Age dependency in the transmission dynamics of the liver fluke, Opisthorchis viverrini and the effectiveness of interventions

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Age dependency in the transmission dynamics of the liver fluke, *Opisthorchis viverrini* and the effectiveness of interventions

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Abstract We introduce a population-based model of the transmission dynamics of the liver fluke *Opisthorchis viverrini*, that allows the mean worm burden in humans to depend on the host age. We parameterise the model using data on intensity of infection in humans and prevalence data for cats, dogs, fish and snails from two island communities in Lao People's Democratic Republic. We evaluate the steady state solution using a fixed point iteration and estimate the basic reproductive number. We optimise the coverage level of MDA in an adapted model of five age groups to compare varying coverages across age groups. Our results suggest that although adults have the strongest contribution to transmission and campaigns should target adults, if such targeting is operationally infeasible, achieving moderate coverage levels in all age groups can still have a substantial impact on reducing worm burden.

Keywords Opisthorchis viverrini · mathematical modelling · partial differential equation · age-dependent model · mass drug administration

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1 Introduction

The liver fluke *Opisthorchis viverrini*, which causes the neglected tropical disease opisthorchiasis, is prevalent in the lower Mekong Subregion in Southeast Asia, mainly in Cambodia, Thailand and Lao People's Democratic Republic (Lao PDR) [9, 19]. It is estimated that about 10 million people are infected with *O. viverrini* worldwide [19] and over 2 million in Lao PDR [14].

The parasite *O. viverrini* has multiple definitive hosts and two intermediate hosts. The definitive hosts include humans, cats, dogs and other mammals, who get infected through the consumption of raw or undercooked fish containing infective larval stages. In the mammalian host, the larvae develop into adults, which migrate to the bile duct. The hermaphrodite adults mate and release eggs that are excreted with the host faeces into the environment. If the eggs are ingested by snails of the genus *Bithynia*, the first intermediate host, they develop into a free swimming larval stage called cercariae. Cercariae can penetrate through the skin of cyprinoid fish, their second intermediate host. The fish is infective as soon as the parasite develops into metacercariae [14].

Different studies on age-related patterns in *O. viverrini* infection show that the mean worm burden and prevalence are lowest in young children (< 5 years). All studies show an increase in prevalence afterwards during school-age. Some studies show a decrease in prevalence in the elderly age group, which is common in other helminth infections [19].

Deterministic models of the mean worm burden of *O. viverrini* have been used to quantify the role of cats and dogs in maintaining transmission in two rural communities in Lao PDR [4]; and compare the effectiveness of three control interventions (behaviour change campaigns, improved sanitation and mass drug administration (MDA)) in reducing transmission [3]. A spatial model including water flow was used to model the impact of environmental drivers on disease transmission [11]. An ecological niche model was created to simulate the distribution of *Bythnia* snails in Thailand to predict the occurrence of snails and link it to the prevalence of opisthorchiasis [12]. However, these models have ignored dependence of the worm burden on human age, which affects the impact of age-specific interventions, such as the intermittent treatment of school children, and potential biases caused by mass drug administration campaigns achieving lower coverage in working age adults. To explore the impact of such interventions, many age-dependent models have been developed for schistosomiasis and other helminths. Schistosomiasis models with age-structure have been used to target age-groups for MDA [23] and predict the outcome of the current coverage levels of recommended treatment strategies [2]. Similarly, a model for soil-transmitted helminths was used to quantify the role of children in onward transmission. The model describes the mean worm burden of humans of a given age of different soil-transmitted helminths as *Ascaris lumbricoides*, *Trichuris trichuria* and hookworm. Applying MDA

to different age groups, as preschool aged and school-aged children, as the World Helath Organization recommends, shows the outcome in 2020 for these soil-tranmitted helminths [20].

Here we likewise develop two new model extensions of a previously published ordinary differential equation (ODE) model for *O. viverrini* [4]. We present a partial differential equation (PDE) model of the age-specific worm burden of the human population assuming continuous age, and an age-structured ODE model assuming discrete age groups. We use these models to (i) define the basic reproduction number which provides a threshold condition for the persistence of transmission; (ii) evaluate the steady state solution of the system with a fixed point iteration; and (iii) estimate model parameters using data from Lao PDR. We run numerical simulations to optimise coverage levels of MDA campaigns and the required change in eating behaviour through education campaigns using the optimal control method. We build different scenarios of mass drug administration campaigns to compare their effectiveness in reducing the mean worm burden in humans when targeting different age groups.

2 Mathematical model

We extend the previously published model with reservoir hosts from [4] to include the dependence of mean worm burden in humans on the host age. We model human age continuously by transforming the system of ODEs to a PDE, where the mean worm burden in humans depends on age and time ($w_h(a,t)$). The number of humans also depends on age ($N_h(a)$) and the additional parameter $\phi(a)$ denotes the proportion of people of age a who eat raw or undercooked fish. This model of *O. viverrini* including age of human is given through the equations:

$$\frac{\partial w_h(a,t)}{\partial t} + \frac{\partial w_h(a,t)}{\partial a} = \phi(a)\beta_{hf} N_f i_f(t) - \mu_{ph} w_h(a,t), \tag{1a}$$

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

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

$$\frac{\mathrm{d}i_s(t)}{\mathrm{d}t} = \left(\beta_{sh} \int_0^{a_{\max}} N_h(a) w_h(a,t) \mathrm{d}a + \beta_{sd} N_d w_d(t) + \beta_{sc} N_c w_c(t) \right) (1 - i_s(t)) - \mu_s i_s(t), \tag{1d}$$

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

Herein, $a_{\max}$ is the maximum age of humans. All state variables are described in Table 1 and parameters in Table 2.

The parameter μ_{ph} is the death rate of the parasite in humans excluding mortality due to the death of humans (since the mortality of humans is explicitly included with an exponential distribution for the human population).

The integral over age of the mean worm burden in humans $w_h(a,t)$ weighted by the number of humans $N_h(a)$ yields the total number of worms in humans. The total human population size is given by the integral over age

$$\bar{N}_h = \int_0^{a_{\max}} N_h(a)\mathrm{d}a.$$

We assume that the number of humans over age is exponentially distributed with the following equation

$$N_h(a) = \frac{c}{\lambda}\exp\left(-\frac{a}{\lambda}\right), \tag{2}$$

where λ is the average life span of a human and c is a scaling factor defined as

$$c = \frac{\bar{N}_h \cdot \lambda}{\int_0^{a_{\max}} \exp\left(-\frac{a}{\lambda}\right)\mathrm{d}a},$$

where we can estimate the total human population, $\bar{N}_h$, and λ from data.

Table 1 State variables of the opisthorchiasis model, see [4, 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

3 Data and numerical simulation

We estimate parameter values for the model (1) using data collected from two islands in Champasack province in Lao PDR between October 2011 to August 2012 [21]. We have a data set of 994 humans which includes infection intensity and habit of eating raw or undercooked fish. The infection intensity is measured in eggs per gram (epg) in stool. We also have data on prevelance in all animals (dogs, cats, snails and fish) [21]. To estimate the age distribution of the human population, we use the UN data of the year 2015 from Lao PDR [1].

Table 2 Parameters of the opisthorchiasis model with interventions; adapted from [4, Table 2].

Parameter	Description	Dimension
$N_h(a)$	Population size of humans dependent on age a	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 (without 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)
$\phi(a)$	proportion of humans of age a eating raw or undercooked fish	Dimensionless
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
λ	Mean life span of humans	Time
c	Scaling factor for human population size	Dimensionless

We fit an exponential distribution for the number of humans, $N_h(a)$, as a function of age, a, (2) by using the population data of Lao PDR [1]. We estimate an average life span of humans of $\lambda = 9628$ days ≈ 26.37 years with a maximum life span of 95 years ($a_{\max} = 95$ yrs) using the maximum likelihood estimation method[1] (MLE). The average life span is so low because the number of humans is only exponentially distributed from around an age of 20 years (see Figure 1). We assume that the total number of humans living on the two islands is $\bar{N}_h = 14541$ [21], leading to the scaling factor $c = 1.5318 \times 10^4$ in the exponential distribution.

