Analysis of Interventions against the Liver Fluke, *Opisthorchis viverrini*

C. Bürli, H. Harbrecht, P. Odermatt,
S. Sayasone and N. Chitnis

Departement Mathematik und Informatik
Fachbereich Mathematik
Universität Basel
CH-4051 Basel

Preprint No. 2017-15
December 2017

www.math.unibas.ch

Analysis of Interventions against the Liver Fluke, *Opisthorchis viverrini*

Christine Bürli[a,d,*], Helmut Harbrecht[d], Peter Odermatt[a,b], Somphou Sayasone[a,b,c], Nakul Chitnis[a,b]

[a]*Swiss Tropical and Public Health Institute, Socinstrasse 57, 4002 Basel, Switzerland*
[b]*University of Basel, Basel, Switzerland*
[c]*National Institute of Public Health, Vientiane, Lao PDR*
[d]*Department of Mathematics and Computer Science, University of Basel, Basel, Switzerland*

Abstract

We adapt a population-based model of *Opisthrochis viverrini* transmission dynamics to determine the effectiveness of three different interventions. The model includes the definitive hosts, humans; the reservoir hosts, dogs and cats; and the intermediate hosts, snails and fish. We consider the interventions: education campaigns to reduce the consumption of raw or undercooked fish, improved sanitation and treatment through mass drug administration. We calculate the control reproduction number, simulate different scenarios and optimise the interventions with optimal control. We look at the potential of the interventions to eliminate transmission within 20 years. The model shows that education and better sanitation need a very high coverage to fulfill the goal of elimination, whereas drug distribution at medium coverage and yearly distribution is enough. The best solution is a combination of drug distribution at a medium level of coverage and as high as possible coverage of education and better sanitation.

Keywords: Opisthorchis viverrini, mathematical modelling, simulation, optimal control, intervention
2010 MSC: 92D30 49N90

*Corresponding author
Email address: christine.buerli@unibas.ch (Christine Bürli)

1. Introduction

The liver fluke *Opisthorchis viverrini* infects people through nutrition-related behaviour such as eating raw or undercooked infected fish. The distribution of *O. viverrini* occurs mainly in Southeast Asia. Over 67.3 million people are at risk of getting infected with this liver fluke [1]. Over 8 million people are infected with *O.viverrini* in the Mekong area in Thailand, Lao People's Democratic Republic (PDR), Cambodia and Vietnam [2]. Infection with *O. viverrini* can, in the worst case, lead to a subtype of liver cancer [3].

The life cycle of *O. viverrini* includes humans, dogs and cats as definitive hosts and snails and fish as first and second intermediate hosts. The adult worm lives in the bile ducts of its definitive hosts. Their eggs reach the external environment through faeces. The eggs are ingested by the first intermediate host, snails of the genus *Bithynia* when they reach freshwater. The free-living cercariae leave the snails and penetrate through skin of the fish of the family Cyprinidae, their second intermediate host. The cerceriae develop inside the fish into metacercariae and the fish reaches its infective stage for the definitive host [4]. The worms can survive in the definitive hosts for about 10 years [5].

Our model analysis is based on a model from a previously published paper [6]. This model includes humans, dogs and cats as definitive hosts and snails and fish as intermediate hosts. Distributions of unknown parameters of this model were estimated by a Bayesian sampling resampling approach and point estimates with maximum likelihood estimation.

There is no published paper on modelling interventions against *O. viverrini*, but there are many publications on interventions against other diseases, such as influenza vaccination, which can be adapted. Optimal control is used to optimise the coverage of the choosen intervention in different influenza models. We can adapt the optimal control method of these influenza models to our model.

To reach the goal of elimination of *O. viverrini* in 20 years, we have to find the optimal coverage of each intervention. We consider three different types of interventions and model their targeted coverage. The first one is education campaign to change people's eating habits, that they stop eating raw or undercooked fish. This results in no new infections in humans. The second one is improved sanitation, which prevents outdoor defecation. We assume that this intervention is perfect, so that no egg is able to reach the environment and be ingested by snails, when people use the latrine. The last

one is treatment. We look at the coverage of people that has to be treated, with the assumption that the drugs have complete efficacy. We also look at the optimal time frequency at which drug distribution takes place. At the moment Praziquantel is the only drug available against *O. viverrini* [1], which has a high efficacy in regard to cure rate and egg reduction rate [2].

After developing the model, we estimate the unknown parameters with the help of data from Lao PDR. We define the basic as well as the control reproduction number of the model. This helps us to define the minimum coverage of each intervention. Then we optimise coverages with the optimal control method. Finally we estimate the time and probability of reaching elimination of *O. viverrini* to investigate more about the potential of the interventions. We also simulate the influence of the sensitivity of the diagnostic test, as it does not have 100 % sensitivity, on the mean worm burden in humans and on the probability of elimination.

2. Mathematical model

We extend the previously published model with reservoir hosts of *O. viverrini* to include the effect of interventions [6]. We assume that the transmission of *O. viverrini* depends on humans, dogs and cats as definitive hosts and snails and fish as intermediate hosts. We simulate the mean worm burden in humans, dogs and cats and the prevalence in fish and snails. We model the interventions as:

(i) education campaign to reduce the consumption of raw or undercooked fish. We let I_e denote the coverage successfully reached by the education campaign, that is, the proportion of people who do not get further infected by eating raw or undercooked fish.

(ii) improved sanitation to stop transmission from humans to snails, we let I_d denote the coverage of sanitation, that is the proportion of people stop defecating outdoors because of the improved sanitation.

(iii) mass drug administration, we let I_m denote the proportion of people treated annually (except for campaigns at lower frequencies as described later).

Assuming γ is the rate per unit time of treating people,

$$\exp(-\gamma \times T_\gamma) = 1 - I_m$$

is the proportion of untreated humans with T_γ as the time interval of treatment in days [7]. It follows that the treatment rate is

$$\gamma = \frac{-\log(1 - I_m)}{T_\gamma}.$$

We consider two modes of mass drug administration: the first is continuous treatment I_m, with $T_\gamma = 1$ day in the model, which refers to a daily treatment rate. The second is a pulsed treatment applied at a fixed frequency. For example treatment once a year is modelled by,

$$I_m(t) = \begin{cases} I_m, & t \mod 365 = 1, \\ 0, & \text{else}, \end{cases}$$

with $T_\gamma = 1$ day. The full model is given by the ordinary differential equation system,

$$\frac{\mathrm{d}w_h(t)}{\mathrm{d}t} = \beta_{hf} N_f i_f(t)(1 - I_e) - \left(\mu_{ph} - \frac{\log(1 - I_m(t))}{T_\gamma}\right) w_h(t), \tag{1a}$$

$$\frac{\mathrm{d}w_d(t)}{\mathrm{d}t} = \beta_{df} N_f i_f(t) - \mu_{pd} w_d(t), \tag{1b}$$

$$\frac{\mathrm{d}w_c(t)}{\mathrm{d}t} = \beta_{cf} N_f i_f(t) - \mu_{pc} w_c(t), \tag{1c}$$

$$\frac{\mathrm{d}i_s(t)}{\mathrm{d}t} = (\beta_{sh} N_h w_h(t)(1 - I_d) + \beta_{sd} N_d w_d(t) + \beta_{sc} N_c w_c(t))(1 - i_s(t)) - \mu_s i_s(t), \tag{1d}$$

$$\frac{\mathrm{d}i_f(t)}{\mathrm{d}t} = \beta_{fs} N_s i_s(t)(1 - i_f(t)) - \mu_f i_f(t), \tag{1e}$$

Variable	Description
w_h	Mean worm burden per human host
w_d	Mean worm burden per dog host
w_c	Mean worm burden per cat host
i_s	Proportion of infectious snails
i_f	Proportion of infectious fish

Table 1: State variables of the opisthrochiasis model, see [6, Table 1]

where the state variables are shown in Table 1 and the parameters in Table 2.

We model the mean worm burden per human host, w_h, so we distribute the total number of worms equally to all humans. w_h is additionally influenced by the proportion of the people who stop eating raw or undercooked fish because of the education campaign with coverage I_e. The transmission rate from fish to humans is proportionally reduced by $(1 - I_e)$. The worms die naturally in humans, $\mu_{ph} w_h$, or because of the treatment, $\frac{-\log(1-I_m(t))}{T_\gamma} w_h$. We make the implicit assumption that there is no correlation between worm burden and the likelihood of being treated so the proportion of people getting treated, with the assumption that treatment is perfect, is equal to killing this proportion of worms of the mean worm burden in human. The infection rate of snails depends on the proportion of people who have access to a latrine and do not defecate outdoors. Making the implicit assumption that access to a latrine is not correlated with worm burden, improved sanitation proportionally reduces the transmission from humans to snails by $(1 - I_d)$.

