}, \\ 1 & \text{if } 4 \text{ kg} \leq W_{g,i}(t) < 5 \text{ kg}. \end{cases} \tag{6c}$$

2.8.1. Cost

The total cost $C_i(t_{\text{term}})$ of farm i over a single production cycle consists of the cost of stocking-sized fish, feed, drug treatment, mechanical treatment, slaughter, and other costs,

$$\begin{aligned} C_i(t_{\text{term}}) = \{ & p_0 N_0 \\ & + c_{\text{feed}} e_{\text{feed}} \sum_{\tau=0}^{t_{\text{term}}-1} B_i(\tau) \\ & + c_{\text{drug}} e_{\text{feed}} \sum_{\tau=0}^{t_{\text{term}}-1} I_{\text{drug},i}(\tau)\, B_i(\tau) \\ & + c_{\text{mech}} \sum_{\tau=0}^{t_{\text{term}}-1} I_{\text{mech},i}(\tau)\, W_i(\tau)\, N_i(\tau) \} (1 + e_{\text{other}}) \\ & + c_{\text{slaughter}}\left(W_{g,i}(t_{\text{term}})\right)\, W_i(t_{\text{term}})\, N_i(t_{\text{term}}), \end{aligned} \tag{6d}$$

where p_0 is the unit price of stocking-sized fish, c_{feed} is the cost of fish feed, e_{feed} is the conversion factor from dry-feed weight to live-fish weight (biological feed-conversion ratio), $B_i(\tau) = E_{\text{gr},i}(\tau)\, \Delta W_i(W_i(\tau))\, N_i(\tau)$ is the total biomass gain of fish on farm i over the time interval from $\tau - 1$ to τ (irrespective of their mortality), c_{drug} is the unit cost of drug treatment, c_{mech} is the unit cost of mechanical treatment, e_{other} is the relative magnitude of additional other costs, and $c_{\text{slaughter}}\left(W_{g,i}(t_{\text{term}})\right)$ is the slaughter cost per unit fish weight. Because the selling price of fish with a gutted weight less than 1 kg is not available, we assume that the slaughter cost and the salvage price of such fish offset each other. Thus, we set $e_{\text{sell},1} = 0$ and

$$c_{\text{slaughter}}\left(W_{g,i}(t_{\text{term}})\right) = \begin{cases} 0 & \text{if } W_{g,i}(t_{\text{term}}) < 1 \text{ kg}, \\ c_{\text{slaughter}} & \text{otherwise.} \end{cases} \tag{6e}$$

2.8.2. Profit

The profit $\Pi_i(t_{\text{term}})$ of farm i over a single production cycle is the difference between the farm's revenue and total cost,

$$\Pi_i(t_{\text{term}}) = R_i(t_{\text{term}}) - C_i(t_{\text{term}}). \tag{6f}$$

2.8.3. Management objective

The goal of the farm management is to maximize the long-term profits P_i over all farms i by choosing the three thresholds specifying the parasite control: D_{depop}, W_{depop}, and either ϵ_{switch} or ρ_{switch}.

2.9. Model initialization

To avoid artifacts caused by synchrony among farms, we spread out the starting times of their first production cycles over the typical duration of one production cycle: therefore, we start each of the 10 farms one after the other with time gaps of 10 weeks. Each farm is stocked with N_0 fish and infested with 10,000 drug-sensitive parasites and 2000 drug-resistant parasites. Before starting to collect the results, the model is equilibrated for 400 weeks.

2.10. Model calibration

We could obtain most of parameters from existing literature cited in Table 2. Unless otherwise stated, economic parameters apply to the year 2016 because many of them could only be obtained from a 2017 report (Iversen et al., 2017). The drug considered is emamectin benzoate, the most frequently administered anti-parasite drug in Norwegian salmon aquaculture since 2016 (Sommerset et al., 2023). Below we explain the derivation of those parameters that could not be directly obtained from the sources.

2.10.1. Critical proportion θ_{min} of cumulatively surviving fish to trigger termination of production cycle and maximum number t_{cycle} of weeks in fish production cycle

These parameters are set well outside the characteristics of normal production cycles (about 80 % and 70 weeks, respectively), such that they become effective only if parasite control fails and fish show greatly reduced growth and/or survival. Consequently, they affect only results on the counterfactual scenarios with failed parasite control shown in Fig. 2 (first and third rows).

2.10.2. Initial fish weight W_0

Size of the salmon released in sea cages varies considerably, from under 100 g to several hundreds of grams. We chose to use "large smolts" that tolerate salmon louse better. This agrees with the general trend towards stocking with larger fish in Norwegian salmon aquaculture (Ytrestøyl et al., 2023).

2.10.3. Asymptotic maximum fish weight W_{max}

Calculated as the average for the "central region" in Table 2 of Thyholdt (2014).

2.10.4. Coefficient of fish growth curve ω

Calculated using equation $\omega = exp(-kT \bullet 1\,\text{w})$ (see the Supplementary methods) with $k = 0.15\ \text{week}^{-1\circ}C^{-1}$ and $T = 8.7^{\circ}\text{C}$, the averages for the last two years in the "central region" in Table 2 and Table 4, respectively, of Thyholdt (2014).

