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, Basel 4002, Switzerland*
[b] *University of Basel, Basel, Switzerland*
[c] *Lao Tropical and Public Health Institute, Vientiane, Lao People's Democratic Republic*
[d] *Department of Mathematics and Computer Science, University of Basel, Basel, Switzerland*

ABSTRACT

We adapt a population-based model of *Opisthorchis 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 fit model parameters to a data set from two islands in southern Lao PDR. 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 improved sanitation need a very high coverage to fulfil the goal of elimination, whereas annual drug distribution at medium coverage is sufficient. The best solution is a combination of drug distribution at a medium level of coverage and as high as possible coverage of education and improved sanitation.

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 cercariae 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 using data collected from two villages in Lao PDR.

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 chosen intervention in different influenza models. We can adapt the optimal control method of these influenza models to our model.

We find the optimal coverage of each intervention to reach the goal of elimination of *O. viverrini* within 20 years. We consider three different types of interventions and model their targeted coverage. The first intervention is the use of education campaigns to change people's eating habits so that they stop eating raw or undercooked fish, reducing 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 intervention is treatment. We consider the coverage of people that need to be treated, with the assumption that the drugs are completely efficacious. We also consider the optimal frequency of drug distribution. Currently, 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].

---

* Corresponding author at: Swiss Tropical and Public Health Institute, Socinstrasse 57, Basel, 4002, Switzerland.
E-mail address: christine.buerli@unibas.ch (C. Bürli).

Other interventions against *O. viverrini*, not considered here, are drug treatment of reservoir hosts and the detection of potential cancer in the liver with ultrasound in humans [7,8]. We did not include the treatment of reservoir hosts, as we showed in the previous paper [6], that is not possible to interrupt transmission without focusing on reducing the mean worm burden in humans. Furthermore, this model of the mean worm burden in humans only considers transmission and does not include the impact of morbidity, which would be focus of interventions against cancer.

After describing the model, we estimate the unknown parameters using data from Lao PDR. We define the basic as well as the control reproduction numbers of the model. This helps us to determine the minimum coverage of each intervention. Then we optimise targeted coverage levels with the optimal control method. Finally we investigate the elimination potential of interventions by estimating the time to and probability of achieving elimination of *O. viverrini*.

2. General 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 of infection 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 improved sanitation, that is the proportion of people who 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 [9]. It follows that the treatment rate is

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

The full model is given by the ordinary differential equation system,

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

(1a)

$$\frac{dw_d(t)}{dt} = \beta_{df} N_f i_f(t) - \mu_{pd} w_d(t),$$

(1b)

$$\frac{dw_c(t)}{dt} = \beta_{cf} N_f i_f(t) - \mu_{pc} w_c(t),$$

(1c)

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

(1d)

$$\frac{di_f(t)}{dt} = \beta_{fs} N_s i_s(t)(1 - i_f(t)) - \mu_f i_f(t),$$

(1e)

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

Table 1
State variables of the opisthorchiasis model, see [6, Table 1].

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

We model the mean worm burden per human host, w_h, assuming a negative binomial distribution for the distribution of worms in humans [6]. We assume no correlation between the worm burden of an individual and the probability of being influenced by the education campaign to stop eating raw fish, so 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 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 in humans. 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 on the intensity of infection in humans (see Table 3). The number of humans is estimated from the study in Champasack province [10], but additional data on the number of animals and death rates are from literature and expert opinion.

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 and no intervention $I_e = I_d = I_m = 0$, followed by the maximum likelihood estimation (MLE) method. We sample 50,000 data sets and resample 500 of them in the Bayesian resampling approach. 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 Fig. 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 Fig. 1.

3. Model with continuous treatment

We first assume continuous treatment with I_m constant throughout the year and $T_\gamma = 365$ days in the model, which refers to a daily treatment rate while coverage is defined as the proportion of people treated within one year (as described above). For the model with continuous treatment, it is possible to calculate the basic and the control reproduction number and to determine the threshold value of coverage where the control reproduction number is equal to one.

3.1. 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 assuming no density dependence and no interventions. It is calculated as the spectral radius of the next-generation matrix [11]. The cubed spectral radius is equal to the number of adult offspring in mammalian hosts from one adult worm in a mammalian host. It follows that when the basic reproduction number is below one ($\mathcal{R}_0 < 1$), the parasite cannot produce

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

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 × Animals)
β_{df}	Transmission rate from infectious fish to dogs per dog per fish	1/(Time × Animals)
β_{cf}	Transmission rate from infectious fish to cats per cat per fish	1/(Time × Animals)
β_{sd}	Infection rate of snails per parasite in a dog host	1/(Time × Animals)
β_{sc}	Infection rate of snails per parasite in a cat host	1/(Time × Animals)
β_{sh}	Infection rate of snails per parasite in a human host	1/(Time × Animals)
β_{fs}	Infection rate of fish per snail	1/(Time × 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 3
Total number tested and positive hosts from two islands in Lao PDR [10], see [6, Table 3].

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

enough offspring to persist. The control reproduction number $\mathcal{R}_c$ includes the impact of interventions on the reproduction number. The next-generation matrix **K** of the model (1), with constant I_m, is given by

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

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

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

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). The basic reproduction number is $\mathcal{R}_0 = 1.1351$ with the MLE parameter values in Table 4.

