Analysis of interventions against the liver fluke, opisthorchis viverrini

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

The life cycle of \textit{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 \textit{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 \cite{4}. The worms can survive in the definitive hosts for about 10 years \cite{5}.

Our model analysis is based on a model from a previously published paper \cite{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 \textit{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 \textit{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 \textit{O. viverrini} \cite{1}, which has a high efficacy in regard to cure rate and egg reduction rate \cite{2}.
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 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 optimize 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 $I_s$ 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 $\gamma$ is the rate per unit time of treating people, \[ \exp(-\gamma \times T_r) = 1 - I_m \]
is the proportion of untreated humans with $T_r$ as the time interval of treatment in days [9]. It follows that the treatment rate is \[ \gamma = -\log(1 - I_m) / T_r. \]

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

\[
\begin{align*}
\frac{dw_h(t)}{dt} &= \beta_{sh} N_h I_s(t) (1 - I_t) - \left( \mu_{ph} - \log(1 - I_m(t)) / T_r \right) w_h(t), \\
\frac{dw_d(t)}{dt} &= \beta_{sh} N_h I_s(t) - \mu_{pd} w_d(t), \\
\frac{dw_c(t)}{dt} &= \beta_{sh} N_h I_s(t) - \mu_{pc} w_c(t), \\
\frac{di_1(t)}{dt} &= (\beta_{sh} N_h w_h(t)(1 - I_d) + \beta_{sc} N_c w_c(t) + \beta_{sh} N_s w_s(t)) (1 - i_1(t)) - \mu_i i_1(t), \\
\frac{dl(t)}{dt} &= \beta_{ph} N_h I_s(t)(1 - I_t) - \mu_i l(t). 
\end{align*}
\]

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].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$w_h$</td>
<td>Mean worm burden per human host</td>
</tr>
<tr>
<td>$w_d$</td>
<td>Mean worm burden per dog host</td>
</tr>
<tr>
<td>$w_c$</td>
<td>Mean worm burden per cat host</td>
</tr>
<tr>
<td>$i_s$</td>
<td>Proportion of infectious snails</td>
</tr>
<tr>
<td>$l$</td>
<td>Proportion of infectious fish</td>
</tr>
</tbody>
</table>

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, $-\log(1 - I_m) w_h$. 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 $(1 - I_s)$. 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 $\beta = (\beta_{sh}, \beta_{s}, \beta_{ph}, \beta_{pc}, \beta_{sh}, \beta_{ph})$, we followed the Bayesian resampling approach in [6] with the same parameter ranges as in Table 4 and no intervention $I_e = I_s = I_m = 0$, 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, $(w_h(0), w_d(0), w_c(0), l(0), i_1(0)) = (33, 3, 13, 0.003, 0.3)$, 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 $T_r = 365$ 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 $R_0$ 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 ($R_0 < 1$), the parasite cannot produce
Table 2
Parameters of the opisthorchiasis model with interventions, adapted from [6, Table 2].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_h$</td>
<td>Population size of humans</td>
<td>Animals</td>
</tr>
<tr>
<td>$N_d$</td>
<td>Population size of dogs</td>
<td>Animals</td>
</tr>
<tr>
<td>$N_c$</td>
<td>Population size of cats</td>
<td>Animals</td>
</tr>
<tr>
<td>$N_s$</td>
<td>Population size of snails</td>
<td>Animals</td>
</tr>
<tr>
<td>$N_f$</td>
<td>Population size of fish</td>
<td>Animals</td>
</tr>
<tr>
<td>$\mu_h$</td>
<td>Per capita death rate of adult parasites in humans (includes additional mortality due to death of humans)</td>
<td>1/Time</td>
</tr>
<tr>
<td>$\mu_d$</td>
<td>Per capita death rate of adult parasites in dogs (includes additional mortality due to death of dogs)</td>
<td>1/Time</td>
</tr>
<tr>
<td>$\mu_c$</td>
<td>Per capita death rate of adult parasites in cats (includes additional mortality due to death of cats)</td>
<td>1/Time</td>
</tr>
<tr>
<td>$\mu_f$</td>
<td>Per capita death rate of snails</td>
<td>1/Time</td>
</tr>
<tr>
<td>$\gamma_f$</td>
<td>Per capita death rate of fish including mortality through fishing by humans</td>
<td>1/Time</td>
</tr>
<tr>
<td>$\beta_f$</td>
<td>Transmission rate from infectious fish to human per person</td>
<td>(Time × Animals)</td>
</tr>
<tr>
<td>$\beta_p$</td>
<td>Transmission rate from infectious fish to dogs per dog per fish</td>
<td>(Time × Animals)</td>
</tr>
<tr>
<td>$\beta_s$</td>
<td>Transmission rate from infectious fish to cats per cat per fish</td>
<td>(Time × Animals)</td>
</tr>
<tr>
<td>$\beta_t$</td>
<td>Transmission rate from infectious fish to fish per snail</td>
<td>(Time × Animals)</td>
</tr>
<tr>
<td>$\beta_n$</td>
<td>Transmission rate from infectious fish to a person in a human host</td>
<td>(Time × Animals)</td>
</tr>
<tr>
<td>$\beta_{sh}$</td>
<td>Transmission rate of fish per snail</td>
<td>(Time × Animals)</td>
</tr>
<tr>
<td>$\beta_{ph}$</td>
<td>Transmission rate of fish per person</td>
<td>(Time × Animals)</td>
</tr>
<tr>
<td>$I_t$</td>
<td>Proportion of people who stop defecating outdoors due to intervention</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$I_d$</td>
<td>Proportion of people who stop defecating outdoors due to intervention</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$I_{td}(0)$</td>
<td>Proportion of people getting treatment (medication) at time t</td>
<td>Dimensionless</td>
</tr>
<tr>
<td>$T$</td>
<td>Interval of drug distribution</td>
<td>Time</td>
</tr>
</tbody>
</table>