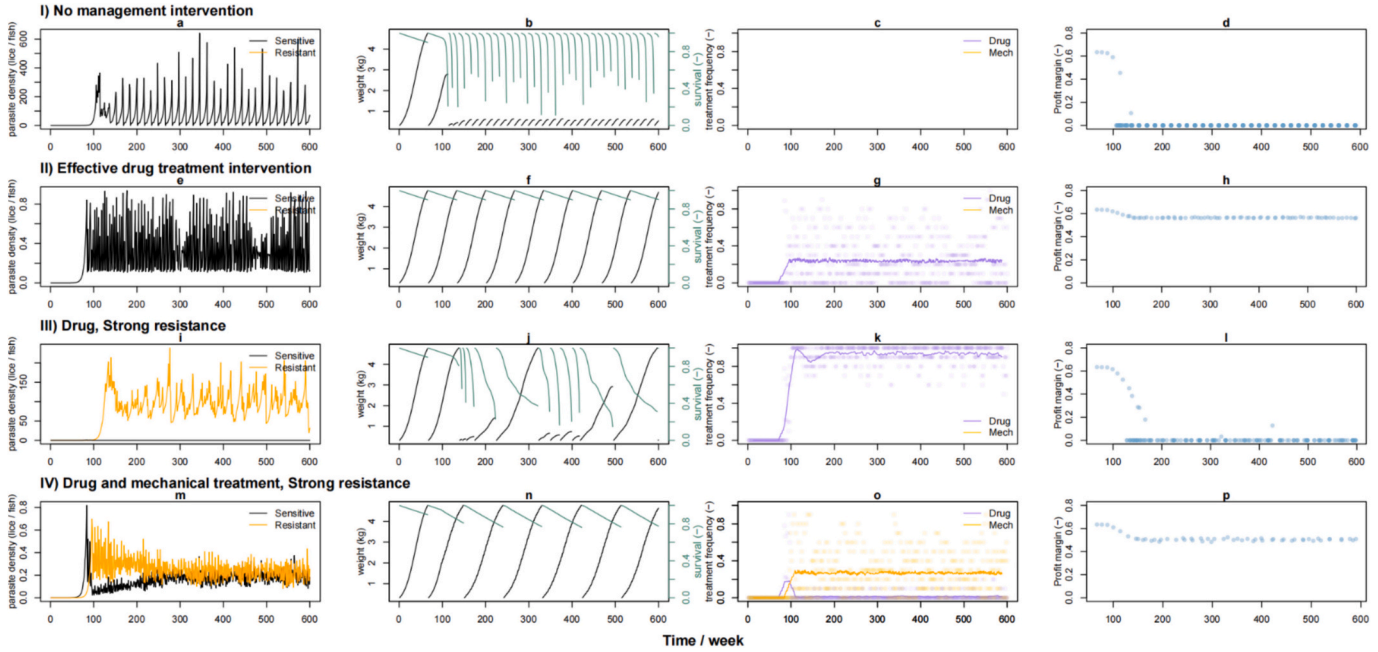

Fig. 2. Model-predicted developments in a collection of aquaculture farms under different scenarios of parasite control. The columns show how parasite density (a, e, i, m), fish weight and survival (b, f, j, n), treatment frequency (c, g, k, o), and profit margin (d, h, l, p) develop over time under four scenarios. First row: Counterfactual scenario without management interventions, with the parasite ruining the farming operations; Second row: Before drug resistance spreads, drug intervention is effective in controlling the parasite; Third row: After drug resistance spreads, the drug loses its ability to control the parasite; Fourth row: A combination of drug treatment and mechanical treatment can control the parasite even when drug resistance is present.

2.10.5. *Sensitivity* δ_{gr} *of fish growth to parasite load*

Estimated using eq. $\left(1+exp\left(\delta_{gr}\left(P_i(t)-P_{gr50}\right)\right)\right)^{-1}$ fitted with the non-linear least squares estimation to fish growth and parasite load data in Fig. 2 of Fjelldal et al. (2022).

2.10.6. *Fish natural survival* s *per week*

Monthly mortality probability of 0.5 % (Oliveira et al., 2021) converted to weekly survival as $(1–0.005)^{(7/30)}$.

2.10.7. *Sensitivity* δ_{surv} *of fish survival to parasite load*

Estimated using eq. $\left(1+exp(\delta_{surv}(P_i(t)-P_{surv50})\right))^{-1}$ fitted with the non-linear least squares estimation to fish mortality and parasite load data in Table 5 of Fjelldal et al. (2020).

2.10.8. *Fecundity* f *of a drug-sensitive parasite*

Calculated by dividing the fecundity per reproductive cycle (2 egg strings with 285 eggs each) with average reproductive cycle length (218 egg strings produced by 44 females over their average lifespan of 52 days) (Heuch et al., 2000), giving about 380 eggs week^{-1} (of which half are assumed to be females).

2.10.9. *Relative cost* q *to parasite of drug resistance*

Espedal et al. (2013) did not find statistically significant fecundity cost, but the results presented in their Fig. 4 are consistent with a small cost of about 10 %.

2.10.10. *Probability* m *of juvenile parasite transitioning to adult stage per week*

Heuch et al. (2000) report mean time of 57 days from infection to first egg strings. This corresponds to weekly maturation probability of 1/(57/7 week) ~ 0.12 week^{-1}.

2.10.11. *Death probability* d_{dr} *of drug-sensitive parasites exposed to drug treatment*

Studies conducted before the spread of emamectin benzoate resistance suggest drug effectiveness between 59 % and 95 %, with most estimates closer to the upper end of this interval (Stone et al., 1999, 2000; Armstrong et al., 2000). We take 90 % as a representative value.

2.10.12. *Strength* r *of drug resistance in parasites*

Strength of resistance is not directly reported in any study, but Espedal et al. (2013) report that the half-maximal effective concentration (EC_{50}) of emamectin benzoate is about 2–5 times higher in drug-resistant than in drug-sensitive salmon lice. Aldrin et al. (2023) report that the realized efficacy in 2017–2020 was 35 %. If $d_{dr} = 0.9$ (see above) and one-third of the lice are drug-sensitive, then the strength of resistance is 0.9.

2.10.13. *Death probability* $d_{J,mech}$ *of juvenile parasites exposed to the mechanical treatment*

Median value of estimates reported for two different mechanical systems by Furberg (2022) is about 0.7.