The control reproduction number depends on the type and coverage of the intervention. Fig. 2, shows the impact of coverage of each intervention applied singly on the control reproduction number for parameter values determined by MLE and $T_\gamma = 365$. The control reproduction number $\mathcal{R}_c$ has a similar dependence on the level of coverage of education campaigns (I_e) and improved sanitation (I_d). The coverage needs to be at least 34% for either of these two interventions for $\mathcal{R}_c$ to be 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 for mass drug administration decreases below 1 at the a low coverage of 10%. Fig. 2 also shows that the incremental effectiveness of the interventions in reducing $\mathcal{R}_c$ increases with coverage for improved sanitation and education campaign but decreases for mass treatment. Therefore, programs should try to achieve as high a coverage of education campaigns and improved sanitation as possible, but a moderate coverage of mass treatment may be sufficient.

The possible combination of the interventions I_e and I_d (without I_m) which are successful in achieving $\mathcal{R}_c < 1$, for MLE parameter values, are shown in Fig. 3. The minimum combination such that $\mathcal{R}_c < 1$ is $I_e = I_d = 0.2025$.

4. Model with pulsed treatment

The second model is a pulsed treatment applied at a fixed frequency. This model takes into account that the number of worms increases in humans in between mass drug administration. For example, treatment once a year, conducted over one day, is modelled by,

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

with $T_\gamma = 1$ day.

This model allows us to additionally consider the frequency of the mass drug administration in determining the effectiveness of interventions on the probability of elimination and time to elimination. We also calculate the optimal coverage of the mass drug administration and education campaigns using optimal control theory.
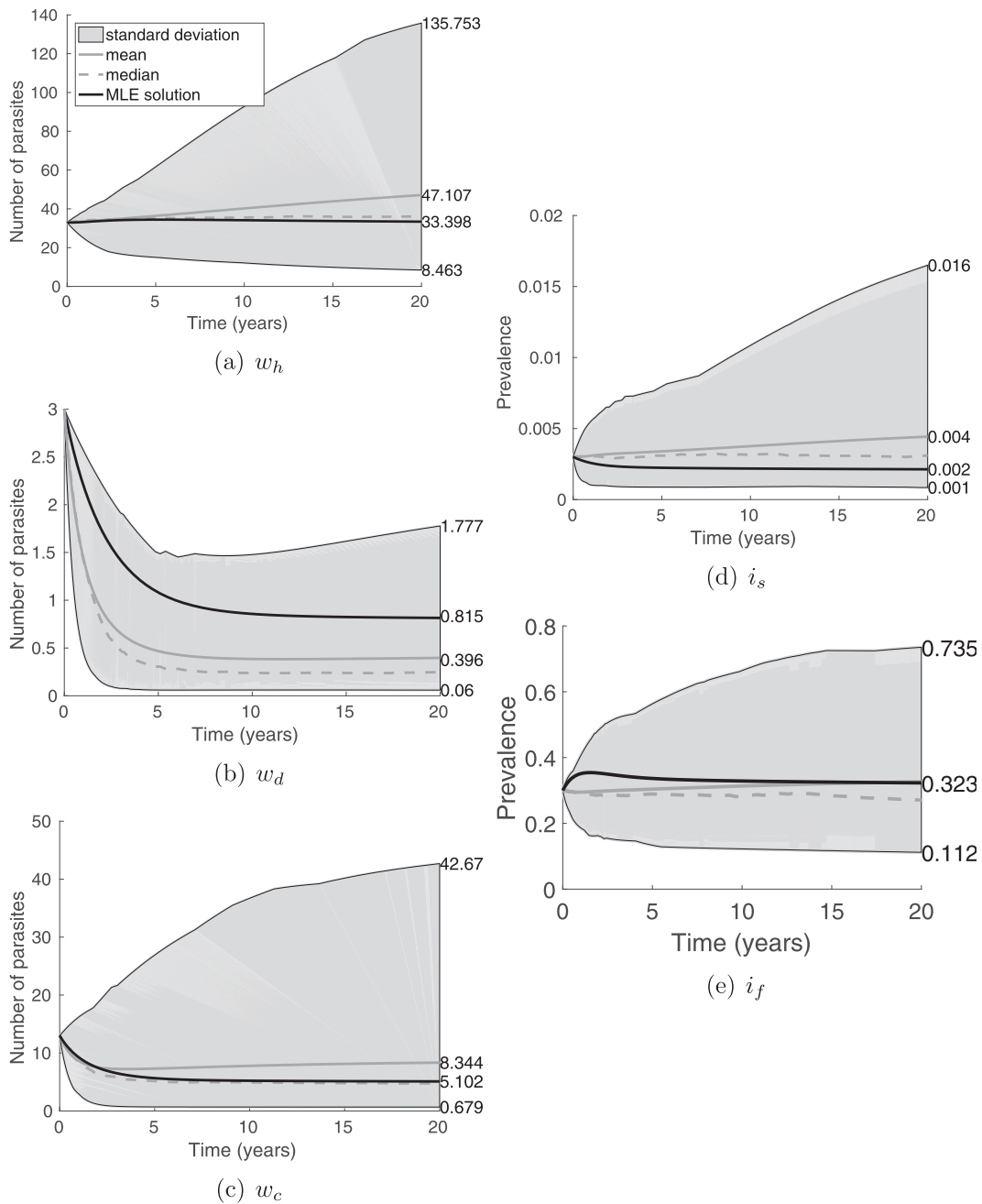
(a) w_h