Table 3
Total number tested and positive hosts from two islands in Lao PDR [10], see [6, Table 3].

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n_h$</td>
<td>Number of tested humans</td>
<td>994</td>
</tr>
<tr>
<td>$p_h$</td>
<td>Number of positive tested humans</td>
<td>603</td>
</tr>
<tr>
<td>$n_d$</td>
<td>Number of tested dogs</td>
<td>68</td>
</tr>
<tr>
<td>$p_d$</td>
<td>Number of positive tested dogs</td>
<td>17</td>
</tr>
<tr>
<td>$n_c$</td>
<td>Number of tested cats</td>
<td>64</td>
</tr>
<tr>
<td>$p_c$</td>
<td>Number of positive tested cats</td>
<td>34</td>
</tr>
<tr>
<td>$n_s$</td>
<td>Number of tested snails</td>
<td>3102</td>
</tr>
<tr>
<td>$p_s$</td>
<td>Number of positive tested snails</td>
<td>9</td>
</tr>
<tr>
<td>$n_f$</td>
<td>Number of tested fish</td>
<td>628</td>
</tr>
<tr>
<td>$p_f$</td>
<td>Number of positive tested fish</td>
<td>169</td>
</tr>
</tbody>
</table>

enough offspring to persist. The control reproduction number $R_c$ includes the impact of interventions on the reproduction number. The next-generation matrix $K$ of the model (1), with constant $I_{td}$, is given by

$$K = \begin{pmatrix}
0 & 0 & 0 & 0 & \frac{\beta_f N(1 - I_d)}{\mu_f} \\
0 & 0 & 0 & 0 & \frac{\beta_p N_I}{\mu_p} \\
0 & 0 & 0 & 0 & \frac{\beta_s N_I}{\mu_s} \\
0 & 0 & 0 & 0 & \frac{\beta_n N_I}{\mu_n} \\
0 & 0 & 0 & 0 & 0
\end{pmatrix},$$

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

$$R_c = \left( \frac{N_h N_f \beta_f (\mu_{sh} T_f - \log(1 - I_{td})) (N_h \beta_f \beta_{ph} \mu_{ph} + N_c \beta_f \beta_{ps} \mu_{ps})}{(\mu_{ph} T_f - \log(1 - I_{td})) \mu_{ph} \mu_{ps}} + \frac{N_c N_f \beta_f (1 - I_d - I_{td} T) (N_d \beta_p \beta_{ph} \mu_{ph} + N_c \beta_p \beta_{ps} \mu_{ps})}{(\mu_{ph} T_f - \log(1 - I_{td})) \mu_{ph} \mu_{ps}} \right)^{\frac{1}{2}}.$$

The basic reproduction number,

$$R_0 = \left( \frac{N_h N_f \beta_f (N_d \beta_f \beta_{ph} \mu_{ph} + N_c \beta_f \beta_{ps} \mu_{ps} + N_s \beta_f \beta_{ph} \mu_{ps})}{\mu_{ph} \mu_{ps}} \right)^{\frac{1}{2}}.$$

is equal to the control reproduction number $R_c$ if the coverage of all interventions is 0 (no interventions in the population). The basic reproduction number is $R_0 = 1.1351$ 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 $T_f = 365$. The control reproduction number $R_c$ has a similar dependence on the level of coverage of education campaigns ($I_e$) and improved sanitation ($I_s$). The coverage needs to be at least 34% for either of these two interventions for $R_c$ 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 ($I_s$). 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 $R_c$ 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 $I_s$ (without $I_m$) which are successful in achieving $R_c < 1$, for MLE parameter values, are shown in Fig. 3. The minimum combination such that $R_c < 1$ is $I_e = I_s = 0.2025$.

