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Understanding How Parasites from Farmed Fish May Influence Wild Fish Declines Using Epidemiological Modelling

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ABSTRACT

Beside various fields of its applications, in this study epidemiological modelling was used to understand how parasites from farmed fish may cause wild fish declines. Two separate strategic models were constructed addressing the transmission of micro-parasites and macro-parasites between farmed and wild fish: A SIR (Susceptible-Infective-Removed) model for micro-parasite infections and a compartmental density-dependent model for macro-parasite infestations. The results indicated that parasites originated in wild fish populations, after infecting farmed fish can cause epizootics. Subsequently, these parasites can be transmitted from farmed to wild fish and might have negative impact on the dynamics of wild fish populations. Sensitivity analysis of the basic model parameters in both models showed that model parameters, which are influenced by abiotic factors and allow passive manipulation, such as pathogen specific transmission rate (β), pathogen specific transmission rate between infected farmed and susceptible wild fish (δ), the rate of production of infective stages by an adult parasite (λ) and transmission rate between host and parasite infective stages (β) are more sensitive compared to model parameters which encompass chemical control and fallowing. This emphasizes the importance of the preventive medicine rather than intervention procedures in aquaculture aiming at eradicating epizootics caused by parasites and protecting wild fish stocks.

Keywords: Aquaculture, parasites, epidemiology, modelling, wild fish

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Kültür Balıklarından Kaynaklanan Parazitlerin Nasıl Yabani Balık Azalmalarını Etkileyebileceğini Epidemiyolojik Modelleme Kullanarak Anlaşılması

Öz: : Çeşitli uygulama alanlarının yanı sıra, bu çalışmada epidemiyolojik modelleme kültür balıklarından kaynaklanan parazitlerinin nasıl yabani balık azalmalarına yol açabileceğinin anlaşılması için kullanılmıştır. Kültür ve yabani balıklar arasındaki mikro-parazitlerin ve makro-parazitlerin yayılımına yönelik iki ayrı stratejik model geliştirilmiştir: mikroparaziter enfeksiyonlar için SIR (Sağlam-Enfektif-Geçiren) modeli ve makro-paraziter enfestasyonlar için bölümlü ve yoğunluğa bağlı model. Sonuçlar, başta yabani balık popülasyonlarında çoğalan parazitlerin kültür balıklarını enfekte ettikten sonra belirli yetiştiricilik şartları altında epizootiklere neden olabileceklerini işaret ettiler. Akabinde, bu parazitler kültür balıklarından yabani balıklara yayılabilirler ve yabani balık popülasyonlarının dinamikleri üzerinde olumsuz etkiye sahip olabilirler. İki modeldeki temel model değişkenlerinin duyarlılık analizleri, abiyotik etmenler tarafından etkilenen ve edilgen yönetime izin veren değişkenler, örneğin mikroparaziter modelde patojene özgü yayılım hızı (β) ve enfektif kültür balıkları ile sağlam yabani balıklar arasındaki patojene özgü yayılım hızı (δ) ve makroparaziter modelde erişkin parazitlerin enfektif evre üretim hızı (λ) ile parazitin enfektif evreleri ile konakçısı arasındaki yayılım hızı (β), kimyasal kontrol ve üretim alanının boş bırakılmasını içeren model parametreleri ile kıyasla daha duyarlı olduklarını göstermiştir. Bu, parazitlerden kaynaklanan epizootiklerin yok edilmesinde ve yabani balık soyunun korunmasını amaçlayan su ürünlerindeki müdahale yöntemlerinden çok koruyucu hekimliğin önemini vurgulamaktadır.

Anahtar kelimeler: Su ürünleri yetiştiriciliği, parazitler, epidemiyoloji, modelleme, yabani balıklar

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Introduction

There has been a steady growing trend in the world fish production in the last few decades, paralleled with world population growth and respectively fish consumption. According to FAO, total world fisheries production in 2020 was estimated as 177.8 million tonnes, from which aquaculture accounted for 87.5 million tonnes (FAO 2022). Whereas capture fisheries shows a relatively steady state, aquaculture production is the true contributor of growth in world fish production with a continuous growing pace of roughly 3.3% annually (FAO 2022). This expansion of the world aquaculture production can be truly regarded as a "Blue Revolution". However, the revolution can be regarded as a reality only if aquaculture growth is sustainable and does not negatively impact and endanger wild fish populations. In this respect, not only demand for fish oil and fishmeal of aquaculture industry must be considered, but also interchangeable status of disease between wild fisheries and farmed fish.

Disease in aquaculture limits the expansion of the sector with different pathogens constraining its growth (Murray and Peeler 2005). Previously existing disease in wild populations can be exacerbated in artificially reared fish due to high population densities and other stresses (Reno 1998; Murray and Peeler 2005). The problem can also be formulated as a double-edged sword where pathogens transmission from wild to farmed and vice versa takes place. Such transmission of pathogens between wild and farmed fish populations named spill-over and spillback can be true cause of emergence of infectious diseases (Krkošek 2010; Reno 1998). Moreover, disease agents which exist in wild populations, if no control measures are taken, might be magnified in farmed populations and itself become a source of pathogens for wild populations, with negligible to significant impact (Miossec et al. 2005; Murray 2009).

A substantial amount of the epizootics, which occur in wild and farmed fish populations with sometimes devastating impact, are parasitic in their nature. Parasitic disease outbreaks account for much of the economic losses in aquaculture and they might also be a cause for wild fish decline elsewhere. Understanding their establishment mechanisms is essential prerequisite for eradicating them (Guo and Woo 2009; Tokşen and Çilli 2010; Costello 2009; Munday et al. 2001; Morris 2011).

Vital tools for understanding the establishment mechanisms of parasitic disease in wild and farmed fishes are risk analysis and epidemiology. Analysing and identifying the risk factors associated with parasitic diseases and conducting epidemiological surveys is the way for prevention of mortality (Soares et al. 2013). Furthermore, focusing on risk analysis, biosecurity and supportive epidemiological studies can improve understanding of the causes of parasitic disease and leads to better management of these diseases in aquaculture and wild fish populations, subsequently informing decision making authorities and policy makers (Rodgers and Peeler 2012). Because aquaculture health issues are mostly based on population medicine, epidemiological methods are used when tackling parasitic diseases in farmed and wild fish (Georgiadis et al.2001; Beaglehole et al. 1993) and effectively implemented in order to passively reduce the risk of parasitic disease occurrence (Murray 2013). Nevertheless, epidemiology is one of the most important tools for identifying risk factors that increase the probability of parasitic disease occurrence and for optimizing the cost efficacy of any intervention or control strategy (Turnbull et al. 2011).

One of the crucial subject areas of veterinary epidemiology is theoretical disease modelling. These models offer solutions to aquatic animal health problems, estimate the impact of the parasitic disease on population level and can be appropriate where there is lack of experimental data (Peeler and Taylor 2011; Murray et al. 2011). However, epidemiological modelling has its constraints as well. Models, which are based on mathematical simulations, vary in their ability to reflect the real world where the onset of disease is a multiplicative process rather than additive process (Reno 1998). For example epidemiology of sea lice *Lepeophtheirus salmonis* (Krøyer 1838) has been regarded as multifactorial in origin with many abiotic and biotic factors interacting in a rather complex way (Revie et al. 2005). In contrast, many epidemiological models assume that any change observed in the output is solely due to the single variable change in the basic input variables and does not take into account the correlation between them (Anonymous 2015). Even the most complex models for many diseases are oversimplified, where many "guesstimated" basic disease parameters make in long run quantitative disease predictions impossible (Roberts and Heesterbeek 1993). Despite these limitations models can be used efficiently because they point important underlying relationships and hypothesises such as basic reproduction ratio (R_o), simulate thought experiments where practical experiments are impossible, highlight the importance of parameters with critical influence on onset of the diseases and eventually they are beneficial for building control strategies. For example, the evidences for farm and wild parasite sea lice exchanges are indirect because infective stages cannot be traced physically but modelling can help predict that exchange (Todd

2007). Besides, against many parasitic diseases there are no effective drugs (Guo and Woo 2009; Munday et al. 2001) and prevention is the best choice, which makes epidemiological modelling inevitable.