We use data from a study on two islands in the Mekong in Champasack province, Lao PDR, conducted from October 2011 to August 2012. We have data on the prevalence of infection in humans, dogs, cats, snails and fish and intensity of infection in in humans, see Table 3. The number of humans is estimated from the study in Champasack province [8], but additional data on the number of animals and death rates are from literature and expert opinions.

To estimate $\beta = (\beta_{hf}, \beta_{df}, \beta_{cf}, \beta_{sd}, \beta_{sc}, \beta_{sh}, \beta_{fs})$, we followed the Bayesian resampling approach in [6] with the same parameter ranges as in Table 4, followed by the maximum likelihood estimation (MLE) method. The final estimate with MLE is found in Table 4.

We simulate the ODE system (1) with the Runge-Kutta 4 method with the initial value we estimate from the data, $(w_h(0), w_d(0), w_c(0), i_s(0), i_f(0)) = (33, 3, 13, 0.003, 0.3)$, and time steps in days up to 20 years. The numerical results of the model with parameter values of the MLE are presented in Figure 1. To show the uncertainty of the parameter sets, we also illustrate the median, the mean and the standard deviation of the 500 data sets in Figure 1.

3. Basic and control reproduction number

The basic reproduction number $\mathcal{R}_0$ is the average number of new offspring per parasite in the next step of the life cycle without interventions. It is calculated as the spectral radius of the next-generation matrix [9]. The cubed

spectral radius is equal to the number of offspring of one adult worm in the next generation. It follows that when the basic reproduction number is below one ($\mathcal{R}_0 < 1$) the parasite cannot produce enough offspring to persist. The control reproduction number $\mathcal{R}_c$ includes interventions in the reproduction number. The next-generation matrix $\mathbf{K}$ of the model (1) is given by

$$\mathbf{K} = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\beta_{hf} N_f (1-I_e)}{\mu_f} \\ 0 & 0 & 0 & 0 & \frac{\beta_{df} N_f}{\mu_f} \\ 0 & 0 & 0 & 0 & \frac{\beta_{cf} N_f}{\mu_f} \\ \frac{\beta_{sh} N_h (1-I_d)}{\mu_{ph} - \frac{\log(1-I_m(t))}{T_\gamma}} & \frac{\beta_{sd} N_d}{\mu_{pd}} & \frac{\beta_{sc} N_c}{\mu_{pc}} & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{fs} N_s}{\mu_s} & 0 \end{bmatrix},$$

assuming that treatment is distributed continuously. Its spectral radius and so the control reproduction number of the model is given by the expression,

$$\mathcal{R}_c = \left(\frac{N_s N_f \beta_{fs} (\mu_{ph} T_\gamma - \log(1 - I_m(t)))(N_d \beta_{df} \beta_{sd} \mu_{pc} + N_c \beta_{cf} \beta_{sc} \mu_{pd})}{(\mu_{ph} T_\gamma - \log(1 - I_m(t)))\mu_{pd} \mu_{pc} \mu_s \mu_f} \right.$$
$$\left. + \frac{N_s N_f \beta_{fs} (1 - I_d - I_e + I_d I_e)(T_\gamma N_h \beta_{hf} \beta_{sh} \mu_{pd} \mu_{pc})}{(\mu_{ph} T_\gamma - \log(1 - I_m(t)))\mu_{pd} \mu_{pc} \mu_s \mu_f} \right)^{\frac{1}{3}}.$$

The control reproduction number depends on the intervention and their coverage. In Figure 2, the graphs show the control reproduction number in dependence of the coverage, each intervention applied singly with the MLE parameter values and $T_\gamma = 365$. The control reproduction number $\mathcal{R}_c$ has a similar dependence on the level of coverage of the interventions of education campaign (I_e) and improved sanitation (I_d). It needs at least a coverage of 25% of these two interventions each to get $\mathcal{R}_c$ below 1. The coverage of the mass drug administration (I_m) has a much stronger effect on the control reproduction number than the coverage of the education campaign (I_e) and improved sanitation (I_d). The control reproduction number decreases below 1 at the a low coverage of 7% of treated people.

The basic reproduction number

$$\mathcal{R}_0 = \left(\frac{N_s N_f \beta_{fs} (N_d \beta_{df} \beta_{sd} \mu_{pc} + N_c \beta_{cf} \beta_{sc} \mu_{pd} + N_h \beta_{hf} \beta_{sh} \mu_{pd} \mu_{pc})}{\mu_{ph} \mu_{pd} \mu_s \mu_f} \right)^{\frac{1}{3}}$$

is equal to the control reproduction number $\mathcal{R}_c$ if the coverage of all interventions is 0 no interventions in the population.

4. Effectiveness of interventions

To find the optimal level of coverage of the interventions, we first look at them separately. We solve the equation $\mathcal{R}_c = 1$ for the coverage of each intervention in absence of the other two interventions (see the intercept points in Figure 2),

$$I_e = I_d = 0.254,$$
$$I_m = 0.0678,$$

the other parameters are set to the MLE solutions in Table 4. As seen in Figure 2, the control reproduction number depends similarly on I_e and I_d. The combination of the interventions I_e and I_d (without I_m) is only successful if $\mathcal{R}_c < 1$. The possible combinations to reach a control reproduction number below 1 and a decreasing worm burden in humans are shown in Figure 3. We use the MLE solutions (Table 4) for the parameters in the model. The minimum combination such that $\mathcal{R}_c < 1$ is the minimum coverage $I_e = I_d = 0.1363$. Figure 2 also shows that the effectiveness of the interventions in reducing $\mathcal{R}_c$ increases with coverage for improved sanitation and education campaign but decreases for mass treatment. Figure 2 describes the minima of coverage we need for each intervention separately to interrupt transmission, assuming I_m is continuous with $T_\gamma = 365$. However, the minimum levels coverage are too small to reach a low number of mean worm burden in humans in 20 years. Hence, we simulate the levels of coverage of $I_e \in \{0.2, 0.4, 0.6\}$ and $I_d, I_m \in \{0.4, 0.6, 0.8\}$ which cover reasonably achievable levels of coverage. Treatment is assumed to be distributed every year once. The numerical simulations of these levels of intervention coverage are shown in Figure 4. We compare the numerical solution without any intervention to the numerical solution including each intervention separately at the different coverage levels. Here we assume a more realistic pulsed distribution of treatment once a year.

The mass drug administration depends on time, more precisely on the frequency which the drug is distributed. We assume different frequencies of drug distribution every 0.5, 1, 2, 3 and 4 years. Hence, $I_m(t)$ is the proportion of humans who receive a drug against *O. viverrini* in every drug distribution

campaign. The influence of the choice of this frequency on the mean worm burden in humans with different levels of coverage is shown in Figure 5.

5. Optimal Control

To synchronously optimise the level of coverage of the education campaign (I_e) and the mass drug administration (I_m) in the model, we use the optimal control method. We do not try to optimise the sanitation coverage because we assume that any program would try to maximise sanitation for all its additional health benefits. We focus on optimising interventions that are targeted against *O. viverrini*. To fulfil the linearity property of the right-hand side of the model (1), we optimise the treatment rate

$$\gamma(t) = -\frac{\log(1 - I_m(t))}{365}$$

instead of the proportion $I_m(t)$, when $I_m(t)$ and correspondingly $\gamma(t)$ are piecewise constant for a pulsed treatment rate. Since treatment distribution occurs once a year, we have a rate $\gamma(t)$ of treated people with the properties,

$$\gamma(t) = \begin{cases} \gamma_k, & t \mod 365 = 1, \\ 0, & \text{else.} \end{cases}$$

with the yearly rate γ_k for $k = 1, \ldots, n$, $n \in \mathbb{N}$. The first equation of the ODE system (1) changes then to

$$\frac{\mathrm{d}w_h(t)}{\mathrm{d}t} = \beta_{hf} N_f i_f(t)(1 - I_e) - (\mu_{ph} + \gamma(t))w_h(t). \tag{2}$$

To minimise the coverage of the interventions affecting humans leads to the optimal control problem

$$\min_{I_e,\gamma} \int_0^T w_h^2(t) + \frac{\alpha^2}{2} \left(I_e(t)^2 + \sum_{k=1}^{n} \gamma_k^2 \right) \mathrm{d}t$$

with the weight $\alpha = 0.001$, the time $T = 20 \times 365$ (in days), $n = \frac{T}{365}$, $0 \leq I_e(t) \leq 0.9$ and $0 \leq \gamma_k \leq 0.0016$, which is equal to $0 \leq I_m = 1 - \exp(\gamma_k \times 365) \leq 0.8$ for each $k = 1, \ldots, n$. The regularisation parameter α priorities the minimisation of the mean worm burden instead of the coverage level.

