Effects of fish-human transmission and different life stages of fish on Clonorchiasis: A novel mathematical model

Wei Wang[a], Xiaohui Huang[a], Hao Wang[b,*]

[a]*College of Mathematics and Systems Science, Shandong University of Science and Technology, Qingdao 266590, China*
[b]*Department of Mathematical and Statistical Sciences, University of Alberta, Edmonton, AB T6G 2G1, Canada*

Abstract

Clonorchiasis is a zoonotic disease mainly caused by eating raw fish and shrimp, and there is no vaccine to prevent it. More than 30 million people are infected worldwide, of which China alone accounts for about half, and is one of the countries most seriously affected by Clonorchiasis. In this work, we formulate a novel Ordinary Differential Equation (ODE) model to discuss the biological attributes of fish within authentic ecosystems and the complex lifecycle of Clonorchis sinensis. This model includes larval fish, adult fish, infected fish, humans, and cercariae. We derive the basic reproduction number and perform a rigorous stability analysis of the proposed model. Numerically, we use data from 2016 to 2021 in Guangxi, China, to discuss outbreaks of Clonorchiasis and obtain the basic reproduction number $R_0 = 1.4764$. The fitted curve appropriately reflects the overall trend and replicates a low peak in the case number of Clonorchiasis. By reducing the release rate of cercariae in 2018, the fitted values of Clonorchiasis cases dropped rapidly and almost disappeared. If we decrease the transmission rate from infected fish to humans, Clonorchiasis can be controlled. Our studies also suggest that strengthening publicity education and cleaning water quality can effectively control the transmission of Clonorchiasis in Guangxi, China.

Keywords: Clonorchiasis; Fish-human transmission; Larval fish; Basic reproduction number; Global stability; Sensitivity analysis.

1. Introduction

Clonorchiasis is a highly neglected global foodborne disease, with a high incidence in East Asia [27]. Initially, the infection only causes digestive discomfort. As it prolongs or worsens the infection, it may lead to disorders such as biliary tract disease and bile duct lesions [17, 45], which can sometimes lead to death. Patients with Clonorchiasis are 4.47 times more likely to develop cholangiocarcinoma than the general population [25]. Nonetheless, the disease has received limited attention in the medical community. In 2010, the World Health Organization (WHO) incorporated it into the category of neglected tropical diseases. Currently, the standard tests used to diagnose Clonorchiasis include hematology, immunology, parasitology, ultrasound, and Computed Tomography (CT) [10]. Detection of liver fluke eggs or specific DNA fragments in stool or bile samples is a definitive diagnostic sign [15]. Eggs can usually be detected in the feces about four weeks after infection [27]. However, even experts have difficulty differentiating the diagnosis of liver fluke eggs from other micro flukes [14, 15]. Therefore, it is essential to take precautions, detect early, and seek medical advice.

The hosts of Clonorchis sinensis commonly comprise humans, cats, and dogs [45]. The life cycle of Clonorchis sinensis mainly includes four stages: egg, cercaria, metacercaria, and adult. Every time it enters a new host, it needs a development period to continue transmission. The complex life cycle further exacerbates the complexity of the disease transmission cycle. The eggs enter the water with the feces

*Corresponding author
Email addresses: weiwang10437@sdust.edu.cn (Wei Wang), xiaohuihuang@sdust.edu.cn (Xiaohui Huang), hao8@ualberta.ca (Hao Wang)

of the infected individual and are ingested by the first intermediate host (the freshwater snail). After a development period, the eggs become cercaria and escape from the snail into the water. Cercariae in the water encounters a second intermediate host (freshwater fish) and invades the muscle tissue of the fish, where they develop into metacercariae [18, 27, 34]. The main cause of Clonorchiasis infection is consuming raw fish and shrimp with metacercariae or drinking infected water [37]. In Guangxi and Guangdong, sashimi is a delicacy for guests of honor [6, 25]. From the local Chaoshan raw marinade to the raw fish slices in Japanese cuisine, these raw foods are on the table of every household and spread parasitic diseases to more families.

Since the first discovery of Clonorchis sinensis in an ancient corpse in Hubei Province, China, in 1975 [3], scholars in various fields have studied Clonorchiasis from multiple perspectives [20, 21, 25, 27, 35, 38, 42, 43]. In order to consider the impact of death and disability with different symptoms on population health, the WHO has initiated a global burden of disease assessment for foodborne diseases, including Clonorchiasis [1]. The burden of disease is often measured by disability-adjusted life years (DALY) [39]. Sun Yat-sen University and Guangdong Provincial Center for Disease Control and Prevention have estimated the burden of Clonorchiasis in various provinces in China, and the three provinces with the largest DALY are Guangxi Zhuang Autonomous Region, Guangdong Province and Heilongjiang Province, showing a continuous upward trend [36]. This is closely related to the local climate, geography, dietary habits, other factors, and the need for more awareness of the disease and the imperfect disease prevention and control measures [5, 36, 46]. Moreover, the infection of Clonorchiasis also has gender and age differences. It was found that men are more likely to be infected with Clonorchiasis than women [25, 27, 43], which may be related to the fact that men favor raw freshwater fish more than women [2, 24]. Qian et al. [27] found that the prevalence of the disease was positively proportional to age, and the prevalence of infection was highest in the age group of 50-59 years old. Qian et al. [26] conducted a cross-sectional survey in two secondary schools in Qiyang County, Hunan Province. They found that children's knowledge of Clonorchiasis is relatively blank, and their families strongly influence their raw food habits. Knowledge education should be strengthened to increase children's alertness to Clonorchiasis.

The development of dynamics based on mathematical modeling has provided a more comprehensive range of ideas for studying infectious diseases [13, 19, 30, 34, 41, 44]. Dai et al. [41] established an ODE model to study the dynamics of Clonorchiasis transmission. Yuan et al. [30] constructed a model for the transmission of Clonorchiasis in humans, snails, and fishes, then proposed that it would be highly feasible to break the cercariae-fish transmission cycle. Zhang et al. [34] considered the dynamic behavior during the development of Clonorchis sinensis to construct a Partial Differential Equation (PDE) model, and predicted the future development trend of Clonorchiasis in Guangxi through numerical simulations. Mainul et al. [13] proposed four mathematical models to study the dynamics of Clonorchiasis with human treatment and fish vaccination with snail control, demonstrating that fish fry control is an effective control method. Vaccination of fish can largely protect fish from Clonorchis to a great extent and cut off the transmission of the disease from fish to humans. The rapid development of the genomics of Clonorchis sinensis provides a new opportunity for the research and development of vaccines [47]. Fish of different ages may have different behaviors and living conditions in natural ecosystems. Larval fish may be more susceptible to infection by Clonorchis sinensis because they typically live in shallow waters and are more likely to come into contact with environments infected with Clonorchis sinensis eggs [8, 28]. Most existing models assumed that the fish was homogeneous, and the stage structure was not considered, which may lead to an overestimation of disease transmission rates. The main cause of human disease is the consumption of sashimi, but the production of sashimi will have some requirements on the weight of the fish, so we assume that only adult fish are involved in the spread of disease. Our subdivision of fish into larval and adult fish can better model these transmission dynamics, help to study the transmission patterns more accurately, and provide a scientific basis for preventing and treating Clonorchiasis.

The paper is structured as follows. Considering the biology of fish in natural ecosystems and the life cycle of Clonorchis sinensis, we divide the fish into two different life stages (larval and adult). In Section 2, we propose and study an ODE model that covers the critical factors of larval fish, adult fish, infected adult fish, humans, and caecilians. The model describes the linked dynamics between the cercaria-fish interaction and the fish-human interaction. We calculate the basic reproduction number of the system and analyze the stability of the disease-free and vector-free equilibrium, and disease-free equilibrium in Section 3. We discuss the stability of the endemic equilibrium in Section 4. In Section 5, we present a case study of the transmission of Clonorchiasis in Guangxi, China, by numerical studies, and the fitting curve is consistent with the development trend of the actual data. We also perform some sensitivity analysis on R_0 according to the model parameters and observe the change of the fitting curve by changing the values of some parameters. Some concluding remarks are presented in Section 6.

2. Model Formulation

Clonorchiasis is a multi-host parasitic disease, which increases the difficulty of disease control and poses a great challenge to public health planning. Mathematical modeling has become an effective tool to transform complex systems into mathematical structures, improve understanding of Clonorchiasis, and help establish better long-term effective disease prevention and control systems and rational allocation of available resources.

We establish a mathematical model to describe the transmission dynamics of Clonorchiasis between human and fish hosts, using cercariae as vectors. Fig 2.1 depicts the transmission of Clonorchiasis between different hosts. We divide the total population N_h into the following epidemiological categories, reflecting the immune response to infection: susceptible humans S_h which are free of Clonorchiasis and are at risk of contracting it from cercariae in the environment, infected humans I_h who have been infected with Clonorchiasis and can shed eggs into the environment, people who have been cured of Clonorchiasis R_h. The total population is given as

$$N_h = S_h + I_h + R_h.$$

G is the concentration of cercariae in water that survived and was infective. We divide the life cycle of fish into larval stage L_f and adult stage N_f.

From an epidemiological view, fry control is a vital vector control measure. We consider that infectivity does not affect vector fecundity b and mortality μ_f. The natural mortality and maturity rates of larval fish are σ and λ_f, respectively. As noted by [9, 28], larval crowding or competition has a general effect on population development. We use α to denote the density dependence of larval developmental mortality. Based on the modeling idea of the classic Ross-MacDonald model [29], adult fish were divided into susceptible fish S_f and infected fish I_f, then we have

$$N_f = S_f + I_f.$$

Susceptible humans are recruited at a positive constant rate Λ, and μ_h is the natural mortality rate. Since infected humans may die from the disease, δ_h is set to be the disease-induced mortality rate for humans. The infected population recovers and gains immunity at a rate of γ_h. Susceptible humans are infected by eating fish infected with Clonorchiasis, and we use β_h to represent the transmission rate between susceptible people and fish multiplied by the probability of transmission of infected fish to susceptible people. The infection rate per unit of susceptible population is given by

$$\frac{\beta_h S_h I_f}{N_h}.$$

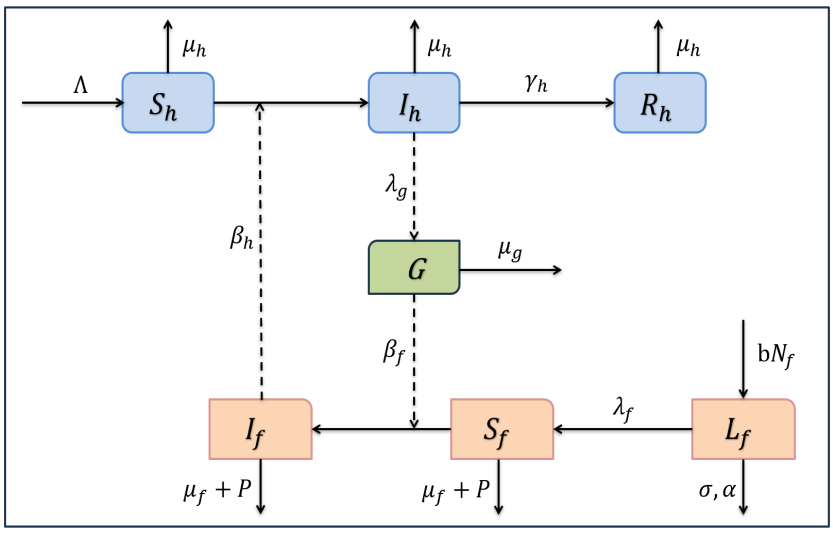


Figure 2.1: Flowchart of the transmission of Clonorchiasis in system (2.1). Solid lines indicate direct transmission between the same species and dashed lines indicate transmission between different species. Different colours represent different meanings: blue for humans, orange for freshwater fish and green for cercariae.