In this study, strategic epidemiological models were constructed to reflect spreading of more easily establishing micro and macroparasites, with direct life cycles, between farmed and wild fish populations. This study was completely theoretical one and was based on hypothetical parameter values. The latter were subsequently evaluated through sensitivity analyses in order to reveal important parameters underlying the basic transmission mechanisms of parasitic diseases between wild and farmed fish populations. This allowed different scenarios to be derived, which might lead to management policy changes.

The present study is not concerned with revealing the true cause and effect relationship responsible for the decline of wild fish populations in European seas, nor is it concerned with parameterising the specific parasitic diseases, which are very complex tasks on their own. The aim of the study is simply to build strategic models in order to understand the basic underlying facts in transmission of parasitic diseases between wild and farmed fish and whether there is any possibility of negative impact on wild fish populations from fish farming activities.

Materials and Methods

The models in the present study were based on the basic principles and differential equations developed in the epidemiological models by Anderson and May (1979a, 1979b). Because both micro and macroparasites have much shorter life span than their respective fish hosts and the duration of the epizootic is relatively shorter compared to the life duration the of the fish, the natural birth rate and death rate of the wild and farmed fish were neglected and omitted from the models in this study. Respectively, the original differential equations by Anderson and May (1979a, 1979b) were changed and simplified (Krkošek 2010).

In addition, it was also preliminary assumed that wild and farmed populations were closed populations, contacts between individuals were random (Anderson and May 1979a), the density of fish was fairly constant in time with negligible addition of new susceptible individuals to both farmed and wild fish populations and eventually farmed fish not being harvested at time of epizootics (Roberts and Heesterbeek 1993).

In both models, densities of farmed hosts were adopted as five times greater than their wild counterparts (Heuch et al. 2005). This had implications on the calculations of the basic reproduction ratio (R_o) of both models. Only densities of farmed fish populations were considered because it was assumed that farmed fish are the real focal point for epidemics.

Another basic assumption was that the physical milieu where epizootics took place was semi - closed sea bay, fjord or loch where transmission of pathogens is enhanced (Amundrud and Murray 2009; Penston et al. 2008; McKenzie et al. 2004). The contact structure of the pathogens was considered to be via water column with the aid of the flowing sea water currents (Krkošek et al. 2005; Salama and Murray 2013), escaped fish (Green et al. 2012; Costello 2006) and presence of feeding wild fish around the sea cages (Esat Çilli`s personal observation).

Estimation of the basic model parameters such as pathogen specific transmission rate, infection removal rate, the rate of production of infective stages of the macroparasites and the mortality rate of the macroparasite infective and adult stages was another sensitive issue due their multifactorial nature. For example, the disease transmission coefficient (=pathogen specific transmission rate) is one of the most difficult parameters to be estimated in any epidemiological model (McCallum et al. 2001). Attempts to calculate it have been concentrated on preliminary knowledge on host-disease behaviour, controlled experiments and deduction of the parameter by observation of real epidemics (McCallum et al. 2001). Reno (1998) proposed that the factors affecting transmission coefficient of a particular disease (=pathogen specific transmission rate) are host resistance factors such as species, age, natural immunity, induced immunity; pathogens factors such as ability to infect species, dose, vertical transmission and finally environmental factors such as population density, temperature, water flow and water chemistry.

In the models presented below, attempts were made where possible to deduce the disease model parameters from existing experimental data (Amundrud and Murray 2009; Munday et al. 2001; Morrison et al. 2004; Wagner et al. 2008; Costello 2006). However, due to the difficulties of parameter estimation mentioned above and relative lack of real epidemiological data about transmission of parasites between farmed and wild fish population, most model parameters were completely arbitrary in order to prevent numerical instability of the models. In each model arbitrary time steps were used, such that they do not denote for particular time period as hour, day or month.

The first epidemiological model attempted to explain the transmission behaviour and onset of epidemics between wild and farmed fish caused by protozoan parasites with direct life cycles such as the causative agent of amoebic gill disease

Neoparamoeba spp., microsporidian parasite such as *Loma* spp. and metazoan parasites with direct life cycle such as *Gyrodactylus* spp.

The second epidemiological model had the main aim to elucidate the epidemiology of macroparasites with direct life cycle such as the copepod parasites *L. salmonis* (Krøyer, 1838) and *Caligus elongatus* (Nordmann, 1832). According to Murray (2009), the first model in this study can be regarded as a direct density-dependent transmission model, respectively the second model as a constant open recruitment model. However, due to lack of enough mathematical information in the study of Murray (2009), for construction of the model for macroparasites differential equations developed in the epidemiological models by Anderson and May (1979a, 1979b) were used.

Microparasite Model

A compartmental density-dependent SIR (Susceptible-Infective-Removed) model consisting of series of differential equations was developed to investigate the epidemiology of microparasitic infections between farmed and wild fish. The overall schematic representation of the model is provided in Figure 1 and the description of all model parameters along with their dimensional analysis are summarised in Table 1.

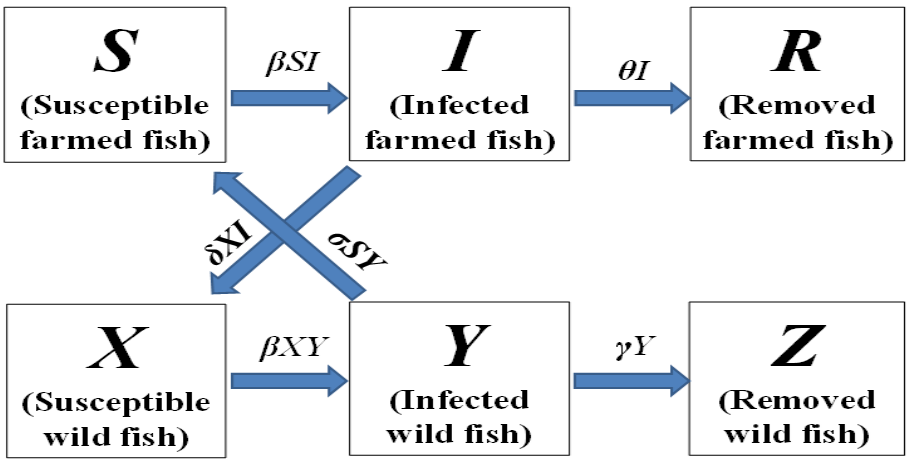

Figure 1. A schematic representation of the compartmental density-dependent SIR (Susceptible-Infective-Removed) model of microparasitic infections between farmed and wild fish (all model parameters are described in Table 1)

Table 1. Description of the model parameters and variables used in the compartmental density-dependent SIR (Susceptible-Infective-Removed) model of microparasitic infection between farmed and wild fish

Parameter symbol	Description	Dimension
S	Susceptible farmed fish density	[M]
I	Infected farmed fish density	[M]
R	Removed farmed fish density	[M]
X	Susceptible wild fish density	[M]
Y	Infected wild fish density	[M]
Z	Removed wild fish density	[M]
β	Pathogen specific transmission rate	$[M]^{-1}[T]^{-1}$
γ	Infection removal rate of wild fish	$[T]^{-1}$
θ	Infection removal rate of farmed fish	$[T]^{-1}$
δ	Pathogen specific transmission rate between infected farmed (I) and susceptible wild (X) fish	$[M]^{-1}[T]^{-1}$
σ	Pathogen specific transmission rate between infected wild (Y) and susceptible farmed (S) fish	$[M]^{-1}[T]^{-1}$

For parameter dimensions, T represents time and M represents host density.