(b) w_d

(c) w_c

(d) i_s

(e) i_f

Fig. 1. Numerical simulation of the *O. viverrini* model (1) with parameter values selected using MLE (black line) and with the 500 parameters sets chosen 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).
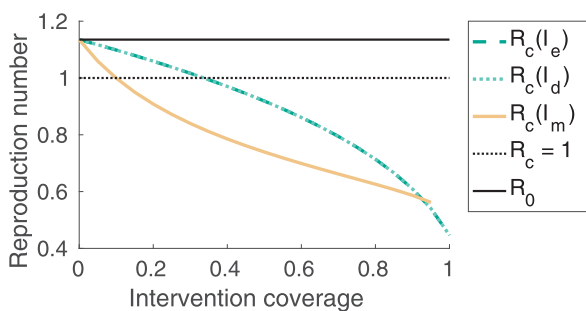

Fig. 2. Control reproduction number as a function of the coverage level for various intervention applied singly and the basic reproduction number, calculated with the parameters from the MLE solution in Table 4.

4.1. Effectiveness of interventions

The minimum levels of coverage we calculated with continuous treatment, where $\mathcal{R}_c = 1$, are not sufficient to reach a low mean worm burden in humans in 20 years. Hence, we simulate reasonably achievable coverage levels of $I_e \in \{0.2, 0.4, 0.6\}$ and $I_d, I_m \in \{0.4, 0.6, 0.8\}$. We choose these coverage levels because we assume that it is more difficult to changes people's eating habit through education campaigns, than it is to convince them to use a latrine or accept treatment. Mass drug administration is assumed to be distributed over one day once a year. Fig. 4 shows the numerical solutions for all state variables for each intervention at these different levels of coverage compared to no interventions.

To investigate the impact of mass drug administration on the frequency of distribution, we simulate campaigns distributing drugs every

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

| Variable	Value	Range	MLE	Unit
N_h	14,542	[7271, 21, 813]	15,705	Animals
N_d	7271	[3635.5, 10906.5]	8437	Animals
N_c	4847	[2423.5, 7270.5]	6098	Animals
N_s	20,000	[2000, 40, 000]	31,019	Animals
N_f	8000	[800, 16, 000]	9701	Animals
μ_{ph}	$\frac{1}{10 \times 365}$	$\left[\frac{1}{20 \times 365}, \frac{1}{1 \times 365}\right]$	$\frac{1}{4.8 \times 365}$	1/Days
μ_{pd}	$\frac{1}{4 \times 365}$	$\left[\frac{1}{8 \times 365}, \frac{1}{0.4 \times 365}\right]$	$\frac{1}{2.2 \times 365}$	1/Days
μ_{pc}	$\frac{1}{4 \times 365}$	$\left[\frac{1}{8 \times 365}, \frac{1}{0.4 \times 365}\right]$	$\frac{1}{1.5 \times 365}$	1/Days
μ_s	$\frac{1}{1 \times 365}$	$\left[\frac{1}{2 \times 365}, \frac{1}{0.1 \times 365}\right]$	$\frac{1}{1 \times 365}$	1/Days
μ_f	$\frac{1}{2.5 \times 365}$	$\left[\frac{1}{5 \times 30}, \frac{1}{0.25 \times 365}\right]$	$\frac{1}{1.5 \times 365}$	1/Days
β_{hf}	4.1111×10^{-6}	$[4.1111 \times 10^{-7}, 8.2222 \times 10^{-6}]$	5.9785×10^{-6}	1/(Animal x Day)
β_{df}	2.0159×10^{-7}	$[2.0159 \times 10^{-8}, 4.0317 \times 10^{-7}]$	3.2337×10^{-7}	1/(Animal x Day)
β_{cf}	4.1077×10^{-6}	$[4.1077 \times 10^{-7}, 8.2155 \times 10^{-6}]$	2.9608×10^{-6}	1/(Animal x Day)
β_{sh}	1.4846×10^{-11}	$[1.4846 \times 10^{-12}, 2.9693 \times 10^{-11}]$	1.0210×10^{-11}	1/(Animal x Day)
β_{sd}	1.4846×10^{-11}	$[1.4846 \times 10^{-12}, 2.9693 \times 10^{-11}]$	2.8635×10^{-11}	1/(Animal x Day)
β_{sc}	1.4846×10^{-11}	$[1.4846 \times 10^{-12}, 2.9693 \times 10^{-11}]$	4.7734×10^{-12}	1/(Animal x Day)
β_{fs}	6.9536×10^{-6}	$[6.9536 \times 10^{-7}, 1.3907 \times 10^{-5}]$	1.2900×10^{-5}	1/(Animal x Day)
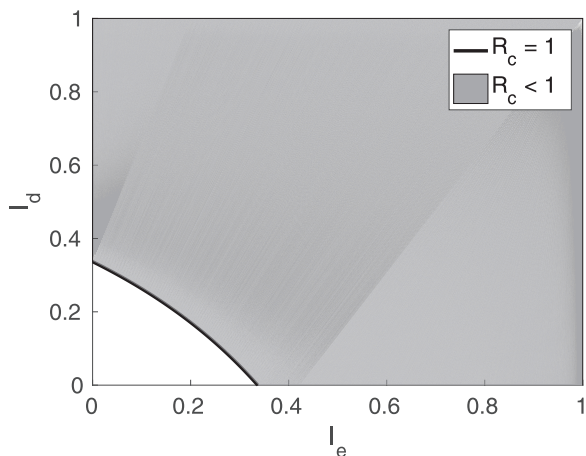
Fig. 3. Combinations of I_e and I_d such that $\mathcal{R}_c < 1$ in absence of I_m ($I_m = 0$). The other parameters are set to their MLE solution in Table 4.

