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Transmission dynamics and control of Gnathostomiasis: Insights from dynamics modelling and Optimal control.

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June 13, 2023

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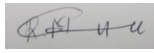
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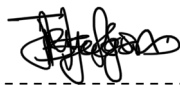


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Abstract

Gnathostomiasis is a system food-borne parasitic disease. Gnathostomiasis is usually consumed/ingested in contaminated raw fish, which is one of the main risk factors. The parasite can infect many animals including domestic and wild felines and canines, domestic and wild pigs. Despite the fact that the disease is common in several regions of Asia and South America, very few patients have been reported in Africa. Control strategies including disinfecting contaminated water sources, providing medical care and reducing contact rate have been introduced to reduce Gnathostomiasis disease. In this thesis, a Gnathostomiasis model was developed and analyzed. Positivity and boundedness of solutions were explored, and computed basic reproduction number (R_0) using the method of the next generation. R_0 was used to find out the disease-free equilibrium's local stability along with the endemic equilibrium's existence. We found out that endemic equilibrium is unique for $R_0 > 1$ and the disease-free equilibrium is globally asymptotically stable when $R_0 < 1$. Sensitivity analysis and numerical results were obtained. We observed that the processes related to contact of individuals to Gnathostoma infected environments, water sources or food have the potential of worsening the disease when increased. In addition, increased shedding of the pathogen into the environment also has the potential of increasing the disease burden. We also extended our force of infection (λ), that is adding the force of infection for consuming food contaminated with the pathogen. We only focused on the numerical simulation for the extended force of infection (λ), considering the contribution of eating contaminated food. Our results showed a higher estimation of the number of infections and hence the disease burden. The model was improved to consider controls that target the reduction in the number of infections. We found that all controls should be implemented to contain the infection. For the optimal control model, we introduced three controls, and implemented objective cost function to reduce the infected population and accompanying costs. We solved the numerical optimal control problem using the forward and backward sweep method. From the numerical results, we deduced that when all the controls are implemented, the disease can be contained.

Dedications

To my daughter Isago.



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I would like to thank God for giving strength and made everything possible. I would also like to thank my supervisor Dr H.J.B Njagarah for guidance, support and patience during tough times of my life. May God richly bless him. I would like to thank the Simons Foundation for funding my studies.



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1. Introduction

Gnathostomiasis is a systemic food-borne parasitic disease caused by a migrating nematode larvae called *Gnathostoma Spinigerum* of the genus *Gnathostoma* [3]. It belongs to one of the largest groups of nematodes called Spirurida. The parasite can infect many animals including domestic and wild felines and canines, domestic and wild pigs, copepods, toads and fish. It is usually consumed/ingested in contaminated raw fish, which is one of the main risk factors [3]. The general life cycle of *Gnathostoma Spinigerum* is given in Figure 1.1.

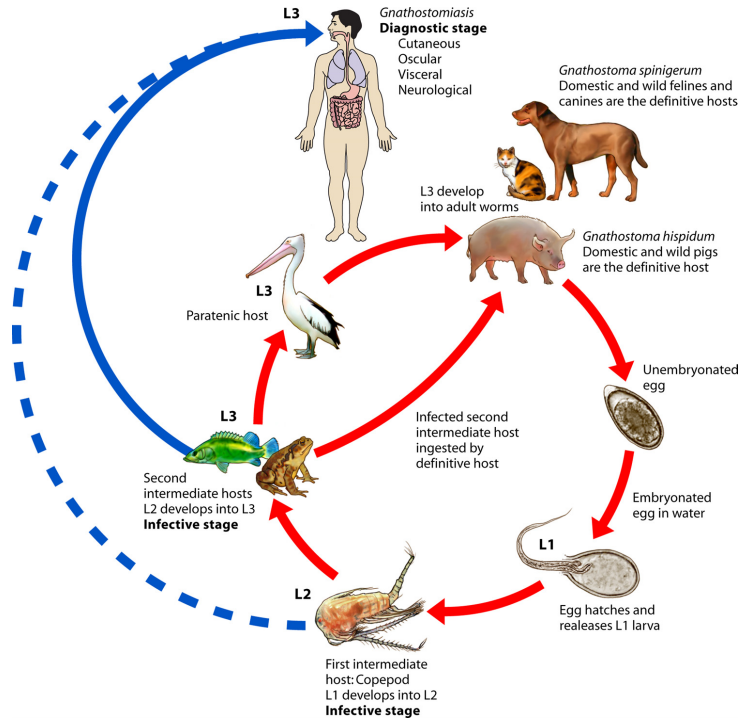


Figure 1.1: Life cycle of *Gnathostoma Spinigerum* [1]

The symptoms of Gnathostomiasis occur when the larvae is at the third-stage, moving through the tissues, creating intermittent cutaneous symptoms (see for example Figure 1.2) or visceral larva migrans [4]. Gnathostomiasis is characterised by cutaneous, visceral, ocular and neurological disease [5]. Cutaneous Gnathostomiasis is when the nematode is travelling through tissues, vital organs such as eyes and central nervous system eventually causing illness [4]. Visceral disease occurs when larvae travel through the internal organs, causing some infections moving through the tissues in the pulmonary system, gastrointestinal tract, genitourinary tract, eye, ear, nose, throat, or central nervous system, causing intermittent cutaneous symptoms [5].

According to Germaine (2018) [6], there are rare cases where larvae can immediately penetrate the skin of people who have been exposed to contaminated food or freshwater. Infection can affect any organ system, although the most prevalent symptom is localized, intermittent, migratory swelling in the skin and subcutaneous tissues. Furthermore, due to larval migration into the CNS, *Gnathostoma* species frequently induce parasitic eosinophilic meningitis. Germaine (2018)



Figure 1.2: Symptoms of Gnathostomiasis on the skin [2]

[6] also stressed that systemic infection is frequently linked with peripheral eosinophilia, in which eosinophils account for more than 50% of the circulating white blood cells. Because it can affect any portion of the body, Gnathostomiasis can last for 10 to 12 years and cause serious morbidity. The primary cause of death, invasion of the CNS, may result in death in 8–25% of patients or long-term consequences in 30% of individuals with neurognathostomiasis [6].

Liu *et al.*(2020) [7] highlighted that Gnathostomiasis is a one of the ignored food-borne zoonosis. Gnathostomiasis is a disease that is frequently reported in developing nations, but it is also an emerging disease in wealthy nations where it is not endemic [7]. Geographically, *Gnathostoma spp.* are distributed all over the world. Since the first instance of Gnathostomiasis in humans was documented in the country of Thailand in 1889, there have been about 5000 cases reported globally [7]. Liu *et al.*(2020) [7] also added that the current increase in Gnathostomiasis cases is primarily due to a higher intake of uncooked freshwater fish, amphibians, and reptiles.

Gnathostomiasis can be prevented by avoiding coming in contact with contaminated water sources as well as avoiding eating raw fish or raw hosts of the disease causing pathogen. Infected individuals can be treated using albendazole (400 mg twice a day) [8]. In addition, a single dose of Ivermectin ($150 - 200\mu g/kg$) is also very effective in the treatment of cutaneous larva migrans (creeping eruption), with cure rates of 100% and the drug is safe in humans [9]. Kraivichian *et al.*(2004) [9] stated that the best treatment for cutaneous Gnathostomiasis is surgical removal of the worm.

Global distribution of Gnathostomiasis

As of 2021, Gnathostomiasis was one of the public health issues in Mexico due to the large number of cases that were reported there [10]. The first cases of Gnathostomiasis were recorded in Mexico in 1970, and the prevalence of gnathostomiasis there appears to be increasing rapidly over time[11]. Between January 1992 and December 1995, 300 cases of cutaneous larva migrans were reported in Culiacán, Sinaloa [12]. In addition, one patient had a *Gnathostoma* larva surgically removed from their eye. Face, neck, arms, and legs were the most common places for cutaneous lesions to be found [12]. Gnathostomiasis has been reported in Peru and Ecuador in South America [1].

Rusnak and Lucey [13] stated that Gnathostomiasis is one of the endemic diseases in Southeast Asia, particularly in Japan and Thailand. Mexico, Japan and Thailand are 3 major endemic countries where people mostly consume raw fish [14]. Nawa *et al.*(2010) [14] also reported a case of cutaneous Gnathostomiasis in a Bangladeshi woman from Germany and some cases from Sri Lanka. Ando *et al.*[15] stated that between the late 1940s to 1960s, many Japanese people, especially those living in the Southwestern part of Japan, often ate snakehead fish (*Channa argus*) infected with *G. spinigerum* and more than 1000 cases were reported. In 1980, Gnathostomiasis infections were found in Hiroshima city, and subsequently, similar mass infections were reported from various areas of Japan. All of the patients had consumed raw loaches imported from Taiwan, Korea, or the Chinese mainland. [15].

Africa has been viewed generally to be free of Gnathostomiasis. However, there have been some reported cases of Gnathostomiasis in Zambia, Tanzania, Botswana [1, 4]. Gnathostomiasis is referred to as one of the emerging imported diseases in Botswana. Herman *et al.*(2009) [1, 4] reported 2 cases of 2 tourists who had Gnathostomiasis in Botswana. The Tourists were fishing between Maun and Shakawe in the North west of Botswana. There were also cases of 2 patients who contracted gnathostomiasis from the Okavango Delta [16].