The age-dependent proportion of people eating raw or undercooked fish, $\phi(a)$, is fitted to a truncated Gaussian distribution in the interval [0, 89]. based on the data from the study in Champasack province Southern Lao PDR [21]. Figure 2 shows the absolute number of humans eating raw or undercooked fish, as well as the proportion and estimated Gaussian distribution of $\phi(a)$. We assume that the proportion of people eating raw or undercooked fish increases with age since young children rarely eat raw fish, until a peak and then decreases. This decrease is most probably presumably due to decreasing dental health with age, which makes it difficult to chew the undercooked fish. Also, Those people who are mots effected have a higher mortality due to resulting opisthorchiasis and severe complications.

To get an initial value for the numerical simulation, we need a distribution of the mean worm burden of humans over age. We fit the distribution of eggs per gram (epg) stool in humans over age to a truncated Gaussian distribution in the interval [0, 89] as shown in Figure 3. We use the data from Lao PDR on epg in stool [21] and transform it into the number of worms per person as described in a previous publication [4] using purging data from a study in Thailand [6]. We assume the same trend in the number of worms over age as in the proportion of people eating raw or undercooked fish due to their eating habits.

To estimate $\beta = (\beta_{hf}, \beta_{df}, \beta_{cf}, \beta_{sh}, \beta_{sd}, \beta_{sc}, \beta_{fs})$ we use the maximum likelihood method, as in the previous model calibration [4]. We use the estimates from this paper as mode, see Table 4. We sample 5000 sets of parameter values from the ranges in Table 4 assuming triangular distributions. The likelihood function L is given by the product of the likelihood functions of humans, dogs, cats, snails and fish,

$$L = L_h L_d L_c L_s L_f,$$

where we assume a negative binomial distribution for the worm burden (and the egg burden)

$$L_h = \prod_{i=1}^{n_h} \frac{(\mathrm{epg}_i + r - 1)!}{\mathrm{epg}_i!(r-1)!} \left(\frac{r}{\mathrm{epg}^* + r}\right)^r \left(\frac{\mathrm{epg}^*}{\mathrm{epg}^* + r}\right)^{\mathrm{epg}_i}$$

with n_h the number of human tested in the data set from Lao PDR (see Table 3) [21], epg_i the eggs per gram of each person, epg^* the steady sate solution

[1] Matlab R2015b: Distribution Fitting App

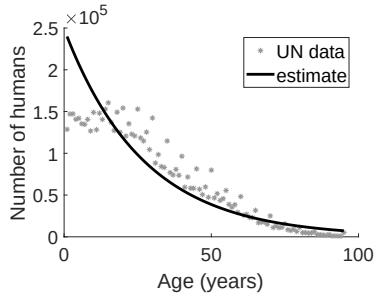


Fig. 1 Number of humans per age in years of the UN data and the the fitting with MLE to an exponential distribution: $f(\text{age}) = \frac{1}{\mu}\exp\left(-\frac{\text{age}}{\mu}\right)$ with $\mu = 9628$.

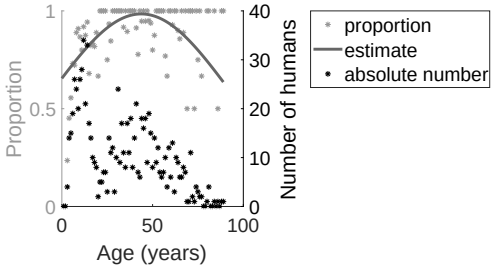


Fig. 2 Estimate of the proportion of humans eating raw or undercooked fish depending on age fitted to a truncated Gaussian distribution from the data set from Lao PDR: $f(\text{age}) = 0.9844 \times \exp\left(-\left(\frac{\text{age}-43.73}{68.51}\right)^2\right)$.

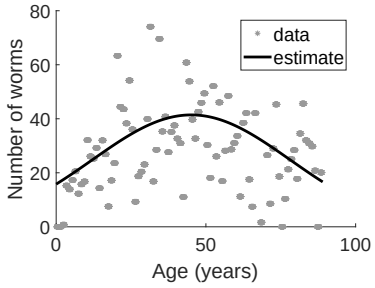


Fig. 3 Estimate of the number of egg per gram stool in humans per age fitted to a truncated Gaussian distribution $f(\text{age}) = 1799 \times \exp\left(-\left(\frac{\text{age}-45.1}{33.1}\right)^2\right)$.

of the mean worm burden transformed into the mean egg per gram burden (see [6] for the calculation) and $r > 0$ a real value. L_d, L_c, L_s and L_f all have binomial distributions,

$$L_d = \frac{n_d!}{p_d!(n_d-p_d)!}\,(i_d^*)^{p_d}\,(1-i_d^*)^{(n_d-p_d)},$$
$$L_c = \frac{n_c!}{p_c!(n_c-p_c)!}\,(i_c^*)^{p_c}\,(1-i_c^*)^{(n_c-p_c)},$$
$$L_s = \frac{n_s!}{p_s!(n_s-p_s)!}\,(i_s^*)^{p_s}\,(1-i_s^*)^{(n_s-p_s)},$$
$$L_f = \frac{n_f!}{p_f!(n_f-p_f)!}\,(i_f^*)^{p_f}\,(1-i_f^*)^{(n_f-p_f)},$$

as in the previous publication [4] with variable in Table 3. For the numerical simulations we take the parameter set with the largest likelihood function value as a starting set and fit β using MLE to the data from Lao PDR. We run numerical simulations of the model (1) with parameter values chosen using MLE from Table 4. We use the method of characteristics [7] to

Table 3 Total number tested and positive hosts from two islands in Lao PDR [21], adapted from [4, Table 3].

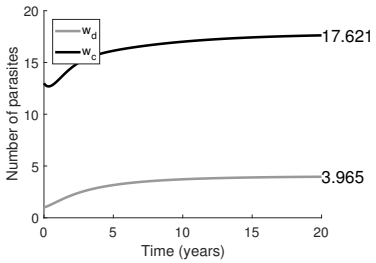
Variable	Description	Value
n_h	number of tested humans	994
n_d	number of tested dogs	68
p_d	number of positive tested dogs	17
n_c	number of tested cats	64
p_c	number of positive tested cats	34
n_s	number of tested snails	3102
p_s	number of positive tested snails	9
n_f	number of tested fish	628
p_f	number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

Table 4 Parameter values of the model and ranges for the sampling. We use the initial value as the mode of the triangular distribution and the range as the minimum maximum value, respectively, to generate the parameter sets. The MLE solution is the parameter set with the highest likelihood and the βs estimated by the MLE method.

