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Highlights

- Humans, snails and fish are a maintenance-hosts and without them transmission of O. viverrini cannot be sustained.
- Cats and dogs are non-maintenance hosts; they cannot sustain transmission in absence of humans as a definitive host.
- The most effective control interventions are targeting death rates of parasites in humans through regular treatment, the transmission rate from humans to snails through improved sanitation and from fish to humans through safe fish production.

Mathematical Analysis of the Transmission Dynamics of the Liver Fluke, *Opisthorchis viverrini*

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Abstract

We develop and analyse two population-based models of the transmission dynamics of the worm parasite *Opisthorchis viverrini*. The life cycle of *O. viverrini* includes humans, cats and dogs as definitive hosts; and snails and fish as intermediate hosts. The first model has only one definitive host (humans) while the second model has two additional hosts: the reservoir hosts, cats and dogs. We define reproduction numbers and endemic equilibrium points for the two models. We use prevalence data for the five hosts from two islands in Lao People's Democratic Republic to estimate distributions of parameter values. We use these distributions to compute the sensitivity index and the partial rank correlation coefficient of the basic reproduction number and the endemic equilibrium point to the parameters. We calculate distributions of the host-specific type-reproduction number to show that humans are necessary to maintain transmission and can sustain transmission without additional reservoir hosts. Therefore interventions targeting humans could be sufficient to interrupt transmission of *O. viverrini*.

Keywords: Opisthorchis viverrini, mathematical modelling, simulation
2000 MSC: 92D30

1. Introduction

Food-borne trematodiases are some of the most neglected of the so-called neglected tropical diseases. They are caused by digenetic trematodes, which live in the biliary duct of their host animal [1]. The disease opisthorchiasis is caused by the worm parasites *Opisthorchis viverrini*, *O. felineus* and *Clonorchis sinensis*. The liver fluke *O. viverrini* is endemic in Asia, mainly in Thailand,

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Lao People's Democratic Republic (Lao PDR) and Cambodia [2]. Worldwide 9–10 million people are infected with this liver fluke [2, 3] and 67.3 million are at risk of infection. Transmission is found in areas where humans have the habit of eating raw, pickled or undercooked fish [4].

Figure 1 shows the life cycle of *O. viverrini* (and correspondingly of *O. felineus* and *C. sinensis*). The first intermediate hosts of *O. viverrini* are snails of the genus *Bithynia* [5]. Freshwater snails ingest eggs, where they hatch to become miracidia. After approximately two months, infected snails release cercariae. The free-swimming cercariae penetrate through the skin of the second intermediate hosts, Cyprinidae fish [6], and become fully infective metacercariae after 21 days [1].

The definitive hosts of *O. viverrini*, humans and other mammals like cats and dogs, get infected through the consumption of undercooked fish infected with metacercariae. A dish with raw fish can contain hundreds of viable *O. viverrini* metacercariae [7]. The immature worm of *O. viverrini* migrates from the duodenum into the biliary tract. After one month the worm matures into an adult worm and mates within the lumen of the bile ducts and gall bladder. The eggs of the worm travel through the bile ducts, enter the lumen and pass out with the faeces [8]. The daily output of infected humans ranges between 3,000 and 36,000 eggs per gram of stool. The life span of the worms in humans is around ten years. The whole life cycle of *O. viverrini* has a duration of four months [2, 6].

Infection with worms leads to many liver diseases including cholangitis, ob-

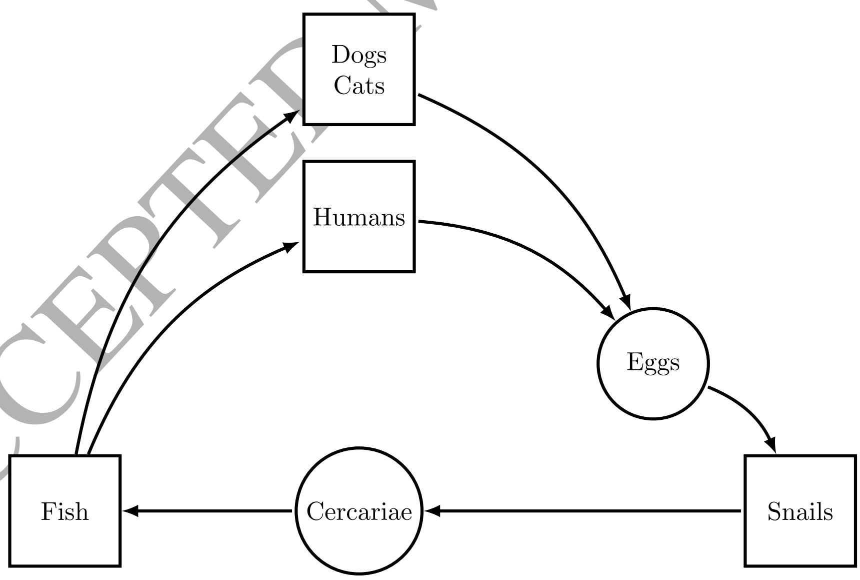


Figure 1: Schematic of the life cycle of *O. viverrini*

structive jaundice, hepatomegaly, biliary periductal fibrosis, cholecystitis, and cholelithiasis. Treatment of worms usually consists of three doses of praziquantel, which is cheap, safe and effective in killing worms. However, treatment of any subsequent liver disease is expensive and difficult. Chronic infection with *O. viverrini* can also lead to the bile duct cancer, cholangiocarcinoma [8]. This kind of cancer is rare but with a poor prognosis [9].

There are no published papers in mathematical modelling of *O. viverrini*, but there is one on modelling the related parasite *C. sinensis*. Song *et al.* developed a catalytic model to estimate equilibrium transmission rates [10]. However, catalytic models are based on linear ordinary differential equations (ODEs) with constant coefficients, so they cannot capture the nonlinear dynamics of transmission.

There are also many publications on modelling schistosomiasis, a similar disease with only one intermediate host, the snail. Schistosome parasites infect the human as cercariae in the free-swimming stage, whereas *O. viverrini* cercariae infect fish [11]. The first model of schistosmiasis was by Hairston in 1965. He used life-tables to calculate the net reproductive rate of the parasite, modelling female and male worms separately [12]. In the same year, Macdonald developed a dynamic model with the probability of pairing worms and the proportion of hosts with paired worms [13]. Goffmann and Warren adopted the Kermack-McKendrick susceptible-infectious-recovered (SIR) model to humans and snails, including the free swimming miracidia and cercariae [14]. Nåsell and Hirsch developed a stochastic model of the intensity of infection [11]. Anderson and May developed an ODE model with the mean worm burden in the human host. They split the snails into three groups: susceptible, latent and shedding [15]. Habbema simulated a stochastic model of the intensity and prevalence in individual humans [16]. We base our model on Anderson and May by tracking the mean worm burden instead of the prevalence of infection in humans, because infectivity to snails and human morbidity depend on the intensity of infection. Similar to previous schistosomiasis models for snails, we use susceptible-infectious models for snails and fish.

To create a basis for the mathematical modelling of food-borne trematodes with population-based models, we develop two different models. We first develop a simple model that only includes infection in fish, snails and humans. We then develop a second model that also includes infection in cats and dogs. These models allow us to better understand the role of domestic pets in the transmission dynamics of *O. viverrini*.

For these models, we define the equilibrium points, the basic reproduction number and the host-specific type-reproduction numbers. We derive these definitions by explicit calculations using Mathematica 10.0.2. We then use data from Lao People's Democratic Republic to estimate reasonable distributions for the parameter values of the models. We conduct sensitivity analysis using these distributions on the equilibrium points and the reproduction numbers for both models to determine weak points in the parasite's life cycle and the role of each mammalian host in maintaining transmission. We perform all the numerical computations in Matlab R2017a.

2. Basic transmission model

In the basic transmission model we assume that only fish, snails and humans are involved in the life cycle of *O. viverrini*, ignoring the reservoir hosts: cats and dogs. We model the mean worm burden in human and the prevalences of infected snails and fish. The deterministic population-based ordinary differential equation (ODE) model represents the base transmission dynamics of *O. viverrini*. It is given by

$$\frac{\mathrm{d}w_h}{\mathrm{d}t} = \beta_{hf} N_f i_f - \mu_{ph} w_h, \tag{1a}$$

$$\frac{\mathrm{d}i_s}{\mathrm{d}t} = \beta_{sh} N_h w_h (1 - i_s) - \mu_s i_s, \tag{1b}$$

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

with the state variables shown in Table 1 and the parameters shown in Table 2.

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

Table 1: State variables of the opisthrochiasis models

The mean worm burden per human host w_h increases with the consumption of infected fish. This includes the number of fish, the proportion of infectious fish and the transmission rate of parasites to humans per fish, $\beta_{hf} N_f i_f$, and decreases with the death of parasites, $\mu_{ph} w_h$. The proportion of infectious snails i_s, depends on the total adult worm population and the eggs they produce that enter the aquatic environment, $\beta_{sh} N_h w_h (1 - i_s)$. Snails are infected until they die at a total rate, $\mu_s i_s$. The proportion of infectious fish has similar dynamics. Their rate of infection depends on the number of infectious snails and the snails' rate of releasing cerceriae, $\beta_{fs} N_s i_s (1 - i_f)$. The fish remain infected until they die at a total rate, $\mu_f i_f$.

This model ignores the intensity of infection in fish, as well as the distribution of intensity in humans. We assume that all humans are the same and are equally likely to be infected by the parasite, and that all infected fish and snails are equal with regards to within- and between-species transmission, so we assume no assortative mixing. We also ignore density-dependent effects in hosts such as acquired immunity and Allee effects.