In August 1988, two men who were fishing in the Zambezi river in Western Zambia contracted Gnathostomiasis by consuming fresh, raw bream marinated in lemon juice [8]. The father and son pair went back to their individual homes, where symptoms started to appear some 12–14 days later. On August 19, 1998, the father, a 70-year-old male, began to experience fever, chills, headache, myalgias, and arthralgias. The 45-year-old son was initially evaluated by his medical practitioner and referred to the South African Institute for Medical Research on September 5, 1998. The son resided in South Africa. His initial signs included muscle soreness, sporadic low-grade fever, nausea, cramping in the abdomen, sweating, chills, chest pain, shortness of breath, and exhaustion.

Herman *et al.*(2009) [4] stated that the first case of a person evaluated for possible Gnathostomiasis contracted in Botswana was a 41-year-old British Caucasian male who arrived at the Hospital for Tropical Diseases (HTD) in London on September 30, 2008, three weeks after leaving Botswana's Okavango Delta. He had been swimming in and consuming river water when swimming, camping, and walking barefoot. He had also consumed raw bream on multiple occasions. Two weeks later, he complained of localized, intermittent stomach pain that shifted to a different location every morning. At the same time, he experienced a palpable enlargement around his spleen, which subsided after 12 days. A painful subcutaneous lump appeared on his anterior chest wall within 24 hours after he started to experience itch under his left arm. Invading other tissues and organs such as the eyes, ears, breasts, lungs, thoracic spinal cord, genitourinary system, and central nervous system (CNS), gnathostoma larvae can travel to the skin through subcutaneous tissue [7, 17, 18]. The clinical features manifest themselves primarily as cutaneous and visceral migrans, depending on which part of the body is affected [7]. Within a day or two of ingestion, Gnathostoma larvae travel through the liver's and gastrointestinal tract's walls [7]. When diagnosing Gnathostomiasis, moving lumps are the most important feature [7].

1.0.1 Aims and objectives

The aim of the research work was focused on developing a mathematical model that describes the transmission dynamics and possible controls of Gnathostomiasis. The objectives of the study are

- To review the work done
- To develop Gnathostomiasis model and examine the dynamical behaviour(stability).
- To identify the control measures and use the optimal control strategies to minimize Gnathostomiasis disease.

1.0.2 The outline of the Thesis

The remaining parts of the thesis are organised as follows. In Chapter 2, the review of the literature and tools used are given. Relevant mathematical preliminaries and definitions are given. In Chapter 3, the basic Gnathostomiasis model is formulated and analysed, positivity and boundedness of the model are shown, the disease free equilibrium and basic reproduction number are determined. In the same chapter, numerical simulations and sensitivity analysis results using the Latin Hypercube Sampling approach are addressed as well. In Chapter 4 we present the Gnathostomiasis extended model, where the controls that minimizes the number of infected individuals are implemented. We also solved the extended model numerically and the results are presented in the same chapter.

2. Literature review

In this Chapter, we review available literature on Gnathostomiasis and present description of tools or methods used in the study and what other researchers have done.

2.1 Preliminaries

Definition 1. *Feasible region is collection of all possible values of the variables that fulfil pre-determined criteria.*

Definition 2. *The disease-free equilibrium is the point in the population where no disease exists.*

Definition 3. *Endemic equilibrium state is the condition when the infection cannot be completely eliminated but still affects the population. For the infection to stay in the population, the classes must not be zero at the equilibrium state that is $E_1 = (S^*, E^*, I_a^*, I_s^*, H^*, R^*, W^*) \neq (0, 0, 0, 0, 0, 0, 0)$.*

Some of the things done in modelling is linearization, Hartman-Grobman theorem [19] stated that the general system is topological equivalent to the behaviour of its linearization near equilibrium point. System of more than two dimensions use the Jacobian matrix, and evaluate the Jacobian at the disease-free equilibrium. Find the characteristic equation and find the roots.

Definition 4. *The Jacobian matrix shows the differentiation of function f at every point where f is differentiable on it can be described as an $m \times n$ matrix where the (i,j) th entry is $J_{ij} = \frac{\partial f_i}{\partial x_j}$.*

$$J_{i,j} = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_m}{\partial x_1} & \cdots & \frac{\partial f_m}{\partial x_n} \end{bmatrix}$$

2.2 Sensitivity analysis

Sensitivity analysis examines the relationship between the uncertainty of reasoning-based models and the uncertainty of model assumption [20]. Marino *et al.*(2008) [21] also added that the technique of sensitivity analysis used to evaluate uncertainty in any model. Sensitivity analysis can help recognize the significant model parameters which in turn can be used to improve the model structure [21, 22]. Local and global sensitivity are the two different types of sensitivity analysis approaches. Local sensitivity analysis is a type of sensitivity analysis that looks at how changes to one input value affect the outputs values and global sensitivity examines the change in the output values brought about by alterations in all parameter values across the parameter ranges [23]. To conduct sensitivity analysis, different methods such as differential sensitivity analysis, one-at-a-time sensitivity measures, factorial design, sensitivity index, importance factors, and

subjective sensitivity analysis have been used [24]. Among these, subjective sensitivity analysis is the only qualitative method, and it is based on the opinions of experienced investigators [24].

The Sobol sensitivity analysis calculates the variance in the overall model output that each input parameter and their interactions contributes to [25]. One option for calculating these variance-based indices is to use Monte Carlo simulation [26]. For Sobol sensitivity analysis, choose the parameters to be varied in the model and include their lower and upper bounds, that is defining parameter ranges. Use the Sobol sequence to generate the parameter sets, then run the parameters through the model and calculate the Sobol indices, now analyze the total, first order and second order sensitivity indices. Sensitivity indices are positive and significant parameters are those with sensitivity indices above 0.05 [25].

Another variance-based method of sensitivity analysis is eFAST. Among the variance-based methods, eFAST has proven to be one of the most dependable methods [27]. The ability to determine both the first-order and total-order sensitivity of each input parameter makes the eFAST method superior to the original FAST [21]. eFAST uses a variance decomposition technique which is similar to ANOVA, in which the model's output is affected by changes to the input parameters [21]. The variance is calculated and divided into portions, calculating the percentage of the variance that can be accounted for by variations in each input parameter [21]. The output of the model is then subjected to Fourier analysis to determine the strength of each parameter's frequency [21]. As a result, the model's sensitivity to a parameter can be determined by seeing how strongly a parameter's frequency propagates from the input to the output through the model [21].

We employed the Latin Hypercube Sampling scheme (LHS), a stratified Monte Carlo sampling that permits concurrent sampling of the broad parameter space, to conduct our sensitivity analysis to our model [28]. LHS is an effective strategy used to sample random parameter vectors, while making sure that each parameter range is evenly covered [29]. Gomero [30] also stated that LHS is a powerful tool often used in uncertainty analysis to look into the entire parameter space of a model. A sensitivity analysis methodology known as partial rank correlation coefficient (PRCC) analysis determines the partial rank correlation coefficients for model inputs and outputs that are sampled using the LHS method [29]. The computed PRCC values ranges from -1 and 1 and their sign reveals shows the qualitative relationship between the model input and model output [29]. A positive PRCC value entails that when the corresponding model input increases, the model output will also increase while a negative PRCC value shows a negative correlation between the model input and output [29]. The size of the PRCC sensitivity determines the importance of the model input in contributing to the model output [29].

2.3 Optimal control

Optimal control theory is a field of optimization in mathematics that focuses on determining a time-dependent control for a dynamical system to optimize an objective function [31]. Pontryagin *et al.* (1962) [32] also defined optimal control theory as a powerful mathematical tool for making choices concerning complex dynamical systems, and it is a common technique for

resolving dynamic optimization problems expressed in continuous time. Optimal control is an optimization strategy for determining control policies, and it deals with the issue of finding controls for a model system in order that optimality model is accomplished [33]. We further note that optimal control can be obtained using Pontryagin's maximum principle. Optimal control was successfully implemented in various contagious disease models, such as Covid [34, 35], Cholera [36], HIV [37, 38] to cite a few. The numerical results displayed that the number of infected people was reduced by 50% compared to continuous vaccination [35]. Optimal control strategies are achieved by lowering the number of people that are exposed and infected individuals while taking into account implementation costs [34]. Optimal control strategies is also used to prevent interactions among the infected and susceptible individuals [39]. In an epidemiological model, the general steps for optimal control process are as follows [40]: (1) determining the model-appropriate permissible controls; (2) setting up the objective function with controls; (3) constructing the Hamiltonian; (4) evaluating costate variables (adjoint functions); and (5) determining the threshold controls that minimize the Hamiltonian. Numerical results shown that optimal control managed to reduce infected individuals. Optimal control was applied to alcohol model with two infected categories being the admitted and non-admitted [39] and Cholera model [36]. Numerical results shown that implementation of controls decreases the infection [36].

2.4 Etiology and life cycle of Gnathostomiasis

The main etiological agent of Gnathostomiasis is the larvae of the genus *Gnathostoma*. These parasitic larvae are found in the intermediate hosts, which include various freshwater and marine animals such as fish, frogs, snakes, and birds. Humans acquire the infection by consuming raw or undercooked infected intermediate hosts, which leads to the transmission of the larvae to the definitive host that is humans [4].