Susceptible, infective and removed compartments of both farmed and wild fish were represented as host densities. In contrast to the viral and bacterial diseases, where hosts acquire long-lasting immunity to reinfection, in the present model it was assumed that there was no recovery from the disease. In parasitic diseases fish do not build significant immune response which can confer them

with immune resistance to microparasites (Guo and Woo 2009). The basic model parameters described in Table 1 were used to formulate the following differential equations reflecting the dynamics of the epizootic:

$$\frac{dS}{dt} = -\beta SI - \sigma SY \quad (1)$$

$$\frac{dI}{dt} = \beta SI + \sigma SY - \theta I \quad (2)$$

$$\frac{dR}{dt} = \theta I \quad (3)$$

$$\frac{dX}{dt} = -\beta XY - \delta XI \quad (4)$$

$$\frac{dY}{dt} = \beta XY + \delta XI - \gamma Y \quad (5)$$

$$\frac{dZ}{dt} = \gamma Y \quad (6)$$

Subsequently, the differential equations above on which the model was based were used for the writing the model code. The Microparasite model as it was schematically outlined in Figure 1 represented two distinct fish populations, wild and farmed denoted in the model as S (susceptible farmed fish density) and X (susceptible wild fish density). Infection started in farmed fish with gradual accumulation of infected farmed fish (I) depending on the pathogen specific transmission rate (β) between S and I. Infection spread to wild fish proportionally to the contact rate between infected farmed fish (I) and susceptible wild fish (X) which in the model was shown as δ. Epizootics in wild and farmed fish populations proceeded by cross infections between both populations (σSY and δXI) and inside the populations (βSI and βXY). Finally, infected fish in the model, both wild and farmed, were removed depending on infection removal rates θ and γ.

The fundamental concept of basic reproduction ratio (R_o) (Anderson and May 1979a; Reno 1998) was adopted to measure the number of the secondary infections caused by single infected hosts in the course of the epizootics. Basically, when $R_o \leq 1$ an epizootic cannot be established, if $R_o > 1$ epizootic will take place. Subsequently this concept proved valuable in calculating the maximum stocking density of farmed fish under which epizootic cannot be established. As it was stated above, only densities of farmed fish were considered, assuming that real focal point for epidemics were farmed fish populations. For measure of the basic reproduction ratio (R_o) of microparasites the following equation adopted from Krkošek (2010) and based on model parameters described in Figure 1 was used.

$$R_o = \frac{\beta S}{\theta} \quad (7)$$

Macroparasite Model

Similar approach as in the compartmental model for microparasites was followed in construction of the model addressing epidemiology of macroparasites with direct life cycle between wild and farmed fish. However, due to the biology of macroparasites and dynamics of the metazoan parasitic epidemics, dividing populations simply to susceptible, infected and removed was not applied (Anderson and May 1979b). Instead division was made upon the existence of five basic populations, respectively two host populations (wild and farmed fish), two adult parasites populations (adult parasites on wild and farmed fish) and one population of infective stages, which was bring into life from the reproductive contribution of the adult parasites infesting both wild and farmed fish. The evidence for only one compartment of infective stages came from the study of Todd (2007), where was claimed that there was actually only one panmictic population of sea lice in North Atlantic. Thus, during the construction of the model it was logical to assume that there is only one compartment for the infective stages. Another assumption specific for the model addressing macroparasitic epidemiology was that the distribution of macroparasites followed Poisson form rather than negative binomial, macroparasites evenly or randomly distributed rather than clumped on their hosts (k→∞, parameter k approaching infinity) (Anderson and May 1979b; Krkošek 2010). The overall schematic representation of the model is provided in Figure 2 and the description of all model parameters along with their dimensional analysis are summarised in Table 2.

All compartments in the model were represented as densities. Again as in the SIR model, it was assumed that there was no recovery from the disease as in metazoan parasitic diseases fish do not build significant immune response to confer them with immune resistance to macroparasites (Guo and Woo 2009). The basic model parameters described in Table 2 were used to formulate the following

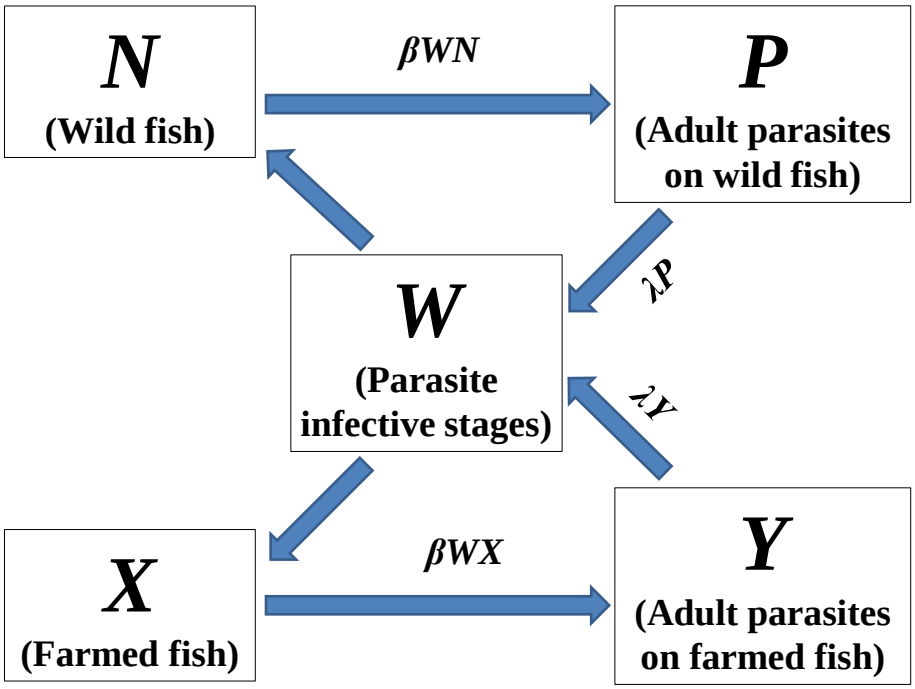

Figure 2. A schematic representation of the compartmental model of macroparasitic infestation between farmed and wild fish (all model parameters are described in Table 2)

Table 2. Description of the model parameters and variables used in the compartmental model of macroparasitic infestation between farmed and wild fish

Parameter symbol	Description	Dimension
N	Wild fish density	[M]
X	Farmed fish density	[M]
P	Density of adult parasites on wild fish	[M]
Y	Density of adult parasites on farmed fish	[M]
W	Density of infective stages	[M]
α	Parasite-induced host death rate	[M]
β	Transmission rate between host and parasite infective stages	$[M]^{-1}[T]^{-1}$
μ	Mortality rate of adult parasites on wild fish	$[T]^{-1}$
θ	Mortality rate of adult parasites on farmed fish	$[T]^{-1}$
c	Mortality rate of infective stages	$[M]^{-1}[T]^{-1}$
λ	The rate of production of infective stages by an adult parasite	$[M]^{-1}[T]^{-1}$

For parameter dimensions, T represents time and M represents host density

differential equations reflecting the dynamics of the epizootic:

$$\frac{dN}{dt} = -\alpha P \quad (8)$$

$$\frac{dX}{dt} = -\alpha Y \quad (9)$$

$$\frac{dP}{dt} = \beta WN - (\mu + \alpha)P - \frac{\alpha P^2}{N} \quad (10)$$

$$\frac{dY}{dt} = \beta WX - (\theta + \alpha)Y - \frac{\alpha Y^2}{X} \quad (11)$$

$$\frac{dW}{dt} = \lambda P + \lambda Y - cW - \beta WN - \beta WX \quad (12)$$

The differential equations above on which the model was based were subsequently used for writing the model code.