Infected humans excrete eggs at a rate of s_1, which enters the first host (freshwater snail) at a rate of s_2 per unit of time, develop and survive in the snail at a rate of s_3, and are ultimately released into the aquatic environment as cercariae. Thus, we define

$$\lambda_g = s_1 s_2 s_3$$

as the concentration of cercariae that are produced through the human population, in which these cercariae survive, and are released into the aquatic environment and removed from the water at a rate of μ_g. β_f is the transmission rate from cercaria to fish.

These assumptions together with the schematic diagram for Clonorchiasis transmission (Fig 2.1) lead to the following ODE model:

$$\begin{cases} \dfrac{dL_f(t)}{dt} = bN_f - \lambda_f L_f - \sigma L_f - \alpha L_f^2, \\ \dfrac{dS_f(t)}{dt} = \lambda_f L_f - \beta_f S_f G - (\mu_f + P) S_f, \\ \dfrac{dI_f(t)}{dt} = \beta_f S_f G - (\mu_f + P) I_f, \\ \dfrac{dG(t)}{dt} = \lambda_g I_h - \mu_g G, \\ \dfrac{dS_h(t)}{dt} = \Lambda - \dfrac{\beta_h S_h I_f}{N_h} - \mu_h S_h, \\ \dfrac{dI_h(t)}{dt} = \dfrac{\beta_h S_h I_f}{N_h} - (\mu_h + \delta_h + \gamma_h) I_h, \\ \dfrac{dR_h(t)}{dt} = \gamma_h I_h - \mu_h R_h. \end{cases} \tag{2.1}$$

Using $N_f = S_f + I_f$, system (2.1) can be described by the following system:

$$\begin{cases} \dfrac{dL_f(t)}{dt} = bN_f - \lambda_f L_f - \sigma L_f - \alpha L_f^2, \\ \dfrac{dN_f(t)}{dt} = \lambda_f L_f - (\mu_f + P)N_f, \\ \dfrac{dI_f(t)}{dt} = \beta_f (N_f - I_f)G - (\mu_f + P)I_f, \\ \dfrac{dG(t)}{dt} = \lambda_g I_h - \mu_g G, \\ \dfrac{dS_h(t)}{dt} = \Lambda - \dfrac{\beta_h S_h I_f}{N_h} - \mu_h S_h, \\ \dfrac{dI_h(t)}{dt} = \dfrac{\beta_h S_h I_f}{N_h} - (\mu_h + \delta_h + \gamma_h)I_h, \\ \dfrac{dR_h(t)}{dt} = \gamma_h I_h - \mu_h R_h, \end{cases} \tag{2.2}$$

with the following initial conditions:

$$L_f(0) = L_f^0 \geq 0,\ N_f(0) = N_f^0 \geq 0,\ I_f(0) = I_f^0 \geq 0,\ G(0) = G^0 \geq 0,$$
$$S_h(0) = S_h^0 \geq 0,\ I_h(0) = I_h^0 \geq 0,\ R_h(0) = R_h^0 \geq 0.$$

The detailed biological considerations and experimental values of all parameters are given in Table 1.

Table 1: Parameter values of system (2.2).

Symbol	Description		Unit	Value
b	Birth rate of larval fish	45	year^{-1}	Fitting
λ_f	Natural maturity rate of adult fish	0.3	year^{-1}	Fitting
σ	Larval fish mortality	0.3	year^{-1}	Fitting
α	Density-dependent development mortality of larval fish	0.0014	year^{-1}	Fitting
$\mu_f + P$	Death rate and predation rate of fish	0.2846	year^{-1}	[34]
λ_g	Rate of release of cercariae into the water	1014	year^{-1}	[31]
μ_g	Clearance rate of cercariae in the water	2.607	year^{-1}	[34]
Λ	Recruitment rate of human	2126468	year^{-1}	Fitting
β_H	Transmission rate from infected fish to human	4×10^{-6}	year^{-1}	Fitting
μ_h	Natural mortality rate of human	1/77	year^{-1}	[34]
δ_h	Disease-induced mortality rate of human	0.00505	year^{-1}	[36]
γ_h	Recovery rate of human	0.73	year^{-1}	[34]
β_f	Transmission rate from cercaria to fish	3.59×10^{-10}	year^{-1}	[34]

Theorem 2.1 *System* (2.2) *has a unique and bounded solution with the initial value*

$$(L_f^0, N_f^0, I_f^0, G^0, S_h^0, I_h^0, R_h^0) \in K := \left\{ (L_f, N_f, I_f, G, S_h, I_h, R_h) \in \mathbb{R}_+^7 : S_h + I_h + R_h > 0,\ I_f \leq N_f \right\}.$$

Moreover, the compact set

$$\Gamma := \left\{ (L_f, N_f, I_f, G, S_h, I_h, R_h) \in K : L_f \leq \frac{b\lambda_f}{\alpha(\mu_f + P)}, N_f \leq \frac{b\lambda_f^2}{\alpha(\mu_f + P)^2}, S_h + I_h + R_h \leq \frac{\Lambda}{\mu_h}, G \leq \frac{\Lambda\lambda_g}{\mu_h\mu_g} \right\}$$

attracts all positive solutions in K.

Proof. It follows from [12, Theorem 5.2.1] that system (2.2) admits a unique nonnegative solution $(L_f(t),N_f(t),I_f(t),G(t),S_h(t),I_h(t),R_h(t))$ through an initial value $(L_f^0,N_f^0,I_f^0,G^0,S_h^0,I_h^0,R_h^0) \in K$ with the maximum interval of existence $[0,\iota)$ for $0<\iota\leq\infty$.

Adding the last three equations in system (2.2), we obtain

$$\begin{aligned}\frac{d(S_h(t)+I_h(t)+R_h(t))}{dt} &= \frac{dN_h(t)}{dt}\\ &= \Lambda-\mu_h N_h-\delta_h I_h\\ &\geq \Lambda-(\mu_h+\delta_h)N_h,\end{aligned}$$

and thus

$$N_h(t)\geq\frac{\Lambda}{\mu_h+\delta_h}\left(1-e^{-(\mu_h+\delta_h)t}\right)+N_h(0)e^{-(\mu_h+\delta_h)t}>0$$

if $N_h(0)>0$ and $t\in[0,\iota)$. For $t\in[0,\iota)$, we have

$$\begin{aligned}\Lambda-(\mu_h+\delta_h)N_h &\leq \frac{dN_h(t)}{dt}\\ &\leq \Lambda-\mu_h N_h.\end{aligned}$$

Then

$$\begin{aligned}\frac{\Lambda}{\mu_h+\delta_h}+\left(N_h(0)-\frac{\Lambda}{\mu_h+\delta_h}\right)e^{-(\mu_h+\delta_h)t} &\leq N_h(t)\\ &\leq \frac{\Lambda}{\mu_h}+\left(N_h(0)-\frac{\Lambda}{\mu_h}\right)e^{-\mu_h t}.\end{aligned}$$

We can see that $N_h(t)$ is bounded for $t\in[0,\iota)$. Now we introduce

$$\frac{dG(t)}{dt}\leq\lambda_g N_h-\mu_g G.$$

Then according to the comparison principle, $G(t)$ is bounded on $[0,\iota)$.

By [40, Corollary 3.2], we have that

$$\begin{cases}\dfrac{dV_1(t)}{dt}=bV_2-\alpha V_1^2,\\ \dfrac{dV_2(t)}{dt}=\lambda_f V_1-(\mu_f+P)V_2,\end{cases}$$

exist a globally asymptotically stable equilibrium $\left(\frac{b\lambda_f}{\alpha(\mu_f+P)},\frac{b\lambda_f^2}{\alpha(\mu_f+P)^2}\right)$ with respect to all initial values in $\mathbb{R}^2_+\setminus\{(0,0)\}$. By system (2.2), we obtain

$$\begin{cases}\dfrac{dL_f(t)}{dt}\leq bN_f-\alpha L_f^2,\\ \dfrac{dN_f(t)}{dt}=\lambda_f L_f-(\mu_f+P)N_f.\end{cases}$$

According to the comparison principle, there exist M_1 and M_2 such that

$$L_f(t) \leq M_1,\ N_f(t) \leq M_2,\ \forall t \in [0, \iota).$$

Thus, we see that $\iota = \infty$ and the solution of system (2.2) exists globally. From the previous arguments, we can see that

$$\limsup_{t\to\infty}(L_f(t), N_f(t)) \leq \left(\frac{b\lambda_f}{\alpha(\mu_f+P)}, \frac{b\lambda_f^2}{\alpha(\mu_f+P)^2}\right),$$

which completes the proof. ■

From system (2.2), we have the following system:

$$\begin{cases} \dfrac{dL_f(t)}{dt} = bN_f - \lambda_f L_f - \sigma L_f - \alpha L_f^2, \\ \dfrac{dN_f(t)}{dt} = \lambda_f L_f - (\mu_f + P)N_f. \end{cases} \tag{2.3}$$

By [44], we define the vector reproduction number as

$$R_v = \frac{b\lambda_f}{(\sigma+\lambda_f)(\mu_f+P)}.$$

System (2.3) has always one trivial equilibrium (0, 0). The positive equilibrium (L_f^*, N_f^*) of system (2.3) exists when $R_v > 1$, where

$$(L_f^*,\ N_f^*) = \left(\frac{\lambda_f+\sigma}{\alpha}(R_v-1), \frac{\lambda_f(\lambda_f+\sigma)}{\alpha(\mu_f+P)}(R_v-1)\right). \tag{2.4}$$

From [44, Lemma 2.1], we have the following result.

Lemma 2.2 *The following statements are valid:*

(i) *If $R_v \leq 1$, the trivial equilibrium $(0,0)$ of system* (2.3) *is globally asymptotically stable in $\mathbb{R}^2_+$;*

(ii) If $R_v > 1$, the positive equilibrium (L_f^*, N_f^*) of system (2.3) is globally asymptotically stable in $\mathbb{R}^2_+ \setminus \{(0,0)\}$.

Remark 2.3 *Lemma 2.2 shows that if the vector reproduction number is less than or equal to one, the vector population will become extinct, while if the vector reproduction number is greater than one, the vector population will eventually stabilize at a positive equilibrium (L_f^*, N_f^*).*

3. Stability Analysis of E_{00} and E_0

System (2.2) always exists one disease-free and vector-free equilibrium $E_{00} = (0,0,0,0,S_h^0,0,0)$ with $S_h^0 = \frac{\Lambda}{\mu_h}$. And system (2.2) admits one disease-free equilibrium $E_0 = (L_f^*, N_f^*, 0, 0, S_h^0, 0, 0)$ when $R_v > 1$.