The life cycle of *Gnathostoma* involves multiple hosts. Adult worms reside in the stomach of definitive hosts such as dogs, cats, or wild animals. They produce eggs, which are then passed through the host's feces. The eggs hatch in water, releasing larvae known as the first-stage larvae (L1)[4]. These L1 larvae are ingested by various species of crustaceans, which act as the first intermediate hosts. The larvae undergo two molts in the first intermediate host, transforming into the infective third-stage larvae (L3). The infected crustaceans are then ingested by the second intermediate hosts, including fish, frogs, or snakes. In these second intermediate hosts, the larvae migrate and encapsulate in the muscle or subcutaneous tissues, awaiting ingestion by the definitive host. Humans become infected with *Gnathostoma* by consuming raw or undercooked second intermediate hosts containing infective larvae. The larvae penetrate the gastrointestinal tract, migrate through various organs, and can cause significant tissue damage as they travel beneath the skin or within the visceral organs[4].

3. Gnathostomiasis Mathematical Model

3.1 Gnathostomiasis model formulation

This chapter, we develop and analyze a new model for the transmission dynamics of the Gnathostomiasis in humans using a system of differential equations. For the model, we classified our population in separate classes being exposed class (E class), susceptible (S class), symptomatically infected (I_s class), asymptotically infected (I_a class), recovered (R class) individuals and the total host population denoted by N . The total host population at any time t is given by

$$N(t) = S(t) + E(t) + I_a(t) + I_s(t) + H(t) + R(t). \quad (3.1)$$

We assume there is recruitment into the susceptible population at rate π accounting for birth and migration. Then the susceptible individuals become exposed to Gnathostomiasis disease. After being exposed to the disease through contact with the pathogen infested environment, some become symptomatically infected and some become asymptotically infected. After some time, the symptomatic (I_s) may become asymptomatic or become hospitalized and treated with medications. We assume that some individuals may develop symptoms in a short time but for some of the small proportion, symptoms may disappear without going to the hospital or reporting. It is only those who have severe conditions that end up being in hospital. Asymptomatic (I_a) infected individuals and hospitalized (H) recover and then move to the recovered (R class). The recovered individuals have some immunity to Gnathostomiasis for some time and then later lose immunity (or immunity wanes) and becomes susceptible (S class) again at a rate of ω . The population is reduced by natural mortality rate μ for each class. Gnathostomiasis can be transmitted through consuming contaminated raw fish or contacting contaminated water sources. Individuals who are susceptible move to the exposed class as a result of contact with pathogen infested aquatic environments by force of infection λ given by

$$\lambda = \beta \frac{W}{K_W + W}, \quad (3.2)$$

where W is the concentration of the pathogen consumed, β is the contact rate and K is half saturation constant of the pathogen. Some of exposed population may develop symptoms immediately and are classified as (I_s) and the remaining ones who did not develop symptoms are classified as (I_a). The symptomatically infected individuals die at a rate $\mu + \delta_1$ and asymptotically individuals die at a rate of $\mu + \delta_2$ where δ_1 and δ_2 are additional mortality rates due to Gnathostomiasis disease. It was reported that Gnathostomiasis caused deaths in 8 – 25% of the infected individuals [6]. The asymptomatic infected individuals become symptomatic at a rate σ_1 , the individuals with mild symptoms may become asymptomatic at a rate σ_2 . The individuals who are symptomatic infected move to the hospitalized class at a rate of ϕ . The recovery rates for asymptotically and hospitalized are γ_1 and γ_2 respectively. Both the symptomatic

and asymptomatic individuals shed the pathogen into the environment at a rate ξ_2 and ξ_1 respectively. In this model developed, we have considered the aspect where the modelling time may be long enough to consider a case when the immunity may have waned during the length of the modelling time. If the modelling time is short, this aspect may not apply.

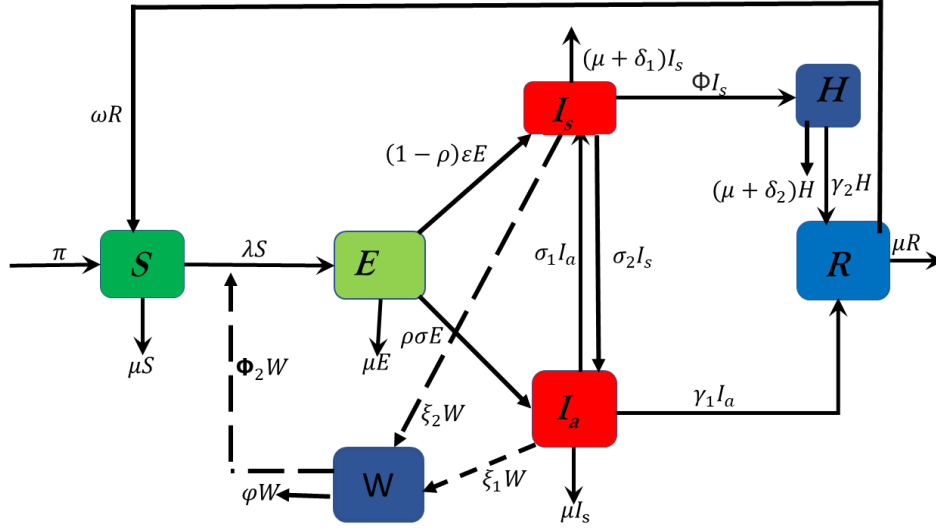


Figure 3.1: Schematic diagram for Gnathostomiasis model.

The model system of equations is given as

$$\frac{dS}{dt} = \pi + \omega R - \lambda S - \mu S, \quad (3.3a)$$

$$\frac{dE}{dt} = \lambda S - Q_1 E, \quad (3.3b)$$

$$\frac{dI_a}{dt} = \rho \epsilon E - Q_2 I_a + \sigma_2 I_s \quad (3.3c)$$

$$\frac{dI_s}{dt} = (1 - \rho) \epsilon E + \sigma_1 I_a - Q_3 I_s, \quad (3.3d)$$

$$\frac{dH}{dt} = \phi I_s - Q_4 H, \quad (3.3e)$$

$$\frac{dR}{dt} = \gamma_2 H + \gamma_1 I_a - Q_5 R, \quad (3.3f)$$

$$\frac{dW}{dt} = \xi_1 I_a + \xi_2 I_s - \varphi W, \quad (3.3g)$$

where $Q_1 = \epsilon + \mu$, $Q_2 = \mu + \sigma_1 + \gamma_1$, $Q_3 = \delta_1 + \mu + \sigma_2 + \phi$, $Q_4 = \gamma_2 + \delta_2 + \mu$ and $Q_5 = \mu + \omega$.

The initial conditions involved in above equations are;

$$S(0) > 0, E(0) \geq 0, I_s(0) > 0, I_a(0) \geq 0, H(0) \geq 0, R(0) \geq 0 \text{ and } W(0) \geq 0. \quad (3.4)$$

The descriptions of model state variables and model parameters are given in Tables (3.1) and (3.2) respectively.

State Variable	Description
S	Susceptible individuals
E	Exposed individuals
I_a	Asymptotically infected individuals
I_s	Symptomatically infected individuals
H	Hospitalized individuals
R	Recovered individuals
W	Freely living bacteria in the environment

Table 3.1: Description of model state variables.

Parameter	Description
π	Recruitment rate into the susceptible individuals population
μ	The natural death rate for individuals
β	Transmission rate
ϵ	The rate at which an exposed individuals becomes infectious
ρ	Proportion of exposed individuals who become asymptotically infected
σ_1	The rate at which asymptotically infected individuals develop symptoms
σ_2	The rate at which the symptomatically infected become asymptomatic
δ_1	Mortality rate of symptomatic individuals due to Gnathostomiasis
δ_2	Mortality rate of asymptomatic individuals due to Gnathostomiasis
γ_2	Recovery rate of hospitalized individuals
γ_1	Recovery rate of asymptotically infected individuals
ω	The rate at which the individuals become susceptible again
ξ_1	Shedding rate of the pathogen by asymptomatic individuals
ξ_2	Shedding rate of the pathogen by symptomatic individuals
φ	Rate of decay of the pathogen
ϕ	Hospitalization rate of symptomatically infected individuals

Table 3.2: Model parameters description

3.2 Model Analysis

Due to the fact that the model tracks population changes which is ever growing, the state parameters and variables are all positive for all $t > 0$. The analysis of the system will therefore be performed in a region of biological significance and the population ought to be bounded.

Theorem 1. *The feasible region Ω for the model defined by*

$$\Omega = \Omega_H \times \Omega_W \in \mathbb{R}_+^6 \times \mathbb{R}_+^1$$

where

$$\Omega_H = \left\{ (S(t), E(t), I_s(t), H(t), I_a(t), R(t)) \in \mathbb{R}_+^6 \mid N_+ \leq \frac{\pi}{\mu} \right\},$$

and

$$\Omega_W = \left\{ W(t) \mid W \leq \frac{(\xi_1 + \xi_2)\frac{\pi}{\mu}}{\varphi} \right\}$$

with initial conditions as given in (3.4), is positively invariant and attracting with respect to the model system (3.3) for all $t > 0$.