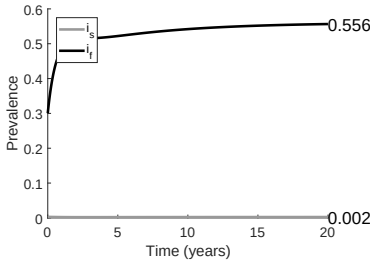
Variable	Mode	Range	MLE	Unit
N_h	15705	$[1571, 23557]$	8679	Animals
N_d	8437	$[844, 12656]$	7991	Animals
N_c	6098	$[610, 9147]$	2552	Animals
N_s	31019	$[3102, 46529]$	33068	Animals
N_f	9701	$[970, 14552]$	12433	Animals
μ_{ph}	$\frac{1}{4.8\times365}$	$\left[\frac{1}{9.6\times365}, \frac{1}{2.2\times365}\right]$	$\frac{1}{3.7\times365}$	1/Days
μ_{pd}	$\frac{1}{2.2\times365}$	$\left[\frac{1}{4.4\times365}, \frac{1}{1.1\times365}\right]$	$\frac{1}{2.9\times365}$	1/Days
μ_{pc}	$\frac{1}{1.5\times365}$	$\left[\frac{1}{3\times365}, \frac{1}{0.8\times365}\right]$	$\frac{1}{1.7\times365}$	1/Days
μ_s	$\frac{1}{1\times365}$	$\left[\frac{1}{2\times365}, \frac{1}{0.5\times365}\right]$	$\frac{1}{1.1\times365}$	1/Days
μ_f	$\frac{1}{1.5\times365}$	$\left[\frac{1}{3\times30}, \frac{1}{0.8\times365}\right]$	$\frac{1}{2.0\times365}$	1/Days
β_{hf}	5.9785×10^{-6}	$[5.9785 \times 10^{-7}, 1.1957 \times 10^{-5}]$	5.1266×10^{-6}	1/(Animal x Day)
β_{df}	3.2337×10^{-7}	$[3.2337 \times 10^{-8}, 6.4674 \times 10^{-7}]$	5.3964×10^{-7}	1/(Animal x Day)
β_{cf}	2.9608×10^{-6}	$[2.9608 \times 10^{-7}, 5.9216 \times 10^{-6}]$	4.2211×10^{-6}	1/(Animal x Day)
β_{sh}	1.0210×10^{-11}	$[1.0210 \times 10^{-12}, 2.0420 \times 10^{-11}]$	1.3490×10^{-11}	1/(Animal x Day)
β_{sd}	2.8635×10^{-11}	$[2.8635 \times 10^{-12}, 5.7270 \times 10^{-11}]$	2.8636×10^{-11}	1/(Animal x Day)
β_{sc}	4.7734×10^{-12}	$[4.7734 \times 10^{-12}, 9.5468 \times 10^{-11}]$	3.8561×10^{-11}	1/(Animal x Day)
β_{fs}	1.2900×10^{-5}	$[1.2900 \times 10^{-6}, 2.5800 \times 10^{-5}]$	2.1769×10^{-5}	1/(Animal x Day)

convert the PDE to a system of ODEs. We numerically integrate the ODEs using the Runge-Kutta method of fourth order with a time step of one day for the simulation. The characteristic lines of the PDE (1a) are $a = \zeta + t$. We solve the PDE along these characteristic lines.

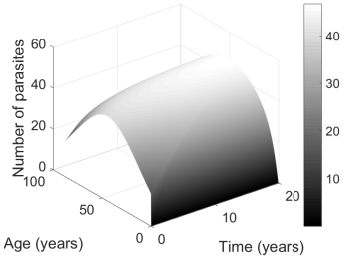
To solve this system of ODEs we use the following initial values at time t_0: the mean worm burden $w_h(a, t_0)$ for every age a as shown in Figure 3 and $(w_d(t_0), w_c(t_0), i_s(t_0), i_f(t_0)) = (1, 13, 0.003, 0.3)$ calculated from [21].



(a) Mean worm burden in dogs w_d and cats w_c.



(b) Prevalence of snails i_s and fish i_f.



(c) Mean worm burden in humans $w_h(a,t)$ over time and age

(d) Mean worm burden in humans $w_h(a,20)$ over age after 20 years.

Fig. 4 Numerical simulation of the model (1) with the parameter values chosen using MLE in Table 4 calculated with the Runge Kutta 4 method.

4 Steady state solution

Definition 1 (Steady state) *The steady state of a system of ODEs is a solution that does not change with time; this means the partial derivative with respect to time is zero [15].*

There is a trivial steady state solution $S_0(a) = (w_h^*(a), w_d^*, w_c^*, i_s^*, i_f^*) = (0,0,0,0,0)$ for all ages $a \in [0, a_{\max}]$. We calculate the endemic steady state solution $S_e(a) = (w_h^*(a), w_d^*, w_c^*, i_s^*, i_f^*)$ solving the following system:

$$\frac{\partial w_h^*(a)}{\partial a} = \phi(a)\beta_{hf} N_f i_f^* - \mu_{ph} w_h^*(a), \tag{3a}$$

$$0 = \beta_{df} N_f i_f^* - \mu_{pd} w_d^*, \tag{3b}$$

$$0 = \beta_{cf} N_f i_f^* - \mu_{pc} w_c^*, \tag{3c}$$

$$0 = \left(\beta_{sh} \int_0^{a_{\max}} N_h(a) w_h^*(a) \mathrm{d}a + \beta_{sd} N_d w_d^* + \beta_{sc} N_c w_c^* \right) (1 - i_s^*) - \mu_s i_s^*, \tag{3d}$$

$$0 = \beta_{fs} N_s i_s^* (1 - i_f^*) - \mu_f i_f^*. \tag{3e}$$

Solving equation (3b), (3c) and (3e) for w_c^*, w_d^* and i_s^*, respectively, leads to

$$w_d^* = \frac{\beta_{df} N_f i_f^*}{\mu_{pd}}, \tag{4a}$$

$$w_c^* = \frac{\beta_{cf} N_f i_f^*}{\mu_{pc}}, \tag{4b}$$

$$i_s^* = \frac{\mu_f i_f^*}{\beta_{fs} N_s - \beta_{fs} N_s i_f^*}. \tag{4c}$$

We rewrite equation (3d) in terms of i_f^* and $w_h^*(a)$:

$$0 = \left(\beta_{sh} \int_0^{a_{\max}} N_h(a) w_h^*(a) \mathrm{d}a + \beta_{sd} N_d \frac{\beta_{df} N_f i_f^*}{\mu_{pd}} + \beta_{sc} N_c \frac{\beta_{cf} N_f i_f^*}{\mu_{pc}} \right) \times \left(1 - \frac{\mu_f i_f^*}{\beta_{fs} N_s - \beta_{fs} N_s i_f^*} \right) - \mu_s \frac{\mu_f i_f^*}{\beta_{fs} N_s - \beta_{fs} N_s i_f^*}.$$

This leads to a quadratic equation with two solutions of i_f^* depending on $w_h^*(a)$. The two solutions are of the form

$$i_{f,1} = \frac{\sqrt{f_1} + f_2 + f_3 - f_4 - f_5}{f_6},$$

$$i_{f,2} = -\frac{\sqrt{f_1} - f_2 - f_3 + f_4 + f_5}{f_6}.$$

The f_i terms are algebraic combinations of the parameters, where $f_i > 0$ for $i = 1, \ldots, 6$ since all parameters are positive. It follows that one solution is positive and one is negative.

We discretise our differential equation by dividing the human population into groups with size of one day $[w_h^*(a_i)]_{i=0}^{a_{\max}}$. We rewrite equation (3a) to calculate $w_h^*(a)$,

$$\begin{aligned} \frac{\partial w_h^*(a_i)}{\partial a} &= \frac{w_h^*(a_{i+1}) - w_h^*(a_i)}{\Delta a} \\ &= \phi(a_i) \beta_{hf} N_f i_f^*(w_h^*(a_i)) - \mu_{ph} w_h^*(a_i), \end{aligned}$$

where $\Delta a = 1$ day for $i = 0 \ldots a_{\max}$ and define the function $\Phi : \left[0, \frac{N_f \beta_{hf}}{\mu_{ph}}\right] \to \left[0, \frac{N_f \beta_{hf}}{\mu_{ph}}\right]$ with

$$\Phi(w_h^*(a_i)) = -\phi(a_i) \beta_{hf} N_f i_f^* \Delta a + \mu_{ph} w_h^*(a_i) \Delta a + w_h^*(a_{i+1}).$$

We use the function Φ for the fixed point iteration

$$w_h^*(a_i)^{k+1} = \Phi(w_h^*(a_i)^k),$$

with k being the iteration index. We set a threshold of $\epsilon = 0.001$ for

$$\left|w_h^*(a_i)^{k+1} - w_h^*(a_i)^k\right| < \epsilon$$

to estimate the steady state solution. If the iteration reaches the limit $k > 100$, we consider the steady state solution not to be calculable.