Following [4, 23], when $R_v > 1$, the basic reproduction number of system (2.2) is given by

$$R_0 = \rho(F_1 V_1^{-1}) = \frac{\beta_h \beta_f \lambda_g N_f^*}{\mu_g(\mu_f+P)(\mu_h+\delta_h+\gamma_h)},$$

where

$$F_1 = \begin{pmatrix} 0 & \beta_f N_f^* & 0 \\ 0 & 0 & 0 \\ \frac{\beta_h S_h^0}{N_h} & 0 & 0 \end{pmatrix}$$

and

$$V_1 = \begin{pmatrix} \mu_f + P & 0 & 0 \\ 0 & \mu_g & -\lambda_g \\ 0 & 0 & \mu_h + \delta_h + \gamma_h \end{pmatrix}.$$

Here, $\frac{1}{\mu_h+\delta_h+\gamma_h}$ is the average life span of a human, $\frac{1}{\mu_g}$ represents the average life span of a cercaria, $\frac{\lambda_g \beta_f N_f^*}{\mu_g}$ denotes the rate at which the cercariae infect the fish, $\frac{1}{\mu_f+P}$ represents the average life span of an adult fish, and $\frac{\beta_h}{\mu_f+P}$ is the rate at which the infected fish infect the susceptible people.

3.1. Local asymptotic stability

The Jacobian matrix taken at $E_{00} = (0,0,0,0,S_h^0,0,0)$ is

$$J_{00} = \begin{pmatrix} -(\lambda_f+\sigma) & b & 0 & 0 & 0 & 0 & 0 \\ \lambda_f & -(\mu_f+P) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -(\mu_f+P) & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_g & 0 & \lambda_g & 0 \\ 0 & 0 & 0 & 0 & -\mu_h & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -(\mu_h+\gamma_h+\delta_h) & 0 \\ 0 & 0 & 0 & 0 & 0 & \gamma_h & -\mu_h \end{pmatrix}.$$

Let $-J_{00} = (a_{ij})$, where $i,j = 1,2,3,4,5,6,7$. Clearly, $a_{ii} > 0$ and $a_{ij} \leq 0$. The leading principal minors of $-J_{00}$ are $\lambda_f+\sigma$, $(\lambda_f+\sigma)(\mu_f+P)(1-R_v)$, $(\lambda_f+\sigma)(\mu_f+P)^2(1-R_v)$, $\mu_g(\lambda_f+\sigma)(\mu_f+P)^2(1-R_v)$, $\mu_h\mu_g(\lambda_f+\sigma)(\mu_f+P)^2(1-R_v)$, $\mu_h\mu_g(\mu_f+P)^2(\mu_h+\gamma_h+\delta_h)(\lambda_f+\sigma)(1-R_v)$, $\mu_h^2\mu_g(\mu_f+P)^2(\mu_h+\gamma_h+\delta_h)(\lambda_f+\sigma)(1-R_v)$. We easily find that they are all positive if and only if $R_v < 1$. By the M-matrix theory [22], we find that $-J_{00}$ is an M-matrix when $R_v < 1$, implies that all eigenvalues of $-J_{00}$ have positive real parts. Accordingly, all eigenvalues of J_{00} have negative real parts when $R_v < 1$. We then conclude that E_{00} is locally asymptotically stable when $R_v < 1$.

Theorem 3.1 *If $R_v < 1$, the disease-free and vector-free equilibrium $E_{00} = (0,0,0,0,S_h^0,0,0)$ of system (2.2) is locally asymptotically stable. If $R_v > 1$, E_{00} is unstable.*

As the proof in Sec. 2, system (2.2) has one disease-free equilibrium $E_0 = (L_f^*, N_f^*, 0, 0, S_h^0, 0, 0)$ when $R_v > 1$. The characteristic polynomial of E_0 is

$$(\lambda+\mu_h)^2 \det(\lambda I - J_{01}) = 0,$$

where

$$J_{01} = \begin{pmatrix} -(\lambda_f+\sigma+2\alpha L_f^*) & b & 0 & 0 & 0 \\ \lambda_f & -(\mu_f+P) & 0 & 0 & 0 \\ 0 & 0 & -(\mu_f+P) & \beta_f N_f^* & 0 \\ 0 & 0 & 0 & -\mu_g & \lambda_g \\ 0 & 0 & \frac{\beta_h S_h^0}{N_h} & 0 & -(\mu_h+\gamma_h+\delta_h) \end{pmatrix}.$$

Let $-J_{01} = (b_{ij})$, where $i, j = 1,2,3,4,5$. Clearly, $b_{ii} > 0$ and $b_{ij} \leq 0$. The leading principal minors of $-J_{01}$ are $\lambda_f + \sigma + 2\alpha L_f^*$, $(\lambda_f + \sigma)(\mu_f + P)(R_v - 1)$, $(\lambda_f + \sigma)(\mu_f + P)^2(R_v - 1)$, $\mu_g(\lambda_f + \sigma)(\mu_f + P)^2(R_v - 1)$, $\mu_g(\lambda_f + \sigma)(\mu_f + P)^2(\mu_h + \gamma_h + \delta_h)(R_v - 1)(1 - R_0)$. Hence, they are all positive if and only if $R_0 < 1$. Clearly, $-J_{01}$ is an M-matrix when $R_v > 1$ and $R_0 < 1$, which means that all eigenvalues of $-J_{01}$ have positive real parts. Accordingly, all eigenvalues of J_{01} have negative real parts when $R_v > 1$ and $R_0 < 1$. We then conclude that E_0 is locally asymptotically stable when $R_v > 1$ and $R_0 < 1$.

Theorem 3.2 *If $R_v > 1$ and $R_0 < 1$, the disease-free equilibrium $E_0 = (L_f^*, N_f^*, 0, 0, S_h^0, 0, 0)$ of system* (2.2) *is locally asymptotically stable.*

3.2. Global stability

Theorem 3.3 *If $R_v < 1$, the disease-free and vector-free equilibrium $E_{00} = (0, 0, 0, 0, S_h^0, 0, 0)$ of system* (2.2) *is globally asymptotically stable in K.*

Proof. As the conclusion in Theorem 3.1, when $R_v < 1$, E_{00} is locally asymptotically stable. It is necessary to prove that $u(t) = (L_f(t), N_f(t), I_f(t), G(t), S_h(t), I_h(t), R_h(t)) \to E_{00}$, as $t \to \infty$, for $u(0) = (L_f(0), N_f(0), I_f(0), G(0), S_h(0), I_h(0), R_h(0)) \in K$. As Lemma 2.2, when $R_v < 1$, we have $(L_f(t), N_f(t)) \to (0,0)$, then $I_f(t) \to 0$, where $t \to \infty$. Then, we have

$$\lim_{t\to\infty}(G(t), S_h(t), I_h(t), R_h(t)) = (0, \frac{\Lambda}{\mu_h}, 0, 0).$$

By [44, Theorem 2.6], we know that $(0, \frac{\Lambda}{\mu_h}, 0, 0)$ is globally attractive in $\mathbb{R}^4$. Thus, E_{00} is globally attractive in K. ■

Theorem 3.4 *If $R_v > 1$ and $R_0 < R_1 := \frac{\mu_h}{\mu_h + \delta_h}$, the disease-free equilibrium $E_0 = (L_f^*, N_f^*, 0, 0, S_h^0, 0, 0)$ of system* (2.2) *is globally asymptotically stable in K with $L_f(0) > 0$ and $N_f(0) > 0$.*

Proof. As Lemma 2.2 and $R_v > 1$, we have $\lim_{t\to\infty}(L_f(t), N_f(t)) = (L_f^*, N_f^*)$, where $L_f(0) > 0$ and $N_f(0) > 0$, then system (2.2) has the following limiting system:

$$\begin{cases} \dfrac{dI_f(t)}{dt} = \beta_f(N_f^* - I_f)G - (\mu_f + P)I_f, \\ \dfrac{dG(t)}{dt} = \lambda_g I_h - \mu_g G, \\ \dfrac{dS_h(t)}{dt} = \Lambda - \dfrac{\beta_h S_h}{N_h} I_f - \mu_h S_h, \\ \dfrac{dI_h(t)}{dt} = \dfrac{\beta_h S_h}{N_h} I_f - (\mu_h + \delta_h + \gamma_h) I_h, \\ \dfrac{dR_h(t)}{dt} = \gamma_h I_h - \mu_h R_h. \end{cases} \tag{3.1}$$

Adding the last three equations of system (3.1) gives

$$\begin{aligned} \Lambda - (\mu_h + \delta_h)N_h &\leq \frac{dN_h(t)}{dt} \\ &= \Lambda - \mu_h N_h - \delta_h I_h \\ &\leq \Lambda - \mu_h N_h. \end{aligned}$$

This implies that $\phi_1 \leq \liminf_{t\to\infty} N_h(t) \leq \limsup_{t\to\infty} N_h(t) \leq S_h^0$, where $\phi_1 = \frac{\Lambda}{\mu_h+\delta_h}$.

By system (3.1), for sufficiently large t,

$$\begin{cases} \dfrac{dI_f(t)}{dt} \leq \beta_f N_f^* G - (\mu_f + P) I_f, \\ \dfrac{dG(t)}{dt} = \lambda_g I_h - \mu_g G, \\ \dfrac{dI_h(t)}{dt} \leq \dfrac{\beta_h S_h^0}{\phi_1} I_f - (\mu_h + \delta_h + \gamma_h) I_h. \end{cases} \tag{3.2}$$

Define the following auxiliary linear system by (3.2):

$$\begin{cases} \dfrac{d\widetilde{I_f}(t)}{dt} = \beta_f N_f^* \widetilde{G} - (\mu_f + P) \widetilde{I_f}, \\ \dfrac{d\widetilde{G}(t)}{dt} = \lambda_g \widetilde{I_h} - \mu_g \widetilde{G}, \\ \dfrac{d\widetilde{I_h}(t)}{dt} = \dfrac{\beta_h S_h^0}{\phi_1} \widetilde{I_f} - (\mu_h + \delta_h + \gamma_h) \widetilde{I_h}. \end{cases} \tag{3.3}$$

The right-hand side of system (3.3) has coefficient matrix J given by

$$\begin{pmatrix} -(\mu_f + P) & \beta_f N_f^* & 0 \\ 0 & -\mu_g & \lambda_g \\ \frac{\beta_h S_h^0}{\phi_1} & 0 & -(\mu_h + \delta_h + \gamma_h) \end{pmatrix}.$$