3.2.1 Positivity of solutions

Since the model being analysed studies the change in the number of organisms, we must ensure that the model is well posed and that the solutions are non-negative and bounded at all times.

Theorem 2. *The solutions for the model system (3.3) with non-negative initials conditions $S(0) = S^0$, $E(0) = E^0$, $I_s(0) = I_s^0$, $I_a(0) = I_a^0$, $H(0) = H^0$, $R(0) = R^0$ and $W(0) = W^0$ are non-negative for all $t \geq 0$.*

Proof. We consider equation (3.3a)

$$\frac{dS}{dt} = \pi + \omega R - (\hat{\lambda}(s) + \mu)S, \text{ where } \hat{\lambda} = \sup_{t \geq 0} \{\lambda(s)\}. \quad (3.5)$$

We want to show that $S(t) > 0$ for all $t \geq 0$. The equation (3.5) can be reduced to the inequality

$$\frac{dS}{dt} \geq -(\hat{\lambda} + \mu)S, \quad (3.6)$$

which can be solved by separation of variables and integration with respect to corresponding variables such that

$$\int \frac{1}{S} dS \geq - \int (\hat{\lambda} + \mu) dt, \quad (3.7)$$

to obtain

$$S(t) \geq S^0 e^{-(\hat{\lambda} + \mu)t} > 0. \quad (3.8)$$

From the inequality (3.8), we observe that $S(t) \rightarrow 0^+$ as $t \rightarrow \infty$. Hence, for every $t > 0$, $S(t)$ is non-negative.

From equation (3.3b), we have

$$\frac{dE}{dt} = \hat{\lambda}(s)S - Q_1E, \quad (3.9)$$

$$\frac{dE}{dt} \geq -Q_1E. \quad (3.10)$$

Then the inequality (3.10) can be solved with respect to the relevant variables to obtain

$$E(t) \geq E^0 e^{-Q_1 t} \geq 0. \quad (3.11)$$

Following a similar approach on equations (3.3c)-(3.3g), we obtain

$$\begin{cases} I_a(t) \geq I_a^0 e^{-Q_2 t}, \\ I_s(t) \geq I_s^0 e^{-Q_3 t}, \\ H(t) \geq H^0 e^{-Q_4 t}, \\ R(t) \geq R^0 e^{-Q_5 t}, \\ W(t) \geq W^0 e^{-\varphi t}. \end{cases} \quad (3.12)$$

Following the results obtained in this section, we observe for every $t \geq 0$, all the state variables are non-negative. This completes the proof. $\square$

3.2.2 Boundedness of solutions

To determine whether the state variables are bounded, or to show that the total population is bounded, we use the system of equations (3.3) and the expression for the total population.

Proof. Using the equations (3.3a)-(3.3f), we obtain the change in the total population as

$$\begin{aligned} \frac{dN}{dt} &= \pi - \mu N - \xi_1 I_a - \delta_2 H - \delta_1 I_s, \\ &\leq \pi - \mu N. \end{aligned}$$

The resulting inequality can be solved to obtain

$$N(t) \leq \frac{\pi}{\mu} + \left(N^0 - \frac{\pi}{\mu} \right) e^{-\mu t}. \quad (3.13)$$

Taking the limit as t approaches infinity on both sides, we obtain

$$\begin{aligned} \lim_{t \rightarrow \infty} N(t) &\leq \frac{\pi}{\mu} + \left(N^0 - \frac{\pi}{\mu} \right) \lim_{t \rightarrow \infty} e^{-\mu t}, \\ &= \frac{\pi}{\mu}. \end{aligned}$$

Therefore, N is bounded above by $\frac{\pi}{\mu}$.

The equation describing the change in the pathogen in the environment is given by

$$\begin{aligned}\frac{dW}{dt} &= \xi_1 I_a + \xi_2 I_s - \varphi W, \\ &\leq (\xi_1 + \xi_2) \frac{\pi}{\mu} - \varphi W.\end{aligned}$$

This can be reorganised to obtain a differential inequality whose solution is given by

$$W(t) \leq \frac{(\xi_1 + \xi_2) \frac{\pi}{\mu}}{\varphi} + \left(W^0 - \frac{(\xi_1 + \xi_2) \frac{\pi}{\mu}}{\varphi} \right) e^{-\varphi t}. \quad (3.14)$$

Taking the limit as t approaches infinity on both sides, we obtain

$$\begin{aligned}\lim_{t \rightarrow \infty} W(t) &\leq \frac{(\xi_1 + \xi_2) \frac{\pi}{\mu}}{\varphi} + \left(W^0 - \frac{(\xi_1 + \xi_2) \frac{\pi}{\mu}}{\varphi} \right) \lim_{t \rightarrow \infty} e^{-\varphi t}, \\ &= \frac{(\xi_1 + \xi_2) \frac{\pi}{\mu}}{\varphi}.\end{aligned}$$

Therefore, W is bounded above by $\frac{(\xi_1 + \xi_2) \frac{\pi}{\mu}}{\varphi}$.

□

Since all the populations are non-negative and the domain of biological significance is shown to be bounded, then the model is well posed and therefore it is right to analyse the model on the domain specified.

3.2.3 The disease-free equilibrium and the basic reproduction number

The disease-free equilibrium is obtained from (3.3), which depicts that absence of Gnathostomiasis in the population. We get our disease-free equilibrium by equating the right hand side of (3.3a) to zero and solve to get the steady state, and the disease-free equilibrium is given as

$$\mathcal{E}_0 = (S^*, E^*, I_a^*, I_s^*, W^*) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0 \right) \quad (3.15)$$

The model's basic reproduction number, R_0 is obtained by using the next generation technique described in [41, 42]. We use the same approach that was used in [41] and adopting the same matrix notations for new terms and transfer terms, and the matrices for new infection and transfer terms between compartments are respectively given by

$$\mathcal{F} = \begin{bmatrix} \lambda S \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \mathcal{V} = \begin{bmatrix} Q_1 E \\ -\rho\epsilon E - \sigma_2 I_s + Q_2 I_a \\ -(1-\rho)\epsilon E - \sigma_1 I_a + Q_3 I_s \\ -\phi I_s + Q_4 H \\ -\xi_1 I_a - \xi_2 I_s + \varphi W \end{bmatrix} \quad (3.16)$$

The Jacobian matrices evaluated at the disease-free equilibrium respectively given as:

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\beta\pi}{K_W\mu} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} Q_1 & 0 & 0 & 0 & 0 \\ -\rho\epsilon & Q_2 & -\sigma_2 & 0 & 0 \\ -(1-\rho)\epsilon & -\sigma_1 & Q_3 & 0 & 0 \\ 0 & 0 & -\phi & Q_4 & 0 \\ 0 & -\xi_1 & -\xi_2 & 0 & \varphi \end{bmatrix}. \quad (3.17)$$

The computed V inverse (V^{-1}) is

$$V^{-1} = \begin{pmatrix} \frac{1}{Q_1} & 0 & 0 & 0 & 0 \\ \frac{\epsilon[\rho Q_3 + (1-\rho)\sigma_2]}{Q_1 Q_2 Q_3 (1-\phi_1)} & \frac{1}{Q_2 (1-\phi_1)} & \frac{\sigma_2}{Q_2 Q_3 (1-\phi_1)} & 0 & 0 \\ \frac{\epsilon[\rho\sigma_1 + (1-\rho)Q_2]}{Q_1 Q_2 Q_3 (1-\phi_1)} & \frac{\sigma_1}{Q_2 Q_3 (1-\phi_1)} & \frac{1}{Q_3 (1-\phi_1)} & 0 & 0 \\ \frac{\phi\epsilon[\rho Q_3 + (1-\rho)\sigma_2]}{Q_1 Q_2 Q_3 Q_4 (1-\phi_1)} & \frac{\phi\sigma_1}{Q_2 Q_3 Q_4 (1-\phi_1)} & \frac{\phi}{Q_3 Q_4 (1-\phi_1)} & \frac{1}{Q_4} & 0 \\ \frac{\epsilon[\rho(Q_3\xi_1 + \xi_2\sigma_1) + (1-\rho)(\xi_1\sigma_2 + Q_2\xi_2)]}{\varphi Q_1 Q_2 Q_3 (1-\phi_1)} & \frac{\xi_1 Q_3 + \xi_2\sigma_1}{\varphi Q_2 Q_3 (1-\phi_1)} & \frac{\xi_2 Q_2 + \xi_1\sigma_2}{\varphi Q_2 Q_3 (1-\phi_1)} & 0 & \frac{1}{\varphi} \end{pmatrix}.$$

The basic reproduction number is given as the spectral radius of the matrix FV^{-1} so that

$$\mathcal{R}_0 = \rho(FV^{-1}) = \mathcal{R}_{01} + \mathcal{R}_{02} \quad (3.18)$$

where

$$\begin{cases} \mathcal{R}_{01} = \frac{\frac{\beta\pi}{\mu K_W} \rho\epsilon(\xi_1 Q_3 + \xi_2\sigma_1)}{\varphi Q_1 Q_2 Q_3 (1-\phi_1)} \\ \mathcal{R}_{02} = \frac{\frac{\beta\pi}{\mu K_W} (1-\rho)\epsilon(\xi_2 Q_2 + \xi_1\sigma_2)}{\varphi Q_1 Q_2 Q_3 (1-\phi_1)}. \end{cases} \quad (3.19)$$

The term $\Phi_1 = \frac{\sigma_1\sigma_2}{Q_2 Q_3}$ is the proportion of individuals who move back and forth between the compartments I_a and I_s .