2.1. Existence and uniqueness of the solution

The system with the equations (1) is well-posed and epidemiologically relevant in the strip $S \subset \mathbb{R}^3$. The strip S is defined by the boundaries of the solutions of the system (w_h, i_s, i_f),

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

The right hand side of the ODE system (1) is continuous with continuous partial derivatives in S. We assume that an initial condition exists in the strip S. We can then show that a solution of the system cannot leave this strip S:

(i) If $w_h = 0$, then

$$\frac{\mathrm{d}w_h}{\mathrm{d}t} = \beta_{hf} N_f i_f - \mu_{ph} \cdot 0 \geq 0,$$

and, if $w_h = \frac{N_f \beta_{hf}}{\mu_{ph}}$, then

$$\frac{\mathrm{d}w_h}{\mathrm{d}t} = \beta_{hf} N_f i_f - \mu_{ph} \cdot \frac{N_f \beta_{hf}}{\mu_{ph}} \leq 0.$$

(ii) If $i_s = 0$, then

$$\frac{\mathrm{d}i_s}{\mathrm{d}t} = \beta_{sh} N_h w_h \cdot 1 - \mu_s \cdot 0 \geq 0,$$

and, if $i_s = 1$, then

$$\frac{\mathrm{d}i_s}{\mathrm{d}t} = \beta_{sh} N_h w_h \cdot 0 - \mu_s \cdot 1 \leq 0.$$

(iii) If $i_f = 0$, then

$$\frac{\mathrm{d}i_f}{\mathrm{d}t} = \beta_{fs} N_s i_s \cdot 1 - \mu_{fs} \cdot 0 \geq 0,$$

and, if $i_f = 1$, then

$$\frac{\mathrm{d}i_f}{\mathrm{d}t} = \beta_{fs} N_s i_s \cdot 0 - \mu_{fs} \cdot 0 \leq 0.$$

It finally follows with the Picard-Lindelöf theorem that a unique solution exists for the ODE system (1) in the strip S.

2.2. Equilibrium points

Definition 1 (Disease free equilibrium point). *The disease free equilibrium, also called trivial equilibrium point, is the steady state solution with no disease in the population.*

Definition 2 (Endemic equilibrium point). *The endemic equilibrium point is the steady state solution with all state variables positive, where the disease persists in the population.*

Setting the derivatives equal to zero, the equilibrium points are given as the solution of

$$\begin{aligned}
0 &= \beta_{hf} N_f i_f^* - \mu_{ph} w_h^*, \\
0 &= \beta_{sh} N_h w_h^* (1 - i_s^*) - \mu_s i_s^*, \\
0 &= \beta_{fs} N_s i_s^* (1 - i_f^*) - \mu_f i_f^*.
\end{aligned}$$

The system has two solutions, the disease free and the endemic equilibrium point. The disease free equilibrium point is characterized by $E_0^{BM} = (w_h^*, i_s^*, i_f^*) = (0, 0, 0)$. The endemic equilibrium point $E_e^{BM} = (w_h^*, i_s^*, i_f^*)$ corresponds to

$$w_h^* = \frac{\beta_{hf}\beta_{sh}\beta_{fs} N_s N_h N_f - \mu_{ph}\mu_s\mu_f}{\beta_{sh} N_h \mu_{ph} (\beta_{fs} N_s + \mu_f)}, \tag{2a}$$

$$i_s^* = \frac{\beta_{hf}\beta_{sh}\beta_{fs} N_s N_h N_f - \mu_{ph}\mu_s\mu_f}{\beta_{fs} N_s (\beta_{hf}\beta_{sh} N_h N_f + \mu_{ph}\mu_s)}, \tag{2b}$$

$$i_f^* = \frac{\beta_{hf}\beta_{sh}\beta_{fs} N_s N_h N_f - \mu_{ph}\mu_s\mu_f}{\beta_{hf}\beta_{sh} N_h N_f (\beta_{fs} N_s + \mu_f)}, \tag{2c}$$

which is in the interior of S if $\beta_{hf}\beta_{sh}\beta_{fs} N_s N_h N_f > \mu_{ph}\mu_s\mu_f$.

2.3. Basic reproduction number

Definition 3 (Basic reproduction number). *The basic reproduction number $\mathcal{R}_0$ is the average number of new cases of an infection (or number of parasite offspring) caused by one typical infected individual (or one parasite), from one generation to the next, in a population with no pre-existing infections.*

To determine $\mathcal{R}_0$, we define the next-generation matrix (NGM) $\mathbf{K}$. This matrix relates the numbers of newly infected individuals or number of adult parasites in consecutive generations. $\mathcal{R}_0$ is then defined as the dominant eigenvalue of $\mathbf{K}$.

The linearised infection subsystem describes the production of newly infected individuals and changes in the states of already infected individuals. To derive the next-generation matrix $\mathbf{K}$, we decompose the matrix, which describes the linearised model, into two matrices, $\mathbf{T}$ and $\mathbf{\Sigma}$. $\mathbf{T}$ describes transmission: the production of new infections; and $\mathbf{\Sigma}$ describes transition: the changes in state. $\mathbf{K}$ is defined as the product of $-\mathbf{T}$ and $\mathbf{\Sigma}^{-1}$ and $\mathcal{R}_0$ is the spectral radius, ρ, of $\mathbf{K}$. Therefore, $\mathcal{R}_0 = \rho(-\mathbf{T}\mathbf{\Sigma}^{-1})$.

The interpretation of the (i,j)-th entry of $\mathbf{\Sigma}^{-1}$ is the expected time that an individual, who presently has the infected state j, will spend in the infected state i. The (i,j)-th entry of $\mathbf{T}$ is the rate at which an individual in the infected state j produces individuals with the infected state i. Therefore, the (i,j)-th entry of the NGM $\mathbf{K}$ is the expected number of the infected offspring with the state i who are infected by an individual currently in infected state j [17].

The transmission matrix is

$$\mathbf{T} = \begin{bmatrix} 0 & 0 & \beta_{hf}N_f \\ \beta_{sh}N_h & 0 & 0 \\ 0 & \beta_{fs}N_s & 0 \end{bmatrix},$$

and the transition matrix is

$$\mathbf{\Sigma} = \begin{bmatrix} -\mu_{ph} & 0 & 0 \\ 0 & -\mu_s & 0 \\ 0 & 0 & -\mu_f \end{bmatrix}.$$

The next-generation matrix of the basic model is therefore

$$\mathbf{K} = -\mathbf{T}\mathbf{\Sigma}^{-1} = \begin{bmatrix} 0 & 0 & \frac{\beta_{hf}N_f}{\mu_f} \\ \frac{\beta_{sh}N_h}{\mu_{ph}} & 0 & 0 \\ 0 & \frac{\beta_{fs}N_s}{\mu_s} & 0 \end{bmatrix}.$$

The eigenvalues of the next-generation matrix $\mathbf{K}$ are

$$\lambda_1 = \sqrt[3]{\frac{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_sN_f}{\mu_{ph}\mu_s\mu_f}},$$

$$\lambda_2 = -(-1)^{\frac{1}{3}}\sqrt[3]{\frac{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_sN_f}{\mu_{ph}\mu_s\mu_f}},$$

$$\lambda_3 = (-1)^{\frac{2}{3}}\sqrt[3]{\frac{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_sN_f}{\mu_{ph}\mu_s\mu_f}}.$$

All eigenvalues have the same modulus, so the (not strictly) dominant eigenvalue is λ_1, the only real and positive eigenvalue of $\mathbf{K}$. Hence, it follows that

$$\mathcal{R}_0 = \sqrt[3]{\frac{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_sN_f}{\mu_{ph}\mu_s\mu_f}}. \tag{3}$$

The ecological definition of the basic reproduction number is the number of offspring adult worms produced by a single adult worm in its life time, in the absence of density-dependence. This number corresponds to the cube of $\mathcal{R}_0$ defined in (3) to include all life stages of the parasite.

2.4. Stability of the equilibrium points

The basic reproduction number provides a threshold condition for the stability of the disease free equilibrium point. If $\mathcal{R}_0 < 1$, then the disease free equilibrium point is locally asymptotically stable, and if $\mathcal{R}_0 > 1$ it is unstable. We conjecture that the disease free equilibrium point is globally asymptotically stable if $\mathcal{R}_0 \leq 1$ because we do not expect any non-equilibrium asymptotic dynamics but we do not have a proof for this.

The endemic equilibrium exists if and only if $\beta_{hf}\beta_{sh}\beta_{fs}N_hN_sN_f > \mu_{ph}\mu_s\mu_f$, that is $\mathcal{R}_0 > 1$. To investigate the local stability of the endemic equilibrium point, we use the Routh-Horwitz Criterion (Proposition 1 in the Appendix) to determine the signs of the real parts of the eigenvalues of the Jacobian matrix.