Macroparasite model, as it was schematically outlined in Figure 2 represented two distinct fish populations, wild and farmed denoted in the model as N (wild fish density) and X (farmed fish density). Infestations, depending on the transmission rate (β) started simultaneously both in farmed and wild fish

by contacts (βWN and βWX) with free swimming infective stages of the parasite (W) , which originated from adult parasites on wild fish (P). After successful infestations, infective stages of the macroparasites attached on wild and farmed fish produced adult parasite stages P and Y. Further production of infective stages (W) by adult parasites continued depending on parameter λ (the rate of production of infective stages by an adult parasite). Gradual accumulation of more infective stages (W) contributed for establishment of epizootics both on farmed and wild fish. Mortality of fish was dependent on parameter α, which in the model was denoted as parasite induced host death rate. Finally, adult parasites on farmed and wild fish were removed at mortality rates μ and θ.

As in the first model about microparasitic epizootics, the important concept of basic reproduction ratio (R_o) (Anderson and May 1979a; Reno 1998) was used to measure the number of the secondary infestations caused by a single macroparasite in the course of the epizootic. Again this concept proved valuable in calculating the maximum stocking density of farmed fish under which epizootic cannot be established. As it was stated above, only densities of farmed fish were considered, assuming that real focal point for epidemics were farmed fish populations. For measure of the basic reproduction ratio (R_o) of macroparasites the following equation adopted from Krkošek (2010) and based on model parameters described in Figure 2 was used:

$$R_o = \left(\frac{\lambda}{\theta+\alpha}\right)\left(\frac{\beta X}{c+\beta X}\right) \qquad (13)$$

Sensitivity Analysis

For the purpose of evaluating the relative importance of the model parameters in the dynamics of the modelled epizootics, the method of sensitivity analysis developed by Bode (1945) was applied. A one-at-a-time approach was followed where one basic input model parameter was changed by 1% keeping other on their default values in order to see what kind of effect it can produce in the model output. The output parameter in the first model addressing microparasitic epizootics was the maximum density of infected wild fish. The output in the second model, reflecting the macroparasitic epizootics, was the final density of wild fish. For measurement of the relative sensitivity of the model parameters following equation was used:

$$S_{x_i}^P = \frac{x_i}{P}\frac{\delta P}{\delta x_i} \qquad (14)$$

Where, $S_{x_i}^P$ was the relative sensitivity of the evaluated parameter, $\frac{\delta P}{\delta x_i}$ was the absolute change in the output in response to a 1% change in the parameter value and $\frac{x_i}{P}$ the ratio between initial output value to initial parameter value.

Writing the Model Codes and Analyses

Codes of the both models were coded in R (A Programming Environment for Data Analysis and Graphics Version 3.2.0 – The R Core Team 2015). Analyses were carried out both in R and Excel (Microsoft Excel, 2010).

Results

Microparasite Model

The simulation of the model started with initial model parameters with following values: $\beta = 0.4$, $\gamma = 0.18$, $\theta = 0.18$, $\delta = 0.02$ and $\sigma = 0.01$, densities of farmed $S = 10.0$ and wild fish $X = 2.0$ and with successful introduction of the microparasite in farmed fish with non-zero value of $I = 0.001$. The epizootic time series for the density-dependent SIR model are shown in Figure 3 where the epizootic follows typical SIR epidemic pattern. Initially, there was a sharp decrease of susceptible farmed fish density (S) as more effective contacts were made and sharp increase in infected farmed fish density (I), with gradual increase of removed farmed fish (R). Almost paralleled in time, with epizootics in farmed fish started the epizootic in wild fish, where microparasites from infected farmed fish were transmitted to wild susceptible fish depending on pathogen specific transmission rate δ. With increasing the infection level in wild fish the opposite trend also proceeded. In other words transmission of the pathogens, depending on pathogen specific transmission rate σ, took place between wild infected and farmed susceptible fish. Finally, the epizootics died off at which the lines in the graph were levelled off.

Sensitivity analysis of the model at default values of the basic parameters was performed (Figure 4). The analyses showed that the most sensitive parameter affecting the density of wild infected fish (denoted in the model as Y) was γ (infection removal rate of wild fish), followed by β (pathogen specific transmission rate), δ (pathogen specific transmission rate between infected farmed (I) and susceptible wild (X) fish) and θ (infection removal rate of farmed fish). Parameter σ (pathogen specific transmission rate between infected wild (Y) and susceptible farmed (S) fish) did not have significant effect on the model outputs. The only parameter in the model which allows direct human intervention such as fallowing, chemotherapeutic applications and

vaccination, with aim to eradicate the epizootic, respectively parameter θ, did not prove to be the most sensitive parameter of the model. In order to evaluate further the importance of this parameter, the model was simulated under three different scenarios (=different epizootic conditions): A) scenario 1: keeping the initial values of all parameters except β, where β was reduced to 0.2 pointing less acute epizootic and less force of infection; B) scenario 2 where the initial values of all parameters were kept except θ, respectively $\theta = 1.2$; C) scenario 3 where again the initial values of all parameters were kept except θ and β, respectively $\theta = 1.2$ and $\beta = 0.2$ (Figure 4).

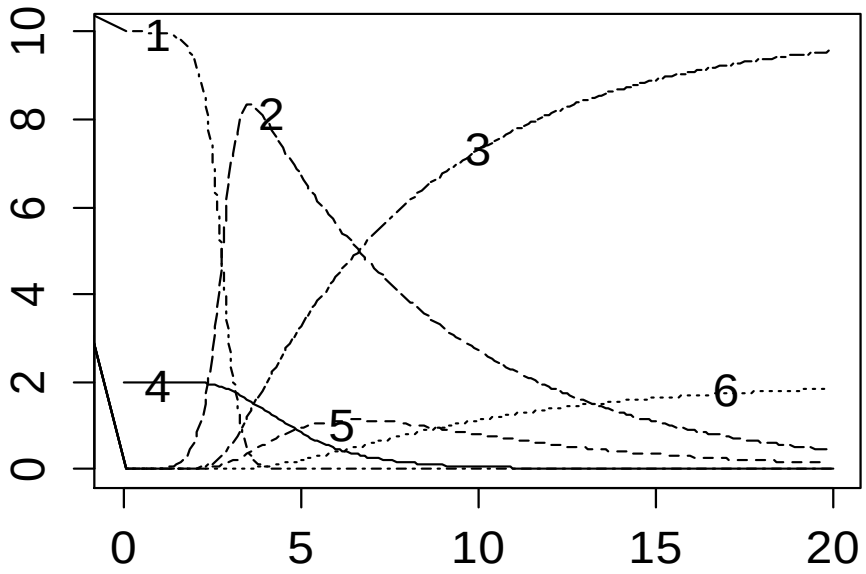

Figure 3. The epizootic time series for the Microparasite model. Line 1 - susceptible farmed fish density (S), line 2 - infected farmed fish density (I), line 3 - removed farmed fish density (R), line 4 - susceptible wild fish density (X), line 5 - infected wild fish density (Y), line 6 - removed wild fish density (Z)