$\mathcal{R}_0$ is sum of the components of the reproduction number representing the contribution of the environment, human to human due to I_a and I_s and human and environment.

Following Theorem 2 in [41], determining $\mathcal{R}_0$ using the next generation matrix method assumes the model's disease-free equilibrium is locally stable. This leads to the following theorem

Theorem 3. *The disease-free equilibrium of the system (3.3) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$ and unstable otherwise.*

Proof. To find the disease-free equilibrium's local stability, we consider a Jacobian matrix and evaluate it at the disease-free equilibrium. The Jacobian matrix is given by

$$J(\mathcal{E}) = \begin{bmatrix} -\lambda - \mu & 0 & 0 & 0 & 0 & \omega & \frac{\beta S(1 - \frac{KW}{K+W})}{K+W} \\ \lambda & -Q_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & \rho\epsilon & -Q_2 & \sigma_2 & 0 & 0 & 0 \\ 0 & (1 - \rho)\epsilon & \sigma_1 & -Q_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & \phi & -Q_4 & 0 & 0 \\ 0 & 0 & \gamma_1 & 0 & \gamma_2 & -Q_5 & 0 \\ 0 & 0 & \xi_1 & \xi_2 & 0 & 0 & -\varphi \end{bmatrix}.$$

When we evaluate the Jacobian at the disease-free equilibrium, we get

$$J(\mathcal{E}_0) = \begin{bmatrix} -\mu & 0 & 0 & 0 & 0 & \omega & \frac{\beta\pi}{\mu K} \\ \lambda & -Q_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & \rho\epsilon & -Q_2 & \sigma_2 & 0 & 0 & 0 \\ 0 & (1 - \rho)\epsilon & \sigma_1 & -Q_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & \phi & -Q_4 & 0 & 0 \\ 0 & 0 & \gamma_1 & 0 & \gamma_2 & -Q_5 & 0 \\ 0 & 0 & \xi_1 & \xi_2 & 0 & 0 & -\varphi \end{bmatrix}.$$

We consider stability by computing the eigenvalues of the Jacobian evaluated at disease-free equilibrium (3.2.3) and the characteristic polynomial is

$$P(x) = (-Q_4 - x)(-Q_5 - x)(-\varphi - x)(-\mu - x)[x^2 + x(Q_2 + Q_3) + Q_2Q_3 - \sigma_1\sigma_2] = 0. \quad (3.20)$$

Note that if all the coefficients of the polynomial are positive then the roots of the polynomial are negative. The eigenvalues are $x = -Q_4 < 0$, $x = -Q_5$, $x = -\varphi$, $x = -\mu$ and the other eigenvalues are obtained as follows

$$x = \frac{-(Q_2 + Q_3) \pm \sqrt{(Q_2 + Q_3)^2 - 4(Q_2Q_3 - \sigma_1\sigma_2)}}{2}$$

which reduces to

$$x = \frac{-(Q_2 + Q_3) \pm \sqrt{(Q_2 - Q_3)^2 + 4\sigma_1\sigma_2}}{2}.$$

Note that $(Q_2 + Q_3) > \sqrt{(Q_2 - Q_3)^2 + 4\sigma_1\sigma_2}$. Then the roots for the polynomial are $x = \frac{-(Q_2 + Q_3) + \sqrt{(Q_2 - Q_3)^2 + 4\sigma_1\sigma_2}}{2} < 0$ or $x = \frac{-(Q_2 + Q_3) - \sqrt{(Q_2 - Q_3)^2 + 4\sigma_1\sigma_2}}{2} < 0$. Since all the eigenvalues are negative, we can conclude that the disease-free equilibrium is locally asymptotically stable when $\mathcal{R}_0 < 1$ and unstable otherwise. $\square$

3.2.4 Global stability of the disease-free steady state

We apply the following theorem to prove the global stability of the disease-free equilibrium when $\mathcal{R}_0 < 1$.

Theorem 4. *The disease-free equilibrium of the system (3.3) is globally asymptotically stable when $\mathcal{R}_0 < 1$ and unstable otherwise.*

Proof. Let

$$V(E, I_a, I_s, H, W) = \alpha_1 E + \alpha_2 I_a + \alpha_3 I_s + \alpha_4 H + \alpha_5 W$$

be a candidate Lyapunov function for some non-negative coefficients $\alpha_i, i = 1, \dots, 5$. We differentiate the Lyapunov function and substitute the relevant terms as follows;

$$\begin{aligned} \frac{dV}{dt} &= \alpha_1 \frac{dE}{dt} + \alpha_2 \frac{dI_a}{dt} + \alpha_3 \frac{dI_s}{dt} + \alpha_4 \frac{dH}{dt} + \alpha_5 \frac{dW}{dt}, \\ &= \alpha_1 [\hat{\lambda}(s)S - Q_1 E] + \alpha_2 [\rho \epsilon E - Q_2 I_a + \sigma_2 I_s] + \alpha_3 [(1 - \rho) \epsilon E + \sigma_1 I_a - Q_3 I_s] + \alpha_4 [\phi I_s - Q_4 H] \\ &\quad + \alpha_5 [\xi_1 I_a + \xi_2 I_s - \varphi W], \\ &\leq \alpha_1 \left[\frac{\beta W \frac{\pi}{\mu}}{K + W} - Q_1 E \right] + \alpha_2 [\rho \epsilon E - Q_2 I_a + \sigma_2 I_s] + \alpha_3 [(1 - \rho) \epsilon E + \sigma_1 I_a - Q_3 I_s] \\ &\quad + \alpha_4 [\phi I_s - Q_4 H] + \alpha_5 [\xi_1 I_a + \xi_2 I_s - \varphi W]. \end{aligned}$$

We note that $S \leq \frac{\pi}{\mu}$ and $\frac{1}{K+W} < \frac{1}{K}$. As a result, the Lyapunov function's derivative becomes

$$\frac{dV}{dt} \leq [\alpha_2 \rho \epsilon + \alpha_3 (1 - \rho) \epsilon] E + [\alpha_3 \sigma_1 + \alpha_5 \xi_1 - \alpha_2 Q_2] I_a + [\alpha_2 \sigma_2 + \alpha_5 \xi_2 + \alpha_4 \phi - \alpha_3 Q_3] I_s - \alpha_4 Q_4 H + \left[\alpha_1 \frac{\beta \pi}{\mu K} - \alpha_5 \varphi \right] W.$$

When we set the coefficients of I_a, I_s, H and W to zero, we obtain

$$\begin{cases} \alpha_1 = \mu \varphi K, \\ \alpha_2 = \frac{\alpha_3 \sigma_1 + \frac{\beta \pi \xi_1}{K}}{Q_2}, \\ \alpha_3 = \frac{\frac{\beta \pi \sigma_1 (\xi_1 \sigma_2 + \xi_2 Q_2)}{Q_2 Q_3 (1 - \phi_1)} + \frac{\beta \pi \xi_1}{K}}{Q_2}, \\ \alpha_4 = 0, \\ \alpha_5 = \beta \pi. \end{cases} \quad (3.21)$$

The coefficients of the Lyapunov function's derivative are substituted, and the result is

$$\frac{dV}{dt} \leq \left[\frac{\rho \epsilon [\sigma_1 \beta \pi (\xi_1 \sigma_2 + \xi_2 Q_2) + \beta \pi \xi_1 (1 - \phi_1) Q_2 Q_3]}{Q_2^2 Q_3 (1 - \phi_1)} + \frac{(1 - \rho) \epsilon (\xi_1 \sigma_2 + \xi_2 \sigma_2)}{Q_2 Q_3 (1 - \phi_1)} - \mu \varphi K \right] E \quad (3.22)$$

which simplifies to

$$\frac{dV}{dt} \leq \mu \varphi K (\mathcal{R}_0 - 1) E.$$

We observe that $\frac{dV}{dt} < 0$ when $\mathcal{R}_0 < 1$. The disease-free equilibrium E_0 is stable and $\frac{dV}{dt} = 0$ when $E = 0$ or when $\mathcal{R}_0 = 1$. By the LaSalle invariance principle [43], this indicates that equilibrium E_0 is globally stable when $\mathcal{R}_0 < 1$. Moreover, we see that the derivative of Lyapunov is positive when $\mathcal{R}_0 > 1$. Therefore, the disease-free equilibrium is unstable if $\mathcal{R}_0 > 1$. $\square$

Theorem 5. *The model has a unique disease persistent equilibrium if $\mathcal{R}_0 > 1$.*