We next discretise the integral by using the Riemann definition

$$\int_0^{a_{\max}} N_h(a) w_h^*(a) \mathrm{d}a = \sum_{i=0}^{a_{\max}} N_h(a_i) w_h^*(a_i).$$

We take the value of $w_h(a)$ at $t = 20$ from the numerical simulation of (3) (as shown in Figure 4(c)) as the initial value of $[w_h^*(a_i)]_{i=0}^{a_{\max}}$ for the fixpoint iteration. The steady state solution $w_h^*(a)$ is shown in Figure 5 and $S_e(a) = (w_h^*(a), 0.9265, 8.6760, 0.0027, 0.3678)$ for all $a \in [0, a_{\max}]$.

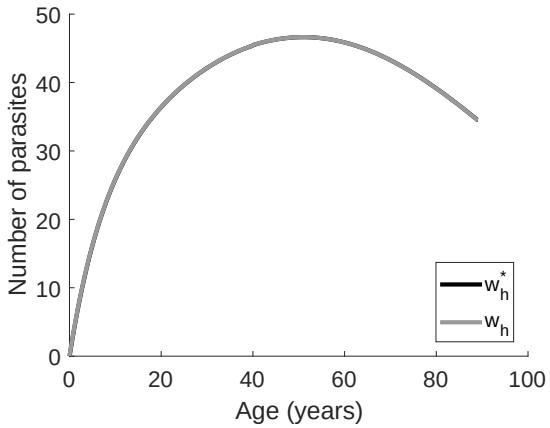


Fig. 5 Steady state solution of the mean worm burden in humans w_h^* calculated by the fixed point iteration.

5 Basic reproduction number

The basic reproduction number, $\mathcal{R}_0$, is the expected number of offspring from one life stage to the next life stage of the parasite. The cube of $\mathcal{R}_0$ is the expected number of offspring of one (hermaphrodite) worm in the absence of density dependence (assuming fully susceptible snail and fish populations) since the worm has three distinct life stages. $\mathcal{R}_0$ is mathematically defined as the spectral radius of the next generation matrix $\mathbf{K}$ [5].

For the sake of simplicity, we divide humans into n age groups and rewrite the model (1) with ODEs. Here, $w_{h,i}$ is the mean worm burden per human

host in the age group i; $N_{h,i}$ is the number of humans in the age group i; and ϕ_i the proportion of people in age group i who consume raw or undercooked fish; for $i = 1, 2, \ldots, n$. ζ_i is the rate of movement of worms from the age group i to $i+1$, which is equal to the rate of movement of humans to the next age group, $\zeta_i = \frac{1}{\text{Duration of age group } i}$ for $i = 1, 2, \ldots, n-1$. This leads to the following model:

$$
\begin{aligned}
\frac{\mathrm{d}w_{h,1}}{\mathrm{d}t} &= \phi_1 \beta_{hf} N_f i_f - (\mu_{ph} + \zeta_1)\, w_{h,1}, \\
&\vdots \\
\frac{\mathrm{d}w_{h,i}}{\mathrm{d}t} &= \phi_i \beta_{hf} N_f i_f - (\mu_{ph} + \zeta_i)\, w_{h,i} + \frac{\zeta_{i-1} N_{h,i-1}}{N_{h,i}} w_{h,i-1}, \\
&\vdots \\
\frac{\mathrm{d}w_{h,n}}{\mathrm{d}t} &= \phi_n \beta_{hf} N_f i_f - \mu_{ph} w_{h,n} + \frac{\zeta_{n-1} N_{h,n-1}}{N_{h,n}} w_{h,n-1}, \\
\frac{\mathrm{d}w_d}{\mathrm{d}t} &= \beta_{df} N_f i_f - \mu_{pd} w_d, \\
\frac{\mathrm{d}w_c}{\mathrm{d}t} &= \beta_{cf} N_f i_f - \mu_{pc} w_c, \\
\frac{\mathrm{d}i_s}{\mathrm{d}t} &= \left(\beta_{sh} \sum_{k=1}^{n} N_{h,k} w_{h,k} + \beta_{sd} N_d w_d + \beta_{sc} N_c w_c \right) (1 - i_s) - \mu_s i_s, \\
\frac{\mathrm{d}i_f}{\mathrm{d}t} &= \beta_{fs} N_s i_s (1 - i_f) - \mu_f i_f.
\end{aligned}
\tag{5}
$$

The next-generation matrix of this model is

$$
\mathbf{K} = \begin{bmatrix}
0 & \ldots & 0 & \cdots & 0 & 0 & 0 & 0 & 0 & \frac{\phi_1 \beta_{hf} N_f}{\mu_{ph}} \\
\vdots & & \vdots & & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & \ldots & 0 & \cdots & 0 & 0 & 0 & 0 & 0 & \frac{\phi_i \beta_{hf} N_f}{\mu_{ph}} \\
\vdots & \ldots & \vdots & \ldots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & \ldots & 0 & \cdots & 0 & 0 & 0 & 0 & 0 & \frac{\phi_n \beta_{hf} N_f}{\mu_{ph}} \\
0 & \ldots & 0 & \cdots & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{df} N_f}{\mu_{pd}} \\
0 & \ldots & 0 & \cdots & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{cf} N_f}{\mu_{pc}} \\
\frac{N_{h,1} \beta_{sh}}{\mu_{ph}} & \ldots & \frac{N_{h,i} \beta_{sh}}{\mu_{ph}} & \ldots & \frac{\beta_{sh} N_{h,n}}{\mu_{ph}} & \frac{\beta_{sh} N_{h,n}}{\mu_{ph}} & \frac{\beta_{sd} N_d}{\mu_{pd}} & \frac{\beta_{sc} N_c}{\mu_{pc}} & 0 & 0 \\
0 & \ldots & 0 & \ldots & 0 & 0 & 0 & 0 & \frac{\beta_f N_s}{\mu_{ph}} & 0
\end{bmatrix}.
$$

We compute its spectral radius for different numbers of age groups starting with three age groups ($n = 3$) and going up to 1000 age groups ($n = 1000$).

The median of the basic reproduction number is 1.38603 and the range of the oscillation for different numbers n of age groups is 1.4856×10^{-02}, so we

conclude $\mathcal{R}_0 = 1.39$ for the adapted model (5) with age groups. To get the basic reproduction number of the model depending on age (1), we let n tend to ∞.

Claim 1 *The basic reproduction number of the model with age groups* (5) *for* $n \to \infty$ *is equal to the basic reproduction number of the continuous age-dependent model* (1).