We assume that it is not possible to reach all people by drug distribution and that the maximum of the treatment coverage is 80%. The maximum of coverage of education on eating raw or undercooked fish is 90%.

To simplify the notation, we write $I_e(t) = I_e$, $\gamma(t) = \gamma$ and $I = (I_e, \gamma_1 \ldots, \gamma_n)$. We use the definitions

$$L(t, w_h, I) := w_h^2(t) + \frac{\alpha^2}{2}\left(I_e^2 + \sum_{k=1}^{n} \gamma_k^2\right)$$

as the integrand, $\frac{\mathrm{d}f}{\mathrm{d}t} = f(x,t)$ with $x = (w_h, w_d, w_c, i_s, i_f)$ as our ODE model (1), so $f_i = f(x(i), t)$ for $i = 1, \ldots, 5$,

$$J(I) = \int_0^T w_h^2(t) + \frac{\alpha^2}{2}\left(I_e^2 + \sum_{k=1}^{n} \gamma_k^2\right) \mathrm{d}t$$

as the integral to minimise and

$$U = \{I(t) | I(t) \in [0, 0.9] \times [0, 0.0016]^n, t \in [0, T]\}.$$

To show that a solution exists to this optimal control problem, we have to prove the following assumptions [10, 11]:

Proposition 1 (Existence)**.** *i) The set of solutions to the system* (1) *is not empty and the right-hand side is continuous and bounded.*

ii) U is closed and convex and f can be written as

$$f(t, w_h, I_e, \gamma) = a(t, w_h) + b(t, w_h) I_e + c(t, w_h)\gamma.$$

iii) $L(t, w_h, \cdot)$ *is convex on* U*.*

Proof. i) The ODE system (1) is well-posed in the strip $S \subseteq \mathbb{R}^5$, which is defined by the boundaries of the system's solution for $(w_h, w_d, w_c, i_s, i_f)$:

$$S = \left[0, \beta_{hf}\frac{N_f}{\mu_{ph}}\right] \times \left[0, \frac{\beta_{df} N_f}{\mu_{pd}}\right] \times \left[0, \frac{\beta_{cf} N_f}{\mu_{pc}}\right] \times [0, 1]^2.$$

The right-hand side of the system is well-posed and with continuous partial derivatives. The prove of existence and uniqueness of the solution of the model (1) can be found in [6, Section 2.1].

The right-hand side of the ODE system (1) is clearly continuous and bounded in the strip $\tilde{S} \subseteq \mathbb{R}^5$, given by

$$\begin{aligned}\tilde{S} = &[-\beta_{hf}N_f, \beta_{hf}N_f] \times [-\beta_{df}N_f, \beta_{df}N_f] \times [-\beta_{cf}N_f, \beta_{cf}N_f] \\ &\times \left[-\mu_s, \frac{\beta_{sh}N_h\beta_{hf}N_f}{\mu_{ph}}\right] \times [-\mu_f, N_s\beta_{fs}].\end{aligned}$$

ii) U is closed and convex because it is a Cartesian product of closed intervals. f can be written as a linear combination according to

$$f(t, w_h, I_e, \gamma) = a(t, w_h) + b(t, w_h)I_e + c(t, w_h)\gamma,$$

where

$$f_1(t, w_h, I_e, \gamma) = \underbrace{\beta_{hf}N_f i_f - w_h}_{a(t,w_h)} + \underbrace{(-\beta_{hf}N_f i_f)}_{b(t,w_h)} I_e + \underbrace{(w_h)}_{c(t,w_h)} \gamma.$$

The linear combination for the other system of equations (f_2, f_3, f_4, f_5) looks similar.

iii) To show that $L(t, w_h, \cdot)$ is convex on U, we must have:

$$L(t, w_h, (1-\epsilon)I_1 + \epsilon I_2) \leq (1-\epsilon)L(t, w_h, I_1) + \epsilon L(t, w_h, I_2),$$

for $I_1, I_2 \in I$.

It holds

$$\begin{aligned}&L(t, w_h, (1-\epsilon)I_1 + \epsilon I_2) \\ &= w_h^2 + ((1-\epsilon)I_{e,1} + \epsilon I_{e,2})^2 + \left((1-\epsilon)\sum_{k=1}^{n}\gamma_{k,1}(t) + \epsilon\sum_{k=1}^{n}\gamma_{k,2}(t)\right)^2 \\ &\leq (1-\epsilon)\left(w_h^2 + \frac{\alpha^2}{2}\left(I_e^2 + \sum_{k=1}^{n}\gamma_k(t)^2\right)\right) + \epsilon\left(w_h^2 + \frac{\alpha^2}{2}\left(I_e^2 + \sum_{k=1}^{n}\gamma_k(t)^2\right)\right).\end{aligned}$$

□

To characterise the optimal solution, we use Pontryagin's maximum principle [12]. The proof can be found in Pontryagin's original text [13].

There exists a piecewise differentiable adjoint variable

$$\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t))$$

such that,

$$\lambda'(t) = \frac{-\partial H(t, x^*(t), I^*(t), \lambda(t))}{\partial x}$$

with the Hamiltonian H

$$H(t, w_h, w_d, w_c, i_s, i_f, I_e, \gamma, \lambda) = L(t, w_h, I) + \sum_{l=1}^{5} \lambda_l(t) f_l(x, t),$$

and $x^* = (w_h^*, w_d^*, w_c^*, i_s^*, i_f^*)$ as the corresponding state variables of the optimal control functions $I^* = (I_e^*, \gamma(t)^*)$.

Proposition 2. *The optimal controls are given by the set*

$$I_e^* = \min\left\{\max\left\{0, \frac{\lambda_1 \beta_{hf} N_f i_f}{\alpha^2}\right\}, 1\right\},$$
$$\gamma^* = \min\left\{\max\left\{0, \frac{\lambda_1 w_h}{\alpha^2}\right\}, 1\right\}.$$

Proof. Let I^* bet the optimal control functions to the corresponding state variables $w_h^*, w_d^*, w_c^*, i_s^*, i_f^*$, which minimise our integral function $J(I)$. It follows with the Pontryagin's maximum principle, that adjoint variables $\lambda(t) = (\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t))$ exist such that

$$\lambda_1' = -2w_h + \lambda_1(\mu_{ph} + \gamma) - \lambda_4 \beta_{sh} N_h (1 - I_d)(1 - i_s), \tag{3a}$$
$$\lambda_2' = \lambda_2 \mu_{pd} - \lambda_4 \beta_{sd} N_d (1 - i_s), \tag{3b}$$
$$\lambda_3' = \lambda_3 \mu_{pc} - \lambda_4 \beta_{sc} N_c (1 - i_s), \tag{3c}$$
$$\lambda_4' = \lambda_4(\beta_{sh} N_h w_h (1 - I_d) + \beta_{sd} N_d w_d + \beta_{sc} N_c w_c + \mu_s) - \lambda_5 \beta_{fs} N_s (1 - i_f), \tag{3d}$$
$$\lambda_5' = \lambda_5(\beta_{fs} N_s i_s + \mu_f) - \lambda_1 \beta_{hf} N_f (1 - I_e) - \lambda_2 \beta_{df} N_f - \lambda_3 \beta_{cf} N_f, \tag{3e}$$

with transversality conditions $\lambda_i(t_1) = 0$ for $i = 1, \ldots, 5$. Considering the optimality condition $\frac{\partial H(t,x^*(t),I^*(t),\lambda(t))}{\partial I} = 0$, we get the solutions

$$I_e^* = \frac{\lambda_1 \beta_{hf} N_f i_f}{\alpha^2}, \tag{4a}$$

$$\gamma^* = \frac{\lambda_1 w_h}{\alpha^2}. \tag{4b}$$

It follows with the characteristics of the control set U that the proposition holds, compare [11]. □

We use the Forward-Backward Sweep method with the Runge-Kutta 4 method to calculate the solution of the optimal control [12]. We calculate the optimal control solution for three different but fixed coverage of I_d, namely 0.4, 0.6, and 0.8. We start with the end value of the MLE solution in Figure 1 as initial value of the state variables

$$(w_h(0), w_d(0), w_c(0), i_s(0), i_f(0)) = (44.807, 0.508, 11.665, 0.003, 0.246).$$

We choose the weight $\alpha = 0.001$ and solve the ODE system (1) with the MLE parameters in Table 4 forward in time with 1,000 iterations, followed by the calculation of ODE system of the adjoint functions (3) backward in time with 1,000 iterations. With the new solution of the adjoint functions, we can update the solution of the intervention I accordingly to the equations (4). We repeat these steps until the relative error of the interventions is smaller than δ,

$$\frac{\left\| I - \tilde{I} \right\|}{\|I\|} \leq \delta,$$

with $\tilde{I}$ being the previous solution. To include the option of $\|I\| = 0$ we transform it to the condition

$$\delta \|I\| - \left\| I - \tilde{I} \right\| \geq 0.$$

The parameter δ is set to $\delta = 0.001$ [12].