The Jacobian matrix of the basic model at the endemic equilibrium point is

$$\begin{aligned}\mathbf{J} &= \begin{bmatrix} -\mu_{ph} & 0 & \beta_{hf}N_f \\ \beta_{sh}N_h(1-i_s^*) & -(\beta_{sh}N_hw_h^* + \mu_s) & 0 \\ 0 & \beta_{fs}N_s(1-i_f^*) & -(\beta_{fs}N_si_s^* + \mu_f) \end{bmatrix} \\ &=: \begin{bmatrix} -j_{1,1} & 0 & j_{1,3} \\ j_{2,1} & -j_{2,2} & 0 \\ 0 & j_{3,2} & -j_{3,3} \end{bmatrix},\end{aligned}$$

for w_h^*, i_s^* and i_f^*, defined in (2). The eigenvalues of the Jacobian matrix are calculated by setting the characteristic polynomial $p(\lambda) = \det(\mathbf{J} - \lambda\mathbf{E})$ to zero. This leads to the equation

$$\begin{aligned}\lambda^3 + \lambda^2(j_{1,1} + j_{2,2} + j_{3,3}) + \lambda(j_{1,1}j_{2,2} + j_{1,1}j_{3,3} + j_{2,2}j_{3,3}) \\ + j_{1,1}j_{2,2}j_{3,3} - j_{1,3}j_{2,1}j_{3,2} \overset{!}{=} 0.\end{aligned}$$

We can determine the a_i of the Routh-Horwitz criterion in Proposition 1 for $i = 0, 1, 2, 3$:

$$\begin{aligned}a_0 &= 1, \\ a_1 &= j_{1,1} + j_{2,2} + j_{3,3}, \\ a_2 &= j_{1,1}j_{2,2} + j_{1,1}j_{3,3} + j_{2,2}j_{3,3}, \\ a_3 &= j_{1,1}j_{2,2}ij_{3,3} - j_{1,3}j_{2,1}j_{3,2}.\end{aligned}$$

With all the a_i's at hand, we can calculate the T_k's for $k = 0, 1, 2$ and see if they are positive or negative:

$$\begin{aligned}T_0 &= a_0 = 1 > 0, \\ T_1 &= a_1 > 0, \\ T_2 &= \det \begin{bmatrix} a_1 & a_0 \\ a_3 & a_2 \end{bmatrix} > 0 \Leftrightarrow \beta_{hf}\beta_{sh}\beta_{fs}N_hN_sN_f > \mu_{ph}\mu_s\mu_f \Leftrightarrow \mathcal{R}_0 > 1.\end{aligned}$$

From the Routh-Hurwitz criterion it follows that the roots of the characteristic polynomial $p(\lambda)$ have negative real parts and thus the eigenvalues of $\mathbf{J}$. This means that the endemic equilibrium is locally asymptotically stable whenever $\mathcal{R}_0 > 1$.

3. Model with reservoir hosts

In the second transmission model we add cats and dogs as reservoir hosts to the basic transmission model. We extend the basic model (1) by including two additional variables: the mean number of adult parasites per hosts in dogs (w_d) and cats (w_c). This leads to

$$\frac{\mathrm{d}w_h}{\mathrm{d}t} = \beta_{hf} N_f i_f - \mu_{ph} w_h, \tag{4a}$$
$$\frac{\mathrm{d}w_d}{\mathrm{d}t} = \beta_{df} N_f i_f - \mu_{pd} w_d, \tag{4b}$$
$$\frac{\mathrm{d}w_c}{\mathrm{d}t} = \beta_{cf} N_f i_f - \mu_{pc} w_c, \tag{4c}$$
$$\frac{\mathrm{d}i_s}{\mathrm{d}t} = (\beta_{sh} N_h w_h + \beta_{sd} N_d w_d + \beta_{sc} N_c w_c)(1 - i_s) - \mu_s i_s, \tag{4d}$$
$$\frac{\mathrm{d}i_f}{\mathrm{d}t} = \beta_{fs} N_s i_s (1 - i_f) - \mu_f i_f. \tag{4e}$$

The additional state variables are given in Table 1 and the additional parameters are given in Table 2.

190 *3.1. Existence and uniqueness of the solution*

The existence and the uniqueness of the solution $(w_h, w_d, w_c, i_s, i_f)$ of the ODE system (4) follows in complete analogy to Section 2.1 in the strip $S \subset \mathbb{R}^5$ given by

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

3.2. Equilibrium points

195 For the model with reservoir hosts (4) we solve the following system

$$\begin{aligned}
0 &= \beta_{hf} N_f i_f^* - \mu_{ph} w_h^*,\\
0 &= \beta_{df} N_f i_f^* - \mu_{pd} w_d^*,\\
0 &= \beta_{cf} N_f i_f^* - \mu_{pc} w_c^*,\\
0 &= (\beta_{sh} N_h w_h^* + \beta_{sd} N_d w_d^* + \beta_{sc} N_c w_c^*)(1 - i_s^*) - \mu_s i_s^*,\\
0 &= \beta_{fs} N_s i_s^* (1 - i_f^*) - \mu_f i_f^*,
\end{aligned}$$

to determine the equilibrium points. We see that $E_0^{RM} = (w_h^*, w_d^*, w_c^*, i_s^*, i_f^*) = (0,0,0,0,0)$ is the disease free equilibrium point and show the existence of at most one endemic equilibrium point. We calculated an analytic expression for this endemic equilibrium but do not present it here because of its length.

200 *3.3. Basic reproduction number*

To define the reproduction number of the model with reservoir hosts (4), we use the same method as for the basic model before. Hence, we obtain the transmission matrix

$$\mathbf{T} = \begin{bmatrix} 0 & 0 & 0 & 0 & \beta_{hf}N_f \\ 0 & 0 & 0 & 0 & \beta_{df}N_f \\ 0 & 0 & 0 & 0 & \beta_{cf}N_f \\ \beta_{sh}N_h & \beta_{sd}N_d & \beta_{sc}N_c & 0 & 0 \\ 0 & 0 & 0 & \beta_{fs}N_s & 0 \end{bmatrix}$$

and the transition matrix

$$\mathbf{\Sigma} = \begin{bmatrix} -\mu_{ph} & 0 & 0 & 0 & 0 \\ 0 & -\mu_{pd} & 0 & 0 & 0 \\ 0 & 0 & -\mu_{pc} & 0 & 0 \\ 0 & 0 & 0 & -\mu_s & 0 \\ 0 & 0 & 0 & 0 & -\mu_f \end{bmatrix}.$$

205 The next-generation matrix is thus defined as

$$\mathbf{K} = -\mathbf{T}\mathbf{\Sigma}^{-1} = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\beta_{hf}N_f}{\mu_f} \\ 0 & 0 & 0 & 0 & \frac{\beta_{df}N_f}{\mu_f} \\ 0 & 0 & 0 & 0 & \frac{\beta_{cf}N_f}{\mu_f} \\ \frac{\beta_{sh}N_h}{\mu_{ph}} & \frac{\beta_{sd}N_d}{\mu_{pd}} & \frac{\beta_{sc}N_c}{\mu_{pc}} & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{fs}N_s}{\mu_s} & 0 \end{bmatrix}.$$

The eigenvalues of the next-generation matrix $\mathbf{K}$ are the roots of the characteristic polynomial:

$$\det(\mathbf{K} - \lambda\mathbf{E}) =$$

$$-\lambda^5 + \lambda^2 \frac{\beta_{fs}N_s}{\mu_s}\left(\frac{\beta_{cf}N_f}{\mu_f}\frac{\beta_{sc}N_c}{\mu_{pc}} + \frac{\beta_{sd}N_d}{\mu_{pd}}\frac{\beta_{df}N_f}{\mu_f} + \frac{\beta_{hf}N_f}{\mu_f}\frac{\beta_{sh}N_h}{\mu_{ph}}\right) \stackrel{!}{=} 0$$

Straightforward calculation yields:

$$\lambda_1 = \lambda_2 = 0,$$

$$\lambda_3 = \sqrt[3]{\frac{\beta_{fs}N_s}{\mu_s}}\sqrt[3]{\frac{\beta_{cf}N_f}{\mu_f}\frac{\beta_{sc}N_c}{\mu_{pc}} + \frac{\beta_{sd}N_d}{\mu_{pd}}\frac{\beta_{df}N_f}{\mu_f} + \frac{\beta_{hf}N_f}{\mu_f}\frac{\beta_{sh}N_h}{\mu_{ph}}},$$

$$\lambda_4 = -(-1)^{\frac{1}{3}}\sqrt[3]{\frac{\beta_{fs}N_s}{\mu_s}}\sqrt[3]{\frac{\beta_{cf}N_f}{\mu_f}\frac{\beta_{sc}N_c}{\mu_{pc}} + \frac{\beta_{sd}N_d}{\mu_{pd}}\frac{\beta_{df}N_f}{\mu_f} + \frac{\beta_{hf}N_f}{\mu_f}\frac{\beta_{sh}N_h}{\mu_{ph}}},$$

$$\lambda_5 = (-1)^{\frac{2}{3}}\sqrt[3]{\frac{\beta_{sf}N_s}{\mu_s}}\sqrt[3]{\frac{\beta_{cf}N_f}{\mu_f}\frac{\beta_{sc}N_c}{\mu_{pc}} + \frac{\beta_{df}N_f}{\mu_f}\frac{\beta_{sd}N_d}{\mu_{pd}} + \frac{\beta_{hf}N_f}{\mu_f}\frac{\beta_{sh}N_h}{\mu_{ph}}}.$$

Since λ_4 and λ_5 are complex numbers, λ_3 is the dominant real eigenvalue of $\mathbf{K}$, and the reproduction number is

$$\mathcal{R}_0 = \sqrt[3]{\frac{\beta_{fs}N_s}{\mu_s}}\sqrt[3]{\frac{\beta_{cf}N_f}{\mu_f}\frac{\beta_{sc}N_c}{\mu_{pc}} + \frac{\beta_{sd}N_d}{\mu_{pd}}\frac{\beta_{df}N_f}{\mu_f} + \frac{\beta_{hf}N_f}{\mu_f}\frac{\beta_{sh}N_h}{\mu_{ph}}}.$$

The endemic equilibrium point exists if and only if $\mathcal{R}_0 > 1$. We expect that is locally asymptotically stable for $\mathcal{R}_0 > 1$ but did not prove this.