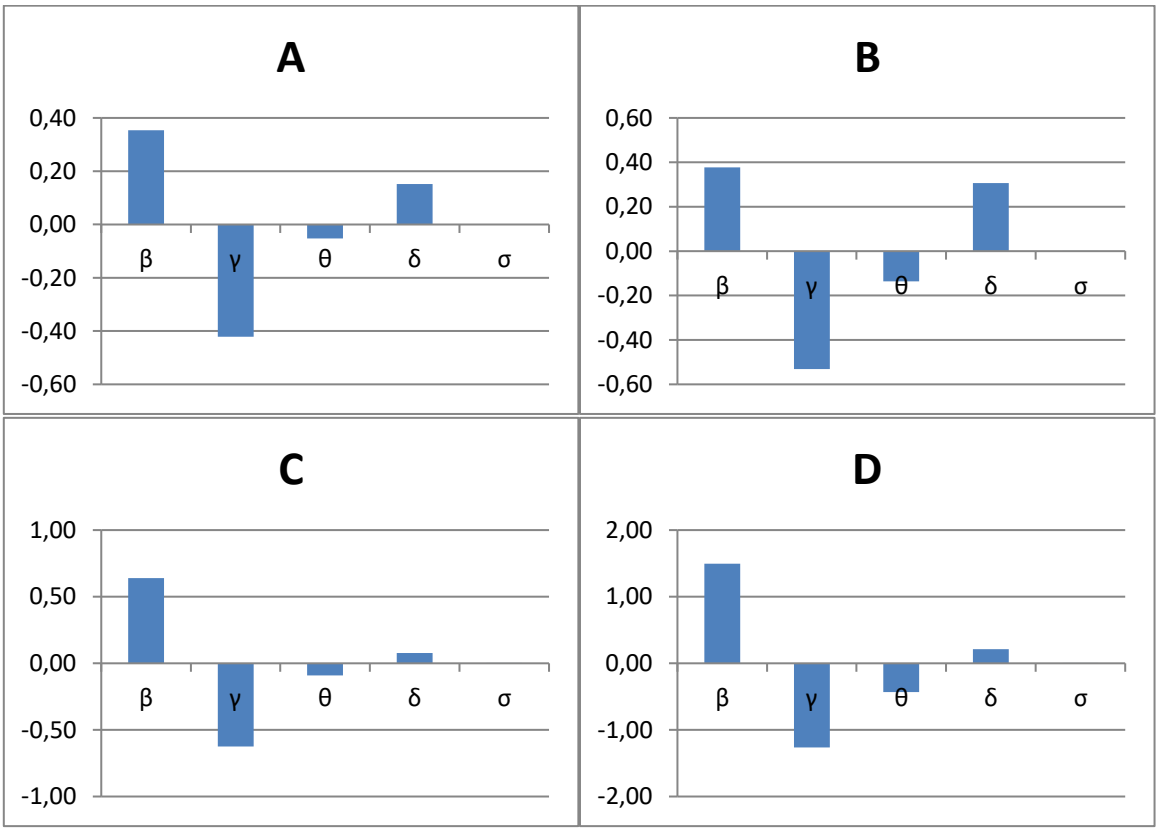

Figure 4. Sensitivity analysis results for the Microparasite model. The panels are: A) model simulated with the initial parameter values; B) scenario 1 - the initial values of all parameters kept except β, where β reduced to 0.2; C) scenario 2 where the initial values of all parameters kept except θ, respectively $\theta = 1.2$; D) scenario 3 where again the initial values of all parameters kept except θ and β, respectively $\theta = 1.2$ and $\beta = 0.2$

In scenario 2 and 3, θ (Infection removal rate of farmed fish) was increased near 6 times ($\theta = 1.2$) indicating more intense intervention procedures in order to eradicate the disease from farmed fish and shorter duration of the disease.

Sensitivity analysis for each scenario was carried out as shown in Figure 4. There was no change in the ranking of the sensitivity of each parameter in scenario 1. However, paralleled with increase in its value, the relative importance of θ (infection removal rate of farmed fish) increased in scenarios 2 and 3. Therefore, infection removal rate of farmed fish became the third most sensitive parameter.

Nevertheless, θ still proved to have relative impact on reducing the density of wild infective fish as shown in Figure 5, where the model was simulated with different θ values representing more effective removal rate of infective farmed fish.

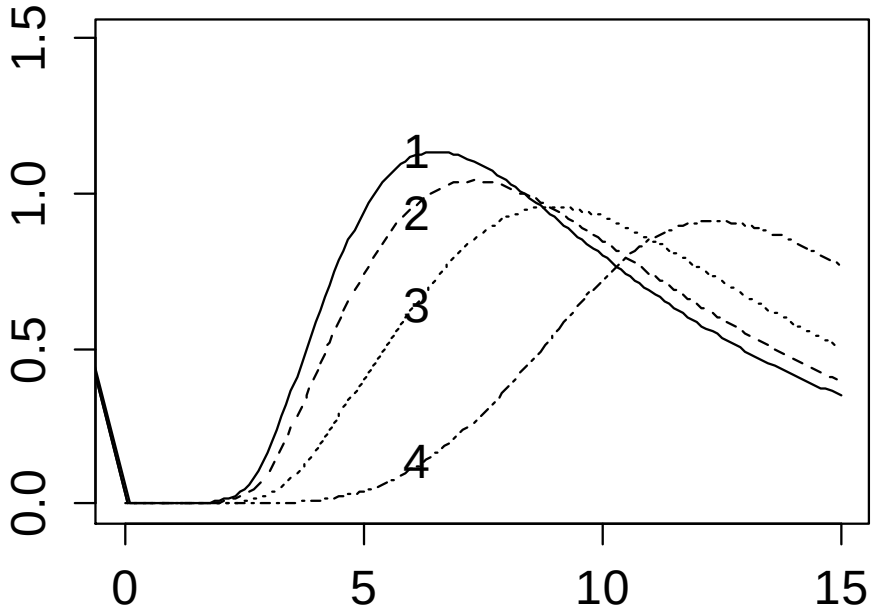

Figure 5. Simulation of the Microparasite model under different values of θ, while keeping other parameters in their default values. Line 1: $\theta = 0.18$; line 2: $\theta = 0.54$; line 3: $\theta = 1.26$; line 4: $\theta = 2.52$. Each line represents the time series of wild infected fish densities.

From the practical viewpoint, it was important to know the maximum density of farmed fish under which epizootic cannot be established. Therefore, in order to calculate the maximum density of stocked (S) fish under each scenario, the basic reproduction ratio (R_o) was set to 1 (the threshold value of R_o for establishment of infection) depending on the values of S, β and θ. The results are shown in Table 3. Although θ was not the most sensitive parameter of the model it was important in calculating the maximum density of stocked fish represented as density of susceptible farmed fish density (S) under different model scenarios.

Table 3. For each scenario in the Microparasitic model, the maximum stocking density of fish represented as density of susceptible farmed fish (S) when the basic reproduction ratio (R_o) is set to 1

Scenario	S	β	θ	R_o
Initial	0.45	0.40	0.18	1.00
1	0.90	0.20	0.18	1.00
2	3.00	0.40	1.20	1.00
3	6.00	0.20	1.20	1.00

1

1

Macroparasite Model

The simulation of the model started with initial model parameters with following values: $\alpha = 0.002$, $\beta = 0.4$, $\mu = 0.01$, $\theta = 0.01$, $c = 0.05$ and $\lambda = 0.3$, densities of farmed $X = 10.0$ and wild fish $N = 2.0$ and with preliminary established population of the

macroparasites in wild fish with non-zero value for $P = 0.2$ and $W = 0.5$. The epizootic time series for the compartmental model of macroparasitic infestation between farmed and wild fishes are shown in Figure 6. Macroparasites both on wild and farmed fish showed exponential growth, more profound in macroparasites on farmed fish. The latter also implied that infective stages mostly originated from farmed fish rather than from wild, which can also be deduced from the very similar slopes of the lines 3 and 5 rather than slopes of lines 4 and 5 (Figure 6). In contrast to the Microparasite model, the epizootics of macroparasites did not die off and the lines in the graph were not levelled off. When the number of the time steps in the simulation of the model was increased, the densities of both wild and farmed fish reached zero value. Therefore, host fish populations were driven by the parasites to extinction.