The solution of the the treatment rate $\gamma(t)$ is transformed back to the proportion $I_m(\gamma) = 1 - \exp(\gamma(t) \times 365)$. The minimisation of the interventions I_e and $I_m(\gamma)$ is shown in Figure 6(a), it is the same solution for

all three assumption of $I_d \in \{0.4, 0.6, 0.8\}$. The mean worm burden in the definitive hosts and the prevalence in the intermediate hosts differs about each assumption on I_d as shown in Figures 6(b)–(f).

The solution of the optimal control problem shows that the optimal coverage for treating people is 44%. The coverage of people that should stop eating raw or undercooked fish is set to the maximum of 90% over the whole time period.

6. Elimination

We define the elimination of *O. viverrini* when either the mean worm burden in humans reaches 1 ($w_h \leq 1$) or only one infected fish ($i_f \times N_f \leq 1$) or snail ($i_s \times N_s \leq 1$) is left. Treatment depends on the relationship between the time to elimination of *O. viverrini* and the frequency of treatment. The application is shown in Figure 7(a). We use the parameter values of the MLE solution (see Table 4). We consider levels of coverage $I_m \in \{0.4, 0.5, 0.6, 0.7, 0.8\}$ for mass drug administration. The probability of reaching elimination is calculated with the 500 data sets we constructed from the Bayesian sampling resampling approach, as the proportion of data sets reaching elimination out of the total number of data sets (500). Elimination is achieved when it reaches the threshold limit of less than one worm per person or one infected fish or snail in 20 years. Time to elimination for the interventions education campaign, improved sanitation and mass drug administration at different frequencies as a function of coverage is shown in Figure 7(b). The probability of elimination depending on the treatment frequency is shown in Figure 7(c). The probability of reaching elimination depending on coverage of the interventions is shown in Figure 7(d).

The test to diagnose humans with *O. viverrini* has an estimated sensitivity of 70 to 95 %. The test is currently used to identify healthy people after treatment. We add a parameter ϕ for the sensitivity of the diagnostic test into the model. This is equal to the assumption that we treat only 70 % to 95 % of the coverage I_m, namely $I_m \times \phi$. Then, the untreated proportion of the coverage $(1 - I_m \times \phi)$ are tested false negative and get no treatment. Including the sensitivity changes the first equation of the model (1) to

$$\frac{\mathrm{d}w_h(t)}{\mathrm{d}t} = \beta_{hf} N_f i_f(t)(1 - I_e) - (\mu_{ph} - \log(1 - I_m(t) \times \phi))w_h(t). \quad (5)$$

The impact of the sensitivity of the diagnostic test on the mean worm bur-

den and the probability of elimination is shown in Figure 8. The time to elimination is calculated with the MLE parameter in Table 4.

7. Discussion

We defined the basic and control reproduction number of the model (1). The influence of coverage on the control reproduction number depends on the interventions as shown in Figure 2. The interventions, education campaign (I_e) and improved sanitation (I_d) behave similarly. The coverage of the intervention mass drug administration (I_m) has a stronger influence on the reproduction number, and the control reproduction number reaches 1 at a low coverage. The minimal coverage of targeted humans with education campaigns is $I_e \approx 0.2540$. The same holds true for coverage of improved sanitation $I_d \approx 0.2540$. The coverage of annual mass drug administration has to reach $I_m \approx 0.07$ at a minimum to decrease the worm burden over time.

The decrease of the worm burden in humans with mass drug administration depends on the frequency of the distribution. The more often the distribution takes place, the faster the mean worm burden decreases. The decrease in mean worm burden in humans is much steeper with distributions once or twice a year, than every 2, 3, or 4 years. At higher coverage of mass drug administration, the less is difference between the effects of the distribution frequencies on the mean worm burden in humans.

The optimal control calculation suggests a yearly mass drug administration coverage of $I_m \approx 0.44$, to achieve elimination in 20 years and that education campaigns should target 90% of people to stop eating raw or undercooked fish. Varying the coverage of $I_d \in \{0.4, 0.6, 0.8\}$ does not have an influence on the optimal control calculations of I_e or I_m.

Considering the probability of reaching elimination in 20 years, mass drug administration has to take place once or twice a year. About 80% of all the 500 parameter sets reach elimination with coverage of the optimal control solution of 44% distributed twice a year. A treatment once a year with the same coverage of 44% leads still to elimination in about 50% of the parameter sets. The other two interventions, education campaign (I_e) and resepctively improved sanitation (I_d), require a very high coverage (over 70%) to reach elimination under 30, respectively 35 years. Also, the probability of elimination of these two interventions is below 50% even with a high coverage level. Therefore, education campaigns and improved sanitation alone

are not enough to reach the elimination goal; and treatment of humans is needed. We need high coverage of education campaign on stopping to eat raw or undercooked fish to exclude reinfection of treated humans. Improved sanitation leads to a lower transmission towards snails and brings additional health benefits. Hence, we seek for a coverage as high as possible of improved sanitation.

The sensitivity of the diagnostic test is negligible in terms of the mean worm burden in humans because the difference in the results is less than one worm apart after 20 years. If we look at the probability, then it is only negligible if the mass drug administration covers 80% of the people.

We ignore seasonality, intensity of infection in fish and the age of humans in this model. The number of fish and snails follow a seasonal pattern. Including seasonality into the model could help to find the best time, in terms of effectiveness, to treat humans. The mean worm burden in the definitive hosts increases as faster as higher the intensity of infection in fish is. In this model we do not distinguish between different level of intensity of infection, we only have infected or uninfected fish. We assume that every human is the same and has the same eating behaviour. In reality older people have more worms, because they accumulate worms over their life time. This has the consequences that we have to target the right age group with the interventions.

Our model suggests that the education campaign reaches as many people as possible and the coverage of improved sanitation is at the highest possible level. In minimum about 40% of the people should receive treatment once or twice a year.

Acknowledgement

CB and SS are supported by the Swiss National Science Foundation under grant number 31003A_163057.

References

[1] T. Fürst, U. Duthaler, B. Sripa, J. Utzinger, J. Keiser, Trematode infections: Liver and lung flukes, Infectious Disease Clinics of North America 26 (2) (2012) 399–419.

[2] S. Sayasone, I. Meister, J. R. Andrews, P. Odermatt, Y. Vonghachack, S. Xayavong, K. Senggnam, K. Phongluxa, J. Hattendorf, I. I. Bogoch,

J. Keiser, Efficacy and safety of praziquantel against light infections of opisthorchis viverrini: A randomized parallel single-blind dose-ranging trial, Clinical Infectious Diseases 64 (4) (2017) 451.

[3] P. J. Brindley, J. M. C. da Costa, B. Sripa, Why does infection with some helminths cause cancer?, Trends in Cancer 1 (3) (2015) 174–182.

[4] S. Kaewkes, Taxonomy and biology of liver flukes, Acta Tropica 88 (3) (2003) 177–186.

[5] P. Sithithaworn, M. Haswell-Elkins, Epidemiology of *Opisthorchis viverrini*, Acta Tropica 88 (3) (2003) 187–194.

[6] C. Bürli, H. Harbrecht, P. Odermatt, S. Sayasone, N. Chitnis, Mathematical analysis of the transmission dynamics of the liver fluke, *Opisthorchis viverrini*, Submitted.

[7] F. Brauer, P. van den Driessche, J. Wu (Eds.), Mathematical Epidemiology, Springer, Berlin-Heidelberg, 2008.