Proof Let h be the length of the age interval of the age groups. We define $\zeta_i = \frac{1}{h}$ for $2 \leq i \leq n-1$. Thus, the system of ODEs for the worm burden in humans becomes

$$\begin{aligned} \frac{\mathrm{d}w_{h,i}}{\mathrm{d}t} &= \phi_i \beta_{hf} N_f i_f - \left(\mu_{ph} + \frac{1}{h}\right) w_{h,i} + \frac{1}{h} \frac{N_{h,i-1}}{N_{h,i}} w_{h,i-1} \\ &= \phi_i \beta_{hf} N_f i_f - \mu_{ph} w_{h,i} - \frac{1}{h}\left(w_{h,i} - \frac{N_{h,i-1}}{N_{h,i}} w_{h,i-1}\right). \end{aligned} \tag{6}$$

We still assume that the human population is exponentially distributed, so $N_{h,i-1} = \int_{k-h}^{k} N_h(a)\,\mathrm{d}a$ is the number of humans between age $k-h$ and k, $N_{h,i} = \int_{k}^{k+h} N_h(a)\,\mathrm{d}a$ for all $i = 1, 2, \ldots, n$ and $k = \frac{a_{max}}{n}(i-1)$. Instead of $n \to \infty$, we can also let $h \to 0$. We look at the last term of the ODE (6)

$$\lim_{h\to 0} \frac{1}{h}\left(w_{h,i} - \frac{N_{h,i-1}}{N_{h,i}} w_{h,i-1}\right) = \frac{\partial w_h}{\partial a}.$$

Then

$$\lim_{h\to 0} \frac{N_{h,i-1}}{N_{h,i}} = \lim_{h\to 0} \frac{\int_{i-h}^{i} N_h(a)\,\mathrm{d}a}{\int_{i}^{i+h} N_h(a)\,\mathrm{d}a} = 1$$

and therefore it follows

$$\frac{\partial w_h}{\partial t} + \frac{\partial w_h}{\partial a} = \phi(a)\beta_{hf} N_f i_f - \mu_{ph} w_h.$$

For $i = 1$ and $i = n$ we are looking at the terms

$$\lim_{h\to 0} \frac{1}{h} w_{h,1}$$

and

$$\lim_{h\to 0} \frac{1}{h} \frac{N_{h,n-1}}{N_{h,n}} w_{h,n-1} = \lim_{h\to 0} \frac{1}{h} w_{h,n-1},$$

which are equal to $\frac{\partial w_h}{\partial a}$ as they are the derivative of age of the first and last age group ODE. We hence obtain exactly the PDE (1a).

It is left to show that the ODE

$$\frac{\mathrm{d}i_s}{\mathrm{d}t} = \left(\beta_{sh} \sum_{k=1}^{n} N_{h,k} w_{h,k} + \beta_{sd} N_d w_d + \beta_{sc} N_c w_c\right)(1 - i_s) - \mu_s i_s$$

is equal to the ODE (1d) for $n \to \infty$. We thus look at the limits of the ODE

$$\begin{aligned}\frac{\mathrm{d}i_s}{\mathrm{d}t} &= \lim_{n\to\infty}\left(\beta_{sh}\sum_{k=1}^{n} N_{h,k}w_{h,k} + \beta_{sd}N_d w_d + \beta_{sc}N_c w_c\right)(1-i_s) - \mu_s i_s \\ &= \left(\beta_{sh}\lim_{n\to\infty}\left(\sum_{k=1}^{n} N_{h,k}w_{h,k} + \beta_{sd}N_d w_d + \beta_{sc}N_c w_c\right)(1-i_s)\right) - \mu_s i_s \\ &= \left(\beta_{sh}\int_0^{a_{\max}} N_h(a)w_h(a)\mathrm{d}a + \beta_{sd}N_d w_d + \beta_{sc}N_c w_c\right)(1-i_s) - \mu_s i_s\end{aligned}$$

with $a_{\max}$ as maximal age. The last step is justified by the Riemann definition of the integral. □

6 Effectiveness of interventions

We simulate the impact of three interventions in reducing the mean worm burden in humans. As modelled previously [4], we consider mass drug administration (MDA) for *O. viverrini* using praziquantel, which is efficacious against all human trematode infections [13]; education campaigns to reduce the consumption of under-cooked fish; and improved sanitation. The implementation in the model is as follows.

- Education campaigns: change the behaviour of eating raw or undercooked fish. This reduces the transmission from fish to humans. We label the proportion of humans who are affected by the education campaign by I_e, assuming that they completely stop eating raw fish.
- Improved sanitation: allows people to stop defecating outdoors and reduces the transmission from humans to snails. We label the coverage of people who have and use improved sanitation I_d, assuming they no longer defecate outdoors.
- MDA: provides people with praziquantel which kills the parasite, increasing the death rate of parasites in humans. We label the coverage of treated people, I_m and assume that the proportion of worms killed corresponds to the coverage of the human population.

We split the human population into 5 age groups and extend the model with age groups (5) to include interventions, as done previously in [3]. The number of humans in each age group is taken accordingly to the exponential distribution. The coverage level of MDA is age group dependent, $I_{m,i}$ for $i =$

$1, \ldots, 5$. The model is given by the ODE system,

$$\frac{\mathrm{d}w_{h,1}(t)}{\mathrm{d}t} = \phi_1\beta_{hf}N_f i_f(t)(1-I_e) - \left(\mu_{ph} + \zeta_1 - \frac{\log(1-I_{m,1}(t))}{T_\gamma}\right)w_{h,1}(t), \tag{7a}$$

$$\frac{\mathrm{d}w_{h,2}(t)}{\mathrm{d}t} = \phi_2\beta_{hf}N_f i_f(t)(1-I_e) - \left(\mu_{ph} + \zeta_2 - \frac{\log(1-I_{m,2}(t))}{T_\gamma}\right) w_{h,2}(t) + \frac{\zeta_1 N_{h,1}}{N_{h,2}}w_{h,1}(t), \tag{7b}$$

$$\frac{\mathrm{d}w_{h,3}(t)}{\mathrm{d}t} = \phi_3\beta_{hf}N_f i_f(t)(1-I_e) - \left(\mu_{ph} + \zeta_3 - \frac{\log(1-I_{m,3}(t))}{T_\gamma}\right) w_{h,3}(t) + \frac{\zeta_2 N_{h,2}}{N_{h,3}}w_{h,2}(t), \tag{7c}$$

$$\frac{\mathrm{d}w_{h,4}(t)}{\mathrm{d}t} = \phi_4\beta_{hf}N_f i_f(t)(1-I_e) - \left(\mu_{ph} + \zeta_4 - \frac{\log(1-I_{m,4}(t))}{T_\gamma}\right) w_{h,4}(t) + \frac{\zeta_3 N_{h,3}}{N_{h,4}}w_{h,3}(t), \tag{7d}$$

$$\frac{\mathrm{d}w_{h,5}(t)}{\mathrm{d}t} = \phi_5\beta_{hf}N_f i_f(t)(1-I_e) - \left(\mu_{ph} - \frac{\log(1-I_{m,5}(t))}{T_\gamma}\right) w_{h,5}(t) + \frac{\zeta_4 N_{h,4}}{N_{h,5}}w_{h,4}(t), \tag{7e}$$

$$\frac{\mathrm{d}w_d(t)}{\mathrm{d}t} = \beta_{df}N_f i_f(t) - \mu_{pd}w_d(t), \tag{7f}$$

$$\frac{\mathrm{d}w_c(t)}{\mathrm{d}t} = \beta_{cf}N_f i_f(t) - \mu_{pc}w_c(t), \tag{7g}$$

$$\frac{\mathrm{d}i_s(t)}{\mathrm{d}t} = \left(\beta_{sh}\sum_{k=1}^{5} w_{h,k}(t)(1-I_d)N_{h,k} + \beta_{sd}N_d w_d(t) + \beta_{sc}N_c w_c(t)\right) (1-i_s(t)) - \mu_s i_s(t), \tag{7h}$$

$$\frac{\mathrm{d}i_f(t)}{\mathrm{d}t} = \beta_{fs}N_s i_s(t)(1-i_f(t)) - \mu_f i_f(t), \tag{7i}$$

with the age groups found in Table 5.