The leading principal minors of $-J$ are $\mu_f + P$, $\mu_g(\mu_f + P)$ and $\beta_h \beta_f N_f^* \lambda_g \left(\frac{1}{R_0} - \frac{\mu_h+\delta_h}{\mu_h} \right)$. Hence, they are all positive if and only if

$$R_0 \frac{\mu_h + \delta_h}{\mu_h} < 1.$$

Namely, $R_0 < R_1 := \frac{\mu_h}{\mu_h+\delta_h}$. Obviously, we obtain $-J$ is an M-matrix when $R_0 < R_1$, which means that all eigenvalues of $-J$ have positive real parts. Consequently, any eigenvalue of J lies in the left half plane. Thus, any nonnegative solution of system (3.3) satisfies $\lim_{t\to\infty}(\widetilde{I_f}, \widetilde{G}, \widetilde{I_h}) = (0,0,0)$. Since system (3.3) is a linear system, the zero solution (0,0,0) of system (3.3) is globally asymptotically stable. As a consequence of the comparison principle, we obtain that any nonnegative solution of system (3.2) satisfies $\lim_{t\to\infty}(I_f, G, I_h) = (0,0,0)$. S_h and R_h in system (3.1) satisfy the following limiting system:

$$\begin{cases} \dfrac{dS_h(t)}{dt} = \Lambda - \mu_h S_h, \\ \dfrac{dR_h(t)}{dt} = -\mu_h R_h. \end{cases}$$

It then follows that $\lim_{t\to\infty}(S_h(t), R_h(t)) = (S_h^0, 0)$ and $E_0 = (L_f^*, N_f^*, 0, 0, S_h^0, 0, 0)$ is globally asymptotically stable when $R_v > 1$ and $R_0 < R_1$. ■

4. Global Stability of the Endemic Equilibrium

4.1. The endemic equilibrium

Let

$$\lambda_1 = \frac{\beta_h I_f}{N_h},\ \lambda_2 = \beta_h G. \tag{4.1}$$

We consider the case when $R_v > 1$, in which case $(L_f, N_f) = (L_f^*, N_f^*)$. The other components of the endemic equilibrium require to satisfy the following conditions:

$$\begin{aligned}
&\Lambda = \lambda_1 S_h + \mu_h S_h,\\
&\lambda_1 S_h = (\mu_h + \delta_h + \gamma_h) I_h,\\
&\gamma_h I_h = \mu_h R_h,\\
&\lambda_g I_h = \mu_g G,\\
&\beta_f (N_f^* - L_f) G = (\mu_f + P) I_f.
\end{aligned} \tag{4.2}$$

Solving Eq. (4.2) in terms of λ_1 and λ_2, we have

$$\begin{aligned}
I_f &= \frac{\lambda_2 N_f^*}{\mu_f + P + \lambda_2},\ G = \frac{\lambda_g \Lambda \lambda_1}{\mu_g(\lambda_1 + \mu_h)(\mu_h + \delta_h + \gamma_h)},\ S_h = \frac{\Lambda}{\lambda_1 + \mu_h},\\
I_h &= \frac{\Lambda \lambda_1}{(\lambda_1 + \mu_h)(\mu_h + \delta_h + \gamma_h)},\ R_h = \frac{\gamma_h \Lambda \lambda_1}{\mu_h(\lambda_1 + \mu_h)(\mu_h + \delta_h + \gamma_h)}.
\end{aligned} \tag{4.3}$$

Then

$$N_h = \frac{\Lambda}{\lambda_1 + \mu_h}\left(1 + \frac{\lambda_1}{\mu_h + \delta_h + \gamma_h} + \frac{\gamma_h \lambda_1}{\mu_h(\mu_h + \delta_h + \gamma_h)}\right). \tag{4.4}$$

Substituting Eqs. (4.3) and (4.4) into Eq. (4.1), we obtain

$$\lambda_1 = \frac{\lambda_1 \lambda_g \beta_h N_f^* K_3}{\lambda_1 K_3 \lambda_g + K_2(\lambda_1 + \mu_h)} \frac{\lambda_1 + \mu_h}{K_1\left[\mu_h(\mu_h + \delta_h + \gamma_h) + \lambda_1 \mu_h + \gamma_h \lambda_1\right]}, \tag{4.5}$$

$$\lambda_2 = \frac{K_3 \lambda_1 \lambda_g}{\mu_g(\lambda_1 + \mu_h)}, \tag{4.6}$$

where

$$K_1 = \frac{\Lambda}{\mu_h(\mu_h + \delta_h + \gamma_h)},\ K_2 = \mu_g(\mu_f + P),\ K_3 = \frac{\Lambda \beta_f}{\mu_h + \delta_h + \gamma_h}.$$

Substituting Eqs. (4.6) into (4.5) and dividing by λ_1, we let

$$1 = \frac{\lambda_g \beta_h N_f^* K_3}{\lambda_1 K_3 \lambda_g + K_2(\lambda_1 + \mu_h)} \frac{\lambda_1 + \mu_h}{K_1\left[\mu_h(\mu_h + \delta_h + \gamma_h) + \lambda_1 \mu_h + \gamma_h \lambda_1\right]}. \tag{4.7}$$

From Eqs. (4.3) and (4.6), we can show that for $\lambda_1 > 0$, and system (2.2) has an endemic equilibrium.

We begin by discussing the case when $\delta_h = 0$, in which case Eq. (4.7) can be written as

$$\begin{aligned}
1 &= \frac{\lambda_g \beta_h N_f^* K_3}{\lambda_1 K_3 \lambda_g + K_2(\lambda_1 + \mu_h)} \frac{\mu_h(\lambda_1 + \mu_h)(\mu_h + \gamma_h)}{\Lambda\left[\mu_h(\mu_h + \gamma_h) + \lambda_1 \mu_h + \gamma_h \lambda_1\right]}\\
&= \frac{\lambda_g \beta_h N_f^* K_3}{\frac{\lambda_1}{\lambda_1 + \mu_h} K_3 \lambda_g + K_2} \frac{\mu_h(\mu_h + \gamma_h)}{\Lambda\left[\mu_h(\mu_h + \gamma_h) + \lambda_1 \mu_h + \gamma_h \lambda_1\right]}.
\end{aligned} \tag{4.8}$$

Let $M(\lambda_1)$ represent the right side of Eq. (4.8), it is clearly to see that $M(\lambda_1)$ is a decreasing function for $\lambda_1 \in (0,\infty)$, which implies that $M(\lambda_1)$ approaches zero when $\lambda_1 \to \infty$. Hence, if $M(0) > 1$, or, equivalently, $R_0 > 1$, (4.8) has a unique positive root such that system (2.2) has a unique endemic equilibrium. In contrast, there is no endemic equilibrium if $M(0) \leq 1$ or, equivalently, $R_0 \leq 1$. Then we obtain the following result.

Theorem 4.1 *Assume that $\delta_h = 0$. If $R_v > 1$ and $R_0 > 1$, then there is a unique endemic equilibrium of system* (2.2)*. Otherwise, there is no endemic equilibrium for system* (2.2)*.*

For $\delta_h \geq 0$, we reorganise the terms in Eq. (4.7) gives

$$D_1\lambda^2 + D_2\lambda + D_3 = 0, \tag{4.9}$$

where

$$\begin{aligned} D_1 &= (\mu_h+\gamma_h)(K_1K_3\lambda_g + K_1K_2),\\ D_2 &= K_1K_2\mu_h(2\mu_h+\delta_h+\gamma_h) + K_1K_3\lambda_g\mu_h(\mu_h+\delta_h+\gamma_h) - K_3\lambda_g\beta_f N_f^*,\\ D_3 &= K_1K_2\mu_h^2(\mu_h+\delta_h+\gamma_h)(1-R_0). \end{aligned} \tag{4.10}$$

It is clear that $D_1 > 0$ and D_3 has the same sign as $1-R_0$. Define

$$h(z) = D_1z^2 + D_2z + D_3, \tag{4.11}$$

then the roots of Eq. (4.11) can be expressed as

$$z_{1,2} = \frac{-D_2 \pm \sqrt{D_2^2 - 4D_1D_3}}{2D_1} = \frac{-D_2 \pm \sqrt{\Delta}}{2D_1}.$$

If $\Delta \leq 0$, then Eq.(4.11) does not have a positive solution, and Eq. (4.10) has no positive real roots. If $\Delta > 0$ and $h(0) = D_3 < 0$, then Eq. (4.11) has a unique positive root, and Eq. (4.10) exists a unique positive solution.

Summarizing the above discussions, we have the following theorem.

Theorem 4.2 *Assume that $R_v > 1$, let Δ be defined by* (4.11)*.*
(i) If $\Delta > 0$ and $R_0 > 1$, then system (2.2) *has a unique endemic equilibrium;*
(ii) If $\Delta \leq 0$, then system (2.2) *has no endemic equilibrium.*

4.2. Global stability of the endemic equilibrium

Theorem 4.3 *If $\Delta > 0$, $R_v > 1$ and $R_0 > 1$, the endemic equilibrium $E^* = (L_f^*, N_f^*, I_f^*, G^*, S_h^*, I_h^*, R_h^*)$ of system* (2.2) *is globally asymptotically stable in* $\mathrm{Int}(K)$*.*

Proof. By Lemma 2.2, the vector population will eventually stabilize at a positive equilibrium (L_f^*, N_f^*) if $R_v > 1$. Hence, the variables I_f, G, I_h and R_h satisfy the following limiting system:

$$\begin{cases} \dfrac{dI_f(t)}{dt} = \beta_f(N_f^* - I_f^*)G - (\mu_h + P)I_f, \\ \dfrac{dG(t)}{dt} = \lambda_g I_h - \mu_g G, \\ \dfrac{dI_h(t)}{dt} = \dfrac{\beta_h(S_h^0 - I_h - R_h)I_f}{S_h^0} - (\mu_h + \delta_h + \gamma_h)I_h, \\ \dfrac{dR_h(t)}{dt} = \gamma_h I_h - \mu_h R_h. \end{cases} \tag{4.12}$$

Let $V = [0, N_f^*] \times \left[0, \frac{\lambda_g}{\mu_g} S_h^0\right] \times [0, S_h^0] \times \left[0, \frac{\gamma_h}{\mu_h} S_h^0\right]$, it then follows that $\omega(I_f(0), G(0), I_h(0), R_h(0)) \in V$, where $\omega(I_f(0), G(0), I_h(0), R_h(0))$ is the omega limit set of $(I_f(0), G(0), I_h(0), R_h(0)) \in \mathbb{R}_+^4$ for the solution semiflow of system (4.12). It is easy to verify that V is positively invariant for system (4.12).