3.4. Type reproduction numbers

To determine the role of cats and dogs in maintaining transmission, we analyse host-specific type-reproduction numbers. They are given by the spectral radii of the next-generation matrices with leaving out one or more host types [18]. U_i is the host-specific and Q_j is the host excluded reproduction number, which are defined as

$$U_i = \rho(\mathbf{K}_i),$$
$$Q_j = \rho(\mathbf{I} - \mathbf{K}_j),$$

where $\mathbf{K}_i$ is the next-generation matrix of only including host i. In this multi-host population with n types of hosts, the reservoir community is defined as the minimum set of hosts with $U > 1$. A maintenance host is the minimum of m ($m \leq n$) different hosts which satisfy $U > 1$ and $Q < 1$ [19]. With the type reproduction number, we can define the reservoir community and subdivide the hosts into maintenance and non-maintenance hosts. Transmission is not possible without snails and fish, so we always include them in the model while determining the role of the three mammalian hosts, that means $i \in \{\text{humans } (h), \text{dogs } (d), \text{cats } (c)\}$.

The different next-generation matrices and their spectral radii are given by

$$U_h (= Q_{d,c}) = \rho(\mathbf{K}_h) = \rho\left(\begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\beta_{hf}N_f}{\mu_f} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_{sh}N_h}{\mu_{ph}} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{fs}N_s}{\mu_s} & 0 \end{bmatrix}\right)$$
$$= \sqrt[3]{\frac{N_f N_h N_s \beta_{hf}\beta_{sh}\beta_{fs}}{\mu_f \mu_{ph} \mu_s}},$$

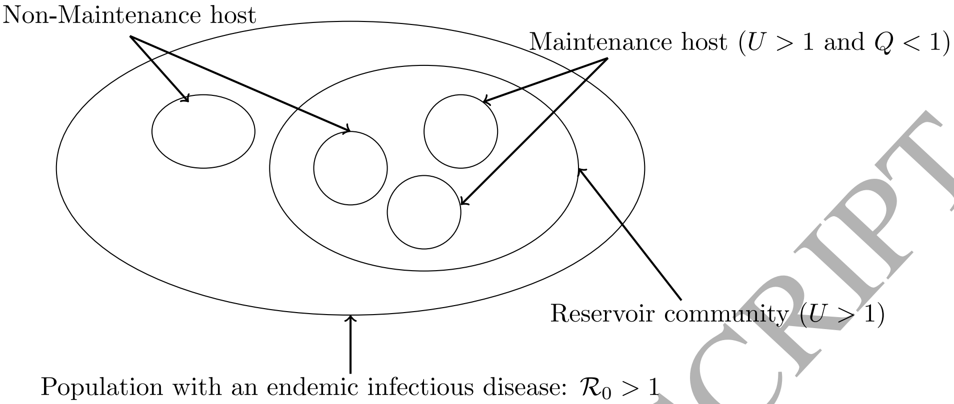


Figure 2: Definition of reservoir, maintenance, and non-maintenance hosts in a population with an endemic infectious disease, figure based on [19, Figure 3]

$$U_d(= Q_{h,c}) = \rho(\mathbf{K}_d) = \rho\left(\begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\beta_{df} N_f}{\mu_f} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\beta_{sd} N_d}{\mu_{pd}} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{fs} N_s}{\mu_s} & 0 \end{bmatrix}\right) = \sqrt[3]{\frac{N_f N_s N_d \beta_{df} \beta_{fs} \beta_{sd}}{\mu_f \mu_{pd} \mu_s}},$$

230

$$U_c(= Q_{h,d}) = \rho(\mathbf{K}_c) = \rho\left(\begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\beta_{cf} N_f}{\mu_f} \\ 0 & 0 & \frac{\beta_{sc} N_c}{\mu_{pc}} & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{fs} N_s}{\mu_s} & 0 \end{bmatrix}\right) = \sqrt[3]{\frac{N_f N_s N_c \beta_{cf} \beta_{fs} \beta_{sc}}{\mu_f \mu_{pc} \mu_s}},$$

$$Q_h(=U_{d,c}) = \rho(\mathbf{K}_{d,c}) = \rho\left(\begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\beta_{df}N_f}{\mu_f} \\ 0 & 0 & 0 & 0 & \frac{\beta_{cf}N_f}{\mu_f} \\ 0 & \frac{\beta_{sd}N_d}{\mu_{pd}} & \frac{\beta_{sc}N_c}{\mu_{pc}} & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{fs}N_s}{\mu_s} & 0 \end{bmatrix}\right)$$
$$= \sqrt[3]{\frac{N_s\beta_{fs}}{\mu_s}\left(\frac{N_fN_d\beta_{df}\beta_{sd}}{\mu_f\mu_{pd}} + \frac{N_fN_c\beta_{cf}\beta_{sc}}{\mu_f\mu_{pc}}\right)},$$

$$Q_c(=U_{h,d}) = \rho(\mathbf{K}_{h,d}) = \rho\left(\begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\beta_{hf}N_f}{\mu_f} \\ 0 & 0 & 0 & 0 & \frac{\beta_{df}N_f}{\mu_f} \\ 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_{sh}N_h}{\mu_{ph}} & \frac{\beta_{sd}N_d}{\mu_{pd}} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{fs}N_s}{\mu_s} & 0 \end{bmatrix}\right)$$
$$= \sqrt[3]{\frac{N_s\beta_{fs}}{\mu_s}\left(\frac{N_fN_h\beta_{hf}\beta_{sh}}{\mu_f\mu_{ph}} + \frac{N_fN_d\beta_{df}\beta_{sd}}{\mu_f\mu_{pd}}\right)},$$

and

$$Q_d(=U_{h,c}) = \rho(\mathbf{K}_{h,c}) = \rho\left(\begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\beta_{hf}N_f}{\mu_f} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\beta_{cf}N_f}{\mu_f} \\ \frac{\beta_{sh}N_h}{\mu_{ph}} & 0 & \frac{\beta_{sc}N_c}{\mu_{pc}} & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{fs}N_s}{\mu_s} & 0 \end{bmatrix}\right)$$
$$= \sqrt[3]{\frac{N_s\beta_{fs}}{\mu_s}\left(\frac{N_fN_h\beta_{hf}\beta_{sh}}{\mu_f\mu_{ph}} + \frac{N_fN_c\beta_{cf}\beta_{sc}}{\mu_f\mu_{pc}}\right)}.$$

4. Sensitivity analysis

235 Sensitivity analysis describes what happens to some dependent variables when one or more independent parameters are changed [20]. Thus, we can see the influence of the different parameter to the basic reproduction number, the host-specific type-reproduction number and the endemic equilibrium point.

4.1. Data and parameter values

240 Data on prevalence of infection in cats, dogs, snails, and fish; and on intensity of infection in humans was collected from two islands Don Khon and Don Som, Champasack province, Lao People's Democratic Republic (Lao PDR), from October 2011 to August 2012. The data was collected in a cross-sectional study for

a pilot community experiment of an integrated intervention package to control schistosomiasis. In the absence of time-series longitudinal data, we assume that this data represents an equilibrium solution, which we use to estimate the unknown parameters. The number of hosts tested and found positive is shown in Table 3 [21]. Additional data on the number of worm eggs per gram of human stool is not shown here.

We assume triangular distributions as prior distributions for the model parameters and estimate ranges and modes from the data in Table 3, literature, and expert opinions, as shown in Tables 4 and 5. We assume that the mean life span of parasite in humans (μ_{ph}) is 10 years, mean life span of a snail (μ_s) is 1 year and of a fish (μ_f) is 2.5 years [22]. We assume that parasites in cats (μ_{pc}) and dogs (μ_{pd}) die after 4 years, which is the average life span of cats and dogs in the area. We use the population sizes of humans from the study in Lao PDR [21]. From discussions with local village chiefs, we assume that there are half as many dogs as humans and a third as many cats as humans. We further expect that there are a lot more snails than fish. We calculate the modes of the transmission parameters (β) by assuming $\beta_{sh} = \beta_{sd} = \beta_{sc}$ and solving the system of equations (4) of the endemic equilibrium point for the data given in Table 3 (after converting the mean worm burden in humans, cats, and dogs to prevalence as described in Section 4.2. For the basic model (1), we multiply β_{sh} from the reservoir model by three to account for increased transmission from humans in the absence of reservoir hosts. We estimate wide ranges for the transmission parameters and the population sizes of snails and fish because we have little data on these values.

4.2. Sample construction and maximum likelihood estimation

We use a Bayesian sampling resampling approach to better estimate parameter distributions. We first draw 100,000 sample sets of parameter values, for both the basic and the reservoir hosts models, from the prior triangular distributions with modes and ranges described in Tables 4 and 5. We filter out samples that correspond to values of $\mathcal{R}_0 < 1$. In the basic model 92,758 (93%) parameter sets correspond to $\mathcal{R}_0 > 1$ and in the reservoir hosts model 84,548 (85%) correspond to $\mathcal{R}_0 > 1$.