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 Fig. 5.

4.2. 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,

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

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

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

Minimising the coverage of the interventions affecting humans leads to the optimal control problem,

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

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 equivalent 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. The optimal control solutions are robust to this parameter, the results are similar even with $\alpha = 1$. We assume that it is not possible to reach all people by either campaign, and that the maximum achievable coverage of drug distribution is 80%, and of the education campaigns 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; $\frac{df}{dt} = f(x, t)$ 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 $i = 1, \ldots, 5$;

$$J(I) = \int_0^T w_h^2(t) + \frac{\alpha^2}{2}\left(I_e^2 + \sum_{k=1}^n \gamma_k^2\right) dt$$
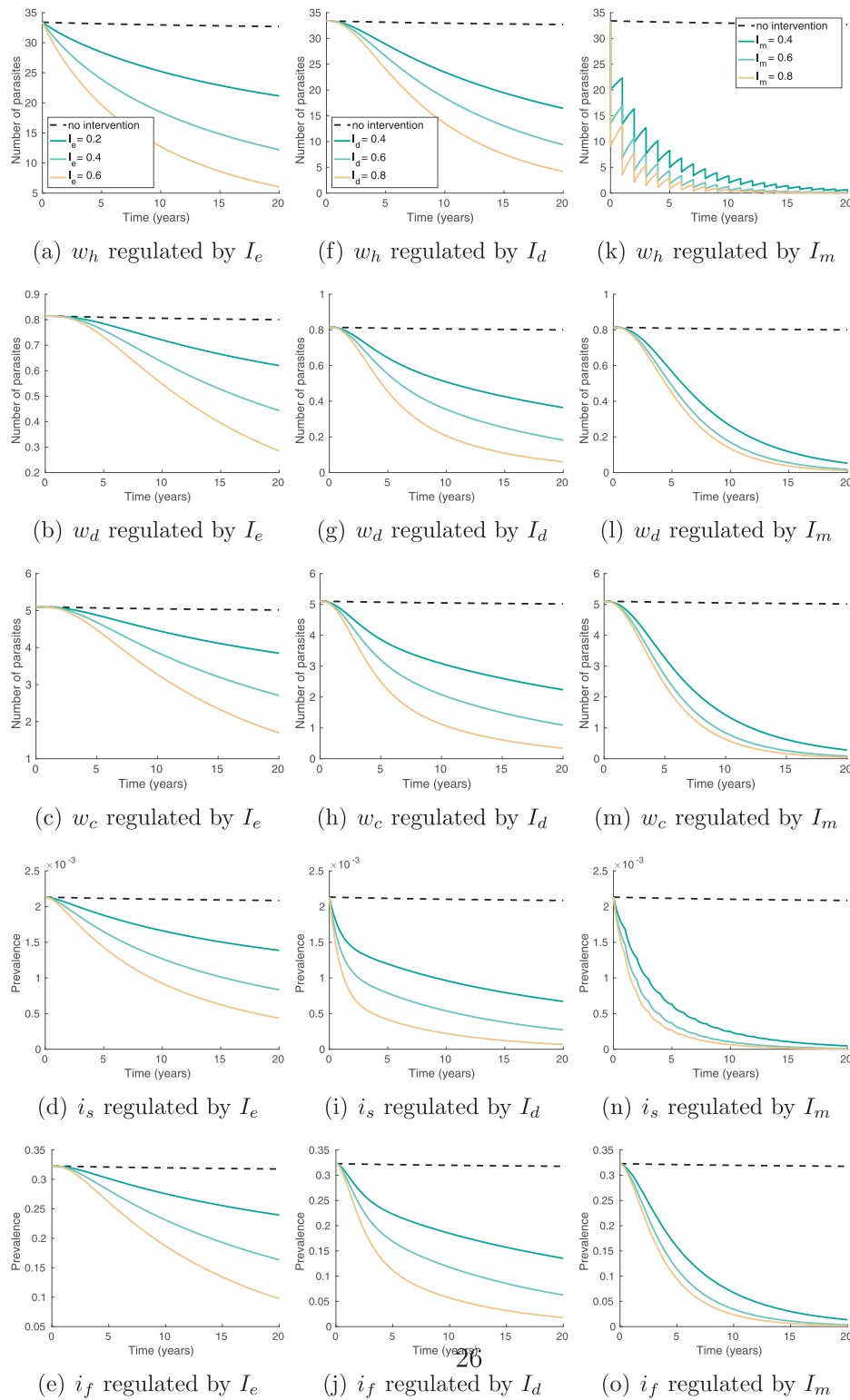
as the integral to minimise and

Fig. 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.

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

To show that a solution exists to this optimal control problem, we have to prove the following assumptions [12,13]:

Proposition 1 (*Existence*).