Let

$$j(u) = \begin{pmatrix} \beta_f(N_f^* - u_1)u_2 - (\mu_f + P)u_1 \\ \lambda_g u_3 - \mu_g u_2 \\ \frac{\beta_h(S_h^0 - u_3 - u_4)u_1}{S_h^0} - (\mu_h + \delta_h + \gamma_h)u_3 \\ \gamma_h u_3 - \mu_h u_4 \end{pmatrix},$$

then $j : \mathbb{R}_+^4 \to \mathbb{R}^4$ is a continuously differentiable map. Clearly, $j(0) = 0$ and $j_m(u) \geq 0$ for all $u \in V$ with $u_m = 0$, $m = 1, 2, 3, 4$. Since

$$D_j(u) = \frac{\partial j_m}{\partial u_n} = \begin{pmatrix} -\beta_f u_2 - (\mu_f + P) & \beta_f(N_f^* - u_1) & 0 & 0 \\ 0 & -\mu_g & \lambda_g & 0 \\ \frac{\beta_h(S_h^0 - u_3 - u_4)}{S_h^0} & 0 & -\frac{\beta_h u_1}{S_h^0} - (\mu_h + \delta_h + \gamma_h) & -\frac{\beta_h u_1}{S_h^0} \\ 0 & 0 & \gamma_h & -\mu_h \end{pmatrix},$$

then $\frac{\partial j_m}{\partial u_n} \geq 0$, $(m \neq n)$ for $u \in V$, thus j is cooperative on V. Clearly, $D_j(u)$ is irreducible for every $u \in V$. For any $\rho \in (0,1)$ and $(u_1, u_2, u_3, u_4) \in \mathrm{Int}(\mathbb{R}_+^4)$, we have

$$\begin{aligned} j_1(\rho u_1, \rho u_2, \rho u_3, \rho u_4) =& \beta_f(N_f^* - \rho u_1)\rho u_2 - (\mu_f + P)\rho u_1 \\ >& \beta_f(N_f^* - u_1)\rho u_2 - (\mu_f + P)\rho u_1 \\ =& \rho\, j_1(u_1, u_2, u_3, u_4). \end{aligned}$$

Similarly, we can show that $j_m(\rho u_1, \rho u_2, \rho u_3, \rho u_4) = \rho\, j_m(u_1, u_2, u_3, u_4)$, $m = 2, 4$ and $j_3(\rho u_1, \rho u_2, \rho u_3, \rho u_4) > \rho\, j_3(u_1, u_2, u_3, u_4)$. Thus, j is strictly sublinear on V. Since

$$D_j(0) = \begin{pmatrix} -(\mu_f + P) & \beta_f N_f^* & 0 & 0 \\ 0 & -\mu_g & \lambda_g & 0 \\ \beta_h & 0 & -(\mu_h + \delta_h + \gamma_h) & 0 \\ 0 & 0 & \gamma_h & -\mu_h \end{pmatrix}, \tag{4.13}$$

the leading principal minors of $-D_j(0)$ are $\mu_f + P$, $\mu_g(\mu_f + P)$ and $\beta_h \beta_f N_f^* \lambda_g \left(\frac{1}{R_0} - 1\right)$. Obviously, $\beta_h \beta_f N_f^* \lambda_g \left(\frac{1}{R_0} - 1\right) < 0$ when $R_0 > 1$. By the M-matrix theory [22], we get $-D_j(0)$ has at least one

eigenvalue with negative real part, which means $D_j(0)$ has at least one eigenvalue with postive real part. Then the spectral bound of $D_j(0)$, $s(D_j(0) := \max\{\mathrm{Re}\lambda : \det(\lambda I - D_j(0)) = 0\} > 0$. It then follows from [40, Corollary 3.2], the positive equilibrium $(I_f^*, S_h^*, I_h^*, R_h^*)$ for system (4.12) is globally asymptotically stable in $\mathbb{R}_+^4 \setminus \{(0,0,0,0)\}$. Therefore,

$$\lim_{t\to\infty} S_h(t) = \lim_{t\to\infty}(N_h(t) - I_h(t) - R_h(t)) = S_h^0 - I_h^* - R_h^* = S_h^*.$$

We finally obtain that the endemic equilibrium $E^* = (L_f^*, N_f^*, I_f^*, G^*, S_h^*, I_h^*, R_h^*)$ of system (2.2) is globally asymptotically stable in $\mathrm{Int}(K)$. ■

Table 2 summarizes the existence and stability conditions for equilibria E_{00}, E_0 and E^*.

Table 2: . Summary of the existence and stability for E_{00} and E_0.

Equilibrium	**Existence**	**LAS**	**GAS**
$E_{00} = (0,0,0,0,S_h^0,0,0)$	**always**	$R_v < 1$	$R_v < 1$
$E_0 = (L_f^*, N_f^*, 0,0,S_h^0,0,0)$	$R_v > 1$	$R_v > 1,\ R_0 < 1$	$R_v > 1,\ R_0 < R_1$
$E^* = (L_f^*, N_f^*, I_f^*, G^*, S_h^*, I_h^*, R_h^*)$	$\Delta > 0,\ R_v > 1,\ R_0 > 1$	$\Delta > 0,\ R_v > 1,\ R_0 > 1$	$\Delta > 0,\ R_v > 1,\ R_0 > 1$

5. A Case Study

In this section, we perform some numerical simulations based on a real case of Clonorchiasis transmission in Guangxi, China.

5.1. Model validation

In 2016, the region with the highest burden of Clonorchiasis disease in China was the Guangxi, China. We simulate the Clonorchiasis transmission case in Guangxi, China based on the data from the Table 3.

Table 3: Population data related to clonorchiasis in Guangxi, China from 2016 to 2021 [11].

Year	2016	2017	2018	2019	2020	2021
Population size$\left(*10^4\right)$	4838	4926	4960	5019	5037	5013
Number of infectious humans	2791332	1442345	2721221	2534064	2165916	2435271

According to the analysis of the disease burden of Clonorchiasis [36], the DALY in Guangxi, China, is 5.05. We assume the disease-induced mortality rate for humans $\delta_h = 0.00505$. For convenience, we define $\beta_H = \frac{\beta_h}{N_h}$. Over 100 freshwater fish species have been identified as intermediate hosts of clonorchis sinensis [32]. Different fish have different effects on disease transmission in the ecological environment. Usually, it takes 3-4 years for fish to become reproductively capable from birth, so we chose $\lambda_f = 0.3$. The lifespan of the larvae fish is about three years, and we choose $\sigma = 0.3$. Table 1 summarises these parameters. We select the initial values: $G^0 = 3 \times 10^5$, $S_h^0 = 35000$, $I_h^0 = 2791332$, $I_f^0 = 12080$, $N_h = 23261104$ from [34], and assume that $L_f^0 = 30800$, $N_f^0 = 20800$.

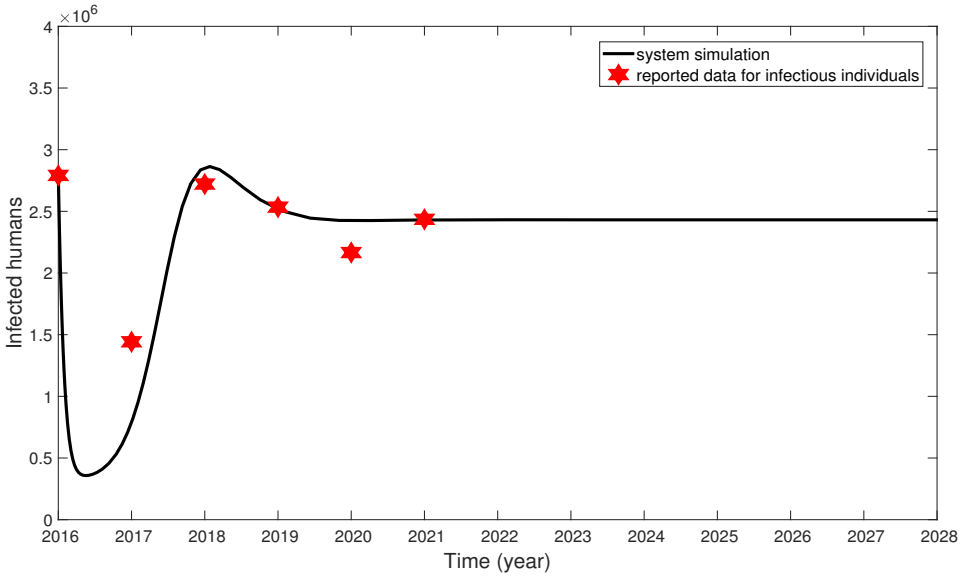


Figure 5.1: The simulation result of Clonorchiasis cases from 2016 to 2021 in Guangxi, China.

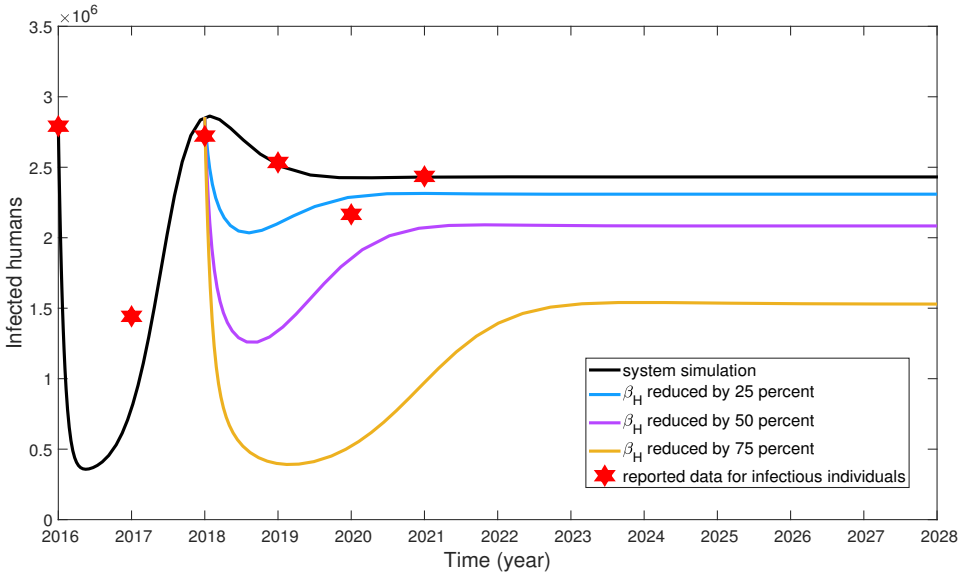


Figure 5.2: The simulation result of Clonorchiasis cases from 2016 to 2021 in Guangxi, China. The black curve is the system simulation. Colored lines is the system simulation when we take control of β_H.

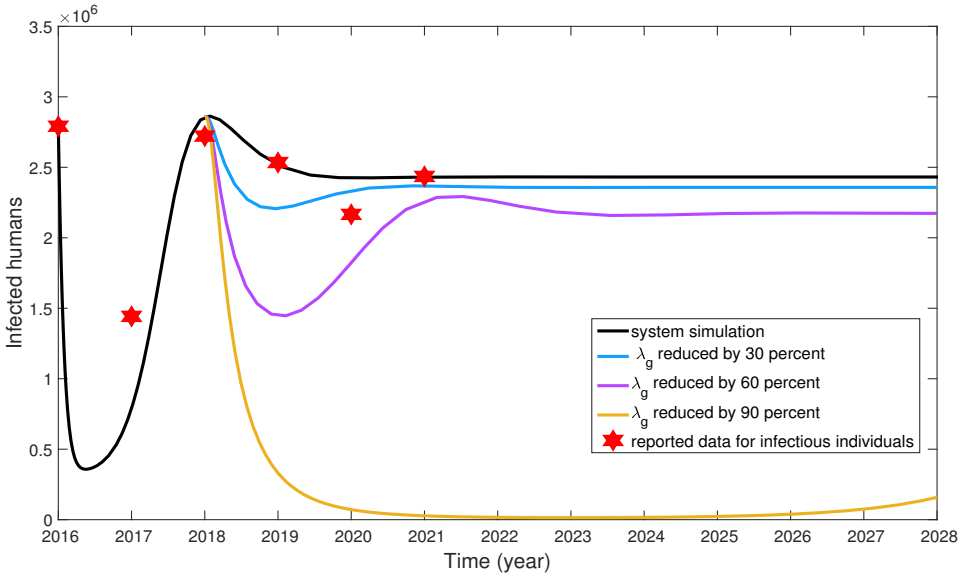


Figure 5.3: The simulation result of Clonorchiasis cases from 2016 to 2021 in Guangxi, China. The black curve is the system simulation. Colored lines is the system simulation when we take control of λ_g.