2.10.14. *Sample size* n_{sample} *for estimating proportion of resistant parasite*

In the surveillance program for resistance in salmon lice in Norway, the resistance is estimated with bioassays is consisting of three groups of 6–59 lice each (Helgesen et al., 2023). This corresponds to approximately 100 lice per bioassay. As the hypothetical more precise case, we assume that the sample size could be increased to 500 lice.

2.10.15. *Threshold parasite density* D_{crit} *for triggering parasite-control measures*

In the Norwegian regulation, the threshold is defined as 0.5 mature female louse per fish (Nærings- og fiskeridepartementet, 2012). Assuming equal sex ratio, this corresponds to 1 adult louse per fish.

2.10.16. *Relative price* $e_{sell,j}$ *of fish in price class j*

Based on the NASDAQ Salmon Index (NQSALMON), available from https://salmonprice.nasdaqomxtrader.com/public/report and calculated as an average of weekly relative prices from 12 different weeks between January 2017 and August 2023. Price for fish with gutted

weight less than 1 kg is not available and is set to zero.

2.10.17. Autocorrelation coefficient α, standard deviation σ of the probability of entering a farm, baseline probability g_0 of entering a farm, and death probability $d_{A,mech}$ of adult parasites exposed to mechanical treatment

For these parameters, no good empirical estimates are available. We calibrate them such that parasite density and profit margin are in good agreement with Norwegian data from 2016, with about 0.4 adult lice per fish (Sommerset et al., 2023) and a profit margin of about 0.36 (Directorate of Fisheries, 2023), respectively. For this calibration, we use the scenario illustrated in the bottom row of Fig. 2, in which parasite control is based on the drug and mechanical treatments, with the drug effectiveness threshold ϵ set at 0.5. While the autocorrelation coefficient α and the standard deviation σ have negligible effects on the parasite density and the profit margin, they are set to provide plausible, moderately temporally correlated fluctuations. The death probability $d_{A,mech}$ of adult parasites exposed to mechanical treatment varies widely, between 50 % and 100 %, but most estimates are in the range 80–95 % (Furberg, 2022). We take a value from this range that, together with baseline probability g_0 of entering a farm, for which no prior information is available, gives a good match with empirical observations.

3. Results

3.1. Adverse biological and economic consequences of salmon louse require management

If left unmanaged, the salmon louse has the potential to cause serious damage to salmon aquaculture, with poor survival and growth of the fish (Fig. 2b). This leads to economic losses (Fig. 2d).

If an effective anti-parasite drug is available, it is possible to keep parasite density at a low level with low costs (Fig. 2e), which allows the fish to have high survival and growth (Fig. 2f). In particular, feed-based drugs are cost-effective, which allows the operation to be highly profitable, despite the parasite (Fig. 2h).

The challenge is that over time, the salmon louse develop resistance against drugs – as has happened repeatedly in the past. If there are no alternative treatments and the resistance is effective, the parasite again leads to a complete loss of profit (Fig. 2l).

If effective non-drug treatment exists, the combination of non-drug treatment and drug treatment can effectively control the parasite density even when drug resistance is present (Fig. 2m). The downside of non-drug treatments, here a mechanical treatment, is that they cause additional mortality, lower growth rate in the fish (Fig. 2n) and high operational costs. Although this is reducing the profit, the operation remains profitable (Fig. 2p). The rest of this paper is focused on how to best combine drug treatment and complementary non-drug measures to control the parasite.

3.2. When using drugs for louse management, the spread of drug resistance is unavoidable

We consider whether a combination of three parasite control measures, drug treatment, mechanical treatment, and depopulation, can control drug resistance while maintaining a good economic performance. A management strategy is defined by three parameters that determine which parasite control measure to use (Fig. 1): a drug-effectiveness threshold that determines when the farmers have to switch away from the drug treatment and a fish-weight threshold and a parasite-density threshold that jointly determine, if either one is exceeded, when the farmers have to perform depopulation.

When the farmers use drugs at least once at the beginning of the production cycle to probe the degree of resistance among the parasites, there is no management strategy that could keep the resistant parasites at a low level (Fig. 3, see Fig. S1 and S2 for higher effectiveness thresholds). As expected, there is a positive correlation between drug