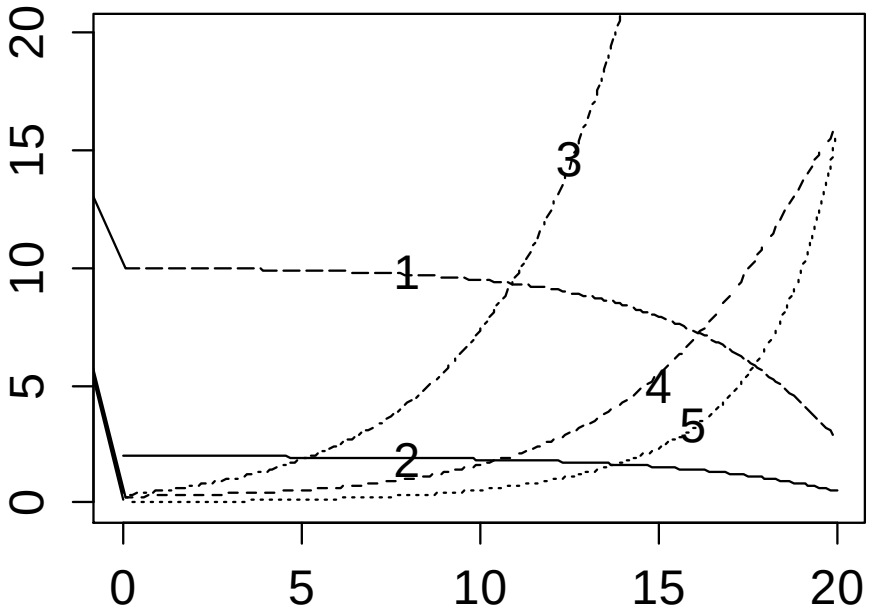

Figure 6. The epizootic time series for the Macroparasite model. Line 1 - Farmed fish density (X), line 2 - Wild fish density (N), line 3 - Density of adult parasites on farmed fish (Y), line 4 - Density of adult parasites on wild fish (P), line 5 - Density of infective stages (W)

Next step was performing the sensitivity analysis of the model with default values of the basic parameters (Figure 7). Analyses showed that the most sensitive parameter affecting the wild fish density was λ (the rate of production of infective stages by an adult parasite), followed by α (parasite-induced host death rate), β (transmission rate between host and parasite infective stages), θ (mortality rate of adult parasites on farmed fish), μ (mortality rate of adult parasites on wild fish) and c (mortality rate of infective stages). Parameter α, which can be influenced by management procedure such as vaccination, turned out to be the second sensitive model parameter in rank. However, the parameter θ in the model which with aim to eradicate the epizootic allows, as well as parameter α, direct human intervention such as fallowing, cleaning fish (wrasse) and chemotherapeutic applications did not prove to be the most sensitive parameter of the model. In order to evaluate further the importance of the parameter θ, the model was simulated under three different scenarios (=different epizootic conditions): A) scenario 1 - the initial values of all parameters were kept except α, where α was reduced to 0.001 B) scenario 2 where the initial values of all parameters were kept except θ, respectively $\theta = 0.1$ C) scenario 3 where again the initial values of all parameters were kept except θ and α, respectively $\theta = 0.1$ and $\alpha = 0.001$. (Figure 7).

In scenario 2 and 3, θ (mortality rate of adult parasites on farmed fish) was increased 10 times ($\theta = 0.1$) indicating more intense intervention procedures in order to eradicate the parasites from farmed fish.

There was no change in the ranking of the sensitivity of each parameter in scenario 1. However, in line with increase in its value, the relative sensitivity of θ (mortality rate of adult parasites on farmed fish), respectively its importance, increased in scenarios 2 and 3 and θ became the third most sensitive parameter.

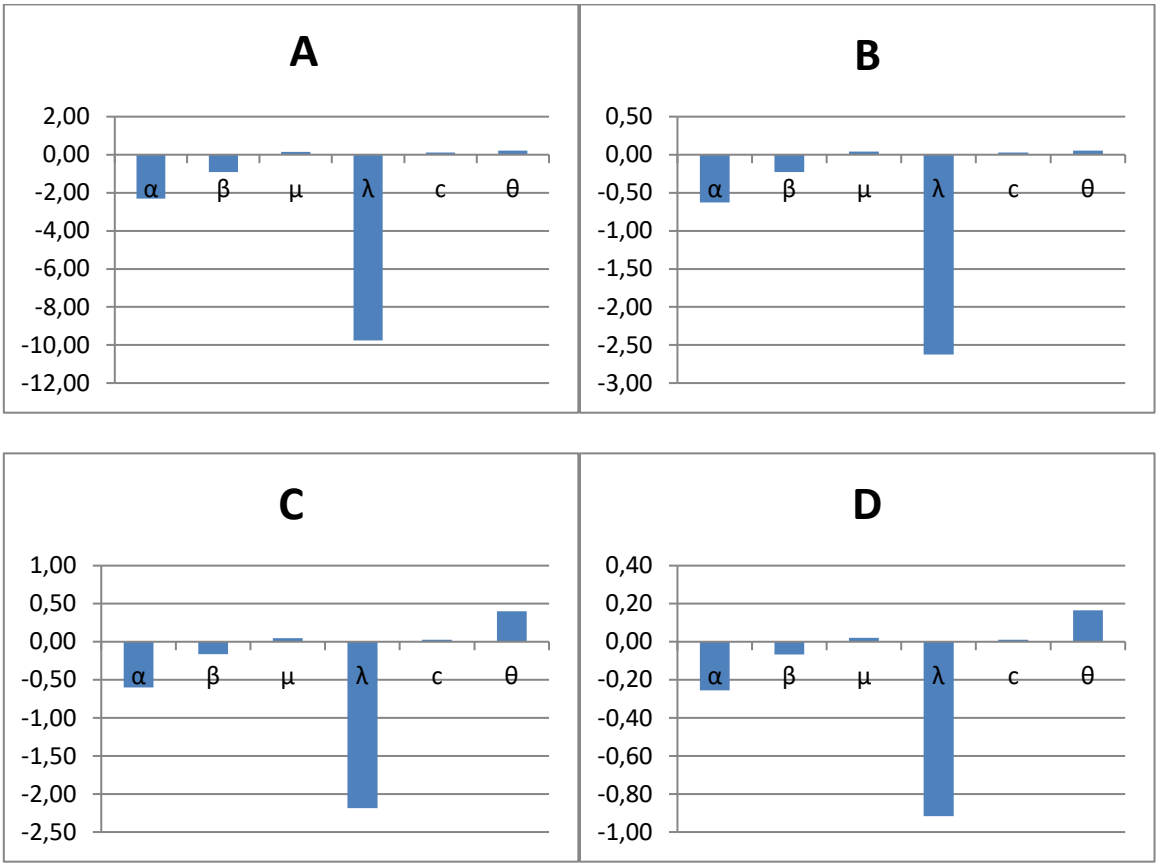

Figure 7. Sensitivity analysis results for the Macroparasite model. The panels are: A) model simulated with the initial parameter values; B) scenario 1 - the initial values of all parameters kept except α, where α reduced to 0.001 C) scenario 2 where the initial values of all parameters kept except θ, respectively $\theta = 0.1$ D) scenario 3 where again the initial values of all parameters kept except θ and α, respectively $\theta = 0.1$ and $\alpha = 0.001$

Furthermore, θ proved to have protective effect on the density of wild fish, which is shown in Figure 8, where the model was simulated with different θ values representing more effective removal rate of parasites on farmed fish (denoted with Y in the model).