To find the best coverage of education campaigns and MDA in each age group where education campaigns are constant over age, we use the optimal control method as in [4] for different coverage levels of improved sanitation. We assume yearly treatment where humans of a certain coverage level are treated once. The treatment rate of humans is $\gamma = -\frac{\log(1-I_m(t))}{T_\gamma}$, where $T_\gamma = 1$ as MDA takes place over one day. For simplicity, we optimise the treatment rate γ instead of the coverage I_m. We optimise the treatment rate of each year separately. This means that we have the treatment sequence $\gamma_{i,1}, \ldots, \gamma_{i,m}$ for

Table 5 Age groups of the age-stratified model (7).

Group	Age (years)
1	< 6
2	$6 - 16$
3	$17 - 36$
4	$37 - 50$
5	> 50

m years and each age group i. γ_i has the following properties

$$\gamma_i(t) = \begin{cases} \gamma_{i,k}, & t \mod 365 = 1 \text{ and } k = \frac{t-1}{365}, \\ 0, & \text{else}, \end{cases}$$

for $i = 1, \dots, 5$ and $k = 1, \dots, m$ the number of years. To simplify the notation we write $\gamma = (\gamma_1(t), \gamma_2(t), \gamma_3(t), \gamma_4(t), \gamma_5(t))$ and $I_e = I_e(t)$.

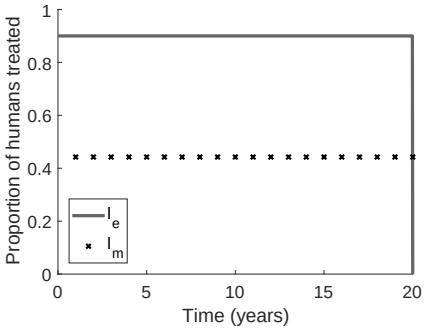
We optimise the functional

$$\min_{I_e, \gamma} \int_0^T \sum_{i=1}^{5} w_{h,i}^2(t) + \frac{\alpha^2}{2} \left(I_e^2 + \sum_{i=1}^{5} \sum_{k=1}^{m} \gamma_{i,k}^2 \right) \mathrm{d}t$$

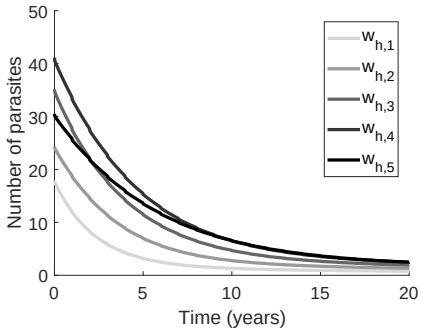
similar to [3]. The constant $\alpha = 0.001$ provides the relative weight of minimising the control efforts when compared to the mean worm burden in humans. The duration of the yearly campaigns is 20 years ($T = 20 \times 365$, $m = 20$) and we assume that the maximum possible coverage we can achieve by education campaigns is 90% and 80% by the mass drug administration. This is equivalent to $0 \leq I_e(t) \leq 0.9$ and $0 \leq \gamma_{i,k}(t) \leq 0.0016$ for $i = 1, \dots, 5$. The initial value is set to the mean number of worms in Figure 3 for humans and $(w_h(a), 1, 13, 0.003, 0.3)$ for the other hosts.

The results of $I_{m,i}(\gamma) = 1 - \exp(\gamma_i \times 365)$ for $i = 1, \dots, 5$ and I_e are shown in Figure 6. The solutions of the optimal control are the same for all age groups. We run the optimisation of the yearly MDA $I_{m,i}(\gamma)$ for $i \in \{1, \dots, 5\}$ and the education campaign I_e for three different levels of coverage of improved sanitation $I_d \in \{0.4, 0.6, 0.8\}$. The results show that a yearly MDA coverage of $I_m = 0.44$ is optimal for all age groups and at all coverage levels of improved sanitation. The optimum of the coverage of education campaign is at the maximum of $I_e = 0.9$. The mean worm burden in humans decreases to less than 3 worms per average in humans, assuming an optimal annual MDA has taken place over the last 20 years for all three coverage levels of improved sanitation.

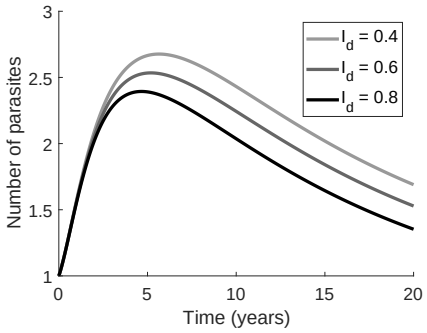
We run thirteen different scenarios to identify the age groups that should be targeted by MDA campaigns. The first three scenarios consider an ideal campaign where all groups are targeted equally with 70% coverage (I), a school-based campaign focusing on children with 80% coverage (II) and a



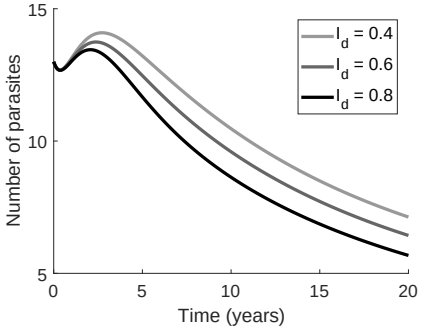
(a) Optimal coverage of intervention strategies with a fixed coverage level of improved sanitation of $I_d = 0.6$ for all age groups. The optimal coverage of intervention strategies with a fixed level of improved sanitation of $I_d = 0.4$ and $I_d = 0.8$ looks similar, but is not shown here.



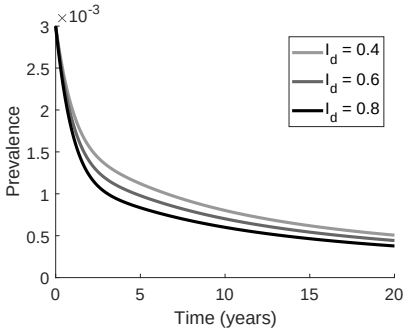
(b) Mean worm burden in humans of each age group with a coverage level of improved sanitation of $I_d = 0.6$ ($w_{h,i}$ for $i \in \{1, \ldots, 5\}$).



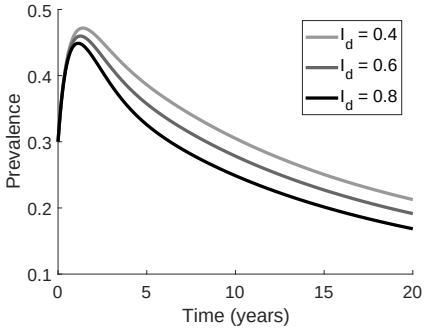
(c) Mean worm burden in dogs (w_d).



(d) Mean worm burden in cats (w_c).



(e) Prevalence in snails (i_s).



(f) Prevalence in fish (i_f).

Fig. 6 Numerical simulation of the optimal control solution with initial value at time t_0: the mean worm burden $w_h(a, t_0)$ for every age a as shown in Figure 3 and $(w_d(t_0), w_c(t_0), i_s(t_0), i_f(t_0)) = (1, 13, 0.003, 0.3)$. The parameter values are shown in Table 4, the maximum likelihood estimates.

Table 6 Coverage of MDA of the age groups for each strategy I, II and III.