[8] Y. Vonghachack, P. Odermatt, K. Taisayyavong, S. Phounsavath, K. Akkhavong, S. Sayasone, Transmission of *Opisthorchis viverrini*, *Schistosoma mekongi* and soil-transmitted helminthes on the Mekong Islands, Southern Lao PDR, Infectious Diseases of Poverty 6 (1) (2017) 131.

[9] O. Diekmann, J. A. P. Heesterbeek, M. G. Roberts, The construction of next-generation matrices for compartmental epidemic models, Journal of The Royal Society Interface 7 (47) (2010) 873–885.

[10] W. H. Fleming, R. W. Rishel, Deterministic and Stochastic Optimal Control, Springer, New York, 1975.

[11] A. Kumar, P. K. Srivastava, Y. Takeuchi, Modeling the role of information and limited optimal treatment on disease prevalence, Journal of Theoretical Biology 414 (2017) 103–119.

[12] S. Lenhart, J. T. Workmann, Optimal Control Applied to Biological Models, Chapman & Hall/CRC, London, 2007.

[13] L. S. Pontryagin, V. G. Boltyanskii, R. V. Gamkrelize, E. F. Mishchenko., The Mathematical Theory of Optimal Processes., Wiley, New York, 1962.

Parameter	Description	Dimension
N_h	Population size of humans	Animals
N_d	Population size of dogs	Animals
N_c	Population size of cats	Animals
N_s	Population size of snails	Animals
N_f	Population size of fish	Animals
μ_{ph}	Per capita death rate of adult parasites in humans (includes additional mortality due to death of humans)	1/Time
μ_{pd}	Per capita death rate of adult parasites in dogs (includes additional mortality due to death of dogs)	1/Time
μ_{pc}	Per capita death rate of adult parasites in cats (includes additional mortality due to death of cats)	1/Time
μ_s	Per capita death rate of snails	1/Time
μ_f	Per capita death rate of fish including mortality through fishing by humans	1/Time
β_{hf}	Transmission rate from infectious fish to humans per person per fish	1/(Time $\times$ Animals)
β_{df}	Transmission rate from infectious fish to dogs per dog per fish	1/(Time $\times$ Animals)
β_{cf}	Transmission rate from infectious fish to cats per cat per fish	1/(Time $\times$ Animals)
β_{sd}	Infection rate of snails per parasite in a dog host	1/(Time $\times$ Animals)
β_{sc}	Infection rate of snails per parasite in a cat host	1/(Time $\times$ Animals)
β_{sh}	Infection rate of snails per parasite in a human host	1/(Time $\times$ Animals)
β_{fs}	Infection rate of fish per snail	1/(Time $\times$ Animals)
I_e	Proportion of people who stop eating raw fish due to intervention	Dimensionless
I_d	Proportion of people who stop defecating outdoors due to intervention	Dimensionless
$I_m(t)$	Proportion of people getting treatment (medication) at time t	Dimensionless
T	Interval of drug distribution	Time

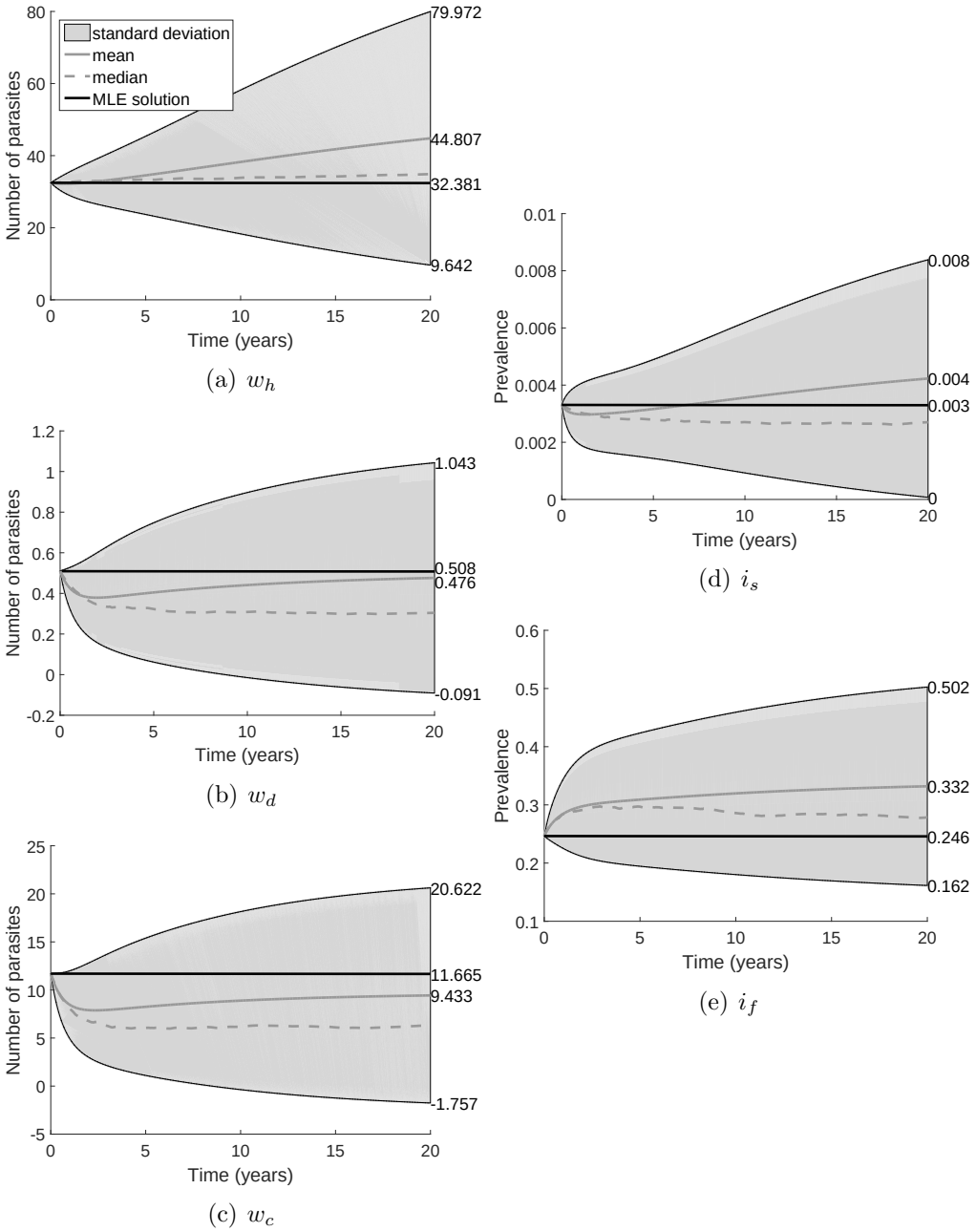
Table 2: Parameters of the opisthorchiasis model with interventions, adapted from [6, Table 2].

Variable	Description	Value
n_h	number of tested humans	994
p_h	number of positive tested humans	603
n_d	number of tested dogs	68
p_d	number of positive tested dogs	17
n_c	number of tested cats	64
p_c	number of positive tested cats	34
n_s	number of tested snails	3102
p_s	number of positive tested snails	9
n_f	number of tested fish	628
p_f	number of positive tested fish	169

Table 3: Total number tested and positive hosts from two islands in Lao PDR [8], see [6, Table 3].