For the resampling, we calculate probabilities from the likelihood that the solution of the equations is at the equilibrium point corresponding to the data in Table 5 (and the eggs per gram in each human tested). We define the likelihood function L of the model with reservoir hosts (4) as

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

and of the basic model (1) as

$$L = L_h L_s L_f,$$

where

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

assuming that the equilibrium prevalences i_h^*, i_d^*, i_c^*, i_s^*, and i_f^* are binomially distributed. For the three mammalian hosts we need to convert the mean worm burden at the endemic equilibrium into prevalence of infection. For humans we have data on both prevalence and intensity of infection (eggs per gram in stool for each human). We use the pre-calculated relationship from literature, $y = x^2 + 2x$ to convert the eggs per gram in stool, y, into mean worm burden, x, [23]. We assume a negative binomial distribution for the number of worms per person, leading to the relation between mean number of eggs per person (M) and the prevalence (P) [24],

$$P = 1 - \left(1 + \frac{M}{k}\right)^{-k}. \tag{5}$$

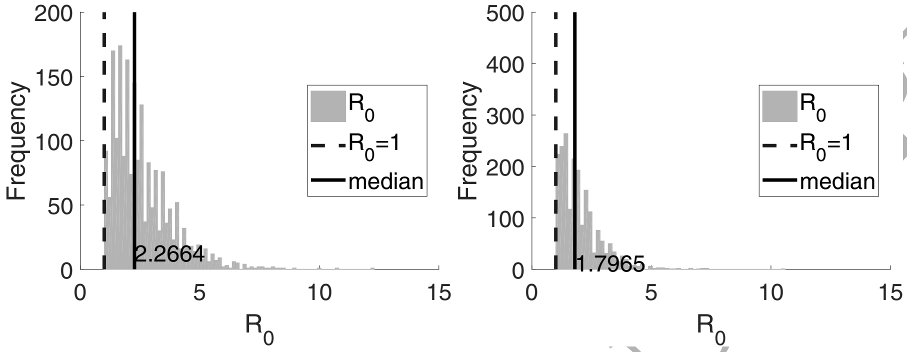
We assume that cats and dogs have the same relationship between mean worm burden and eggs per gram in stool and the same distribution for the number of worms per host as humans. The prevalence of infection in humans is $P = 0.6066$ (calculated from Table 3) and the mean number of eggs per person is $M = 1108.2$, so from equation (5), $k = 0.10020566$. It follows that the prevalences in cats and dogs are

$$i_c^* = 1 - \left(1 + \frac{(w_c^*)^2}{k}\right)^{-k},$$
$$i_d^* = 1 - \left(1 + \frac{(w_d^*)^2}{k}\right)^{-k}.$$

We resample 2,000 sets of parameter values with probability proportional to the likelihood function with replacement[1] [25, 26].

[1] MatlabR2017a: bootstrp

To optimize all the infection rates (β), we maximize[2] the logarithm of the likelihood function starting from the resampled parameter set with the highest likelihood [27, 28]. The maximum likelihood estimates are shown in Table 6.



(a) Basic model

(b) Model with reservoir hosts

Figure 3: Distributions of the basic reproduction number $\mathcal{R}_0$ of the basic (1) and the model with reservoir hosts (4) calculated for the resampled parameter distributions from Section 4.2.

4.3. Threshold conditions

The basic reproduction number $\mathcal{R}_0$ calculated for each of these 2,000 samples is shown in Figure 3. Note that values of $\mathcal{R}_0 < 1$ are excluded because we assume the existence of the endemic equilibrium point. For this equilibrium point, we numerically show that all eigenvalues of the Jacobian matrix have negative real parts so it is locally asymptotically stable.

We calculate the distributions of the type reproduction numbers from the resampled distributions of the parameter values (Figure 4). Humans, snails, and fish belong to the reservoir community because their host-specific type-reproduction number is likely bigger than 1 ($U > 1$) and their host excluded type-reproduction number is likely smaller than 1 ($Q < 1$). Humans, snails, and fish are also maintenance-hosts, because they are the minimum set which satisfies $U > 1$. The host specific type-reproduction number of cats and dogs is smaller than 1 ($U_d, U_c < 1$), so they are non-maintenance hosts.

The host-specific type-reproduction numbers, calculated with the parameter values in Table 6 from the maximum likelihood estimation, are

$$
\begin{aligned}
U_h &= 1.0935, & Q_h &= 0.4016,\\
U_d &= 0.2548, & Q_d &= 1.1067,\\
U_c &= 0.3640, & Q_c &= 1.0981.
\end{aligned}
$$

[2] MatlabR2017a: fminsearch

4.4. Local sensitivity analysis

The local sensitivity index is the ratio of the relative change in the variable and the relative change in the variable. Hence, we define the normalized forward sensitivity index of a variable u and the parameter p as, see [29],

$$\Upsilon_p^u := \frac{\mathrm{d}u}{\mathrm{d}p} \times \frac{p}{u}. \tag{6}$$

We first use the formula in (6) to calculate the sensitivity index of $\mathcal{R}_0$ in the basic model (1) with respect to β_{hf}:

$$\begin{aligned}\Upsilon_{\beta_{hf}}^{\mathcal{R}_0} &= \frac{\mathrm{d}\mathcal{R}_0}{\mathrm{d}\beta_{hf}} \times \frac{\beta_{hf}}{\mathcal{R}_0} = \frac{1}{3\beta_{hf}^{\frac{2}{3}}} \sqrt[3]{\frac{\beta_{sh}\beta_{fs}N_hN_sN_f}{\mu_{ph}\mu_s\mu_f}} \times \frac{\beta_{hf}}{\sqrt[3]{\frac{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_sN_f}{\mu_{ph}\mu_s\mu_f}}}\\ &= \frac{1}{3}.\end{aligned}$$

The calculation is similar for the sensitivity indices of $\mathcal{R}_0$ with respect to β_{sh},β_{fs},N_h,N_s and N_f. For the sensitivity indices of $\mathcal{R}_0$ with respect to μ_{ph}, μ_s and μ_f we have, for example,

$$\begin{aligned}\Upsilon_{\mu_{ph}}^{\mathcal{R}_0} &= \frac{\mathrm{d}\mathcal{R}_0}{\mathrm{d}\mu_{ph}} \times \frac{\mu_{ph}}{\mathcal{R}_0} = -\frac{1}{3\mu_{ph}^{\frac{4}{3}}} \sqrt[3]{\frac{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_sN_f}{\mu_s\mu_f}} \times \frac{\mu_{ph}}{\sqrt[3]{\frac{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_sN_f}{\mu_{ph}\mu_s\mu_f}}}\\ &= -\frac{1}{3}.\end{aligned}$$

Therefore if, for example, β_{hf} increases by 100%, then $\mathcal{R}_0$ increases by 33%. If μ_{ph} increases by 100%, then $\mathcal{R}_0$ decreases by 33%. Since the sensitivity index of $\mathcal{R}_0$ is independent of any other parameters, it is valid locally and globally. Due to the same absolute value of the sensitivity index, all parameters are equally important for $\mathcal{R}_0$.

The sensitivity index of the state variables at the endemic equilibrium of the basic model is for example

$$\begin{aligned}\frac{\mathrm{d}w_h^*}{\mathrm{d}\beta_{hf}} \times \frac{\beta_{hf}}{w_h^*} &= \frac{\beta_{sh}\beta_{fs}N_hN_fN_s}{\beta_{sh}N_h\mu_{ph}(\beta_{fs}N_s+\mu_f)} \times \beta_{hf}\frac{\beta_{sh}N_h\mu_{ph}(\beta_{fs}N_s+\mu_f)}{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_fN_s - \mu_{ph}\mu_s\mu_f}\\ &= \frac{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_fN_s}{\beta_{hf}\beta_{sh}\beta_{fs}N_hN_fN_s - \mu_{ph}\mu_s\mu_f}.\end{aligned}$$

Figure 6 (a) shows the sensitivity index of w_h^* for the parameter values from Table 4. The local sensitivity analysis for the model with reservoirs host (4) is performed as described in formula (6). The results for $\mathcal{R}_0$ are shown in Figure 5 (b) and the results for w_h^* are shown in Figure 6 (b).

4.5. Global sensitivity analysis and numerical simulation

We use partial rank correlation coefficients (PRCC) to analyse the sensitivity globally and to compare the influence of the parameters on $\mathcal{R}_0$ and on the endemic equilibrium point. To calculate the PRCC, we used the Matlab implementation of the PRCC function developed in [30][3]. The function was run on the 2,000 samples from Section 4.2.

Figures 5 (c) and (d) show, from the top to the bottom, the influence of the change in the parameter on $\mathcal{R}_0$ and Figures 6 (c) and (d) show the influence on w_h^* in the basic model (1) and in the model with reservoir hosts (4). The closer the absolute value is to one, the more influence the parameter has on the output.

In the basic model (1), the death rate of snails (μ_s) has the most global influence on $\mathcal{R}_0$, followed by the death rate of parasites in humans (μ_{ph}) and the death rate of fish (μ_f). However there is little difference between the parameter values, so the basic model is not able to differentiate between the sensitivity of the parameters on $\mathcal{R}_0$. For the model with reservoir hosts (4), the death rates of snails and fish (μ_s, μ_f), followed by death rate of parasites in humans (μ_{ph}) have the most global influence on $\mathcal{R}_0$.

The death rate of parasites in humans (μ_{ph}) has the most global influence on the mean worm burden of humans at the endemic equilibrium point w_h^* in both models, followed by the fish to human transmission rate (β_{hf}) and the number of fish (N_f).

In Figure 7 we show two dimensional sensitivity analysis of $\mathcal{R}_0$ (of both models) to the population sizes of the five hosts with all other parameters as in Table 6. Figure 7 (a) shows the dependence of $\mathcal{R}_0$ of the basic model (1) when the numbers of snails (N_s) and fish (N_f) are varied. $\mathcal{R}_0$ depends more strongly on the population size of snails than of fish. The sensitivity of $\mathcal{R}_0$ for the model with reservoir hosts (4) is presented in Figures 7 (b)–(d). Figure 7 (b) shows the variation of $\mathcal{R}_0$ to the number of snails (N_s) and fish (N_f). Similar to the basic model, $\mathcal{R}_0$ increases faster with more snails faster than with more fish. In Figure 7 (c), we see that $\mathcal{R}_0$ increases faster with the number of dogs (N_d) than with the number of cats (N_c). Figure 7 (d) shows that when the numbers of humans (N_h) and cats (N_c) are varied, $\mathcal{R}_0$ increases more rapidly with the number of cats.

We show numerical simulations of the basic model (1) and of the model with reservoir hosts (4) in Figure 8. For both models the parameter values are given in Table 6 and the initial conditions are $w_h = 1$, $w_d = 1$, $w_c = 1$, $i_s = 0$ and $i_f = 0$. We use the Dormand-Prince method [4] to integrate over the time interval [0, 70000], which corresponds to a time period of 190 years.