Strategy		Age group				
		< 6	$6-16$	$17-36$	$37-50$	> 50
I:	ideal MDA	0.7	0.7	0.7	0.7	0.7
II:	school-based treatment	0	0.8	0	0	0
III:	realistic MDA	0.7	0.7	0.5	0.5	0.7

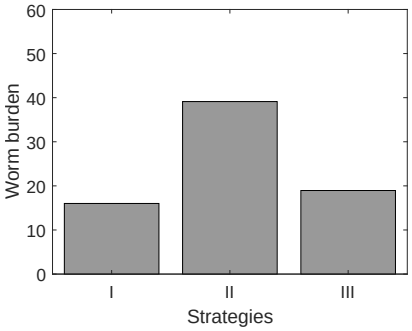
Table 7 Coverage of MDA of the age groups for each strategy $IV - VIII$.

Strategy		Age group				
		< 6	$6-16$	$17-36$	$37-50$	> 50
IV:	ignoring age group < 6	0	0.8867	0.8867	0.8867	0.8867
V:	ignoring age group $6-16$	0.9739	0	0.9739	0.9739	0.9739
VI:	ignoring age group $17-36$	0.9844	0.9844	0	0.9844	0.9844
VII:	ignoring age group $37-50$	0.7770	0.7770	0.7770	0	0.7770
$VIII$:	ignoring age group > 50	0.7956	0.7956	0.7956	0.7956	0

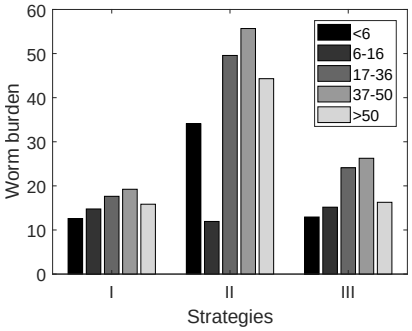
realistic campaign with lower coverage of working-age adults (50%) and 70% of other age groups (III). Strategies IV–$VIII$ consider MDA with equal coverage of four age groups and 0% of one age group (to determine the impact of not reducing transmission from that age group) with an overall population coverage of 70% (to account for the fact that not all age groups have the same population size). Strategies IX–$XIII$ consider campaigns with 70% coverage of each age group singly to determine the impact of transmission from that age group. The strategies are described in Tables 6–8 and the simulation results of the mean worm burden of each age group after 10 years are shown in Figure 7.

Applying the annual MDA strategies to the population for 10 years shows that strategies I and III are much more effective in reducing the overall worm burden. The mean worm burden after 10 years is between 15 and 20 worms per person in strategies I and III. Whereas focusing on school children keeps the mean worm burden high at around 40 worms per person on average. The same pattern is seen when looking at the mean worm burden in each age group. Strategy II does not affect the high mean worm burden of the young and old age group, as we assume the school children do not take place in any education campaigns and so they do not change their behaviour of eating raw or undercooked fish. In particular, reducing the worm burden of school children does not sufficiently reduce onward transmission.

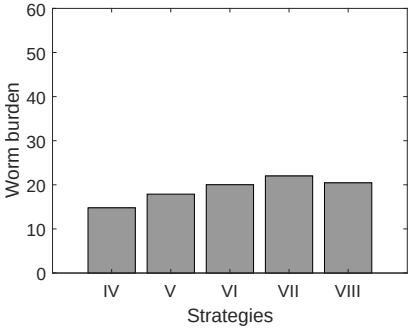
In strategies IV–VII we focus on 4 age groups out of the 5, so one age group does not get any treatment. The overall coverage is held at 70% of the human population. Neglecting the youngest age group has the best effect of strategies IV–VII and neglecting the fourth age group of $37-50$ years has the worst effect. Strategies IX–XII focus on one age group with a coverage level of 70%. The mean worm burden over all age groups shows that focusing on the third, $17-36$ years, or fourth age group, $37-50$ years, has the highest positive effect and focusing on the youngest age group has the least.



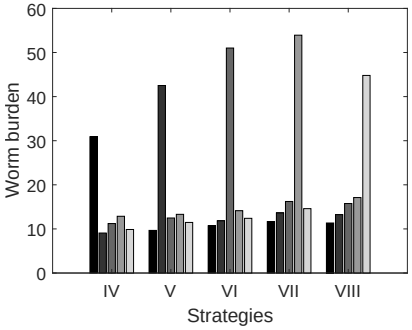
(a) Mean worm burden in humans over all age groups for strategies I–III.



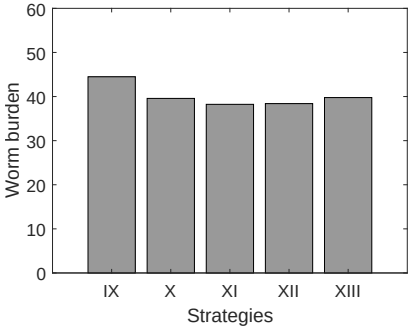
(d) Mean worm burden in humans for each age group for strategies I–III.



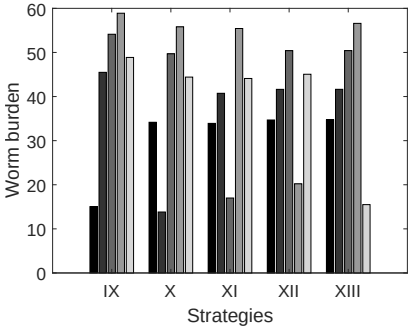
(b) Mean worm burden in humans over all age groups for strategies IV–$VIII$.



(e) Mean worm burden in humans for each age group for strategies IV–$VIII$.



(c) Mean worm burden in humans over all age groups for strategies IX–$XIII$.



(f) Mean worm burden in humans for each age group for strategies IX–$XIII$.

Fig. 7 Intervention strategies (Table 6–8) applied annually for 10 years. The effect of the intervention on the mean worm burden of each age group and overall population.

Table 8 Coverage of MDA of the age groups for each strategy $IX - XIII$.

Strategy		Age group				
		< 6	$6 - 16$	$17 - 36$	$37 - 50$	> 50
IX:	focusing on age group < 6	0.7	0	0	0	0
X:	focusing on age group $6 - 16$	0	0.7	0	0	0
XI:	focusing on age group $17 - 36$	0	0	0.7	0	0
XII:	focusing on age group $37 - 50$	0	0	0	0.7	0
$XIII$:	focusing on age group > 50	0	0	0	0	0.7

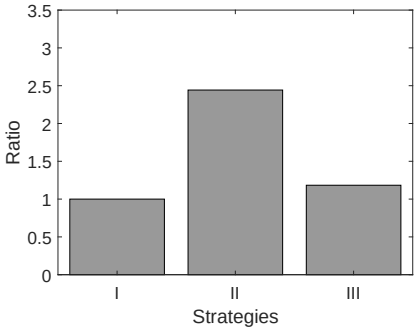
We compare each strategy with strategy I of 70% coverage of all age groups. We calculate the ratio of the mean worm burden of strategy K and the mean worm burden of the baseline strategy I; $r = \frac{w_{h,K}}{w_{h,I}}$ for $K = II, \ldots, XIII$ [23]. The ratio r helps to describe the additional reduction or increase of this strategy in comparison with the baseline strategy I; the additional reduction or increase is $1 - r$. The results are shown in Figure 8. Overall strategy II has 2.44 times more worms per person than strategy I. Strategy III has only 1.18 times more worms than the baseline strategy. In comparison with the baseline strategy I, strategy IV even has 8% less worms and strategy VII has 1.37 times more worms than the baseline strategy. Focusing on only one age group as in strategies IX–XII increases the mean worm burden between $2.39 - 2.78$ times more than the baseline strategy.