(i) *The set of solutions of 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*

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

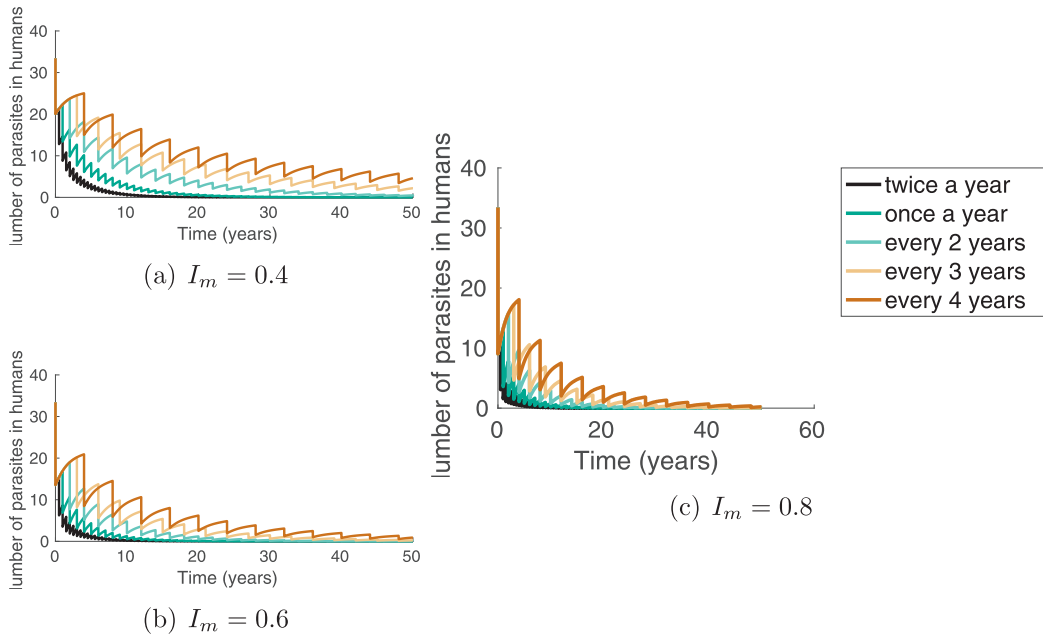(iii) *$L(t, w_h, \cdot)$ is convex on U.*

Fig. 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.

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 proof of the 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 $\widetilde{S} \subseteq \mathbb{R}^5$, given by

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

(ii) U is closed and convex because it is a Cartesian product of closed intervals. f can be written as a linear combination in the form

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

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:

$$L(t, w_h, (1-\varepsilon)I_1 + \varepsilon I_2) \le (1-\varepsilon)L(t, w_h, I_1) + \varepsilon L(t, w_h, I_2),$$

for $I_1, I_2 \in I$.

It holds

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

$$= w_h^2 + ((1-\varepsilon)I_{e,1} + \varepsilon I_{e,2})^2 + \left((1-\varepsilon)\sum_{k=1}^n \gamma_{k,1}(t) + \varepsilon \sum_{k=1}^n \gamma_{k,2}(t)\right)^2$$

$$\le (1-\varepsilon)\left(w_h^2 + \frac{\alpha^2}{2}\left(I_e^2 + \sum_{k=1}^n \gamma_k(t)^2\right)\right)$$

$$+ \varepsilon\left(w_h^2 + \frac{\alpha^2}{2}\left(I_e^2 + \sum_{k=1}^n \gamma_k(t)^2\right)\right). \qquad \square$$

To characterise the optimal solution, we use Pontryagin's maximum principle [14]. The proof can be found in Pontryagin's original text [15].

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,

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

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^* be 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

$$\lambda_1' = -2w_h + \lambda_1(\mu_{ph} + \gamma) - \lambda_4\beta_{sh}N_h(1 - I_d)(1 - i_s), \tag{3a}$$

$$\lambda_2' = \lambda_2\mu_{pd} - \lambda_4\beta_{sd}N_d(1 - i_s), \tag{3b}$$

$$\lambda_3' = \lambda_3\mu_{pc} - \lambda_4\beta_{sc}N_c(1 - i_s), \tag{3c}$$

$$\lambda_4' = \lambda_4(\beta_{sh}N_hw_h(1 - I_d) + \beta_{sd}N_dw_d + \beta_{sc}N_cw_c + \mu_s) - \lambda_5\beta_{fs}N_s(1 - i_f), \tag{3d}$$

$$\lambda_5' = \lambda_5(\beta_{fs}N_si_s + \mu_f) - \lambda_1\beta_{hf}N_f(1 - I_e) - \lambda_2\beta_{df}N_f - \lambda_3\beta_{cf}N_f, \tag{3e}$$

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

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

$$\gamma^* = \frac{\lambda_1w_h}{\alpha^2}. \tag{4b}$$

It follows with the characteristics of the control set U that the proposition holds (compare [13]). □

We use the Forward-Backward Sweep method with the Runge-Kutta 4 method to calculate the solution of the optimal control [14]. We calculate the optimal control solution for three different, but fixed, coverage levels of I_d: 0.4, 0.6, and 0.8. We start with the end value of the MLE solution in Fig. 1 as initial value of the state variables,

$$(w_h(0), w_d(0), w_c(0), i_s(0), i_f(0)) = (47.107, 0.815, 5.120, 0.002, 0.323).$$

We choose the weight $\alpha = 0.001$ and solve the ODE system (1) with the MLE parameters in Table 4 forward in time with 1000 iterations, followed by the calculation of ODE system of the adjoint functions (3) backward in time with 1000 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,

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

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

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

The parameter δ is set to $\delta = 0.001$ [14].