According to the above-estimated parameter values and the initial values, we fitted the Guangxi, China Clonorchiasis cases by system (2.2). The reported data and the simulation result based on our model, are shown in Fig. 5.1. As we can see, they match very well. We compute the basic reproduction number in this case, $R_v = 79.0583$ and $R_0 = 1.4764 > 1$. To explore the impact of control measures on long-term trends in Clonorchiasis, we adjust the values of β_H and λ_g. In Figs. 5.2 and 5.3, we observe that reducing λ_g is the most effective method, and just a single control of β_H cannot eradicate the disease. Reducing the concentration of cercariae in the water environment can effectively decrease the rate of disease in fish, then control the spread of Clonorchiasis in the population.

5.2. Sensitivity analysis

The basic reproduction number reflects the outbreak potential and severity of the disease. In order to take more targeted and effective measures to control the prevalence of Clonorchiasis, we evaluate the influence of parameters on R_0 by sensitivity analysis of the model. Therefore, we use the Latin Hypercube Sampling (LHS) method to evaluate partial rank correlation coefficients (PRCC) for various input parameters against output variables, to determine which parameters can be adjusted to more effectively intervene in the transmission of Clonorchiasis [33]. Parameters with larger absolute values of PRCC have a more significant effect on disease, where the positive PRCC value represents a positive effect on the basic reproduction number and a negative impact on disease control, and the negative PRCC value is the opposite.

We obtain the sensitivity index of R_0 to all the parameters of the system in Table 4 and plot the sensitivity analysis of R_0. Fig. 5.4 shows the global sensitivity analysis of R_0. $\mu_f + P$, λ_f and β_f are the parameters that affect R_0 to a large extent, suggesting that fish play a vital role in the propagation of Clonorchiasis. Obviously, R_0 is an increasing function of parameters $b, \lambda_f, \lambda_g, \beta_H, \beta_f$, respectively. As $\mu_f + P, \mu_g, \mu_h, \gamma_h, \delta_h$ increase, R_0 is reducing but insensitive to the parameters μ_h and δ_h. It means that when controlling the transmission of Clonorchiasis, effective measures need to be taken, such as purifying water quality, cultural education, or strengthening treatment, to reduce λ_g, β_H, β_f, and increase μ_g, γ_h, δ_h.

Table 4: Sensitivity index of R_0.

Input parameter	PRCC	Input parameter	PRCC
b	0.193729	β_H	0.272050
λ_f	0.356660	μ_h	-0.016188
$\mu_f + P$	-0.552336	γ_h	-0.194397
λ_g	0.217804	δ_h	-0.013166
μ_g	-0.212093	β_f	0.311500

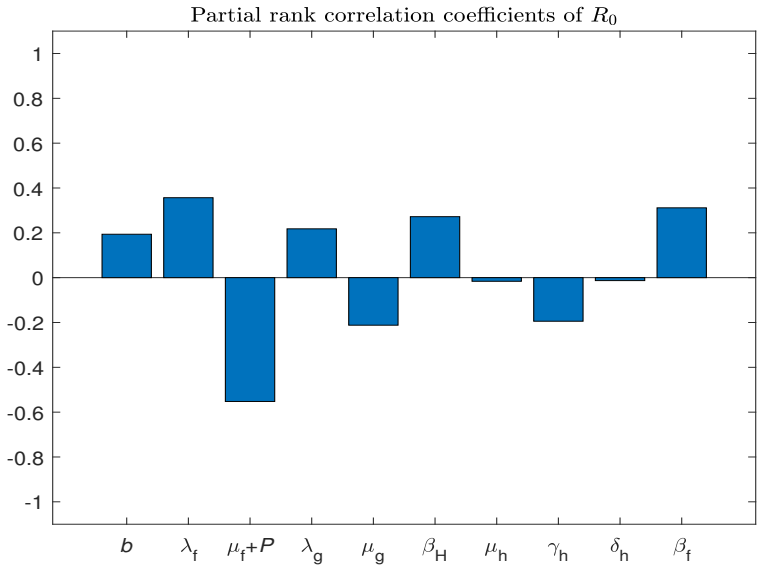


Figure 5.4: Sensitivity analysis diagram of R_0.

5.3. R_0 and long-term behaviors

To simulate the long-term behavior of Clonorchiasis, we change some parameters to satisfy the theorem in Section. 3. In Fig. 5.5, we change b, λ_f and $\mu_f + P$, then we get $R_v < 1$ and $R_0 < 1$. By Theorem 3.3, the disease-free and vector-free equilibrium E_{00} is globally asymptotically stable. In Fig. 5.7, we change λ_g, μ_g, β_H, β_f and $\mu_f + P$, then we get $R_v > 1$ and $R_0 < 1$. Theorem 3.4 implies that the solution converges to the disease-free equilibrium E_0, and the disease eventually becomes extinct.

Then, we explore the effect of different parameters on the basic reproduction number R_0. From Fig. 5.6 (a), we have $R_0 = 1.2655$ when the disease recovery rate $\gamma_h = 1$. This means that the disease is still prevalent even if all patients can recover. It can be seen that prevention is better than cure for Clonorchiasis. Larval fish have relatively weak immune mechanisms and are more susceptible to infection by caecilians in the water. In fact, regular water system cleaning is feasible. To introduce water system cleaning in system (2.2), we replace λ_g with $(1-\pi)\lambda_g$, where $\pi \in [0.2, 1]$ denotes the degree of completion of water system cleaning. Keeping other parameter values the same as in Table 1, Fig. 5.6 (b) shows that R_0 decreases with increasing π. Therefore, to improve the water quality monitoring system, regular clean water, and dismantle toilets at the edge of ponds may effectively control Clonorchiasis.

The infection rate of the host by the parasite plays an important role in disease transmission. Fig. 5.8 simulates the effect of β_H and β_f on R_0, which is an increasing function with respect to β_H and β_f, respectively. A sufficiently small basic reproduction number can be achieved by controlling either β_H or β_f. Although there is no commercially produced vaccine against Clonorchiasis, the possibility of

developing a fish vaccine has been proposed [47]. To reduce the basic reproduction number to less than one, we need to reduce the prevalence of Clonorchiasis infection in fish by at least 56%. In addition to enhancing cultural education to reduce the consumption of raw fish, using non-polluted water for fish farming may also be a reasonable measure to reduce β_f and β_H effectively.

In Fig. 5.9, we demonstrate the relationship between R_0 and (β_H, β_f) in three-dimensional space. We can observe the value of R_0 by changing the value of the parameter β_H and β_f with the other parameters unchanged. We can see that even if β_H is large, R_0 can be smaller than one as long as the value of β_f is small enough. Meanwhile, when β_f is large, R_0 can be smaller than one as long as β_H is small enough. The parameters β_H and β_f are important in Clonorchiasis transmission, and they determine the trend of R_0 together. Fish health is a key factor affecting the prevalence of Clonorchiasis, and cultural education should be strengthened to avoid eating raw freshwater fish.

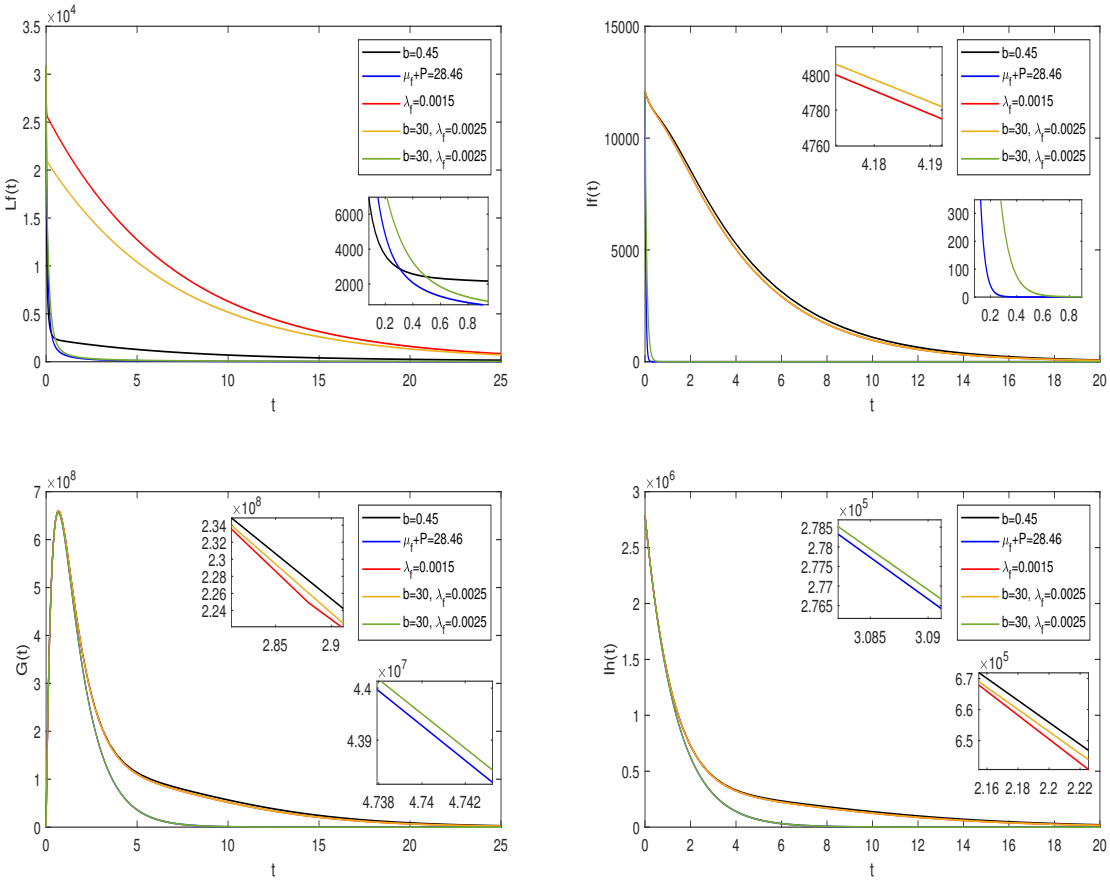


Figure 5.5: Long-term behavior of L_f, I_f, G and I_h when $R_v < 1$ and $R_0 < 1$. Blake line: $b = 0.45$, $R_v = 0.7906$, $R_0 = 0.1476$. Blue line: $\mu_f + P = 28.46$, $R_v = 0.7906$, $R_0 = 0.0015$. Red line: $\lambda_f = 0.0015$, $R_v = 0.7867$, $R_0 = 0.0074$. Blake line: $b = 0.45$, $R_v = 0.7906$, $R_0 = 0.1476$. Yellow line: $b = 30$, $\lambda_f = 0.0025$, $R_v = 0.8712$, $R_0 = 0.1$. Green line: $b = 25$, $\lambda_f = 12.846$, $R_v = 0.9731$, $R_0 = 0.0036$.