Variable	Value	Range	MLE	Unit
N_h	14542	$[7271, 21813]$	20394	Animals
N_d	7271	$[3635.5, 10906.5]$	6981	Animals
N_c	4847	$[2423.5, 7270.5]$	3618	Animals
N_s	20000	$[2000, 40000]$	15233	Animals
N_f	8000	$[800, 16000]$	12488	Animals
μ_{ph}	$\frac{1}{10\times365}$	$\left[\frac{1}{20\times365}, \frac{1}{1\times365}\right]$	$\frac{1}{4.8\times365}$	1/Days
μ_{pd}	$\frac{1}{4\times365}$	$\left[\frac{1}{8\times365}, \frac{1}{0.4\times365}\right]$	$\frac{1}{4.1\times365}$	1/Days
μ_{pc}	$\frac{1}{4\times365}$	$\left[\frac{1}{8\times365}, \frac{1}{0.4\times365}\right]$	$\frac{1}{2.9\times365}$	1/Days
μ_s	$\frac{1}{1\times365}$	$\left[\frac{1}{2\times365}, \frac{1}{0.1\times365}\right]$	$\frac{1}{0.6\times365}$	1/Days
μ_f	$\frac{1}{2.5\times365}$	$\left[\frac{1}{5\times30}, \frac{1}{0.25\times365}\right]$	$\frac{1}{1.6\times365}$	1/Days
β_{hf}	4.1111×10^{-6}	$[4.1111 \times 10^{-7}, 8.2222 \times 10^{-6}]$	5.9549×10^{-6}	1/(Animal x Day)
β_{df}	2.0159×10^{-7}	$[2.0159 \times 10^{-8}, 4.0317 \times 10^{-7}]$	1.1062×10^{-7}	1/(Animal x Day)
β_{cf}	4.1077×10^{-6}	$[4.1077 \times 10^{-7}, 8.2155 \times 10^{-6}]$	3.6374×10^{-6}	1/(Animal x Day)
β_{sh}	1.4846×10^{-11}	$[1.4846 \times 10^{-12}, 2.9693 \times 10^{-11}]$	2.1600×10^{-11}	1/(Animal x Day)
β_{sd}	1.4846×10^{-11}	$[1.4846 \times 10^{-12}, 2.9693 \times 10^{-11}]$	5.6595×10^{-12}	1/(Animal x Day)
β_{sc}	1.4846×10^{-11}	$[1.4846 \times 10^{-12}, 2.9693 \times 10^{-11}]$	7.8199×10^{-12}	1/(Animal x Day)
β_{fs}	6.9536×10^{-6}	$[6.9536 \times 10^{-7}, 1.3907 \times 10^{-5}]$	1.1209×10^{-5}	1/(Animal x Day)

Table 4: Parameter values of the model and ranges for the sampling, adapted from [6, Table 5].



(a) w_h

(d) i_s

(b) w_d

(e) i_f

(c) w_c

Figure 1: Numerical simulation of the *O. viverrini* model (1) with parameter values selected using MLE (black line) and with the 500 parameters sets choosen with the Bayesian sampling-resampling without any interventions ($I_e = I_d = I_m = 0$) the mean (grey line), median (grey dashed line) and standard deviation (grey area).

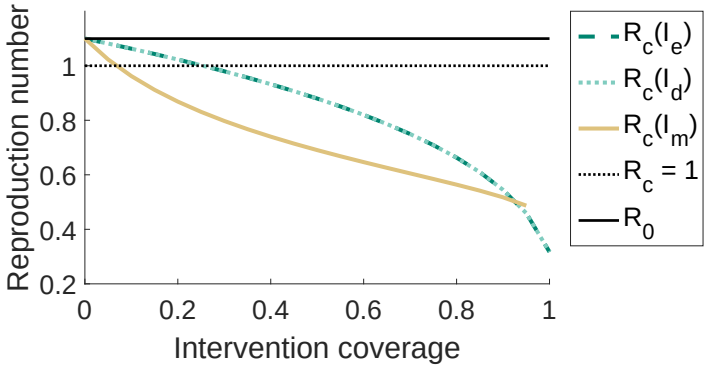


Figure 2: Control reproduction number as a function of the coverage level for various intervention applied singly and the basic reproduction number, calculated with the parameters from the MLE solution in Table 4.

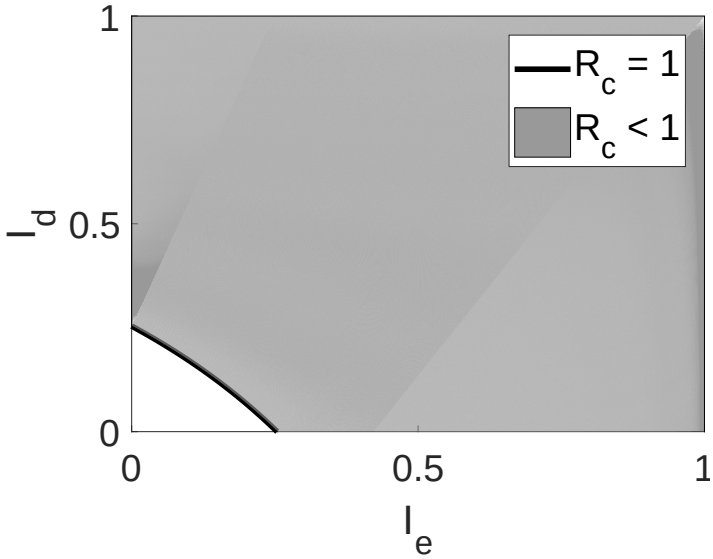
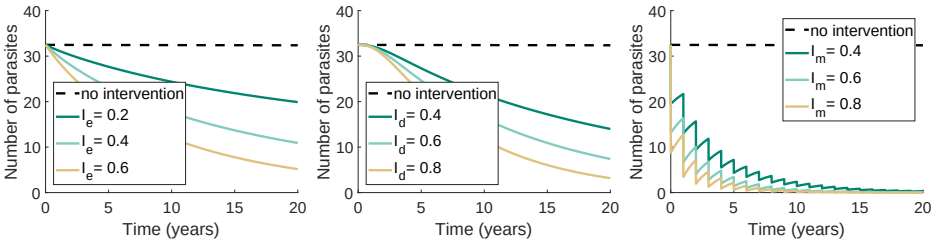


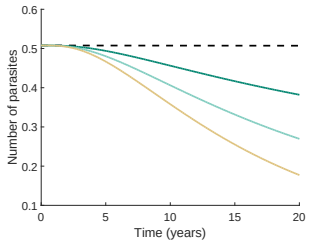
Figure 3: Combinations of I_e and I_d such that $R_c < 1$ in absence of I_m ($I_m = 0$). The other parameters are set to their MLE solution in Table 4.