7 Discussion

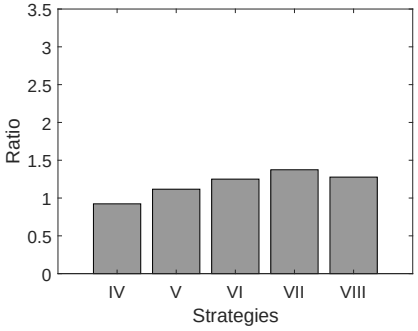
We developed a deterministic model of *O. viverrini* transmission that included age dependence in the worm burden of humans. This allowed us to capture the phenomenon that the worm burden typically increases with age, since older individuals have had more time to accumulate worms and, on average, adults eat more raw fish than children until a peak of around 50 years. The average worm burden of humans does not saturate but decreases with age after 50, possibly because deteriorating dental health (in particular, due to the high prevalence of betel nut consumption) makes chewing raw fish more difficult. This has been modelled through the parameter, $\phi(a)$, which denotes the proportion of people eating raw or undercooked fish at age a. The steady state solution of the model for mean worm burden in humans replicates these dynamics in line with the data for the age distribution of eggs per gram in human stool from two rural communities in Lao PDR.

We defined the basic reproduction number, R_0, for the model (1) and estimated a value of 1.2311, suggesting that each adult worm has 1.866 ($= 1.2311^3$) offspring in the absence of density dependence and fully susceptible snail and fish populations. The value of R_0 is not very large, so the elimination of transmission may be feasible with sufficient control interventions.

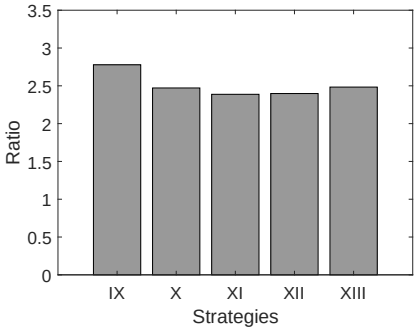
Simulating the effectiveness of interventions in the model with age groups suggests that we should aim for a minimum coverage of 40% for MDA. The



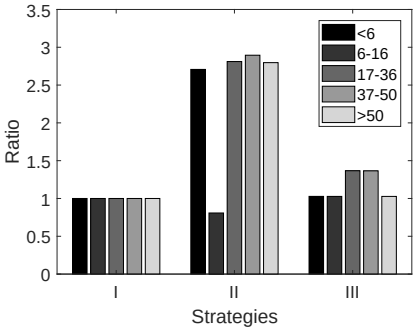
(a) Ratio of the mean worm burden of strategies I–III to the baseline strategy.



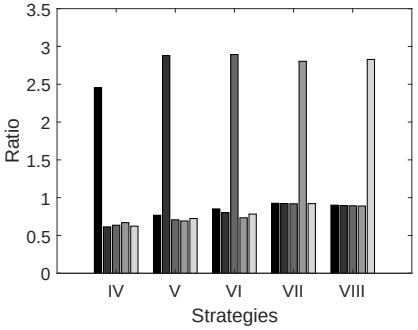
(b) Ratio of the mean worm burden of strategies IV–$VIII$ to the baseline strategy.



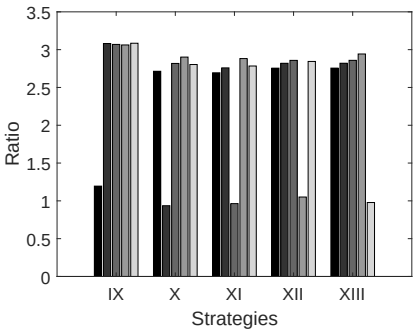
(c) Ratio of the mean worm burden of strategies IX–$XIII$ to the baseline strategy.



(d) Ratio of the mean worm burden in each age group of strategies I–III to the baseline strategy.



(e) Ratio of the mean worm burden in each age group of strategies IV–$VIII$ to the baseline strategy.



(f) Ratio of the mean worm burden in each age group of strategies IX–$XIII$ to the baseline strategy.

Fig. 8 The ratio of the mean worm burden compared to the baseline strategy I.

coverage of improved sanitation and education campaigns should be as high as possible, especially when noting the additional benefits of improved sanitation on other diseases.

School-based mass treatment has been a common strategy for reducing transmission and morbidity of the related trematode disease, schistosomiasis, with mixed results [8, 10]. Mathematical models of schistosomiasis have suggested that school-based programmes can be successful if the pre-treatment prevalence is low, but are unlikely to achieve global control targets if pre-treatment prevalence is high [22]. Our results show that school-based treatment campaigns, even if they are able to achieve very high coverage, do not have a large impact on reducing the worm burden of the overall population, although they can have a substantial reduction in the burden of school-aged children. Therefore, control efforts should focus on community-wide campaigns. The realistic MDA (strategy III) has a lower coverage of the age groups 17–36 years and 37–50 years. However, after 10 years of annual treatment the mean worm burden was not much higher across all age groups than the ideal MDA strategy (I), even though it was higher in those particular age groups. This implies that although campaigns should aim at a coverage which is as high as possible in all age groups, an exceptional effort to reach the same coverage across all age groups is unlikely to be necessary.

We also considered the impact that each age group had on maintaining transmission by simulating MDA campaigns in only one age group, or by excluding only one age group. The simulations for excluding a group allows an increased treatment coverage of the other groups, so that the overall population coverage was 70% (accounting for the fact that not all groups had same the population size). The simulations targeting only one group assumed a fixed coverage in that age group of 80%. Hence, the results also depend on the population size of that age group. As expected, treating only children (< 6 years old) had the least impact, and excluding children was even better than the baseline strategy, since on average humans with more worms were treated. Excluding any other age group resulted in a worse outcome than the baseline strategy, suggesting that all age groups above 6 play an above-average role in maintaining transmission. Excluding the middle aged adults (37–50 years old) results in the worst outcome, suggesting that on a per capita basis, they play the biggest role in maintaining transmission. Treating only the young adult and middle age group (17–50 years old) had the best outcomes. However, the differences between the impact of treating adults of different ages was relatively small.

The models considered here make many simplifying assumptions. We did not consider the seasonality in transmission due to seasonal variation in snail and fish populations [17]. We expect MDA campaigns to be most effective if they are conducted after the peak in transmission but this is not always possible due to operational reasons. Including seasonality in such a model would allow us to compare the potential loss in effectiveness if the timing of MDA campaigns is not optimal.

The dynamics of *O. viverrini* infection in fish are more similar to those of the parasite in humans than in snails, because fish can be superinfected and the number of metacercariae in fish correspond to the number of potential adult worms in humans. However, little data is available on the intensity of infection in fish, so we make the simplifying assumption of susceptible-infectious dynamics for fish based on available prevalence data.

We assumed perfect efficaciousness of all interventions at the given coverage level — although this would be equivalent to imperfect interventions at higher coverage levels. We also assumed no decay in the use of improved sanitation and behavioural change. Sustaining the effectiveness of such interventions is possible but would in turn require sustained efforts by national control programs.

We also only considered the impact of interventions in reducing transmission and not on reducing disease burden. This may have a substantial impact on the results because while differently treating particular age groups may have a minor impact on transmission, they may substantially impact consequent disease burden. However, the relationship between worm burden and morbidity for opisthorchiasis is complicated, as field studies have shown that repeated treatment of high intensity infections may increase the risk of cancer [16]. Capturing such relationships is not possible with mean worm burden models and would require an individual-based model that can track the worm burden of each person over time. Such a model would also allow us to estimate the impact of additional clinical interventions including ultrasound scans to detect potential complications and cancers in the bile duct [18].

Nevertheless, analysis of this model of age-dependent transmission suggests that mass drug administration campaigns can be effective in reducing transmission, especially when combined with improved sanitation and behaviour change campaigns. Although these campaigns should target adults since treating adults has the most impact on reducing transmission, if such targeting is operationally infeasible, achieving moderate coverage levels in all age groups can still have a substantial impact on reducing worm burden.

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