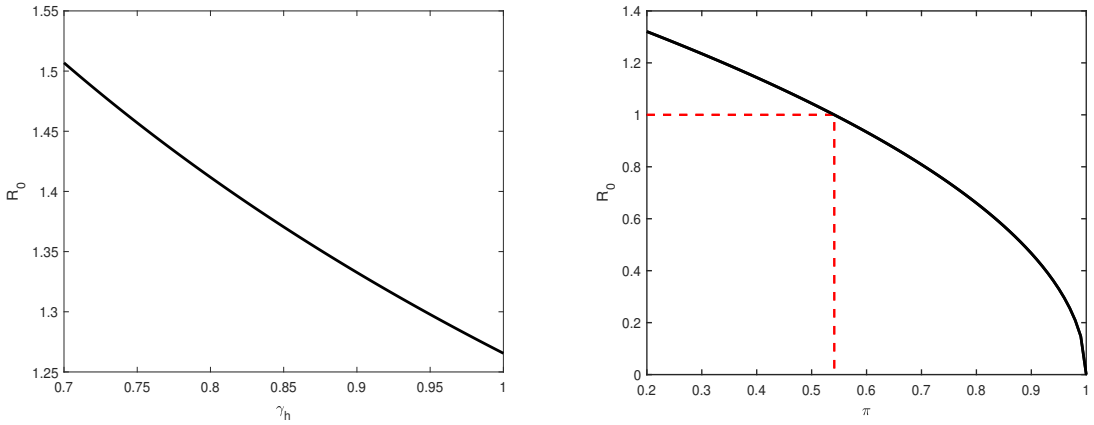


Figure 5.6: The effect of parameters π and γ_h on R_0.

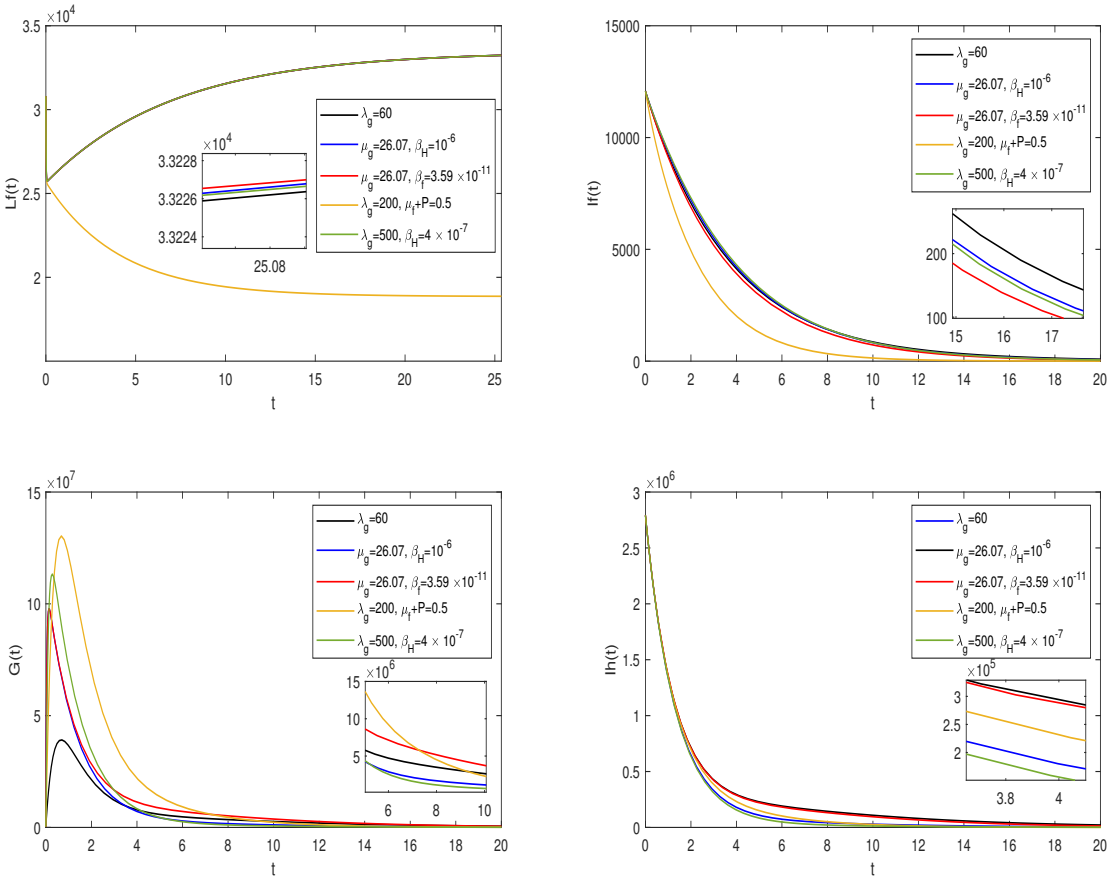
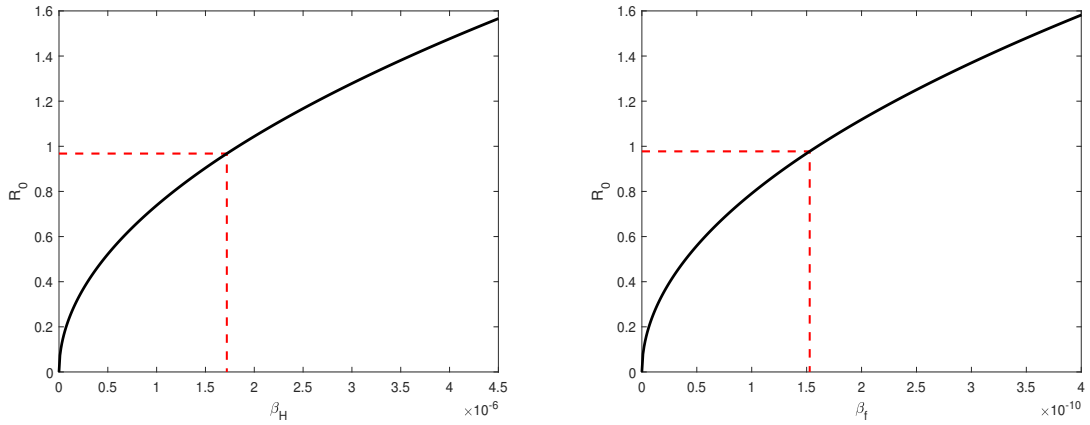
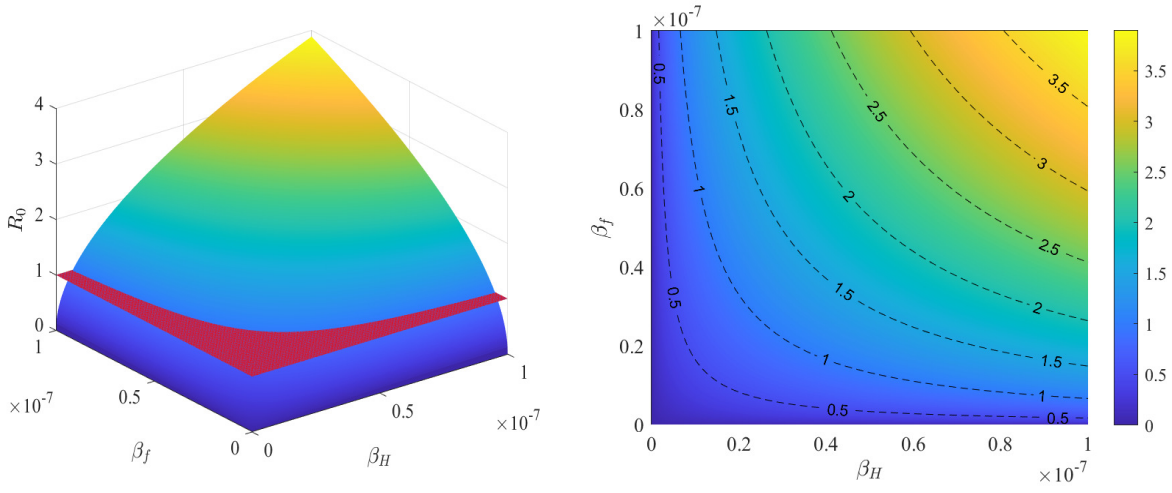


Figure 5.7: Long-term behavior of L_f, I_f, G and I_h when $R_v > 1$ and $R_0 < 1$. Blake line: $\lambda_g = 60$, $R_0 = 0.3591$. Blue line: $\mu_g = 26.07$, $\beta_H = 10^{-6}$, $R_0 = 0.2334$. Red line: $\mu_g = 26.07$, $\beta_f = 3.59 \times 10^{-11}$, $R_0 = 0.1476$. Yellow line: $\lambda_g = 200$, $\mu_f + P = 0.5$, $R_0 = 0.2816$. Green line: $\lambda_g = 500$, $\beta_H = 4 \times 10^{-7}$, $R_0 = 0.1674$.



(a) (b)

Figure 5.8: The effect of parameters β_H and β_f on R_0.



(a) (b)

Figure 5.9: The contour plot of the R_0 as a function of β_H and β_f. (a) The red plane represents $R_0 = 1$, above the red lane $R_0 > 1$, below the red plane $R_0 < 1$. (b) The dashed line represents the value of R_0.

6. Concluding Remarks

Based on the mechanisms of transmission and related studies of Clonorchiasis, fish is the most essential link in transmitting the disease to humans. In this work, we propose a novel mathematical model to study the dynamics of Clonorchiasis around humans and vectors. Due to their biological considerations, fish are divided into two stages: larval and adult. Larval fish may be more susceptible to Clonorchiasis because they usually live in shallow waters and are more likely to come into contact with environments contaminated with Clonorchis sinensis eggs. The mathematical results show that (i) the disease-free and vector-free equilibrium E_{00} is GAS if $R_v < 1$ holds; (ii) if $R_v > 1$, the disease-free equilibrium E_0 exists and is GAS for $R_0 < R_1 := \frac{\mu_h}{\mu_h+\delta_h}$; (iii) the endemic equilibrium E^* exists and is GAS if $\Delta > 0$, $R_v > 1$ and $R_0 > 1$.

To demonstrate the practical value of the parameters of system (2.2), Fig. 5.1 conducted a case study on the transmission dynamics of Clonorchiasis from 2016-2021 using data from Guangxi, China. We

obtain the basic reproduction number as $R_0 = 1.4764$, which means that the disease will persist if no action is taken. Figs. 5.2 and 5.3 predict the development of Clonorchiasis in Guangxi, China under the control of β_H and λ_g, respectively.