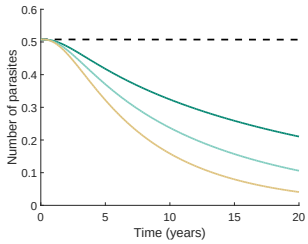
(a) w_h regulated by I_e

(f) w_h regulated by I_d

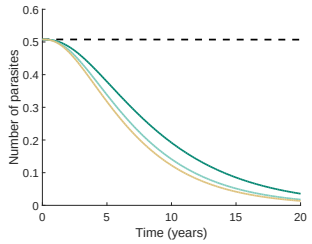
(k) w_h regulated by I_m



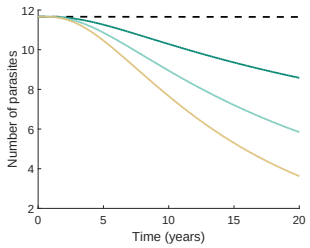
(b) w_d regulated by I_e



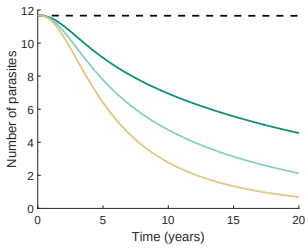
(g) w_d regulated by I_d



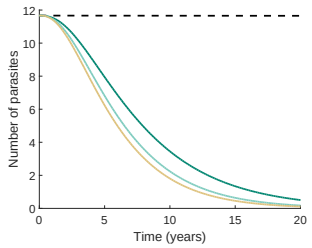
(l) w_d regulated by I_m



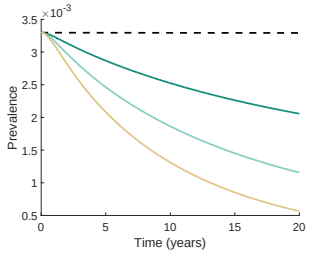
(c) w_c regulated by I_e



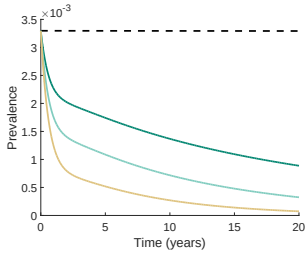
(h) w_c regulated by I_d



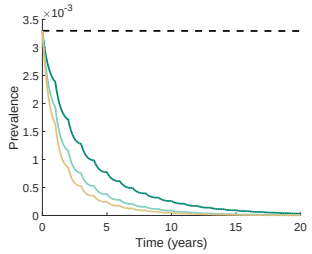
(m) w_c regulated by I_m



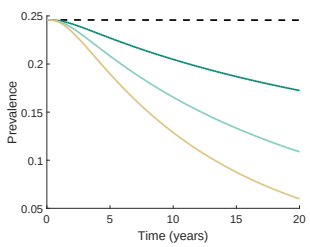
(d) i_s regulated by I_e



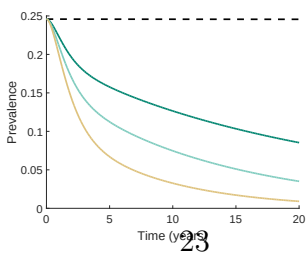
(i) i_s regulated by I_d



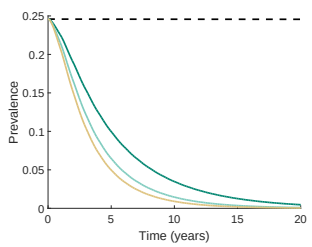
(n) i_s regulated by I_m



(e) i_f regulated by I_e

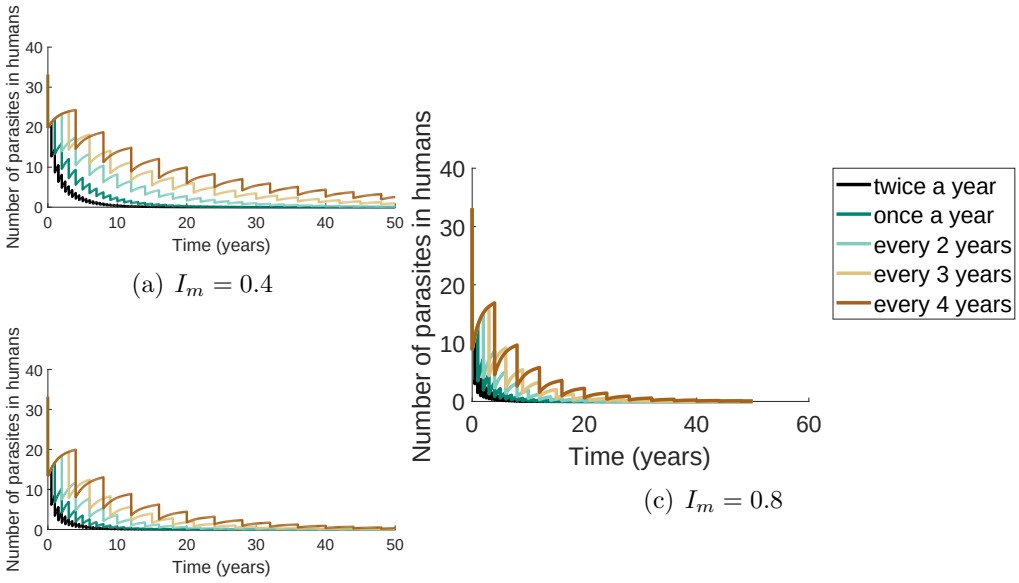


(j) i_f regulated by I_d



(o) i_f regulated by I_m

Figure 4: Numerical simulations of the model (1) with different coverage levels of the interventions compared to the baseline scenarios with no intervention. The parameters are set to the MLE solution in Table 4.

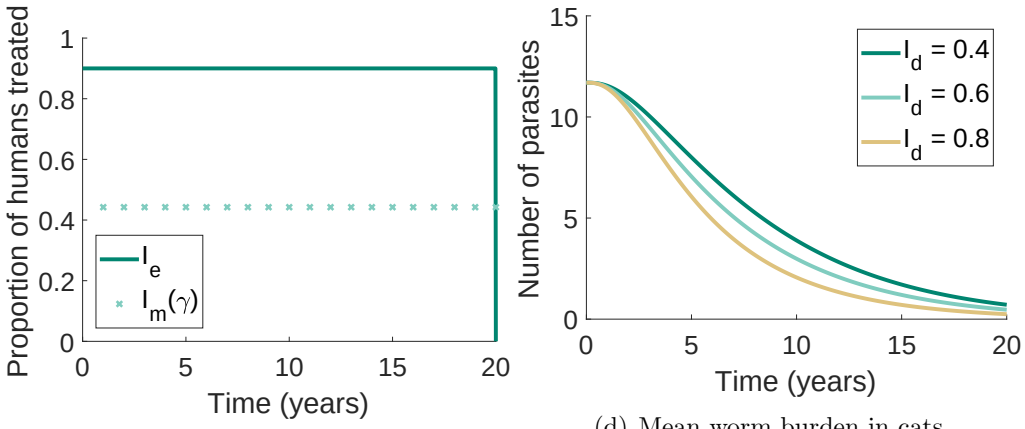


(a) $I_m = 0.4$

(b) $I_m = 0.6$

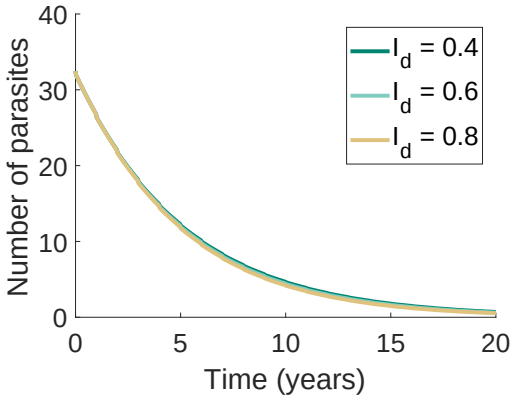
(c) $I_m = 0.8$

Figure 5: Numerical simulations of the frequency of treatment every 0.5, 1, 2, 3 and 4 years and its effect on the mean worm burden in humans. The parameters of the MLE solution in Table 4 are used for the calculation.

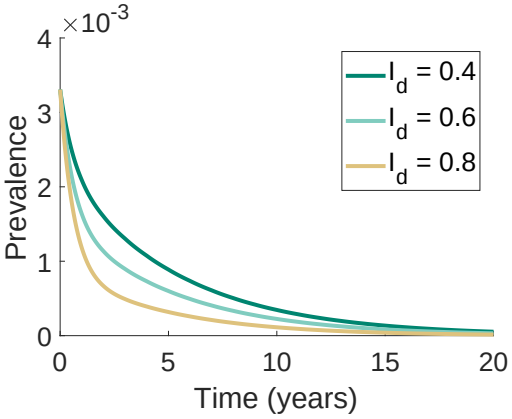


(a) Interventions

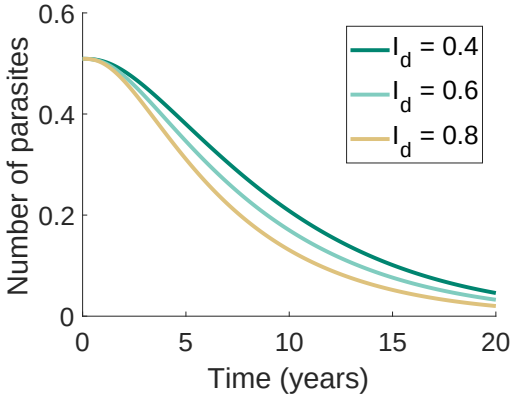
(d) Mean worm burden in cats



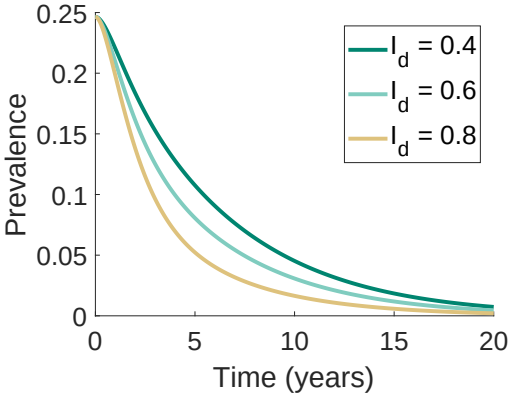
(b) Mean worm burden in humans



(e) Prevalence in snails

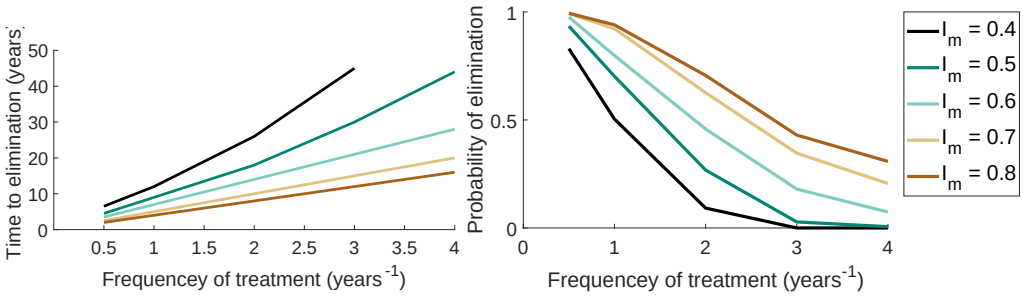


(c) Mean worm burden in dogs



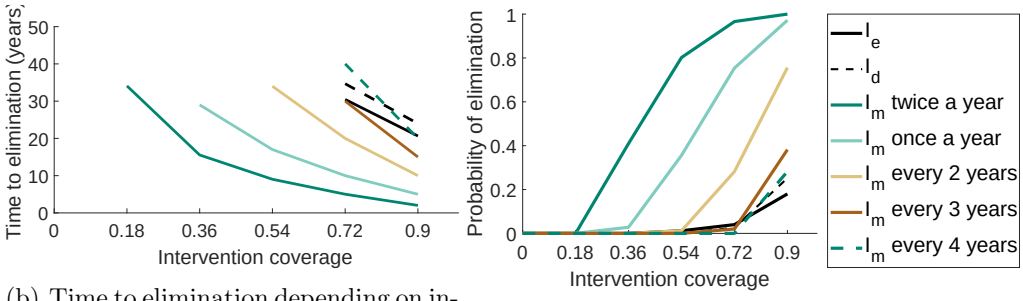
(f) Prevalence in fish

Figure 6: Optimal control results of the interventions and the solution of the model calculated with the Forward-Backward Sweep method for the different assumptions on I_d. The MLE solution parameter (Table 4) are used for the calculation.