The solution of 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 Fig. 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 depends on the coverage of improved sanitation, I_d, as shown in Fig. 6(b)–(f).

The solution of the optimal control problem shows that the optimal coverage for treatment 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.

4.3. Elimination

We define the elimination of *O. viverrini* as in Definition 1 when there is less than one worm per person ($w_h \leq 1$) or less than one infected fish ($i_f \times N_f \leq 1$) or snail ($i_s \times N_s \leq 1$).

Definition 1 (*Elimination*). Elimination of *O. viverrini* is reached if at least one of the following statements is true:

(i) $w_h \leq 1$
(ii) $i_f \times N_f \leq 1$

(iii) $i_s \times N_s \leq 1$,

within a default timeframe of 20 years.

Fig. 7 shows the time to elimination and probability of elimination at varying frequencies of mass treatment and at varying levels of coverage for all three interventions. We estimate the time to elimination for MLE parameter values (see Table 4) assuming that interventions are deployed at time $t = 0$ with the endemic equilibrium in the absence of interventions as the initial condition. Fig. 7(a) shows the time to elimination at different frequencies of mass treatment at coverage levels of $I_m \in \{0.4, 0.5, 0.6, 0.7, 0.8\}$. Fig. 7(b) shows the time to elimination for all interventions as the coverage of each intervention increases. We estimate the probability of reaching elimination as the proportion of the 500 resampled parameter sets that achieve the definition of elimination above. The probability of elimination as a function of treatment frequency is shown in Fig. 7(c) and as a function of intervention coverage is shown in Fig. 7(d). The results show that mass treatment, even at very low frequencies is more effective and faster in achieving elimination than improved sanitation or education campaigns and even relatively low coverage of treatment at a high frequency is as effective if not more than high coverage of the other interventions or of treatment at low frequencies.

5. Discussion

We defined the basic and control reproduction number of the model with continuous treatment (1). Education campaigns (I_e) and improved sanitation (I_d) show a similar relationship between coverage and the control reproduction number, with a sharper decrease as coverage increases. Since increasing coverage leads to larger gains, if these interventions are deployed, high coverage should be targeted. The coverage of mass treatment (I_m) has a stronger influence on the reproduction number, and a lower coverage is sufficient to reach the threshold of 1. The minimal coverage of successfully targeted humans with education campaigns is $I_e \approx 0.34$. The same is true for coverage of improved sanitation, $I_d \approx 0.34$. The coverage of continuous treatment has to reach $I_m \approx 0.10$ within a year at a minimum to eventually lead to elimination.

The decrease of the worm burden in humans with mass drug administration in the model with pulsed treatment also 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. However, as the coverage of mass drug administration increases, the impact of the frequency of distribution decreases.

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 underlying coverage of improved sanitation, $I_d \in \{0.4, 0.6, 0.8\}$ does not have an influence on the optimal control calculations of the coverage of mass treatment or education campaigns.

The World Health Organization promotes regular mass drug administration to reduce the parasite burden in the community and the subsequent development of severe morbidity. Today, Praziquantel is the only efficacious medicine against trematodes such as Opisthorchis and Schistosoma. It has been widely and intensively used in human trematode infection control, but so far no resistance has been identified. However, there is a potential risk that resistance might develop. Therefore, in addition to researching new drug candidates, such as Tribendimidine [16], preventive control measures such as promoting well-cooked fish consumption and improved sanitation is essential (although behaviour change remains challenging to achieve).