[3]http://malthus.micro.med.umich.edu/lab/usanalysis.html (24.10.2016)
[4]MatlabR2017a: ode45

5. Discussion

We analysed two population-based models of transmission dynamics of the *O. viverrini*. The basic model (1) includes the intermediate hosts snails and fish, and humans as definitive hosts. We extended this model to a model with reservoir hosts (4) by including cats and dogs as additional definitive hosts. We proved that the models are mathematically and epidemiologically well-posed. We obtained an explicit expression for the basic reproduction number $\mathcal{R}_0$. We defined the disease-free and the endemic equilibrium points, showed the criterion for the existence of these points points, and investigated their stability with respect to $\mathcal{R}_0$. We used Bayesian sampling-resampling with data from two islands in Lao PDR to construct distributions for the parameter values. We finally simulated the mean worm burden in the definitive hosts and the prevalence in the intermediate hosts over time.

The host-specific type-reproduction number defines the number of new infection from one infected individual when certain types of hosts are excluded from the model. It helps to identify the reservoir community and their maintenance hosts. We showed that humans, snails, and fish are maintenance-hosts because they can sustain transmission on their own. Furthermore, transmission is not possible if any of these species is removed from the cycle, so they are also reservoir hosts. This implies that it is possible to interrupt transmission with interventions that only target humans and ignore cats and dogs. For example, improving sanitation to an high enough level would be sufficient to eliminate opisthorchis transmission in Lao PDR.

The basic model could not differentiate between the sensitivity of the parameters on the basic reproduction number, $\mathcal{R}_0$. Sensitivity analysis of the model with reservoir hosts showed that $\mathcal{R}_0$ depends mostly on the death rate of parasites in humans (μ_{ph}), of snails (μ_s), and of fish (μ_f), and the population sizes of snails (N_s) and fish (N_f). Increasing the death rate of parasites in humans (μ_{ph}) is possible through regular treatment of humans with praziquantel. Increasing the death rates of snails (μ_s) and fish (μ_f) is more difficult, but reducing the number of snails is possible through snail control. Improved sanitation (which lowers β_{sh}) and safe fish production (which lowers β_{hf}) have a moderate effect on reducing $\mathcal{R}_0$.

There are some differences in the sensitivity indices of the equilibrium mean worm burden in humans (w_h^*) between the basic and the model with reservoir hosts and between the local and global analysis (Figure 6). However, the death rate of parasites in humans (μ_{ph}), the transmission rate from fish to humans (β_{fs}) and the number of fish (N_f) most often have a high sensitivity index. This suggests that regular treatment of humans and safe fish production are the most effective intervention in reducing the parasite burden in humans. Sensitivity analysis of the model with reservoir hosts (4) showed that the cats have more influence on the worm burden in humans than dogs.

In both models, we ignored seasonality, the age of humans, the dynamics of infection in fish and the latent period in snails and fish. Transmission of *O. viverrini* follows a seasonal pattern because of increases in the number of snails and fish in the rainy season. This implies that interventions could be more effective if targeted in the right season. Additionally it may also be possible that in the rainy season, cats or dogs could sustain transmission.

The results of the sensitivity analysis depend on the data we used to fit the models. This data was collected in 2011–2012 from a cross-sectional survey in two islands so, in the absence of any time-series data, we made the parsimonious assumption that the system was at an endemic equilibrium and that the coverage of any interventions (such as improved sanitation) was constant, with their effects included in the model parameters. Although there may have been intermittent mass drug administration campaigns in the past, a consistent nationwide schistosomiasis elimination program, with annual mass drug administration (with praziquantel which also kills *O. viverrini* worms) combined with improved access to sanitation and safe water, was only started later in 2015.

In the models, we assumed all humans are the same and ignored the fact that babies are born without infection and children have a lower worm burden than adults. Since humans accumulate parasites over their life times, heterogeneity in the distribution of worms in humans may lead to sustained transmission even at lower mean worm burdens. At high parasite density there are likely to be effects of density-dependence such as competition and immune regulation, but we ignore these effects in our simple model. A more complete analysis of heterogeneity in human exposure, density-dependent effects at high parasite densities, and the impact of high density infections on morbidity and mortality would likely require an individual-based model, that includes the intensity of infection in each human. Additionally, detailed data on the densities of worms in humans would be necessary to parameterise such a model.

O. viverrini is a hermaphrodite — it has both male and female reproductive organs — so any two worms in one definitive host can reproduce and Allee effects at low worm densities are less relevant for this species [31] (although they could also be included in an individual-based model). Assortative mixing between species is unlikely because cats and dogs are domestic pets so all definitive hosts live in the same households, eat the same fish, and are likely the infect the same fish..

The infection rate from fish to the definitive hosts ($\beta_{hf}, \beta_{df}, \beta_{cf}$) depends on the intensity of infection in fish. We ignore the intensity of infection in fish, but model the prevalence of infected fish. Similar to the heterogeneity in humans, the heterogeneity of intensity of infection in fish could lead to higher transmission. Infected snails and fish are not infectious immediately but need some time for the parasite to develop. This latent period could lead to a lower prevalence of infectious snails and fish, because infected snails and fish can die before becoming infectious. We plan to investigate the implication of these assumptions in future work.

This work suggests that including cats and dogs in a model of opisthorchis allows us to better differentiate the most important parameters for maintaining transmission and reducing worm burden in humans. However cats and dogs are not necessary to maintain transmission so it would be possible to eliminate *O. viverrini* by only targeting humans with effective interventions such as regular treatment, safe fish production and improved sanitation.

Appendix

Proposition 1 (Routh-Horwitz criterion, see [32]). *For a polynomial*

$$f(x) = a_0x^3 + a_1x^2 + a_2x + a_3 = 0 \tag{.1}$$

with $a_i \in \mathbb{R}$ for $i = 0, 1, 2, 3$, the number of roots with positive real parts is equal to the number of sign changes in either one of the sequences

$$T_0, T_1, \frac{T_2}{T_1}$$

or

$$T_0, T_1, T_1T_2,$$

where

$$T_0 = a_0 > 0, \quad T_1 = a_1, \quad T_2 = \det \begin{bmatrix} a_1 & a_0 \\ a_3 & a_2 \end{bmatrix}.$$

Given $a_0 > 0$, all roots have negative real parts if and only if T_0, T_1 and T_2 are all positive.

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Parameter	Description	Dimension
N_h	Population size of humans	Animals
N_d	Population size of dogs	Animals
N_c	Population size of cats	Animals
N_s	Population size of snails	Animals
N_f	Population size of fish	Animals
μ_{ph}	Per capita death rate of adult parasites in humans (includes additional mortality due to death of humans)	1/Time
μ_{pd}	Per capita death rate of adult parasites in dogs (includes additional mortality due to death of dogs)	1/Time
μ_{pc}	Per capita death rate of adult parasites in cats (includes additional mortality due to death of cats)	1/Time
μ_s	Per capita death rate of snails	1/Time
μ_f	Per capita death rate of fish including mortality through fishing by humans	1/Time
β_{hf}	Transmission rate from infectious fish to humans per person per fish	1/(Time $\times$ Animals)
β_{df}	Transmission rate from infectious fish to dogs per dog per fish	1/(Time $\times$ Animals)
β_{cf}	Transmission rate from infectious fish to cats per cat per fish	1/(Time $\times$ Animals)
β_{sd}	Infection rate of snails per parasite in a dog host	1/(Time $\times$ Animals)
β_{sc}	Infection rate of snails per parasite in a cat host	1/(Time $\times$ Animals)
β_{sh}	Infection rate of snails per parasite in a human host	1/(Time $\times$ Animals)
β_{fs}	Infection rate of fish per snail	1/(Time $\times$ Animals)

Table 2: Parameters of the opisthorchiasis model

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

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

Variable	Value	Range	Unit
β_{hf}	4.898×10^{-5}	$\left[4.898 \times 10^{-6}, 9.795 \times 10^{-5}\right]$	1/(Animal x Day)
β_{sh}	9.160×10^{-11}	$\left[9.160 \times 10^{-12}, 1.832 \times 10^{-10}\right]$	1/(Animal x Day)
β_{fs}	3.477×10^{-5}	$\left[3.477 \times 10^{-6}, 6.954 \times 10^{-5}\right]$	1/(Animal x Day)
N_h	14542	$[1454.2, 29084]$	Animals
N_s	20000	$[2000, 40000]$	Animals
N_f	8000	$[800, 16000]$	Animals
μ_{ph}	$\frac{1}{10\times365}$	$\left[\frac{1}{20\times365}, \frac{1}{1\times365}\right]$	1/Days
μ_s	$\frac{1}{1\times365}$	$\left[\frac{1}{2\times365}, \frac{1}{0.1\times365}\right]$	1/Days
μ_f	$\frac{1}{2.5\times365}$	$\left[\frac{1}{5\times365}, \frac{1}{0.25\times365}\right]$	1/Days