Proof. Let the steady state $E = (S^*, E^*, I_a^*, I_s^*, H^*, R^*, W^*)$ at the endemic equilibrium. At the

equilibrium points, we have that

$$0 = \pi + \omega R^* - \lambda S^* - \mu S^*, \quad (3.23a)$$

$$0 = \lambda S^* - Q_1 E^*, \quad (3.23b)$$

$$0 = \rho \epsilon E^* + \sigma_2 I_s^* - Q_2 I_a^* \quad (3.23c)$$

$$0 = (1 - \rho) \epsilon E^* + \sigma_1 I_a^* - Q_3 I_s^*, \quad (3.23d)$$

$$0 = \phi I_s^* - Q_4 H^*, \quad (3.23e)$$

$$0 = \gamma_2 H^* + \gamma_1 I_a^* - Q_5 R^*, \quad (3.23f)$$

$$0 = \xi_1 I_a^* + \xi_2 I_s^* - \varphi W^*, \quad (3.23g)$$

$$(3.23h)$$

From equation (3.23e)

$$I_s^* = \frac{Q_4}{\phi} H^*. \quad (3.24)$$

From equation (3.23d)

$$I_s^* = \frac{(1 - \rho) \epsilon E^* + \sigma_1 I_a^*}{Q_3}. \quad (3.25)$$

From equation (3.23c)

$$I_a^* = \frac{\rho \epsilon E^* + \sigma_2 I_s^*}{Q_2}. \quad (3.26)$$

We now substitute equation (3.26) into equation (3.25) to get

$$I_s^* = \frac{((1 - \rho) Q_2 \epsilon + \sigma_1 \rho \epsilon) E^*}{Q_2 Q_3 [1 - \Phi_1]}. \quad (3.27)$$

We can now express I_a^* in terms of E^* .

We substitute equation (3.27) into equation (3.26) to obtain

$$I_a^* = \frac{[\rho \epsilon Q_3 + \sigma_2 (1 - \rho) \epsilon] E^*}{Q_2 Q_3 [1 - \Phi_1]}. \quad (3.28)$$

Expressing H in terms of E^* , from (3.23e)

$$H^* = \frac{\phi}{Q_4} I_s^* \quad (3.29)$$

and substituting (3.27) into (3.29) we get

$$H^* = \frac{Q_4 [(1 - \rho) Q_2 \epsilon + \sigma_1 \rho \epsilon] E^*}{\phi Q_2 Q_3 [1 - \Phi_1]}. \quad (3.30)$$

We now express R^* in terms of E^* , from equation (3.23f) to obtain

$$R^* = \frac{\gamma_2 H^* + \gamma_1 I_a^*}{Q_5}. \quad (3.31)$$

Substituting equation (3.30) and equation (3.28) into equation (3.31) we obtain

$$R^* = \Phi_2 E^* \quad (3.32)$$

$$\text{where } \Phi_2 = \frac{\gamma_2 Q_4 [(1-\rho)Q_2 \epsilon + \sigma_1 \rho \epsilon] + \gamma_1 \phi [\rho Q_3 + \sigma_2 (1-\rho)] \epsilon}{\phi Q_2 Q_3 Q_5 [1-\Phi_1]}.$$

From (3.23g)

$$W^* = \frac{\xi_1 I_a^* + \xi_2 I_s^*}{\varphi}. \quad (3.33)$$

We substitute equation (3.28) and (3.27) into (3.33) to obtain

$$W^* = \Phi_3 E^* \quad (3.34)$$

$$\text{where } \Phi_3 = \frac{\xi_1 [\rho \epsilon Q_3 + \sigma_2 (1-\rho) \epsilon] + \xi_2 [(1-\rho)Q_2 \epsilon + \sigma_1 \rho \epsilon]}{\varphi Q_2 Q_3 [1-\Phi_1]}.$$

We now express λ^* in terms of E^*

$$\lambda^* = \frac{\beta \Phi_3 E^*}{K_W + \Phi_3 E^*}. \quad (3.35)$$

Combining equation (3.23a) and equation (3.23b) we get

$$S^* = \frac{\pi}{\mu} - \frac{(Q_1 - \omega \Phi_2) E^*}{\mu} \quad (3.36)$$

We now substitute expression (3.35) and expression (3.36) into equation (3.23b) to obtain

$$0 = \frac{\beta \Phi_3 E^*}{K_W + \Phi_3 E^*} \left(\frac{\pi}{\mu} - \frac{(Q_1 - \omega \Phi_2) E^*}{\mu} \right) - Q_1 E^* \quad (3.37)$$

We note that $E^* = 0$ is one of the solutions of the above equation and this corresponds to the disease-free equilibrium. If $E^* \neq 0$, we have

$$0 = \frac{\beta \Phi_3}{K_W + \Phi_3 E^*} \left(\frac{\pi}{\mu} - \frac{(Q_1 - \omega \Phi_2) E^*}{\mu} \right) - Q_1 \quad (3.38)$$

which can be re-arranged to obtain

$$E^* = \frac{\mu Q_1 K_W [R_0 - 1]}{[\beta \Phi_3 (Q_1 - \omega \Phi_2) + \mu Q_1 Q_3]}. \quad (3.39)$$

Suppose the immunity does not wane during the modelling time, that is $\omega = 0$, the expression for E^* reduces to

$$E^* = \frac{\mu Q_1 K_W [R_0 - 1]}{[\beta \Phi_3 Q_1 + \mu Q_1 Q_3]}, \quad (3.40)$$

and if the immunity wanes the expression of E^* will be (3.39). Note the term $Q_1 - \omega\Phi_2$ in the expression (3.39) which indicated that in the case of waning of immunity we would be dividing by a smaller denominator which implies that a higher number of exposed individuals at the endemic equilibrium. Then the sign of (3.39) is determined by the magnitude of R_0 . We note that when $R_0 > 1$, then $E^* > 0$ which indicates the existence of an endemic equilibrium on the other hand, when $R_0 \leq 1$, the expression E^* will be non positive which indicates non existence of the endemic equilibrium, then the rest of the state variables can be found by substituting E^* . Therefore the model system of equations (3.3) has a unique endemic equilibrium when $R_0 > 1$. $\square$

3.3 Numerical Results

3.3.1 Parameter Estimation

The average life expectancy in Africa for males is 62 years and for females is 65 years and average life expectancy globally for males is 70 years and for females is 75 years [44]. In Botswana the current life expectancy for males is 63.6 years and for females is 68.4 years and the average life expectancy is 66.1 years [45] corresponding to mortality rate of 0.0000431 per day, 0.0000401 per day and 0.0000414 per day respectively. According to [8] exposed individuals take about 12.5 – 16.7 days to become infectious and we chose our infectious rate to be $\epsilon = 0.075$ per day. We estimated that about 20% of exposed individuals become symptomatically infected. Patients of Gnathostomiasis may be symptomatically infected or asymptotically infected. Symptoms of Gnathostomiasis occur when the larvae is at the third-stage [4]. According to Strady *et al.* (2009) [46] symptoms shows from 24 – 48 hours and median being 2 months and while Hale *et al.* (2009) [8] indicated that symptoms showed after 12 – 14 days in two fisher men. For our numerical simulations, we considered σ_1 to 0.165 per day and we estimated the rate at which symptomatically infected become asymptotically infected to be between 6 days and 60 days and our nominal value of σ_2 to be 0.165 per day. The main cause of mortality is due to invasion of the central nervous system [6]. The additional mortality rate due to Gnathostomiasis, being δ_1 and δ_2 are 0.0625 and 0.056 per day respectively [47] and Germaine [6] also added that mortality rate of Gnathostomiasis patients is between 8–25%. We estimated that symptomatically infected individuals go to hospitals 2 days after after showing symptoms and maximum of 30 days. The recovery rate for asymptotically infected, γ_1 , is estimated to be between 15 days and 240 days and we chose 0.025 per day to be our nominal value. According to Hale *et al.* (2009) [8] South African oldman was treated with antibiotics on September 5 and on the 14th of the same month he was recovered, that is a treated individual took 9 days to recover. In addition, Strady *et al.* (2009) [46] reported that the recovery was a month. In this work, we considered an average recovery rate of 20 days which corresponds to $\gamma_2 = 0.05day^{-1}$. Asymptotically and symptomatically infected individuals shed the pathogen to the environment at a rate of 0.2445 per day and 0.03315 per day respectively. The mortality rate of the pathogen is estimated to be between 250 days and 40000 days, and we choose φ to be 0.095 per day. Individuals who recover from Gnathostomiasis become susceptible again, we estimated it to be in range (0.00274, 0.033).