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,

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

with $T_f = 1$ 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.
4.1. Effectiveness of interventions

The minimum levels of coverage we calculated with continuous treatment, where $R_0 = 1$, 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 change people's eating habits 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
The in...conence of the choice of this frequency on the mean worm burden...with the annual rate $\gamma_k$ for $k = 1, ...n$, $n \in \mathbb{N}$. The first equation of the ODE system (1) becomes
\[
\frac{d w_h(t)}{dt} = \beta_{Bd} N_h I_w(t) (1 - I_f) - (\mu_{wh} + \gamma(t)) w_h(t).
\] (2)

Minimising the coverage of the interventions affecting humans leads to the optimal control problem,
\[
\min_{L_f, \gamma} \int_0^T w_h(t) + \frac{\alpha^2}{2} \left( I_f(t)^2 + \sum_{k=1}^n \gamma_k^2 \right) dt,
\]
with the weight $\alpha = 0.001$, the time $T = 20 \times 365$ (in days), $n = \frac{T}{365}$, $0 \leq I_f(t) \leq 0.9$, and $0 \leq \gamma_k \leq 0.0016$, which is equivalent to $0 \leq I_f(t) = 1 - \exp(\gamma_k \times 365) \leq 0.8$ for each $k = 1, ...n$. The regularisation parameter $\alpha$ priorises 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 $I_h(t) = I_h$, $\gamma(t) = \gamma$ and $I = (I_f, \gamma_1, ..., \gamma_n)$. We use the definitions
\[
L(t, w_h, I) = w_h(t) + \frac{\alpha^2}{2} \left( I_f(t)^2 + \sum_{k=1}^n \gamma_k^2 \right)
\]
as the integrand; $\frac{d w_h(t)}{dt} = f(x(t), t) + x = (w_h(t), w_f(t), I_f(t), \gamma(t))$ as our ODE model (1), so $f_i = f(x(t), t)$ for $i = 1, ..., 5$;
\[
J(I) = \int_0^T w_h(t) + \frac{\alpha^2}{2} \left( I_f(t)^2 + \sum_{k=1}^n \gamma_k^2 \right) dt
\]
as the integral to minimise and

--

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Range</th>
<th>MLE</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_h$</td>
<td>14,542</td>
<td>[7271, 21,813]</td>
<td>15,705</td>
<td>Animals</td>
</tr>
<tr>
<td>$N_f$</td>
<td>7271</td>
<td>[3635.5, 10906.5]</td>
<td>8437</td>
<td>Animals</td>
</tr>
<tr>
<td>$N_t$</td>
<td>4847</td>
<td>[2423.5, 7270.5]</td>
<td>9701</td>
<td>Animals</td>
</tr>
<tr>
<td>$N_d$</td>
<td>20,000</td>
<td>[2000, 40,000]</td>
<td>31,019</td>
<td>Animals</td>
</tr>
<tr>
<td>$N_s$</td>
<td>8000</td>
<td>[805, 16,000]</td>
<td>9701</td>
<td>Animals</td>
</tr>
<tr>
<td>$\mu_h$</td>
<td>70.92</td>
<td>[10 x 365]</td>
<td>1/48 x 365</td>
<td>1/Days</td>
</tr>
<tr>
<td>$\mu_d$</td>
<td>4 x 365</td>
<td>1/4 x 365</td>
<td>1/2 x 365</td>
<td>1/Days</td>
</tr>
<tr>
<td>$\mu_c$</td>
<td>1 x 365</td>
<td>1/4 x 365</td>
<td>1/13 x 365</td>
<td>1/Days</td>
</tr>
<tr>
<td>$\mu_t$</td>
<td>1 x 365</td>
<td>1/8 x 365</td>
<td>1/1 x 365</td>
<td>1/Days</td>
</tr>
<tr>
<td>$\beta_{Bd}$</td>
<td>4.1111 x 10^{-6}</td>
<td>[4.1111 x 10^{-7}, 8.2222 x 10^{-6}]</td>
<td>5.9785 x 10^{-6}</td>
<td>1/(Animal x Day)</td>
</tr>
<tr>
<td>$\beta_{Bf}$</td>
<td>2.0159 x 10^{-7}</td>
<td>[2.0159 x 10^{-8}, 4.0317 x 10^{-7}]</td>
<td>2.3327 x 10^{-7}</td>
<td>1/(Animal x Day)</td>
</tr>
<tr>
<td>$\beta_{Bf}$</td>
<td>4.1077 x 10^{-6}</td>
<td>[4.1077 x 10^{-7}, 8.2155 x 10^{-6}]</td>
<td>2.9608 x 10^{-6}</td>
<td>1/(Animal x Day)</td>
</tr>
<tr>
<td>$\beta_{Bh}$</td>
<td>1.4846 x 10^{-11}</td>
<td>[1.4846 x 10^{-12}, 2.9693 x 10^{-11}]</td>
<td>1.0210 x 10^{-11}</td>
<td>1/(Animal x Day)</td>
</tr>
<tr>
<td>$\beta_{Bf}$</td>
<td>1.4846 x 10^{-11}</td>
<td>[1.4846 x 10^{-12}, 2.9693 x 10^{-11}]</td>
<td>2.8365 x 10^{-11}</td>
<td>1/(Animal x Day)</td>
</tr>
<tr>
<td>$\beta_{Bf}$</td>
<td>1.4846 x 10^{-11}</td>
<td>[1.4846 x 10^{-12}, 2.9693 x 10^{-11}]</td>
<td>4.7734 x 10^{-12}</td>
<td>1/(Animal x Day)</td>
</tr>
<tr>
<td>$\beta_{Bf}$</td>
<td>6.9536 x 10^{-6}</td>
<td>[6.9536 x 10^{-7}, 1.3907 x 10^{-6}]</td>
<td>1.2900 x 10^{-6}</td>
<td>1/(Animal x Day)</td>
</tr>
</tbody>
</table>