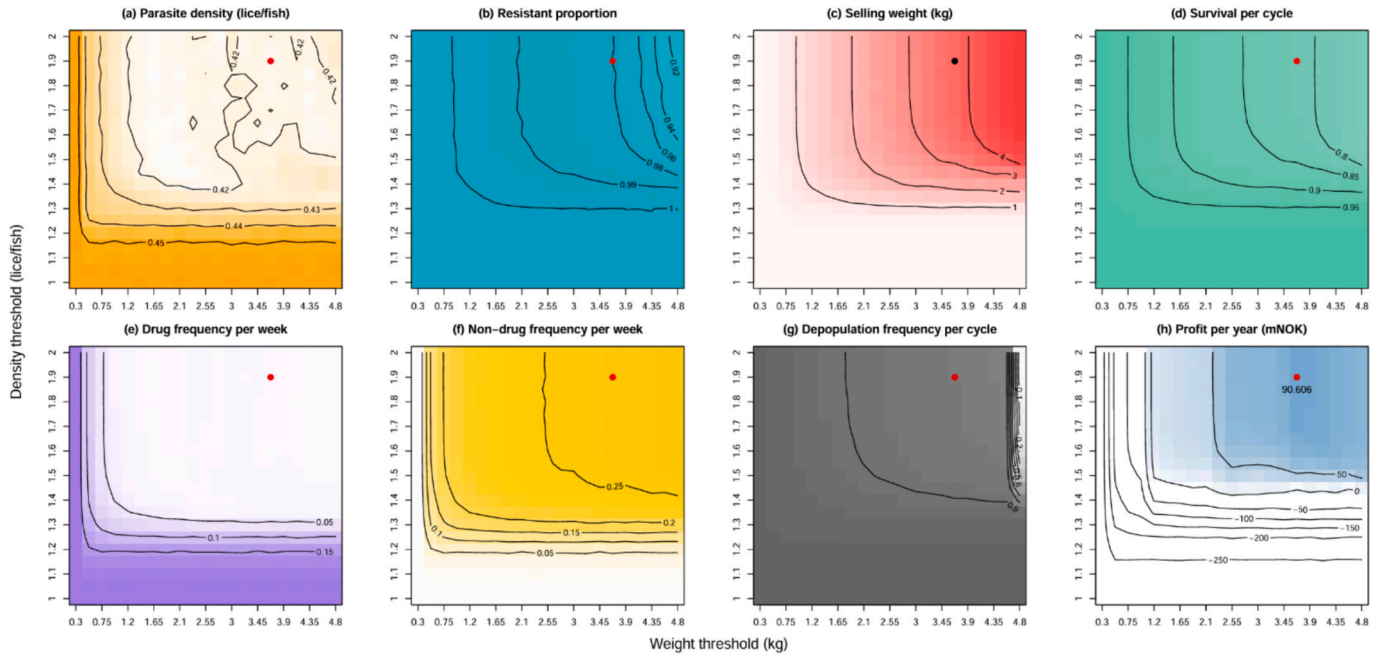

Fig. 3. Contour plot showing the influence of different parasite-control strategies on fish-farming operations. We considered farmers who use a drug to control the parasite until drug effectiveness ϵ (proportion of the parasites killed by a single drug treatment) drops below a critical threshold ϵ_{switch} and then switch to a non-drug (mechanical) treatment. The production cycle may be ended prematurely by depopulation; depopulation is triggered when the fish weight is higher than the weight threshold W_{depop} (horizontal axis) or when the parasite density is higher than the density threshold D_{depop} (vertical axis). The panels show the consequences of different parasite-control strategies on the parasites (a, b), the farmed fish (c, d), treatment frequency (e, f, g), and economic performance (h). Here effectiveness threshold $\epsilon_{switch} = 0.1$ is used, but the results are not sensitive to this parameter (see Fig. 4). The displayed values are means over a 200-week period, after an initial transient of 400 weeks. Color scale is adjusted independently for each panel, with white corresponding to zero and most separated color to panel specific maximum. The red dot indicates the optimal profit. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

use and the proportion of resistant parasites (Fig. 3b). The proportion of resistant parasites is the lowest when the non-drug treatment is the main management measure and the weight threshold for depopulation is high, such that depopulation is rare (Fig. 3g).

The most profitable management strategy to control the parasite, indicated by the red dot in Fig. 3, primarily relies on the mechanical treatment. Because this treatment reduces fish growth rate and survival, it is optimal to terminate the production cycle at a lower fish weight than in the absence of a parasite (Fig. 3c). The profits are not sensitive to exactly which management strategy is used, as long as depopulation is not triggered too early.

Our results suggest that using depopulation to control the parasite leads to high drug resistance and poor economic performance (Fig. S3). In practice, the parasite density can trigger depopulation only when the depopulation threshold is set very low. This will lead to early termination of the production cycle. When the production cycles are short, the drug use frequency is relatively high, which leads to a higher resistant proportion.

3.3. Costly drug resistance has economically beneficial aspects

Once lice have become resistant to the drug treatment, the actual proportion of resistant lice has only modest consequences for the parasite's population dynamics and the farms' economic performance. When the drug-effectiveness threshold is varied, the highest profit occurs at the threshold implying maximal drug use before switching to non-drug treatments, which corresponds to the highest resistant proportion. This suggests that, if drug resistance cannot be avoided, the next-best option is to take advantage of its beneficial aspect, the cost of resistance. Specifically, we assume that resistant parasites produce fewer eggs, leading to lower total egg production (Fig. 4c), despite slightly higher parasite density (Fig. 4d). This can offset the negative effect of the drug becoming less effective.

The beneficial aspect of drug resistance becomes more evident with a hypothetically higher cost of resistance ($q = 0.25$; orange curves in Fig. 4). Compared to the default cost of resistance ($q = 0.1$), a higher cost of resistance causes the resistant proportion to decline faster with an increasing drug-effectiveness threshold, making the beneficial aspects of resistance more prominent in terms of economic performance (Fig. 4a) and reduced egg production (Fig. 4c). This allows for more cost-effective parasite management relying more on the low-cost drug treatment and less on the costly non-drug treatment. Conversely, a lower cost of resistance ($q = 0.05$; blue curves in Fig. 4) diminishes the beneficial aspect of drug resistance. A lower cost leads to higher resistant proportion and parasite control relying more on non-drug treatments.

When resistance is costly enough (i.e., $q = 0.25$), it becomes possible to push the resistant proportion almost to zero by using a high drug-effectiveness threshold (Fig. 4b). This implies that the farmers use the drug only once per production cycle, switching to the non-drug treatment afterward. While such a near-eradication of drug resistance is attractive in principle, it actually causes an abrupt decline in profit (Fig. 4a) and an abrupt increase in the non-drug treatment frequency (Fig. 4f). This happens because, as long as the resistant proportion is low, the drug treatment is cost-effective. Therefore, using this cost-effective drug treatment only minimally causes the resultant economic benefits to remain unrealized.