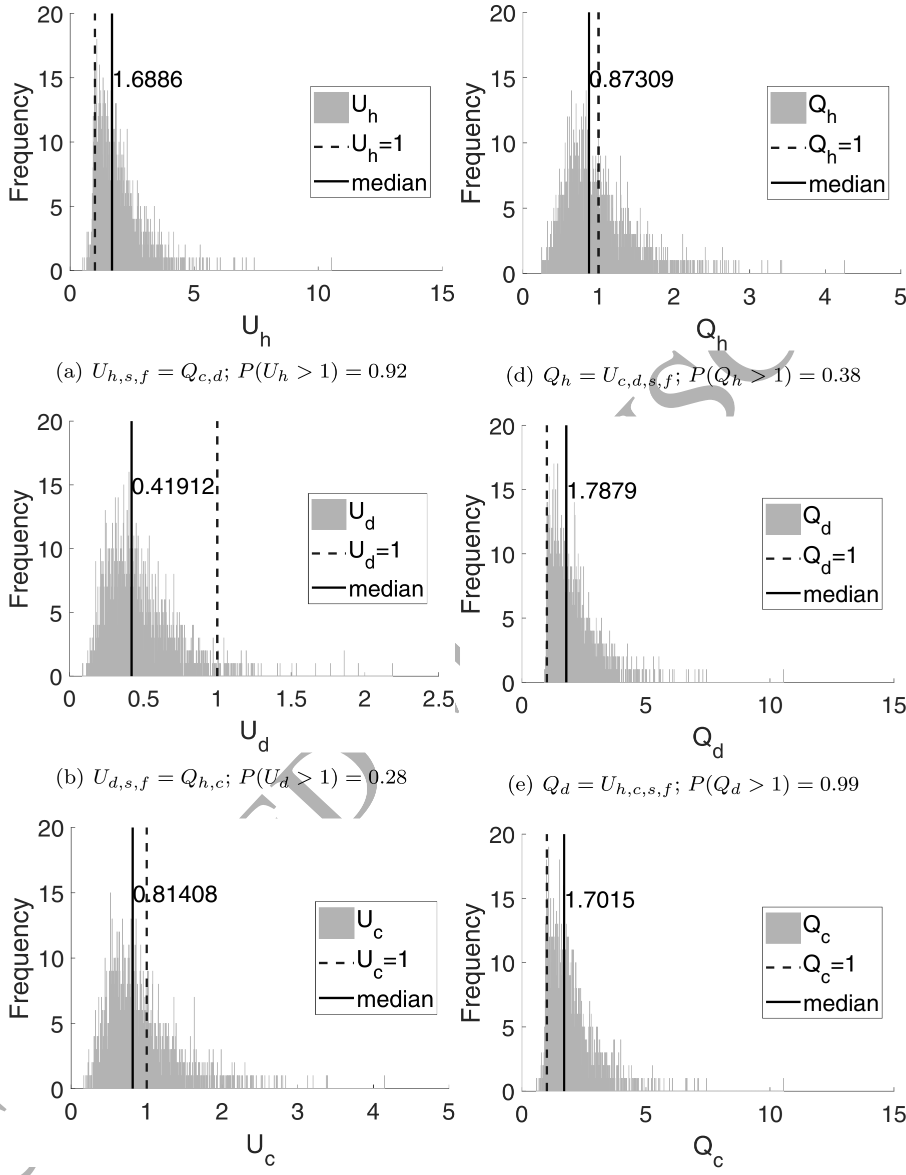
Table 4: Parameter values and ranges of the basic model (1)

Variable	Value	Range	Unit
β_{hf}	4.898×10^{-5}	$\left[4.898 \times 10^{-6}, 9.795 \times 10^{-5}\right]$	1/(Animal x Day)
β_{df}	4.110×10^{-6}	$\left[4.110 \times 10^{-7}, 8.220 \times 10^{-6}\right]$	1/(Animal x Day)
β_{cf}	4.414×10^{-5}	$\left[4.414 \times 10^{-6}, 8.829 \times 10^{-5}\right]$	1/(Animal x Day)
β_{sh}	3.053×10^{-11}	$\left[3.053 \times 10^{-12}, 6.107 \times 10^{-11}\right]$	1/(Animal x Day)
β_{sd}	3.053×10^{-11}	$\left[3.053 \times 10^{-12}, 6.107 \times 10^{-11}\right]$	1/(Animal x Day)
β_{sc}	3.053×10^{-11}	$\left[3.053 \times 10^{-12}, 6.107 \times 10^{-11}\right]$	1/(Animal x Day)
β_{fs}	3.477×10^{-5}	$\left[3.477 \times 10^{-6}, 6.954 \times 10^{-5}\right]$	1/(Animal x Day)
N_h	14542	$[7271, 21813]$	Animals
N_d	7271	$[3635.5, 10906.5]$	Animals
N_c	4847	$[2423.5, 7270.5]$	Animals
N_s	20000	$[2000, 40000]$	Animals
N_f	8000	$[800, 16000]$	Animals
μ_{ph}	$\frac{1}{10\times365}$	$\left[\frac{1}{20\times365}, \frac{1}{1\times365}\right]$	1/Days
μ_{pd}	$\frac{1}{4\times365}$	$\left[\frac{1}{8\times365}, \frac{1}{0.4\times365}\right]$	1/Days
μ_{pc}	$\frac{1}{4\times365}$	$\left[\frac{1}{8\times365}, \frac{1}{0.4\times365}\right]$	1/Days
μ_s	$\frac{1}{1\times365}$	$\left[\frac{1}{2\times365}, \frac{1}{0.1\times365}\right]$	1/Days
μ_f	$\frac{1}{2.5\times365}$	$\left[\frac{1}{5\times30}, \frac{1}{0.25\times365}\right]$	1/Days

Table 5: Parameter values and ranges of the model with reservoir hosts (4)

	Basic model	Model with reservoir hosts
Parameter	MLE	MLE
β_{hf}	3.4891×10^{-5}	1.6850×10^{-5}
β_{df}	-	1.2733×10^{-6}
β_{cf}	-	1.1851×10^{-5}
β_{sh}	5.6002×10^{-11}	3.3575×10^{-11}
β_{sd}	-	5.2889×10^{-11}
β_{sc}	-	7.5833×10^{-12}
β_{fs}	4.1682×10^{-5}	2.5073×10^{-5}
N_h	$12,231$	$15,143$
N_d	-	$6,236$
N_c	-	$6,220$
N_s	$18,862$	$6,261$
N_f	$6,969$	$6,824$
μ_{ph}	$\frac{1}{1.3526\times365}$	$\frac{1}{2.8603\times365}$
μ_{pd}	-	$\frac{1}{0.7424\times365}$
μ_{pc}	-	$\frac{1}{1.6392\times365}$
μ_s	$\frac{1}{0.3580\times365}$	$\frac{1}{0.4600\times365}$
μ_f	$\frac{1}{0.4479\times365}$	$\frac{1}{2.2044\times365}$
Reproduction number		
$\mathcal{R}_0$	1.1112	1.1112

Table 6: Maximum likelihood estimation (MLE) and the corresponding basic reproduction number ($\mathcal{R}_0$)



(a) $U_{h,s,f} = Q_{c,d}$; $P(U_h > 1) = 0.92$

(b) $U_{d,s,f} = Q_{h,c}$; $P(U_d > 1) = 0.28$

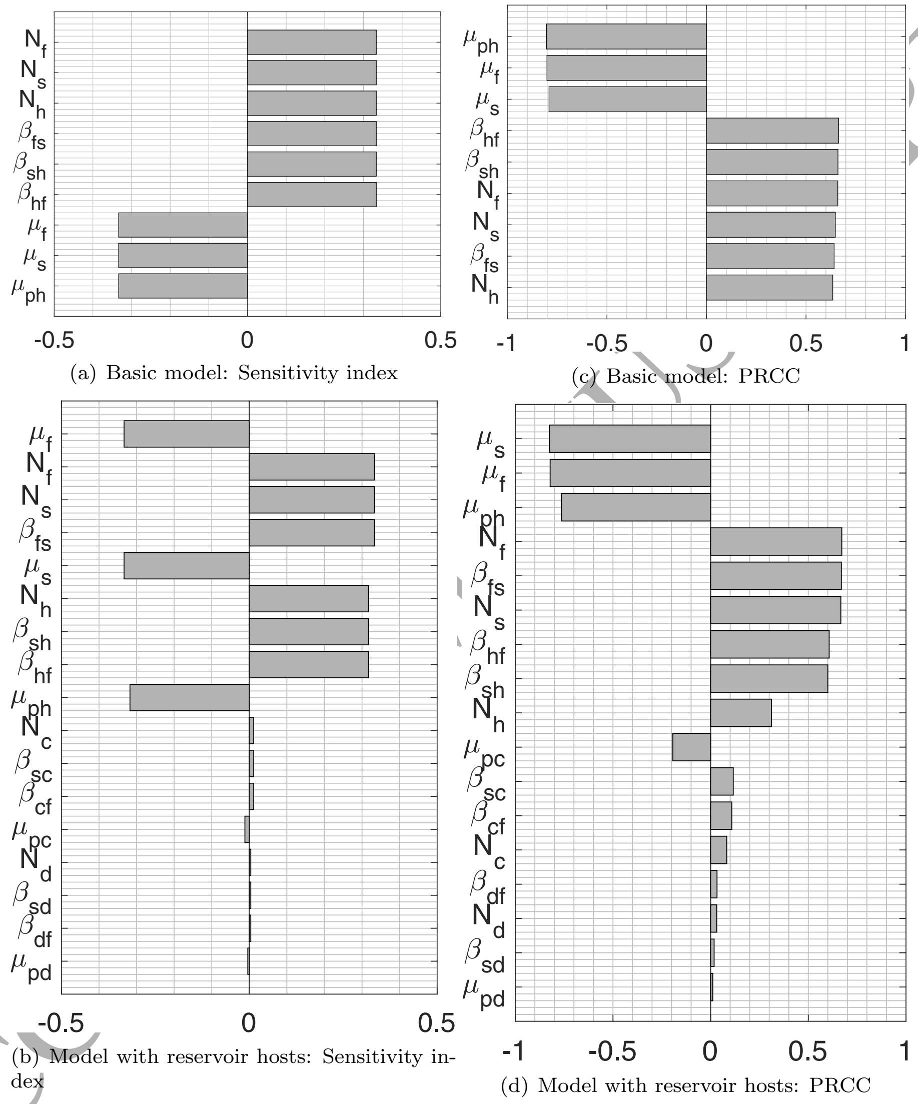
(c) $U_{c,s,f} = Q_{h,d}$; $P(U_c > 1) = 0.33$

(d) $Q_h = U_{c,d,s,f}$; $P(Q_h > 1) = 0.38$

(e) $Q_d = U_{h,c,s,f}$; $P(Q_d > 1) = 0.99$

(f) $Q_c = U_{h,d,s,f}$; $P(Q_c > 1) = 0.94$

Figure 4: Distributions of the host-specific type-reproduction numbers of the model with reservoir hosts (4) calculated from the resampled parameter distributions from Section 4.2 and the probability that the number is above 1.