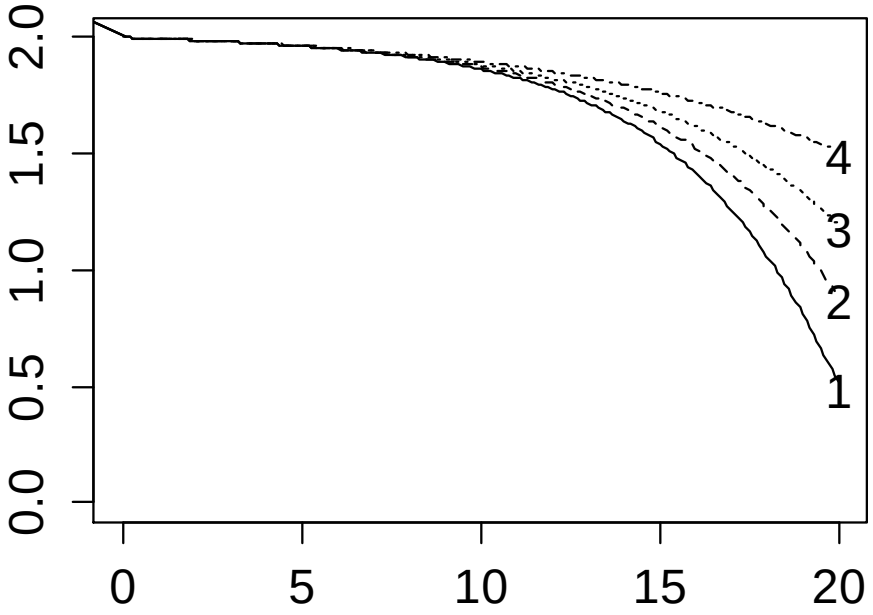

Figure 8. Simulation of the Macroparasite model under different values of θ, while keeping other parameters in their default values. Line 1: $\theta = 0.01$; line 2: $\theta = 0.05$; line 3: $\theta = 0.1$; line 4: $\theta = 0.2$. Each line represents the time series of the wild fish densities

In spite of θ not being the most sensitive parameter of the model, θ was important for calculation of the maximum density of stocked fish (X) under different model scenarios. For each scenario, depending on the values of X, α, β, λ, c and θ, the basic reproduction ratio (R_o) was set to 1 (the threshold value of R_o for establishment of infection) in order to calculate the maximum density of stocked fish (X). The results are shown in Table 4.

Table 4. For each scenario in the Macroparasitic model, the maximum stocking density of fish represented as density of farmed fish (X) when the basic reproduction ratio (R_o) is set to 1

Scenario	X	λ	θ	α	β	c	R_o
Initial	0.005	0.300	0.010	0.002	0.400	0.050	1.000
1	0.005	0.300	0.010	0.001	0.400	0.050	1.000
2	0.064	0.300	0.100	0.002	0.400	0.050	1.000
3	0.063	0.300	0.100	0.001	0.400	0.050	1.000

Discussion

The result of the present study indicate that parasitic pathogens first originated in wild fish populations after infecting and infesting farmed fish, subsequently causing epizootics under certain farming conditions in cultured fish, might have negative impact on wild fish populations. Similar views were expressed by Krkošek et al. (2005), Costello (2009) and Heuch et al. (2005) dealing with sea lice infestations on wild fish. Krkošek et al. (2005) suggested that fish farms were responsible for increasing sea lice infection pressure four times of magnitude than ambient levels and salmonid declines in Europe and North America may be attributed to salmon fish farming industry (Costello 2006, 2009). Heuch et al. (2005) claimed that there is a causal relation between salmon farming and sea lice epizootics on Norwegian South West coast due to high fish farming activity and low stocks of wild salmonids to generate these epizootics, but it was uncertain whether these epizootics effectively regulated the population size of Arctic char and sea trout.

Although in the present study, through computer models, testable hypothesis was generated, the results obtained *in silico* does not necessarily implied causation in reality (Turnbull et al. 2011). Indeed, this is in accord with findings of Green et al. (2012) who pointed out that paralleled to growing fish farming industry on the west coast of Scotland there was also decline in wild fisheries on the East coast, where fish farming is absent and answer might be simply lack of fishing effort instead of fish farming. Alleviating confounding factors in studying disease and observations supported by experimental data sufficiently repeated over time are needed to indicate that such correlation is based on cause and effect relationship (Costello 2009).

The present study models assumed homogenous dispersion of the wild fish populations similar to farmed fish. In reality, wild fish populations can have very patchy and chaotic distribution reducing contact rate, respectively protecting proportion of the wild fish populations from spreading of the diseases (Reno 1998; Green 2010). Thus, the results of the present models represented the worst-case scenarios, where wild fish populations were homogenously dispersed with enhanced disease transmission.

Another aspect of the present study was if under the developed models the hosts might be driven to extinction. According to Murray (2009), direct density-dependent transmission between hosts, as in the Microparasite model, cannot drive hosts to extinction, whereas macroparastic epizootics as in the Model II can. The results obtained indicated that after certain time microparasitic epizootics did not reach the state of equilibrium with their hosts and exterminated the host populations. Similarly, macroparasitic epizootics modelled in model II, did not reach the state of equilibrium and macroparasites continued their growth exponentially until reducing their host population density to zero. The latter was also consistent with the results obtained by Todd (2007) where the genetic distinction between wild and farmed populations was not discovered, dictating impossibility of eradicating sea lice as a pest from wild and farmed fish.

In the present models spreading of the microparasites as well as transmission of the macroparasite infective stages and their respective hosts was modelled under density dependency. Support for the latter and especially for microparasitic transmission came from the studies of Morrison et al. (2004) on amoebic gill disease (AGD), where infection was strictly amoeba density dependent and AGD function of amoeba cell density. In contrast, McCallum et al. (2001) proposed that simple mass action is not the proper model to explain effectively many terrestrial epizootics and does not account for the observed prevalence of many

diseases, with frequency dependence more accurately describing the disease patterns. However, due to the more contagious nature of the aquatic environment (Green 2010), assumptions of McCallum et al. (2001) were rejected while constructing the models and density dependency transmission finally adopted. With the correct models in place, it was easier to evaluate intervention steps and propose control procedures (Roberts and Heesterbeek 1993).

Results from the simulation of the Microparasite model indicated that the model parameter which is the least prone to management intervention, respectively infection removal rate of wild fish (γ) was the most sensitive parameter. It was evident that any attempt to apply chemotherapeutic agents for reduction of number wild infected fish is practically impossible and financially not feasible. Attempts to vaccinate wild fish from application viewpoint are simply futile when planning changes in (γ).

However, the second most sensitive parameter in model I respectively pathogen specific transmission rate (β) can be to certain degree manipulated. This parameter is influenced by the environmental factors such as population density, temperature, water flow and water chemistry (Reno 1998) so aquaculture can be geographically placed in areas (i.e. site selection) where the latter abiotic factors contribute to minimizing survivability of microparasites by reduction of basic reproduction ratio (R_o) (Krkošek 2010). Indeed, examples for reduction of β came from studies of Munday et al. (2001) who found that infections of salmonids with causative agent of amoebic gill disease (AGD) *Neoparamoeba pemaquidensis* occurred at high temperatures and high salinities and AGD can be easily managed and controlled at low temperatures and low salinities.

Equally important should be the measures applied to reduce the next sensitive parameter in the Microparasite model, pathogen specific transmission rate between infected farmed and susceptible wild fish (δ). This can be achieved by reducing the number of contacts between escaped farmed fish and wild (Heuch et al. 2005) and situating aquaculture production sites on places with greater residual current flow which leads to greater pathogen decay rate (Salama and Murray 2013 Green 2010).

Next sensitive parameter in the model evaluation, infection removal rate of farmed fish (θ), increased in importance paralleled to increase in its value and become the third most important model parameter. This had the most valuable implications for the model because the latter parameter encompassed all practically applicable procedures from aquaculture intervention viewpoint such as fallowing, application of chemotherapeutic agents and vaccination. All these procedures can inevitably affect infection removal rate of farmed fish (θ) and have protective impact on wild fish populations.

Beside the influence of aforementioned parameters susceptible farmed fish density had also important impact on onset of the parasitic epizootics via its influence on basic reproduction ratio (R_o). The lesser the density of susceptible farmed fish the lower R_o was and minimization of the microparasitic epizootics (Anderson and May 1979a; Roberts and Heesterbeek 1993; Reno 1998; Krkošek 2010). Reduction of farmed fish density at which R_o was still equal to 1 or below 1 dropped from 10.0 to 6.00. At density of 6.00 farmed fish can still be effectively and feasibly stocked (Table 3).