Fig. 3. Combinations of $I_f$ and $I_d$ such that $R_f < 1$ in absence of $I_d$ ($I_h = 0$). The other parameters are set to their MLE solution in Table 4.

0.5, 1, 2, 3 and 4 years. Hence, $I_h(t)$ 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 ($I_f$) and the mass drug administration ($I_h$) 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 ful...
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

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

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

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$U = \{I(t) | I(t) \in [0, 0.9] \times [0, 0.0016]^6, \ t \in [0, T]\}$.

To show that a solution exists to this optimal control problem, we have to prove the following assumptions [12,13]:
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 $(w_0, w_0, w_0, i_0, i_0)$:

$$S = \left[ 0, \beta_N N_I \mu_p \right] \times \left[ 0, \beta_N N_I \mu_p \right] \times \left[ 0, \beta_N N_I \mu_p \right] \times [0, 1]^2.$$  

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 $S \subseteq \mathbb{R}^5$, given by

$$\bar{S} = \left[ -\beta_N N_I \mu_p, \beta_N N_I \mu_p \right] \times \left[ -\beta_N N_I \mu_p, \beta_N N_I \mu_p \right] \times \left[ -\beta_N N_I \mu_p, N_N \beta_p \right].$$

(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

$$f(t, w_0, w_0, w_0, i_0, i_0) = a(t, w_0) + b(t, w_0)l + c(t, w_0),$$

where

$$f(t, w_0, w_0, i_0, i_0) = \beta_N N_I i_0 - w_0 + \frac{-\beta_N N_I i_0}{a(t, w_0)} l + \frac{(w_0)}{c(t, w_0)}.$$  

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

(iii) To show that $L(t, w_0, \cdot)$ is convex on $U$, we must have:

$$L(t, w_0, (1 - \epsilon)l + \epsilon l_2) \leq (1 - \epsilon)L(t, w_0, l) + \epsilon L(t, w_0, l_2)$$

for $l_1, l_2 \in I$.

It holds

$$L(t, w_0, (1 - \epsilon)l + \epsilon l_2) = w_0^2 + ((1 - \epsilon)I_{c,1} + \epsilon I_{c,2})^2 + \left(1 - \epsilon\right) \sum_{k=1}^{n} \gamma_{c,k}(t) + \epsilon \sum_{k=1}^{n} \gamma_{c,k}(t)^2 \leq (1 - \epsilon) \left( w_0^2 + \frac{\alpha^2}{2} \left( l_1^2 + \sum_{k=1}^{n} \gamma_{c,k}(t)^2 \right) \right) + \epsilon \left( w_0^2 + \frac{\alpha^2}{2} \left( l_2^2 + \sum_{k=1}^{n} \gamma_{c,k}(t)^2 \right) \right).$$