If the cost of resistance is sufficiently low ($q = 0.05$), the resistance proportion is always high (Fig. 4b) because the selection against the

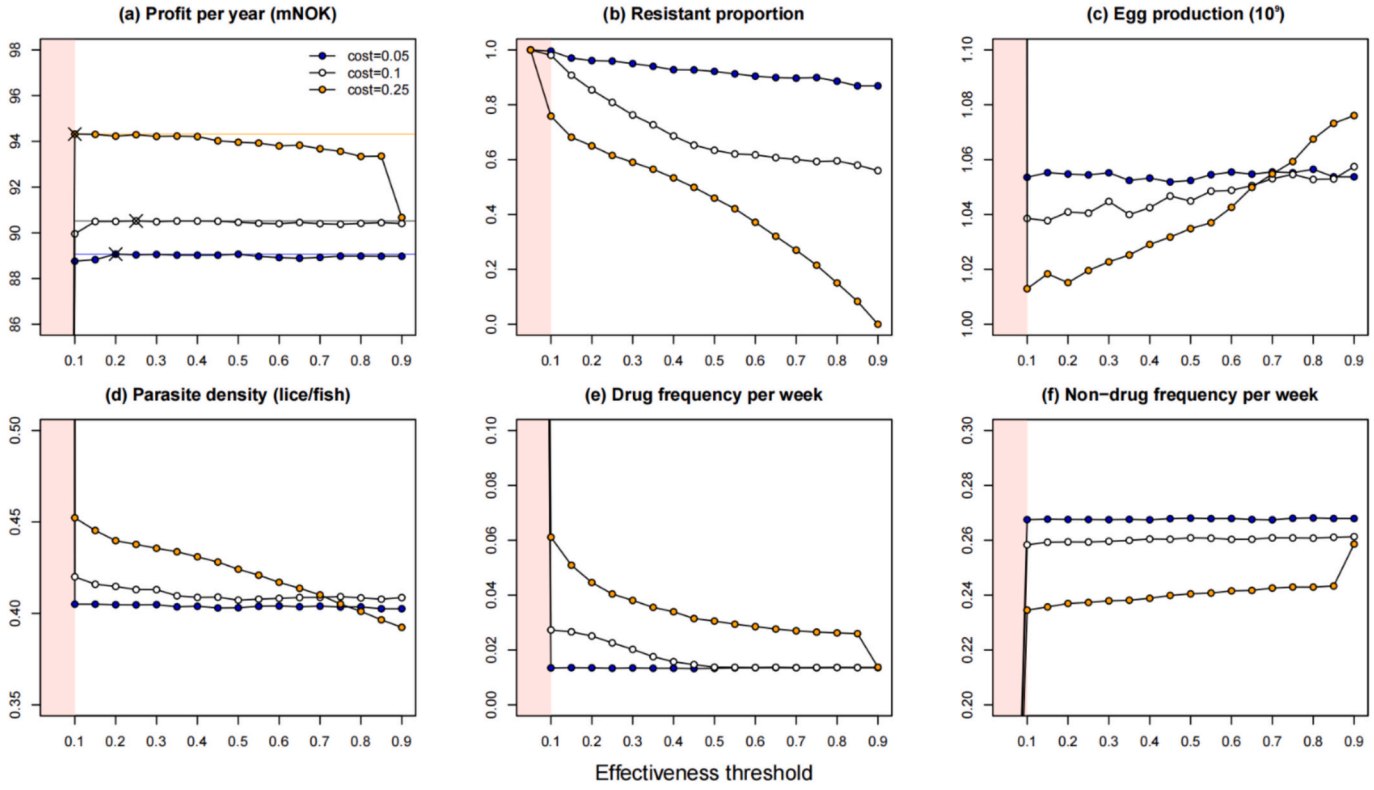

Fig. 4. Influence of different effectiveness thresholds ϵ_{switch} on fish farming operation. Effectiveness ϵ is the proportion of the parasites killed by a single drug treatment; when the effectiveness drops below a critical threshold, the farmers switch to a non-drug (mechanical) treatment and possibly depopulation. The figure shows the consequences of different effectiveness thresholds on profit (a), resistant proportion (b), egg production (c), parasite density (d), and treatment frequency (e, f) for economically optimal depopulation thresholds based on 200 replicates. The results are shown for low ($q = 0.0.5$), medium ($q = 0.1$), and high ($q = 0.25$) fecundity cost of resistance. Because drug resistance is not complete ($r < 1$), the effectiveness can never reach zero. With our default parameter values, the lowest possible drug effectiveness is $d_{dr}(1 - r) \approx 0.09$, hence only drug is ever used for effectiveness thresholds below this value (shaded area). The cross sign and horizontal line in (a) indicate the maximum profit, which is achieved at the drug effectiveness threshold that corresponds to the lowest reachable drug effectiveness.

drug resistance is weak and the parasite population becomes dominated by resistant parasites even when the drug is used only once per production cycle. The little variation in drug resistance that remains no longer has significant economic consequences (Fig. 4a).

3.4. Neither minimum nor maximum resistances are economically optimal

Our results suggest that when farmers must use drug to know the resistant proportion of the lice on their farm, it is not economically optimal to push the resistant proportion to the lowest achievable level (Fig. 4ab). We investigate this result further by considering a counterfactual scenario in which farmers can directly estimate the resistant proportion of the lice on their farm through a sample of lice, without probing it with drug treatment, and use a resistant-proportion threshold instead of the less precise drug-effectiveness threshold. This leads to a strong correlation between the resistant-proportion threshold and the actual resistant proportion (Fig. 5b), making the resistant proportion directly manageable.

Having more direct information on the resistant proportion of the lice is economically beneficial: compared to the resistant proportion estimated through drug application (Fig. 4a), the profits increase, especially when the cost of resistance is high (Fig. 5a). By making the information more precise through a larger sample size brings further benefits (thick and thin lines in Fig. 5a).

Even with direct information on the resistant proportion, pushing the resistant lice towards eradication brings no clear economic benefits (Fig. 5a): at the economic optimum, the resistant proportion is about 50 % for the default cost of resistance ($q = 0.1$). However, the profits are insensitive to the resistant-proportion threshold unless the threshold is either high or very low. In particular, a complete eradication would require abandoning the drug treatment, which is economically disadvantageous.