Macroparasite model results revealed that the most important, respectively the most sensitive parameter was the rate of production of infective stages by an adult parasite (λ), significantly surpassing the importance of all model parameters. Fortunately, compared to the most sensitive parameter of the Model I which was unaffected by human intervention, the rate of production of infective stages by an adult parasite (λ) can be to certain degree manipulated in order to protect wild fish. The higher the sea temperature the faster is the development and production of eggs by gravid female sea lice, which leads to higher infestation pressure on farmed and farmed fish stocks (Costello 2006; Guo and Woo 2009; Wagner et al. 2008). Support for the latter fact came from the modelling studies of Revie et al. (2005) in which they found that the second sensitive parameter in their model was the feedback rate at which gravid female louse produce viable eggs. Thus, in order to achieve effective eradication of the macroparasite epizootics, farm facilities must be located in areas where environmental factors, in that case temperature, hinder the development and production of viable eggs.

The next sensitive parameter in the Macroparasite model was parasite-induced host death rate (α), which can be influenced by management procedure such as vaccination. However, macroparasitic infestations do not confer their respective fish hosts with significant immune response and development of vaccines against macroparasites seems distant future (Anderson and May 1979b; Krkošek 2010). Consequently, if preventive intervention strategy are to be built over the model parameter (α), it should not be based on vaccination but on supporting the immune system of the host and reduction of environmentally caused stress in fish.

Transmission rate between host and parasite infective stages (β) was the third most sensitive parameter in the Macroparasite model reflecting

infestations between free infective stages of the macroparasites and their hosts. This parameter can be manipulated by relative physical isolation of captive fish populations in order to avoid contact with their wild counterparts (Reno 1998) by selecting farming areas which avoid spreading of infective stages by wind-driven circulation (Amundrud and Murray 2009; Salama and Murray 2013; Penston et al. 2008; Costello 2006). Similarly, stimulating migratory allopatry and avoiding migratory sympatry, in other words avoiding contact between migratory juvenile fish with adult farmed or escaped farmed fish (Costello 2009).

Special attention is deserved by the parameter θ (mortality rate of adult parasites on farmed fish) in the Macroparasite model which comprises the core of the integrated intervention strategy because this parameter can be modified by such control procedures as fallowing, use of cleaner fish (wrasse) and chemical control (use of parasiticides). Increase in the numerical value of the parameter led to increase in the sensitivity and relative importance of the parameter such as θ became the third most sensitive parameter in the second model. As Werkman et al. (2011) reported, synchronised fallowing is highly effective tool in disease control and eradication despite the common long distance contacts. However, there has been significant amount of accumulating data that even synchronised fallowing was not effective in reducing the abundance of sea lice *Caligus elongatus* (Nordmann,1832) on cultured Atlantic salmon in Scotland (Revie et al. 2002). Even when farms in Loch Torridon (Scotland) were synchronously allowed empty for 10 weeks before restocking greatest densities of sea lice nauplii were recovered around farms during the production season (Penston et al. 2008). McKenzie et al. (2004) reported that despite treatment applications against *Caligus elongatus* (Nordmann,1832) in Loch Sunart (Scotland) there was no significant impact on the parasitic infestations and there is substantial evidence that sea lice have been acquiring resistance against widely used and still effective chemotherapeutic agents such as Hydrogen peroxide and Emamectin benzoate (Guo and Woo 2009). Nevertheless, recent introduction of cleaner fish such as wrasse for biological control have had very promising results in reduction of sea lice infestations on salmonid fishes (Costello 2006). Wrasse can be used very efficiently against macroparasites such as sea lice.

In contrast to model I where farmed fish density had important impact on reducing basic reproduction ratio (R_o), in the Macroparasite model farmed fish density did not contribute significantly in reduction of R_o. Reduction of farmed fish density at which R_o was still equal to 1 or below 1 dropped from 10.0 to 6.00 in the Microparasite model, respectively these values in model II were 10.0 to 0.0634 (Table 4). The latter explicitly indicates that macroparasitic epizootics under farming conditions are very difficult to be eradicated.

Strategic models built in this study implicitly showed that parasites can be transmitted between farmed and wild fish populations in both directions and have potential to negatively impact both of them.

In conclusion, the strategic models presented in this study demonstrate the importance of epidemiological modelling in aquaculture disease management and prevention of epizootics caused by uncontrolled parasitic infestations in farmed fish, which can be transmitted to wild stocks with negative impacts on population dynamics. More refined biological data based on experimental and field data is needed for establishment of separate epidemiological models parameterised for specific parasitic disease. These disease specific models can reflect the dynamics of parasitic epizootics better and lead to better control and more effective environmental protection. New models, due to the impact on shortening of generation time of parasites, should mirror in their basic parameters the rise of global water temperatures predicted by climate change scenarios. Increase in the resistance of parasites against chemotherapeutic agents must also be a concern for future modelling efforts. This will be certainly advantageous to both wild fish defenders and aquaculturists.

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APPENDIX A. Code for the Microparasite Model

```
beta <- 0.4
gamma <- 0.18
teta <- 0.18
delta <-0.02
sigma<- 0.01
S <- 10.000
I <- 0.001
R <- 0
X <- 2.000
Y <- 0.000
Z <- 0
dt <- 0.1
t <- 0
max_time <- 20
time_steps <- max_time/dt
results<-c(t,S,I,R,X,Y,Z)
for (i in 1:time_steps) {
t <- t+dt
newI <- beta*S*I*dt+sigma*S*Y*dt
newR <- teta*I*dt
I <- I+newI-newR
S <- S-newI
R <- R+newR
newY <- beta*X*Y*dt+delta*X*I*dt
newZ <- gamma*Y*dt
Y <- Y+newY-newZ
X <- X-newY
Z <- Z+newZ
results<-rbind(results,c(t,S,I,R,X,Y,Z))}
colnames(results)<-
    c("t","S","I","R","X","Y","Z")
results<-as.data.frame(results)
plot(results$t,results$X,type="l",
    ylim=c(0,10))
lines(results$t,results$Y,lty=2)
lines(results$t,results$Z,lty=3)
lines(results$t,results$S,lty=4)
lines(results$t,results$I,lty=5)
lines(results$t,results$R,lty=6)
text (1,10,"1")
text (4.2,8.2,"2")
text (10,7.4,"3")
text (1,2,"4")
text (6.2,1.1,"5")
text (17,1.9,"6")
```

APPENDIX B. Code for the Macroparasite Model

```
alfa <- 0.002
beta <- 0.4
mu <- 0.01
lambda <- 0.3
si <- 0.05
teta <- 0.01
N <- 2.000
P <- 0.200
X <- 10.000
Y <- 0
W <- 0.500
dt <- 0.1
t <- 0
max_time <- 20
time_steps <- max_time/dt
results<-c(t,N,P,X,Y,W)
for (i in 1:time_steps) {
t <- t+dt
newP <- (beta*W*N-(mu+alfa)*P-
    alfa*P*P/N)*dt
newY <- (beta*W*X-(teta+alfa)*Y-
    alfa*Y*Y/X)*dt
newW <- (lambda*P+lambda*Y-si*W-
    beta*W*N-beta*W*X)*dt
P <- P+newP
N <- N-alfa*P
Y <- Y+newY
X <- X-alfa*Y
W <- W+newW
results<-rbind(results,c(t,N,P,X,Y,W))}
colnames(results)<-
    c("t","N","P","X","Y","W")
results<-as.data.frame(results)
plot(results$t,results$N,type="l",
    ylim=c(0,20))
lines(results$t,results$P,lty=2)
lines(results$t,results$W,lty=3)
lines(results$t,results$Y,lty=4)
lines(results$t,results$X,lty=5)
text (8,10,"1")
text (8,2,"2")
text (12.5,14.8,"3")
text (15,5.2,"4")
text (16,3.5,"5")
```