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, $\lambda(t) = (\lambda_0(t), \lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t))$, such that,

$$\dot{x}(t) = -\frac{\partial H(t, x^*(t), I^*(t), \lambda(t))}{\partial x}$$

with the Hamiltonian,

$$H(t, w_0, w_0, w_0, i_0, i_0, i_0, i_0, \lambda, \gamma) = L(t, w_0, I) + \sum_{k=1}^{s} \lambda_k I_{k}(t, I, \lambda, \gamma).$$

and $x^*(w_0, w_0, w_0, i_0, i_0, i_0, \gamma^*(t))$ as the corresponding state variables of the optimal control functions $I^* = (I^*_0, \gamma(t)^*)$.

Proposition 2. The optimal controls are given by the set

$$I^*_0 = \min \left\{ \max \left\{ 0, \frac{\lambda_0 \beta_N N_I i_0}{\alpha^2} \right\}, \frac{1}{2} \right\};$$

$$\gamma^* = \min \left\{ \max \left\{ 0, \frac{\lambda_0 w_0}{\alpha^2} \right\}, \frac{1}{2} \right\}.$$  

Proof. Let $I^*$ be the optimal control functions to the corresponding state variables $w_0^*, w_0^*, w_0^*, i_0^*, \gamma^*$, which minimise our integral function $J(I)$. It follows with the Pontryagin’s maximum principle that adjoint variables $\lambda(t) = (\lambda_0(t), \lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t))$ exist such that

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.
\[ l_i^I = -2 \omega_i + \lambda_i (\mu_i + \gamma) - \lambda_i \beta_{pi} N_i (1 - I_i), \quad (3a) \]
\[ l_i^j = \lambda_i \beta_{pi} - \lambda_i \beta_{pi} N_i (1 - i), \quad (3b) \]
\[ l_i^1 = \lambda_i \beta_{pi} - \lambda_i \beta_{pi} N_i (1 - i), \quad (3c) \]
\[ l_i^j = \lambda_i (\beta_{pi} N_i w_i (1 - I_i) + \beta_{pi} w_i + \beta_{pi} N_i w_i + \mu_i) - \lambda_i \beta_{pi} N_i (1 - i), \quad (3d) \]
\[ l_i^j = \lambda_i (\beta_{pi} N_i i_i + \mu_i) - \lambda_i \beta_{pi} N_i (1 - I_i) - \lambda_i \beta_{pi} N_i - \lambda_i \beta_{pi} N_i, \quad (3e) \]

with transversality conditions \( l_i(t_0) = 0 \) for \( i = 1, ..., 5 \). Considering the optimality condition \( \frac{\partial H}{\partial \lambda(t)} = 0 \), we get the solutions
\[ I^* = \frac{\lambda_i \beta_{pi} N_i}{\alpha^2}, \quad (4a) \]
\[ \gamma^* = \frac{\lambda_i w_i}{\alpha^2}. \quad (4b) \]

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 \( I_e \). The 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 \( \delta \),
\[ ||I - I^*|| \leq \delta, \]

with \( I \) being the previous solution. To include the option of \( ||I|| = 0 \) we transform it to the condition
\[ \delta ||I|| - ||I^* - I|| \geq 0. \]

The parameter \( \delta \) is set to \( \delta = 0.001 \) [14].

The solution of the treatment rate \( \gamma(t) \) is transformed back to the proportion \( L_e(\gamma) = 1 - \exp(\gamma(t) \times 365) \). The minimisation of the interventions \( I_e \) and \( L_e(\gamma) \) is shown in Fig. 6(a) — it is the same solution for all three assumption of \( I_e \) and \( L_e(\gamma) \). The mean worm burden in the definitive hosts and the prevalence in the intermediate hosts depends on the coverage of improved sanitation, \( I_e \), as shown in Fig. 6(b–d).

The solution of the optimal control problem shows that the optimal coverage for treatment is 44%. The coverage of people who 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 \( w_i \leq 1 \) 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) \( w_i \leq 1 \)
(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 \( I_e \in \{0.4, 0.5, 0.6, 0.7, 0.8\} \). 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 minimal coverage of successfully targeted humans with education campaigns is \( I_e \approx 0.34 \). The same is true for coverage of improved sanitation, \( I_s \approx 0.34 \). The coverage of continuous treatment has to reach \( I_n = 0.10 \) 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 \( I_m = 0.44 \), 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, \( I_e \in \{0.4, 0.6, 0.8\} \) 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.
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 reinfection 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...
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 unequaly 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.

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References