Parameter	Range	Nominal values	Units	Source
π		4	personsday ⁻¹	Assumed
μ	[0-0.02]	$\frac{1}{66.1 \times 365}$	day ⁻¹	[45]
ρ	[0-1]	0.8	day ⁻¹	Assumed
ϵ	[0.06-0.08]	0.075	day ⁻¹	[8]
σ_1	[0.01667-0.155]	0.165	day ⁻¹	[8]
σ_2	[0.01667-0.155]	0.165	day ⁻¹	Assumed
δ_1	[0-1]	0.0625	day ⁻¹	[47]
δ_2	[0.04-0.25]	0.056	day ⁻¹	[6, 47]
γ_1	[0.0167-0.067]	0.025	day ⁻¹	Assumed
γ_2	[0.033-0.11]	0.05	day ⁻¹	[46]
ω	[0.00274-0.033]	0.0153	day ⁻¹	Assumed
ξ_1	[0.017-0.63]	0.12445	day ⁻¹	Assumed
ξ_2	[0.0167-0.63]	0.13315	day ⁻¹	Assumed
φ	[0.000228-0.000274]	0.000249	day ⁻¹	[6]
ϕ	[0.0033-0.2]	0.1	day ⁻¹	Assumed

Table 3.3: Nominal values of the model's parameters

3.3.2 Sensitivity analysis

Sensitivity analysis is a method for assessing model uncertainty [21]. Sensitivity analysis can be used to discover important model parameters and to better the model structure [21, 22]. In this work, we use the Latin Hypercube Sampling scheme (LHS) to do sensitivity analysis. We conducted our sensitivity analysis to the model using the LHS, a stratified Monte Carlo sampling technique that allows simultaneous sampling of the multi-dimensional parameter space. [28]. With 1000 simulations each run, the partial rank correlation coefficients (PRCCs) were calculated. Blower and Dowlatabadi, (1994) [28] indicated that the relationship between the parameter and the output is indicated by the PRCCs sign. The PRCCs for the sampled parameters were calculated, they ranged from -1 and 1 [28]. We computed p -values for each parameter in order to identify which ones are crucial. The Fisher's transformation $\rho(r) = 0.5 \log(\frac{1+r}{1-r})$, which is typically used to convert the skew distribution into a normal distribution, was performed on the PRCCs before computing used the p-values. The parameters having a significant p-value of $p < 0.05$ are shown in the Table by "TRUE," whereas those with a non-significant p-value of $p > 0.05$ are denoted by "FALSE."

Sensitivity analysis based on the reproduction number

As PRCCs demonstrate the extent to which each parameter influences the number of infections, the objective of this analysis is to identify variables that have the greatest influence on the reproduction number [48]. When positive PRCC parameters are increased, reproduction number ($\mathcal{R}_0$) increases, and when the process described parameters with negative PRCC are increased, $\mathcal{R}_0$ decreases [48]. The resulting Partial Rank Correlation Coefficients (PRCCs) were calculated using MATLAB, and tornado plot and box plot were also produced. The tornado plot of the PRCCs shows the significance of each parameter's uncertainty in influencing the variability in the time to clear the Gnathostomiasis infection. The PRCC values' sign reveals the qualitative relationship between the model's input and output [29]. When the relevant model input rises, a positive PRCC value implies that the model output will likewise increase, whereas a negative

PRCC value indicates a negative correlation between the model input and output [29]. In our case, if the PRCC is positive, it means that as the process described by the corresponding parameter is enhanced, the number of Gnathostomiasis cases will rise as well, and if it is negative, it means the number of Gnathostomiasis cases decline and can be contained. The contribution of the model input to the model output is determined by the size of the PRCC sensitivity [29]. From the tornado plot, the contact rate β was observed as a parameter that has the highest potential for worsening the disease when increased, followed by shedding rates, ξ_1, ξ_2 . This can be prevented by avoiding coming in contact with contaminated water sources as well as avoiding eating raw meat from hosts of the disease causing pathogen.

We also observed that hospitalisation rate ϕ , φ which is the rate of decay of the pathogen and recovery rate γ_1 are some of the parameters that, when maximised, have the ability to contain the Gnathostomiasis disease. A decrease in the number of infected individuals is due to increase in recovery rates. Due to small magnitude of PRCC, ω have very little effect on the reproduction number.

From the boxplot the minimum value of R_0 is 0.0066, the lower quartile is approximately 0.46, the upper quartile is approximately 1.88 with a median of approximately 0.998 and the maximum of 4.002.

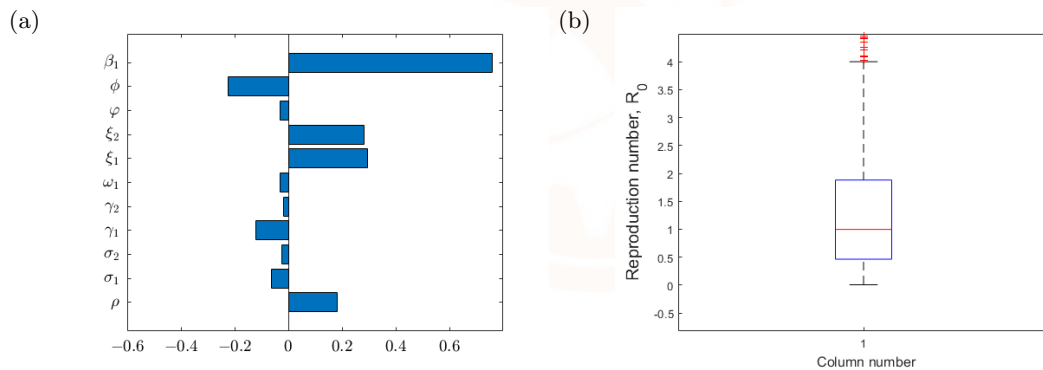


Figure 3.2: Tornado plot and box plot displaying the Partial Rank Correlation Coefficients (PRCCs) for the whole range of model parameters in Table (3.3)

The p-values for each parameter were calculated using the R. The Fisher's transformation $\rho(r) = 0.5 \log(\frac{1+r}{1-r})$, which is normally used to convert the skew distribution into a normal distribution, was used to compute the p-values.

Additionally, we produced scatter plots of Monte Carlo simulations for the parameters that most significantly impacted the reproduction number. We observed that R_0 is monotone increasing with β, ξ_1 and ξ_2 and monotone decreasing with ϕ .

To determine whether pairs of parameters are significantly different, a pairwise comparison of parameters with p-values less than 0.5 was conducted. We observe that most parameters are significantly different. When compared to other parameters, we find that the parameters $\rho, \sigma_1, \gamma_1, \xi_1, \phi$ and β are significant. Using the FDR-adjusted p-values we present our findings

Parameter	PRCC	p-value	Significance
ρ	0.2713	0.000000e+00	TRUE
σ_1	-0.1849	7.681700e-09	TRUE
σ_2	0.0102	9.149796e-01	FALSE
γ_1	-0.1265	1.014057e-04	TRUE
γ_2	-0.0052	9.572519e-01	FALSE
ω	0.0130	9.149796e-01	FALSE
ξ_1	0.3148	0.000000e+00	TRUE
ξ_2	0.2921	0.000000e+00	TRUE
φ	0.0010	9.749373e-01	FALSE
ϕ	-0.2169	9.643442e-12	TRUE
β	0.7515	0.000000e+00	TRUE

Table 3.4: Parameter PRCC Significance (FDR Adjusted P-values)

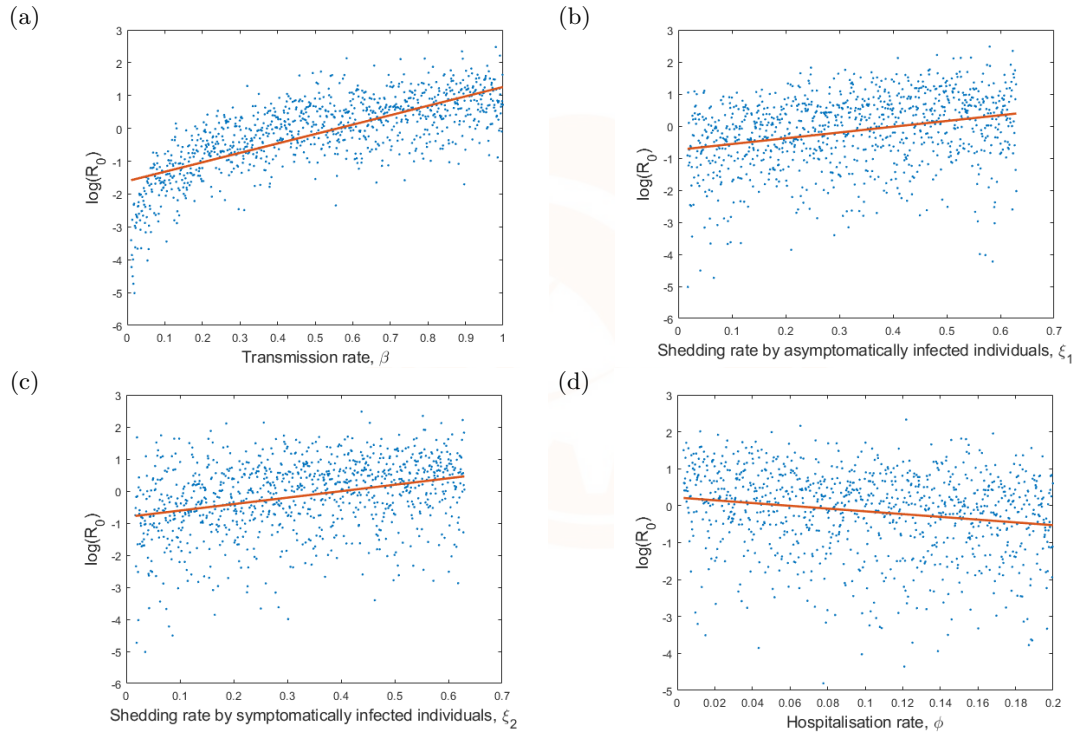


Figure 3.3: Monte Carlo simulations for parameters with the greatest PRCC magnitude

	ρ	σ_1	γ_1	ξ_1	ξ_2	ϕ	β
ρ		0	0	0.29034	0.61572	0	0
σ_1			0.18352	0	0	0.45878	0
γ_1				0	0	0.038372	0
ξ_1					0.57858	0	0
ξ_2						0	0
ϕ							0
β							

Table 3.5: Pairwise PRCC Comparisons (Unadjusted P-values)

	ρ	σ_1	γ_1	ξ_1	ξ_2	ϕ	β
ρ		0	0	0.33873	0.61572	0	0
σ_1			0.22670	0	0	0.50708	0
γ_1				0	0	0.05036	0
ξ_1					0.60751	0	0
ξ_2						0	0
ϕ							0
β							

Table 3.6: **Pairwise PRCC Comparisons (FDR Adjusted P-values)**

	ρ	σ_1	γ_1	ξ_1	ξ_2	ϕ	β
ρ		TRUE	TRUE	FALSE	FALSE	TRUE	TRUE
σ_1			FALSE	TRUE	TRUE	FALSE	TRUE
γ_1				TRUE	TRUE	FALSE	TRUE
ξ_1					FALSE	TRUE	TRUE
ξ_2						TRUE	TRUE
ϕ							TRUE
β							

Table 3.7: **Parameters different after FDR adjustment?**

in Table (3.7), where TRUE denotes a significant difference between the parameters compared and FALSE denotes no significant difference.