According to our simulation results, mass drug administration has to take place once or twice a year to achieve elimination within 20 years.
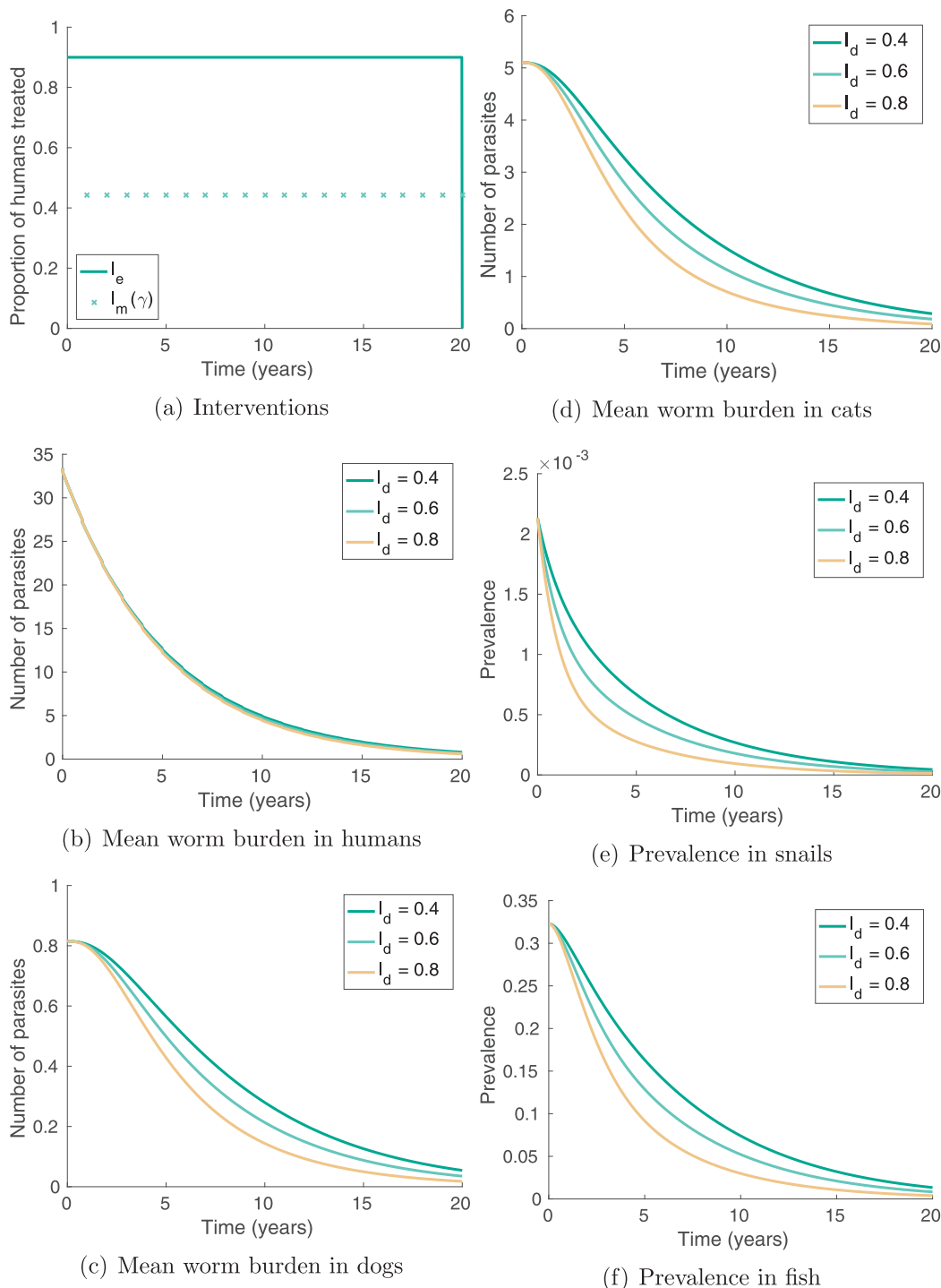
(a) Interventions

(b) Mean worm burden in humans

(c) Mean worm burden in dogs

(d) Mean worm burden in cats

(e) Prevalence in snails

(f) Prevalence in fish

Fig. 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 parameters (Table 4) are used for the calculations.

About 97% of the 500 resampled parameter sets reach elimination with a mass treatment coverage of the optimal control solution of 44% administered twice a year. A treatment once a year with the same coverage of 44% leads still to elimination in about 78% of the parameter sets. The other two interventions, education campaigns (I_e) and (respectively) improved sanitation (I_d), require a very high coverage (over 60%) to reach elimination within 49, and (respectively) 45 years. Also, the probability of elimination of these two interventions within 20 years is below 18% respectively 51% even with a high coverage level. Therefore, education campaigns and improved sanitation alone are not

enough to reach the elimination goal; and mass treatment of humans is necessary.

However, high coverage of education campaigns reduces the re-infection of treated humans, and improved sanitation reduces transmission to snails and brings additional health benefits. Hence, we should seek as high a coverage as possible of these interventions. In this analysis we have defined the coverage of the education campaigns as the proportion of people who stop eating raw or undercooked fish and consequently do not reinfect themselves. We have similarly defined the coverage of improved sanitation as the proportion of defecations that
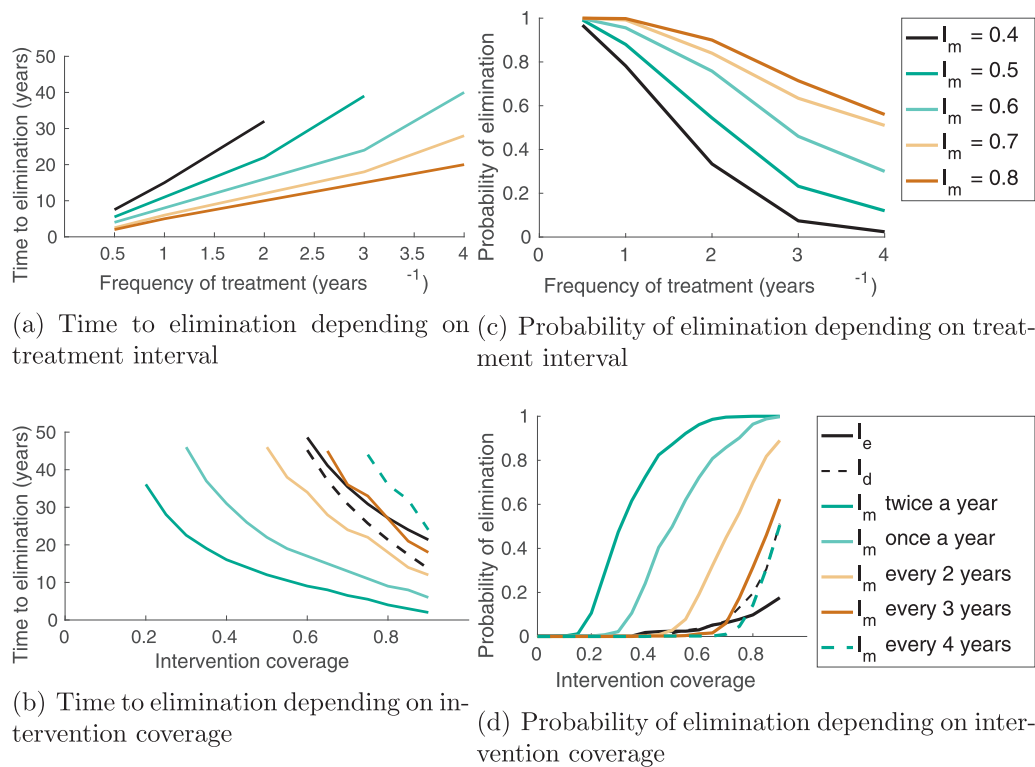
(a) Time to elimination depending on treatment interval