(a) Time to elimination depending on treatment interval

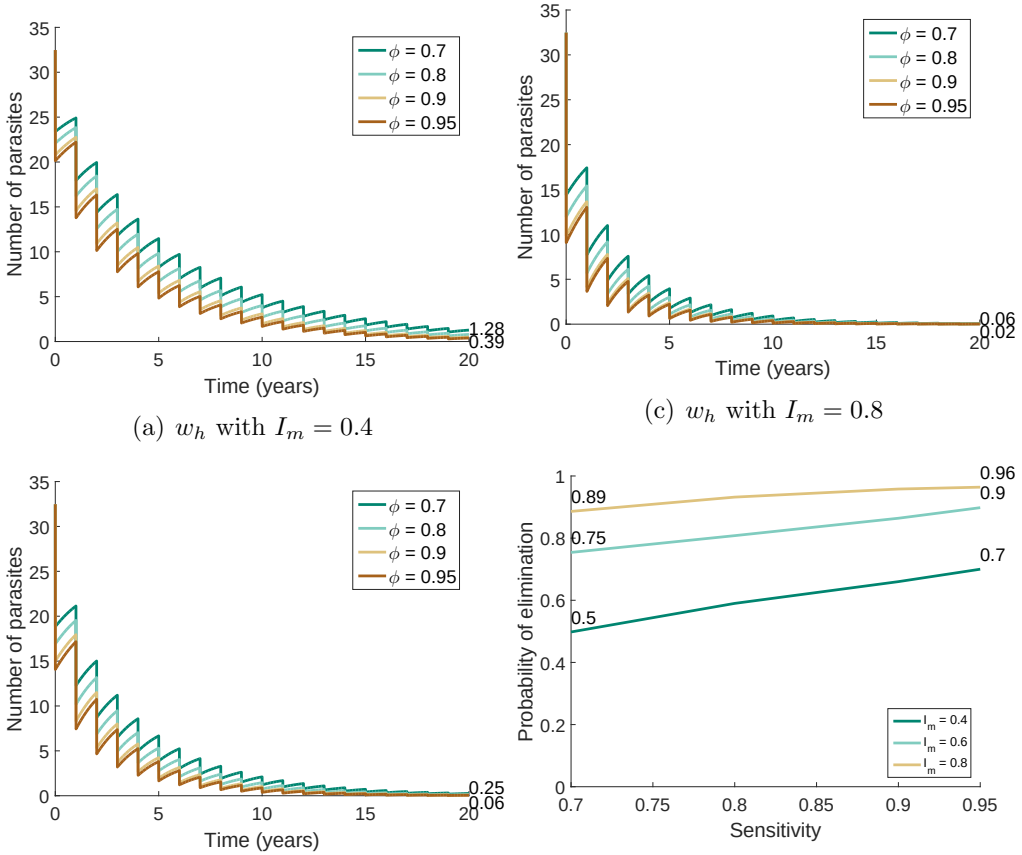
(c) Probability of elimination depending on treatment interval



(b) Time to elimination depending on intervention coverage

(d) Probability of elimination depending on intervention coverage

Figure 7: Time and probability of elimination of the different interventions with different settings. We use the parameter of the MLE solution in Table 4 for the calculation of the time to elimination.



(a) w_h with $I_m = 0.4$

(c) w_h with $I_m = 0.8$

(b) w_h with $I_m = 0.6$

(d) Probability of elimination depending on senstivity of the diagnose test

Figure 8: Impact of the sensitivity of the diagnose test on mean worm burden and the probability of elimination of the 500 data sets. We use the parameter of the MLE solution in Table 4 to simulate the mean worm burden in humans.

LATEST PREPRINTS

No.	Author: *Title*
2016-25	**W. D. Brownawell, D. W. Masser** *Zero estimates with moving targets*
2016-26	**H. Derksen, D. Masser** *Linear equations over multiplicative groups, recurrences, and mixing III*
2016-27	**D. Bertrand, D. Masser, A. Pillay, U. Zannier** *Relative Manin-Mumford for semi-abelian surfaces*
2016-28	**L. Capuano, D. Masser, J. Pila, U. Zannier** *Rational points on Grassmannians and unlikely intersections in tori*
2016-29	**C. Nobili, F. Otto** *Limitations of the background field method applied to Rayleigh-Bénard convection*
2016-30	**W. D. Brownawell, D. W. Masser** *Unlikely intersections for curves in additive groups over positive characteristic*
2016-31	**M. Dambrine, H. Harbrecht, M. D. Peters, B. Puig** *On Bernoulli's free boundary problem with a random boundary*
2016-32	**H. Harbrecht, J. Tausch** *A fast sparse grid based space-time boundary element method for the nonstationary heat equation*
2016-33	**S. Iula** *A note on the Moser-Trudinger inequality in Sobolev-Slobodeckij spaces in dimension one*
2016-34	**C. Bürli, H. Harbrecht, P. Odermatt, S. Sayasone, N. Chitnis** *Mathematical analysis of the transmission dynamics of the liver fluke, Opisthorchis viverrini*
2017-01	**J. Dölz and T. Gerig, M. Lüthi, H. Harbrecht and T. Vetter** *Efficient computation of low-rank Gaussian process models for surface and image registration*
2017-02	**M. J. Grote, M. Mehlin, S. A. Sauter** *Convergence analysis of energy conserving explicit local time-stepping methods for the wave equation*
2017-03	**Y. Bilu, F. Luca, D. Masser** *Collinear CM-points*

Preprints are available under *https://math.unibas.ch/research/publications*

LATEST PREPRINTS

No.	Author: *Title*
2017-04	**P. Zaspel** *Ensemble Kalman filters for reliability estimation in perfusion inference*
2017-05	**J. Dölz and H. Harbrecht** *Hierarchical Matrix Approximation for the Uncertainty Quantification of Potentials on Random Domains*
2017-06	**P. Zaspel** *Analysis and parallelization strategies for Ruge-Stüben AMG on many-core processors*
2017-07	**H. Harbrecht and M. Schmidlin** *Multilevel Methods for Uncertainty Quantification of Elliptic PDEs with Random Anisotropic Diffusion*
2017-08	**M. Griebel and H. Harbrecht** *Singular value decomposition versus sparse grids: Refined complexity Estimates*
2017-09	**J. Garcke and I. Kalmykov** *Efficient Higher Order Time Discretization Schemes for Hamilton-Jacobi-Bellman Equations Based on Diagonally Implicit Symplectic Runge-Kutta Methods*
2017-10	**M. J. Grote and U. Nahum** *Adaptive Eigenspace Regularization For Inverse Scattering Problems*
2017-11	**J. Dölz, H. Harbrecht, S. Kurz, S. Schöps and F. Wolf** *A Fast Isogeometric BEM for the Three Dimensional Laplace- and Helmholtz Problems*
2017-12	**P. Zaspel** *Algorithmic patterns for $\mathcal{H}$-matrices on many-core processors*
2017-13	**R. Brügger, R. Croce and H. Harbrecht** *Solving a free boundary problem with non-constant coefficients*
2017-14	**M. Dambrine, H. Harbrecht and B. Puig** *Incorporating knowledge on the measurement noise in electrical impedance tomography*
2017-15	**C. Bürli, H. Harbrecht, P. Odermatt, S. Sayasone and N. Chitnis** *Analysis of Interventions against the Liver Fluke, Opisthorchis viverrini*

Preprints are available under *https://math.unibas.ch/research/publications*