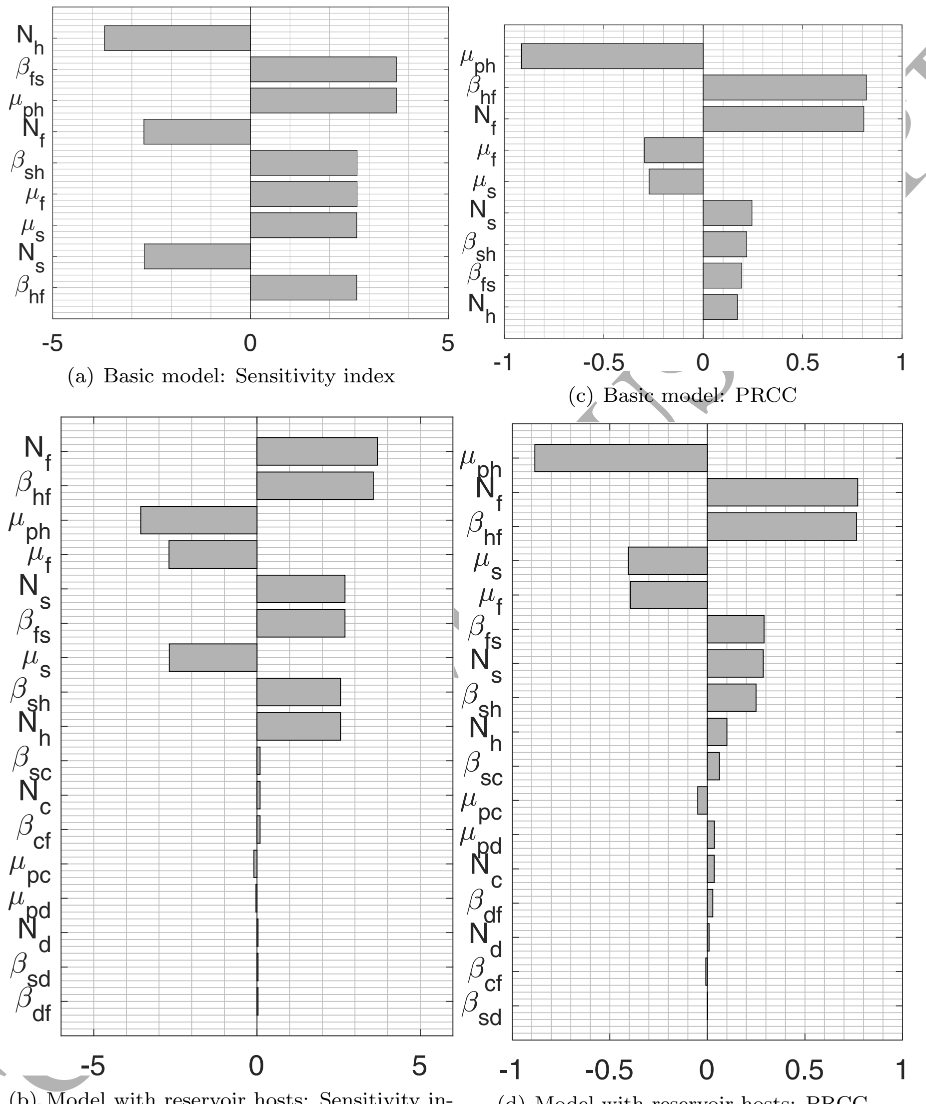
(a) Basic model: Sensitivity index

(c) Basic model: PRCC

(b) Model with reservoir hosts: Sensitivity index

(d) Model with reservoir hosts: PRCC

Figure 5: Local sensitivity indices and partial rank correlation coefficients (PRCC) of the basic reproduction number $\mathcal{R}_0$ for the basic model (1) and the model with reservoir hosts (4).



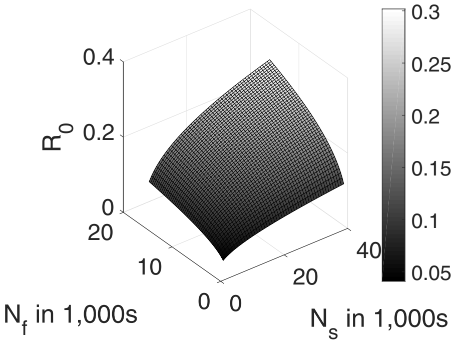
(a) Basic model: Sensitivity index

(c) Basic model: PRCC

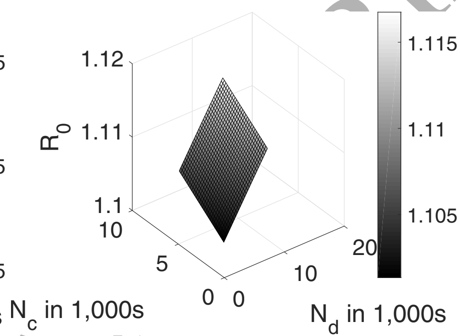
(b) Model with reservoir hosts: Sensitivity index

(d) Model with reservoir hosts: PRCC

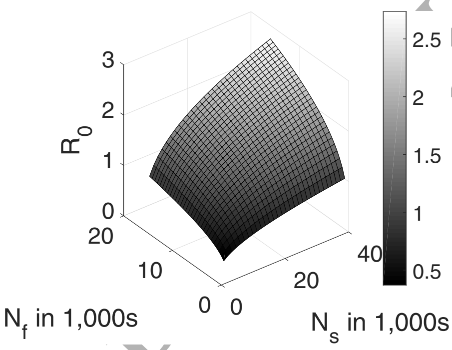
Figure 6: Local sensitivity indices and partial rank correlation coefficients (PRCC) of mean worm burden in humans at the endemic equilibrium point w_h^* of the basic model (1) and the model with reservoir hosts (4).



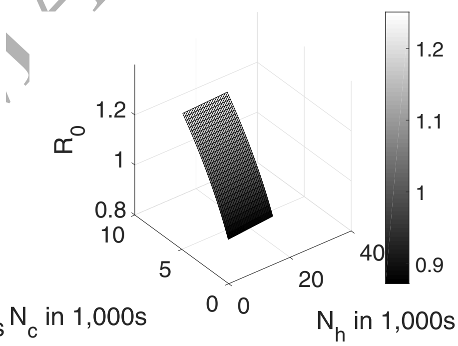
(a) Basic model: N_s and N_f



(c) Model with reservoir hosts: N_d and N_c

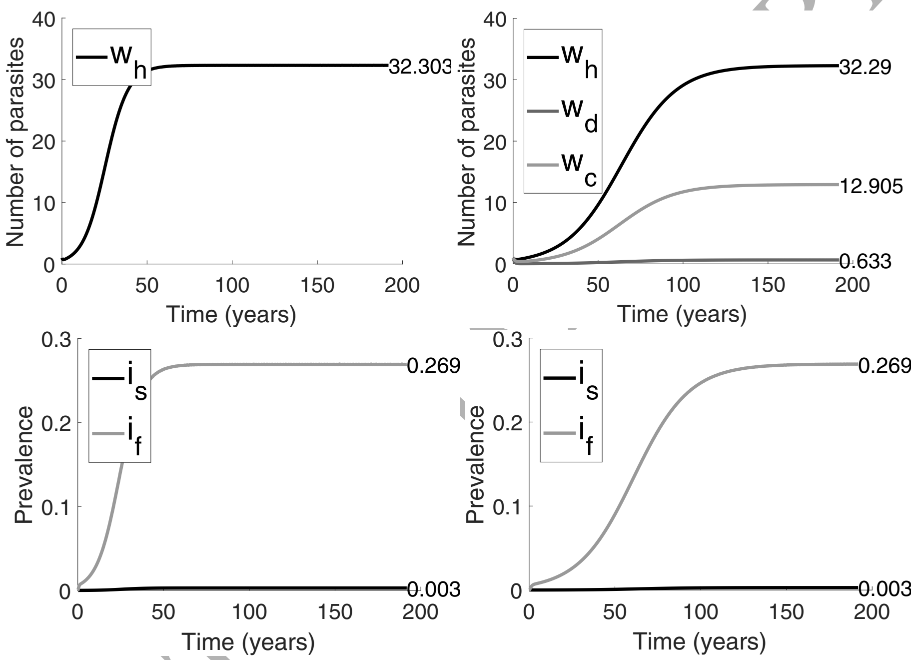


(b) Model with reservoir hosts: N_s and N_f



(d) Model with reservoir hosts; N_h and N_c

Figure 7: Basic reproduction number $\mathcal{R}_0$ for the basic model (1) and the model with reservoir hosts (4) varying population sizes of two hosts with all other parameters as in Table 6.



(a) Basic model

(b) Model with reservoir hosts

Figure 8: Numerical simulations of the opisthorchiasis models (1) and (4) with the Dormand-Prince method over a time line of 70,000 days. The initial values are 1 for the worm burdens and 0 for the prevalences. The parameter values are in Table 6.