(c) Probability of elimination depending on treatment interval

(b) Time to elimination depending on intervention coverage

(d) Probability of elimination depending on intervention coverage

Fig. 7. Time to elimination 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 and the resampled parameter sets to determine the probability of elimination.

occur within improved sanitation. Neither of these definitions of coverage are easy to measure in the field may be approximated through questionnaires.

Here, we ignore seasonality, intensity of infection in fish, the age of humans and the secondary impacts of overdispersion of worms in this model. Fish and snail populations follow a seasonal pattern. Including seasonality in the model could help to optimise the timing of interventions to more effectively reduce worm burden. The mean worm burden in the definitive hosts increases as the intensity of infection in fish increases. However, here we only modelled the prevalence of infection in fish since we lacked data on the intensity of infection in fish. Also, in reality older people have more worms, because they accumulate worms over their life time. This implies that interventions could be more or less effective depending on the age group of humans that is targeted (such as education campaigns in schools) but our model ignores this targeting.

The worms are not only unequally distributed over age but are generally heterogeneous with an overdispersed distribution over the population (that is, a few people have an extremely high number of worms while the majority have zero to a few worms). We modelled this by assuming a negative binomial distribution for the worm burden in the human population [6] but ignored the secondary impacts of this overdispersion. These effects — such as the impact of worm burden on morbidity; the nonlinear relationship between treatment and worm burden on morbidity; and the impact of targeted interventions — would be better analysed with an individual-based model that can separately track the worm burden of each human and the impact of interventions on that human.

We also did not consider the sustainability of the interventions. It has been shown that governmental control programmes are often only successful during the implementation [17]. We assume here that the interventions will continue to be active and equally efficacious over the simulation period; that is the human population will maintain the behaviour change of not eating raw fish and that the improved sanitation

will be maintained. Acknowledging these assumptions, our model suggests that elimination of *O. viverrini* in Lao PDR is feasible within 20 years, if at least reasonable coverage of annual mass drug administration campaigns is maintained and efforts are made to change the population's eating habits and sanitation is improved.

References

[1] T. Fürst, U. Duthaler, B. Sripa, J. Utzinger, J. Keiser, Trematode infections: liver and lung flukes, Infect. Dis. Clin. North Am. 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, Clin. Infect. Dis. 64 (4) (2017) 451.

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

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

[5] P. Sithithaworn, M. Haswell-Elkins, Epidemiology of *opisthorchis viverrini*, Acta Trop. 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*, J. Theor. Biol. 439 (2018) 181–194.

[7] B. Sripa, S. Tangkawattana, T. Laha, S. Kaewkes, F.F. Mallory, J.F. Smith, B.A. Wilcox, Toward integrated opisthorchiasis control in northeast thailand: the lawa project, Acta Trop. 141 (2015) 361–367. Progress in research and control of helminth infections in Asia.

[8] B. Sripa, S. Tangkawattana, T. Sangnikul, The lawa model: a sustainable, integrated opisthorchiasis control program using the ecohealth approach in the lawa lake region of thailand, Parasitol. Int. 66 (4) (2017) 346–354. Special Issue: Opisthorchiasis: 100 Years of Discovery.

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

[10] 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, Infect Dis. Poverty 6 (1) (2017) 131.

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

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

[13] A. Kumar, P.K. Srivastava, Y. Takeuchi, Modeling the role of information and limited optimal treatment on disease prevalence, J. Theor. Biol. 414 (2017) 103–119.

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

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

[16] S. Sayasone, J. Keiser, I. Meister, Y. Vonghachack, S. Xayavong, K. Senggnam, K. Phongluxa, J. Hattendorf, P. Odermatt, Efficacy and safety of tribendimidine versus praziquantel against opisthorchis viverrini in laos: an open-label, randomised, non-inferiority, phase 2 trial, Lancet Infect. Dis. 18 (2) (2018) 155–161.

[17] P. Sithithaworn, R.H. Andrews, N.V. De, T. Wongsaroj, M. Sinuon, P. Odermatt, Y. Nawa, S. Liang, P.J. Brindley, B. Sripa, The current status of opisthorchiasis and clonorchiasis in the mekong basin, Parasitol. Int. 61 (1) (2012) 10–16. Opisthorchiasis and clonorchiasis: Major neglected tropical diseases in Eurasia.