Considering a cost of resistance in excess ($q = 0.25$) of its empirically-motivated default value ($q = 0.1$) again makes the beneficial aspects of resistance more visible: the maximum profit increases by more than 5 % and the economically optimal management relies more on the drug treatment and less on the mechanical treatment (Fig. 5ef). The economic optimum corresponds to an even higher proportion of drug-resistant parasites. Conversely, when the cost of resistance is lower ($q = 0.05$) than the default value, the profits and optimal proportion of drug-resistant parasites are reduced.

3.5. Economic profitability trades off with animal welfare

Our results suggest that economically optimal parasite management should rely heavily on non-drug treatments, here represented by the mechanical treatment. This is potentially problematic from an animal-welfare perspective: mechanical treatment is stressful for the fish, reduces their growth, and increases their mortality. The latter is visible as the negative association between the mechanical-treatment frequency and fish survival in Figure 3df.

Animal-welfare concerns could be addressed by mandating a minimum allowed survival of fish per production cycle or a maximum allowed frequency of the mechanical treatment. However, improving animal welfare through such measures is potentially very costly. Mandating a survival improvement as small as from 80 % to 85 % would already reduce the profit by 19 % (Fig. 6b). Similarly, mandating a moderately constraining maximum mechanical-treatment frequency of 0.25 would already reduce the profit by 23 % (Fig. 6c). Larger

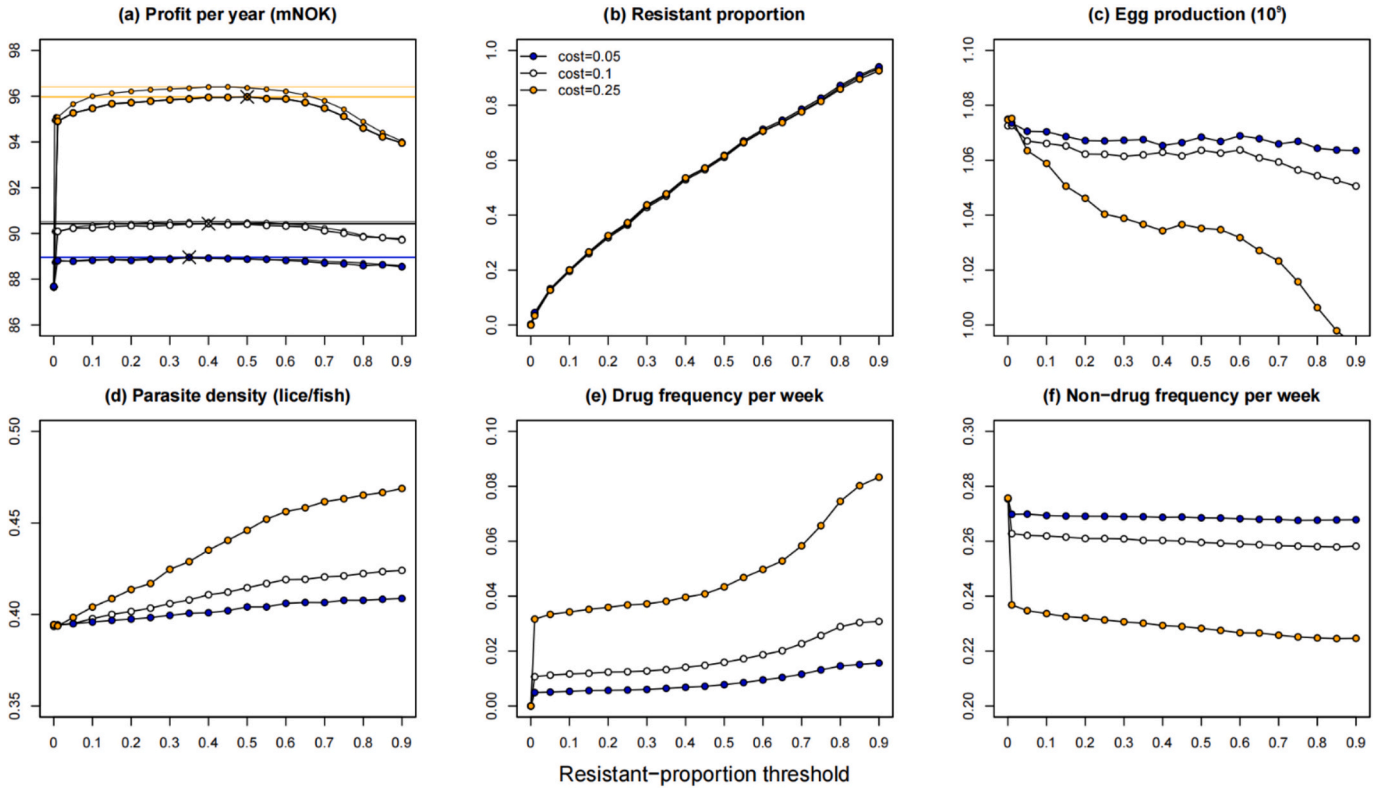

Fig. 5. Influence of different resistant-proportion thresholds ρ_{switch} on fish farming operation when the resistant proportion ρ is estimated through a sample of 100 lice. When the estimated resistant proportion ρ exceeds a critical threshold, the farmers switch to a non-drug (mechanical) treatment and possibly to depopulation. The figure shows the consequences of different resistant-proportion thresholds on profit (a), resistant proportion (b), egg production (c), parasite density (d), and treatment frequency (e, f) for economically optimal depopulation thresholds based on 200 replicates. The results are shown for low ($q = 0.05$), medium ($q = 0.1$), and high ($q = 0.25$) fecundity cost of resistance. The cross sign and horizontal line in (a) indicate the maximum profit for each level of the fecundity cost of resistance. The thin lines with small dots in panel (a) indicate the profit when the sample size is increased to 500 lice.