The basic reproduction number plays a decisive role in the spread of infectious diseases, and only by figuring out which factors affect the basic reproduction number can we better provide reasonable control measures. We conduct a sensitivity analysis of the parameters that may affect R_0 in Fig. 5.4. The results show that fish is a key factor influencing the spread of disease and λ_g, β_H, and β_f are important in influencing the spread of disease. After that, we explore the effect of these parameters on R_0 in Figs. 5.6 (b), 5.8 and 5.9. Fig. 5.6 (a) implies that improving medical care is not enough and that integrated prevention and treatment measures must be taken. Clonorchis sinensis cannot attack humans directly to cause infection. They must invade the human body through food such as fish and shrimp, and the only way for organisms such as fish and shrimp to become infected is through caecilians in the water. Therefore, to eliminate Clonorchiasis, attention must be paid to controlling the concentration of cercariae in the water to reduce the probability of fish becoming infected with Clonorchiasis. This can be achieved through water purification and vaccination of fish.

The current treatment of Clonorchiasis is mainly praziquantel, but praziquantel is associated with serious adverse effects [7]. Studies have shown that Clonorchiasis can be prevented to a large extent by controlling the health status of fish. Raw fish consumption and cutting boards that do not distinguish between raw and cooked food can lead to disease infection, which requires the health sector to strengthen the culture and education of the people to raise their awareness and vigilance against Clonorchiasis. Preventive chemotherapy can be administered for risk groups such as schoolchildren and fishermen [25]. The entire life cycle of Clonorchis sinensis is limited by temperature and rainfall, and the growth state of the cercariae also heavily depends on temperature [33]. For future study, it would be interesting to incorporate these environmental drivers into the model and study their impact on Clonorchiasis transmission.

Acknowledgements

We thank the anonymous referees and the handling editor for their valuable comments which have led to a substantial improvement in the revision. Wei Wang gratefully acknowledges support from the National Natural Science Foundation of China (No. 12271308, 11901360). Hao Wang gratefully acknowledges support from the Natural Sciences and Engineering Research Council of Canada (Discovery Grant RGPIN-2020-03911 and Accelerator Grant RGPAS-2020-00090) and the CRC program (Tier 1 Canada Research Chair Award).

References

[1] A. Havelaar, M. Kirk, P. Torgerson, et al., 2015. World health organization global estimates and regional comparisons of the burden of foodborne disease in 2010. Plos Medicine 12, e1001923.

[2] Y. Chen, C. Zhou, L. Xu, 2012. Analysis of the results of two nationwide surveys on clonorchis sinensis infection in China. Biomedical and Environmental Sciences 25, 163-166.

[3] D. Wei, W. Yang, S. Huang, et al. 1981. Parasitological investigation on the ancient corpse of the Western Han Dynasty unearthed from tomb No. 168 on Phoenix Hill in Jiangling county. Medical Journal of Wuhan University 1, 16-23.

[4] O. Diekman, J.A.P. Heesterbeek, M.G. Roberts, 2010. The construction of next-generation matrices for compartmental epidemic models. Journal of The Royal Society Interface 7, 873-885.

[5] Z. Deng, Y. Fang, 2016. Epidemic situation and prevention and control strategy of clonorchiasis in Guangdong province, China. Chinese Journal of Schistosomiasis Control 28, 5.

[6] Z. Deng, Y. Fang, 2020. The control of clonorchiasis in Guangdong province, southern China. Acta Tropica 202, 105246.

[7] D. Chen, X. Liu, 1997. Clinical observation on treatment of 150 cases of clonorchiasis with praziquantel of different dosages. Journal of Tropical Diseases and Parasitology 5, 28-29.

[8] D. Fan, H. Sun, Y. Peng, et al., 2022. Living Status and Perspective of the Silver Carp (Hypophthalmichthys molitrix) in the Lower Reach of the Yangtze River: Insights from Population Distribution, Age Structure, and Habitat Preference Analyses. Fishes 7, 254.

[9] G. Ruggerone, D. Rogers, 2003. Multi-year effects of high densities of sockeye salmon spawners on juvenile salmon growth and survival: a case study from the Exxon Valdez oil spill. Fisheries Research 63, 379-392.

[10] G. Chelomina, 2014. Current methods for the diagnosis of human and animal clonorchiasis. Meditsinskaia Parazitologiia i Parazitarnye Bolezni, 54-57.

[11] Guangxi Zhuang Autonomous Region Bureau of Statistics, 2022. Guangxi statistical yearbook. http://tjj.gxzf.gov.cn/tjsj/tjnj/.

[12] H. Smith, 1995. Monotone dynamical systems: an introduction to the theory of competitive and cooperative systems: an introduction to the theory of competitive and cooperative systems. American Mathematical Society.

[13] M. Haque, F.A. Basir, E. Venturino, et al., 2023. Mathematical modelling of clonorchiasis with human treatment and fish vaccination versus snail control. Chaos, Solitons and Fractals 167, 113048.

[14] J. Kim, C. Ahn, B. Sripa, et al., 2019. Clonorchis sinensis omega-class glutathione transferases are reliable biomarkers for serodiagnosis of clonorchiasis and opisthorchiasis. Clinical Microbiology and Infection 25, 109.e1-109.e6.

[15] J. Lee, B. Jung, H. Lim, et al., 2012. Comparative morphology of minute intestinal fluke eggs that can occur in human stools in the republic of Korea. The Korean Journal of Parasitology 50, 207-213.

[16] J. Liu, M. Han, T. Zhang, 2023. Global dynamics in a model for anthrax transmission in animal populations. International Journal of Biomathematics 16, 2250119.

[17] K. Jennifer, J. Utzinger, 2009. Food-borne trematodiases. Clinical Microbiology Reviews 22, 466-483.

[18] M. Chen, Y. Lu, X. Hua, et al., 1994. Progress in assessment of morbidity due to Clonorchis sinensis infection: A review of recent literature. Tropical Diseases Bulletin 91, R7-R65.

[19] M. He, B. Tang, X. Yan, S. Tang, 2023. Transmission dynamics informed neural network with application to COVID-19 infections. Computers in Biology and Medicine 165, 107431.

[20] M. Choi, Y. Chang, M. Lim, et al., 2011. Clonorchis sinensis infection is positively associated with atopy in endemic area. Clinical and Experimental Allergy 41, 697-705.

[21] B. Na, J. Pak, S. Jong, 2019. Clonorchis sinensis and clonorchiasis. Acta Tropica 203, 105309.

[22] P. George, B. Thomas, 1974. A survey on M-matrices. SIAM Review 16, 419-427.

[23] P. van den Driessche, J. Watmough, 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Mathematical Biosciences 180, 29-48.

[24] M. Qian, Y. Chen, Y. Yang, et al., 2014. Increasing prevalence and intensity of foodborne clonorchiasis, hengxian county, China, 1989-2011. Emerging Infectious Diseases 20, 1872-1875.

[25] M. Qian, Y. Chen, S. Liang, et al., 2012. The global epidemiology of clonorchiasis and its relation with Cholangiocarcinoma. Infectious Diseases of Poverty 1, 4.

[26] M. Qian, S. Zhuang, S. Zhu, et al., 2021. Epidemiology and determinants of clonorchiasis in school children in southeastern China. Acta Tropica 216, 105752.

[27] M. Qian, J. Utzinger, J. Keiser, et al., 2015. Clonorchiasis. The Lancet 387, 800-810.

[28] A. Richard, F. Cattaneo, J. Rubin, 2015. Biotic and abiotic regulation of a low-density stream-dwelling brown trout (salmo trutta l.) population: effects on juvenile survival and growth. Ecology of Freshwater Fish 24, 1-14.

[29] R. Anderson, 1982. The population dynamics of infectious diseases: Theory and applications. Population and Community Biology. Springer, Boston, MA.

[30] R. Yuan, J. Huang, X. Zhang, S. Ruan, 2018. Modeling the transmission dynamics of clonorchiasis in Foshan, China. Scientific Reports 8, 15176.

[31] M. Ronoh, F. Chirove, S. Pedro, et al., 2021. Modelling the spread of schistosomiasis in humans with environmental transmission. Applied Mathematical Modelling 95, 159-175.

[32] S. Dai, Y. Qing, X. Ma, et al., 2021. Prevalence of clonorchis sinensis infections in freshwater fish in mainland China: A meta-analysis. Chinese Journal of Schistosomiasis Control 34, 16-27.

[33] T. Zhang, X. Zhao, 2020. Mathematical modeling for schistosomiasis with seasonal influence: A case study in Hubei, China. SIAM Journal on Applied Dynamical Systems 19, 1438-1471.

[34] T. Zhang, Z. Li, L. Ma, X. Song, 2022. Threshold dynamics in a clonorchiasis model with time delays. Applied Mathematical Modelling 102, 351-370.

[35] T. Li, Z. Yang, M. Wang, 2014. Correlation between clonorchiasis incidences and climatic factors in guangzhou, China. Parasites and Vectors 7, 1-6.

[36] T. Zhao, Y. Fang, Y. Lai, 2021. Assessment of the burden of clonorchiasis and its temporal changes in China. Chinese Journal of Schistosomiasis Control 33, 162-168.

[37] T. Zhu, Y. Chen, M. Qian, et al., 2020. Surveillance of clonorchiasis in China in 2016. Acta Tropica 203, 105320.

[38] T. Thi Cam, A. Yajima, K. Viet, et al., 2008. Prevalence, intensity and risk factors for clonorchiasis and possible use of questionnaires to detect individuals at risk in northern vietnam. Transactions of the Royal Society of Tropical Medicine and Hygiene 102, 1263-1268.

[39] WHO, 2015. WHO estimates of the global burden of foodborne diseases: foodborne disease burden epidemiology reference group 2007-2015. Geneva: WHO

[40] X. Zhao, Z. Jing, 1996. Global asymptotic behavior in some cooperative systems of functional differential equations. Canadian Applied Mathematics Quarterly 4, 421-444.

[41] Y. Dai, S. Gao, F. Zhang, Y. Luo, 2013. Threshold and stability results for clonorchiasis epidemic model. International Journal of Environmental Science and Technology 2, 13.

[42] Y. Kim, S. Lee, G. Choi, et al., 2010. Performance of an enzyme-linked immunosorbent assay for detection of clonorchis sinensis infestation in high- and low-risk groups. Journal of Clinical Microbiology 48, 2365-2367.

[43] Y. Fang, Y. Chen, X. Li, et al., 2008. Current prevalence of clonorchis sinensis infection in endemic areas of China. Chinese Journal of Parasitology and Parasitic Diseases 26, 99-103.

[44] Y. Lou, X. Zhao, 2011. Modelling malaria control by introduction of larvivorous fish. Bulletin of Mathematical Biology 73, 2384-2407.

[45] Y. Yoshida, 2012. Clonorchiasis-a historical review of contributions of Japanese parasitologists. Parasitology International 61, 5-9.

[46] Z. Lu, M. Su, 2019. Epidemic situation and prevention and control strategy of clonorchiasis in GuangXi. International Journal of Epidemiology and Infectious Disease 46, 229-233.

[47] Z. Tang, Y. Huang, X. Yu, 2016. Current status and perspectives of clonorchis sinensis and clonorchiasis: epidemiology, pathogenesis, omics, prevention and control. Infectious Diseases of Poverty 5, 14-25.