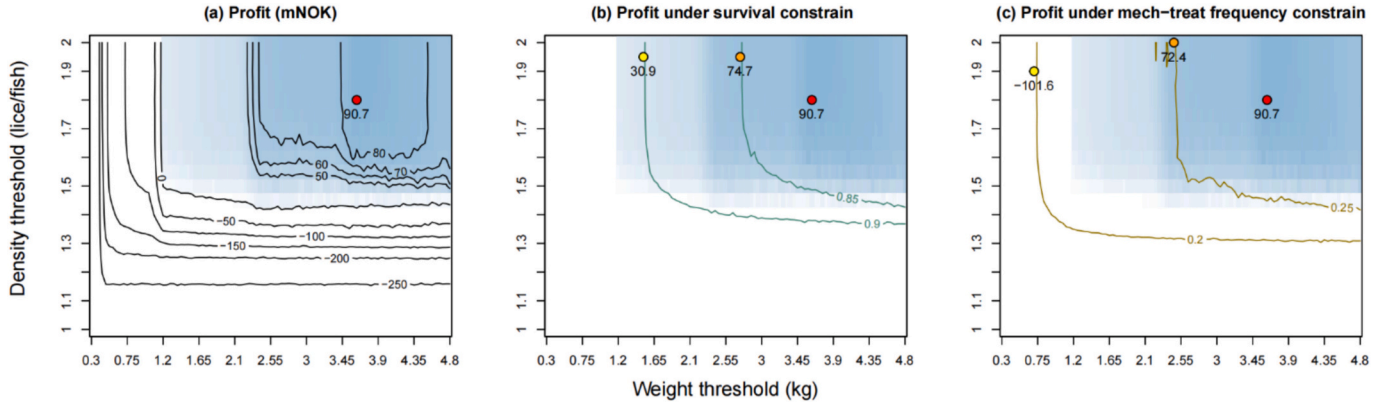

Fig. 6. Influence of different restrictions aimed at improving animal welfare on profits (mNOK per year). The controls for switching from drug to non-drug treatment and for triggering depopulation are the same as in Fig. 2. The figure shows the profit without any welfare restrictions in (a), when a minimum survival (0.85 or 0.9 per production cycle) is prescribed (b) (survival is increasing downwards and to the left, see Fig. 3d), and when a maximum mechanical treatment frequency (0.2 or 0.25 per week) is prescribed in (c) (frequency is decreasing downwards and to the left, see Fig. 3f). The optimal profit under specific restrictions is indicated by the different color of the dot. The red dot stands for the profit without animal-welfare restrictions, orange dot for the profit under moderate animal-welfare restrictions, and yellow dot for the profit under strong animal-welfare restrictions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

improvements in animal welfare would lead to even greater economic losses.

4. Discussion

Here we have analyzed economically optimal strategies to manage drug-resistant parasites in a system of fish farms. We found that even with a combination of drug treatment, mechanical treatment, and depopulation, the spread of drug resistance is inevitable in an open-cage system. This is not a mere technical challenge: it may not even be economically beneficial to drive the resistant proportion to the lowest possible level. This finding underscores the complexity of managing parasites in such systems, the importance of using quantitative models for this purpose, and the additional insights to be gained from jointly considering multiple treatments.

Recent trends in salmon-louse management in Norway are in qualitative agreement with our model predictions. First, the model predicts that, in the presence of drug resistance, drugs can no longer serve as the primary means of controlling the parasite. Indeed, because of widespread drug resistance, there has been a general trend towards parasite control that relies less on drug treatments and more on non-drug measures (Overton et al., 2019; Barrett et al., 2022). Second, because of reduced fish growth and survival caused by the mechanical treatments used to combat salmon louse, our model predicts that lower slaughter weights become optimal. This agrees with the documented trend towards reduced slaughter weights (Barrett et al., 2022). Third, our model results indicate that drug treatments should not be abandoned even when they partly lose their effectiveness due to drug resistance. In accordance with this, significant amounts of anti-parasite drugs continue to be used in Norwegian salmon aquaculture (Myhre Jensen et al., 2020; Sommerset et al., 2023), particularly for small fish (Barrett et al., 2022).

Our study is the first bioeconomic analysis of the management of salmon louse when drug resistance is present. Our model predicts that the economically optimal parasite-management strategy in the presence of drug resistance involves a combination of three parasite-control measures. Each of the three measures contributing to the optimal combination plays a different role after infestation: mechanical treatment serves as the primary measure to reduce louse infestations, depopulation achieves shorter production cycles that become optimal under reduced salmon growth and survival resulting from frequent mechanical treatment, and drug use not only provides parasite control but also keeps the drug-resistant parasites prevalent. That the last function can be beneficial has hitherto been unrecognized.

Even though drug resistance has been a longstanding challenge in salmon aquaculture, many studies of parasite-management strategies have, until recently, ignored it, instead assuming that drug efficacy remains constant over time (Revie et al., 2005; Liu and Bjelland, 2014; Adams et al., 2015; Abolofia et al., 2017; Kragesteen et al., 2019, 2023; Godwin et al., 2021). This is perplexing given that all but one of these papers mention drug resistance, at least in passing, and already Adams et al. (2015) mentioned it as “a pressing topic for investigation”. We are aware of only four papers that have considered the management consequences of drug resistance in salmon louse (Murray, 2011; Coates et al., 2022, 2023; Trombetta et al., 2023). Their main characteristics are summarized in Table S1. These papers have aimed at identifying, first, key factors affecting salmon-louse abundance and resistant proportion, and second, management scenarios that could allow for maintaining louse densities at acceptable levels. In terms of resistance evolution, they reach conclusions that broadly agree with ours: whenever drugs are used, avoiding evolution of drug resistance is difficult. The preceding studies have not, however, attempted to identify management strategies that are optimal from bioeconomic or veterinary perspectives, instead, they have compared small numbers of alternative scenarios. While Murray (2011) and Trombetta et al. (2023) included simplified accounting of some costs of salmon-louse infestations, Coates et al. (2022, 2023) did not include any economic considerations.

Our results show that the fitness cost of drug resistance, even when it is relatively low, can have important implications for parasite management: it may not be economically beneficial to minimize drug use so as to drive resistance to the lowest possible level. This is because resistant lice in our model have slightly reduced fecundity, which means that fewer mechanical treatments are needed to control drug-resistant parasites than drug-sensitive ones. Some earlier modeling studies have chosen to overlook the cost of drug resistance (Coates et al., 2022, 2023; Trombetta et al., 2023), with the first two papers citing earlier empirical research (Fallang et al., 2004; Fjørtoft et al., 2017) that seems to rule out any major fitness cost of drug resistance. In fact, however, Fjørtoft et al. (2017) discuss a relatively rapid increase in lice sensitive to organophosphates after use of these drugs was reduced, indeed suggesting a non-negligible fitness cost of drug resistance among salmon lice in real-world conditions. The only quantitative evaluation of such fitness cost, by Espedal et al. (2013), did not find a statistically significant cost of emamectin benzoate resistance in egg production, hatching success, or offspring survival. However, they acknowledged that the cost might occur in other fitness components that were not measured in their study

and that the cost might not become evident under the laboratory conditions they have applied. Moreover, their results (Espedal et al., 2013, Fig. 5) are well consistent with a fecundity cost of about 10 %, which we have used as the default in our modeling. Murray (2011) assumed a similar cost, without citing a source. Importantly, our main results are not sensitive to the precise level of this cost.

While at the moment we do not have much certainty about the magnitude or exact nature of fitness costs of drug resistance in salmon louse, the existence of such costs is, furthermore, consistent with the general understanding that drug resistance is typically costly for any parasite (Huijben, 2022; Villa et al., 2022). Our results underscore that a better understanding of the fitness cost of drug resistance, both in salmon louse and in parasites more generally, is urgently needed and that reassessing the management consequences of such costs is inevitable.

Our model is also the first to highlight the potential beneficial aspects of drug resistance in parasites in the context of animal husbandry. Interestingly, arguments of a similar structure in human medicine and parasitology underscore the wider relevance of our results. The first mention of positive aspects of resistance we have been able to find is by Zaccarelli et al. (2004). They discovered that antiretroviral drug resistance could potentially have two benefits when fighting the HIV virus: it could reduce viral fitness, thereby decreasing the viruses' replication capacity, and it could induce so-called viral hypersusceptibility, thereby increasing the viruses' sensitivity to other drugs. The first benefit is important when it is not possible to get rid of the virus entirely, in analogy with our findings with drug-resistant salmon lice. A mechanism similar to hypersusceptibility has also been discussed in the context of cancer treatments: Gatenby et al. (2009) introduced the term "evolutionary double bind" to refer to a strategy in which one drug is used to cause an increase in the susceptibility of the evolving disease (such as cancer) to another drug. Wang and Bernards (2018) arrived at a similar idea, apparently independently, and referred to the underlying mechanism as "collateral sensitivity".

The aforementioned examples from human medicine apply to resistance evolution within single hosts. The only example of potentially beneficial resistance evolution in macroparasites utilizing multiple hosts of which we are aware is from the malaria parasite *Plasmodium*: Villa et al. (2022) found that drug resistance may reduce transmission of these parasites. Huijben (2022) pointed out that this reduction could potentially be used in disease management. Nevertheless, the recognition that drug resistance has positive aspects that could be used in disease and parasite management is still very rare, and the potentials of translating this recognition into concrete management actions, to our knowledge, remain untapped.

Like all models, our model contains simplifications that could be relaxed in future efforts. We did not account for seasonal variations, which are known to influence the growth rates of both salmon and parasites (Nordgarden et al., 2003; Coates et al., 2022) and the selling price of salmon (Forsberg and Guttormsen, 2006). We have only considered a single drug treatment, emamectin benzoate administered through the feed. Other drugs will have different effectiveness as well as economic and biological costs, especially if requiring handling of fish. We have not considered the uneven distribution of salmon lice among fish (Jeong and Revie, 2020), but given the louse densities generally well below pathological levels, this is unlikely to be important. Furthermore, the considered decision-making process could be made more realistic by giving farmers agency to make individual decisions (Kragesteen et al., 2019; Trombetta et al., 2023), possibly including coordination or social learning among the farmers. Perhaps most importantly, dispersal dynamics in our model are simple and likely not describing dispersal well in large networks of aquaculture facilities where connectivity varies. Recent research has shown that farm connectivity strongly affects the spread of both salmon louse and drug resistance (Adams et al., 2015; Coates et al., 2022, 2023; Trombetta et al., 2023). Including these insights in our bioeconomic framework is an exciting future research avenue.

In conclusion, our findings suggest that the economically optimal approach to managing drug-resistant salmon lice involves adapting to it and capitalizing on its possible positive effects. Instead of viewing drug resistance as something always to be suppressed, it can be seen as an inevitable outcome that can be managed, and to some extent, even be utilized. This perspective represents a paradigm shift in how we view and manage drug resistance in aquaculture: there is great potential in future research exploring how and when to leverage the biological and economic benefits of drug resistance for managing human and animal health.

CRediT authorship contribution statement

Duo Xu: Writing – original draft, Software, Investigation, Formal analysis, Conceptualization. **Ulf Dieckmann:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Mikko Heino:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aquaculture.2025.742578.

Data availability

Data will be made available on request.

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