3.3.3 Sensitivity analysis based on the full model

The reproduction number is an important factor in determining whether a disease will spread or be contained in the community, but the sensitivity analysis results from above subsection do not take into account situations where parameter values affect the dynamics of the disease differently at various times and more so the cases for which the parameters describing vital processes may not be directly linked to the reproduction number. Using the approach described in Marino *et al.*(2008) [21], we do a time-varying sensitivity analysis of the model parameters. We analyze the PRCCs of model parameters with regard to certain state variables at chosen time periods in the epidemic in order to better know the processes that directly or indirectly influence particular state variables. PRCCs were drawn out at different time intervals being $T = 10$ days, $T = 100$ days and $T = 250$ days. P-values were computed to find their significance. The parameters with significant p-value, that is $p < 0.05$ are indicated by "TRUE" in the table and for $p > 0.05$ are not significant and they are indicated by "FALSE" in the Table.

PRCCs of parameters based on asymptotically infected population

Over continuous time, we notice that the parameters such as σ and ρ are sensitive on asymptotically infected population. The parameters γ_2, ξ_2, ω and β appear to be both sensitive and not significantly sensitive to the change in the asymptotically infected population continuously over time. The parameters like γ_2 and ξ_2 are sensitive at the beginning and become not significantly sensitive. β is sensitive around 10 days and 100 days and becomes not significantly sensitive as time goes on. ω kept on changing sensitivity, it started as not significantly sensitive

Variable	T=10			T = 100			T =250		
	PRCC	p-value	significance	PRCC	p-value	significance	PRCC	p-value	significance
ρ	0.08169	1.853e-02	TRUE	0.05720	1.131649e-01	FALSE	0.05561	0.08031	FALSE
σ_1	-0.51749	0.000e+00	TRUE	-0.86607	0.000000e+00	TRUE	-0.88554	0.00000	TRUE
σ_2	0.91492	0.000e+00	TRUE	0.93609	0.000000e+00	TRUE	0.94809	0.00000	TRUE
γ_1	-0.18833	4.665e-09	TRUE	-0.57850	0.000000e+00	TRUE	-0.55040	0.00000	TRUE
γ_2	0.06983	4.396e-02	TRUE	0.24871	2.849572e-15	TRUE	0.33098	0.00000	TRUE
ω	0.01827	6.226e-01	FALSE	0.60701	0.000000e+00	TRUE	0.28406	0.00000	TRUE
ξ_1	-0.04046	2.486e-01	FALSE	-0.05458	1.183444e-01	FALSE	-0.05436	0.08735	FALSE
ξ_2	0.05947	8.443e-02	FALSE	0.02633	4.987016e-01	FALSE	0.03443	0.27920	FALSE
φ	0.01094	7.311e-01	FALSE	0.01826	6.228114e-01	FALSE	0.02044	0.52060	FALSE
ϕ	-0.51536161	0.000e+00	TRUE	-0.79426445	0.000000e+00	TRUE	-0.79696029	0.00000	TRUE
β	0.81018246	0.000e+00	TRUE	-0.01256287	6.930622e-01	FALSE	0.03378013	0.28840	FALSE

Table 3.8: Asymptomatic class parameter PRCC Significance(FDR Adjusted P-values)

and became sensitive, and switched to not significantly sensitive again. Parameters such as $\sigma_1, \gamma_1, \xi_1, \varphi$ are ϕ are observed to be not significantly sensitive throughout the continuous time.

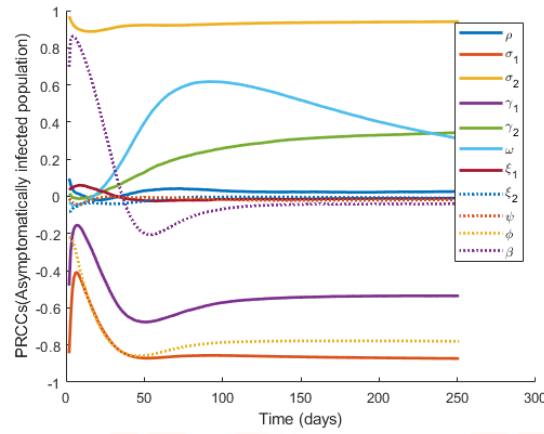


Figure 3.4: Sensitivity analysis PRCCs of asymptotically infected class.

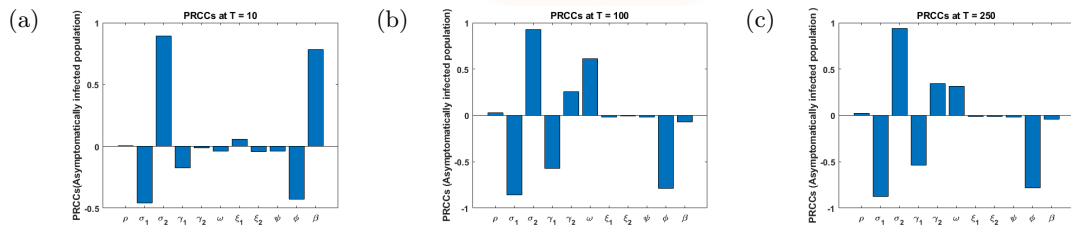


Figure 3.5: PRCCs of asymptotically infected class at T = 10 days, T = 100 days, and T = 250 days.

PRCCs of parameters based on symptomatically infected population

Parameters such as $\rho, \sigma_1, \sigma_2, \gamma_1, \varphi$ and ϕ are observed not to be significantly sensitive to changes in the symptomatically infected population while γ_2 is sensitive over the entire modelling time. The parameters ξ_2, ω and β appear to be both sensitive and not sensitive to changes in the symptomatically infected population during specific times of the epidemic. ω is observed not be sensitive at the beginning of the disease but becomes sensitive as time progress. For ξ_2 and β , they were sensitive when $t = 10$ days and switched to less sensitive as time goes on. Increasing

Variable	T=10			T = 100			T =250		
	PRCC	p-value	significance	PRCC	p-value	significance	PRCC	p-value	significance
ρ	0.033651287	2.902e-01	FALSE	-0.007647614	8.101e-01	FALSE	0.0000257412	0.9994	FALSE
σ_1	0.243707885	5.551e-15	TRUE	0.180070971	1.068e-08	TRUE	0.0246651550	0.8036	FALSE
σ_2	-0.583678027	0.000e+00	TRUE	-0.160011743	3.966e-07	TRUE	-0.0011031840	0.9994	FALSE
γ_1	-0.023224001	4.655e-01	FALSE	-0.105848081	8.442e-04	TRUE	0.0161440730	0.8415	FALSE
γ_2	0.056095705	7.770e-02	FALSE	0.538668658	0.000e+00	TRUE	0.7040683780	0.0000	TRUE
ω	-0.019823128	5.334e-01	FALSE	0.864884370	0.000e+00	TRUE	0.5865995370	0.0000	TRUE
ξ_1	-0.007327639	8.179e-01	FALSE	-0.058299531	6.671e-02	FALSE	-0.0633266810	0.1275	FALSE
ξ_2	0.050498953	1.123e-01	FALSE	-0.008002597	8.015e-01	FALSE	0.0016625260	0.9994	FALSE
φ	0.041151785	1.958e-01	FALSE	0.033966363	2.857e-01	FALSE	0.0393995840	0.4742	FALSE
ϕ	-0.804606817	0.000e+00	TRUE	-0.949628955	0.000e+00	TRUE	-0.9667727160	0.0000	TRUE
β	0.810461579	0.000e+00	TRUE	-0.067117467	3.471e-02	TRUE	-0.0180475240	0.8415	FALSE

Table 3.9: Symptomatic class parameter PRCC Significance(FDR Adjusted p-values)

transmission rate(ϵ), force of infection(λ) and recruitment rate(π) may aggravate the disease. However, increasing ϕ , γ_1 and γ_2 has potential of alleviating the disease burden.

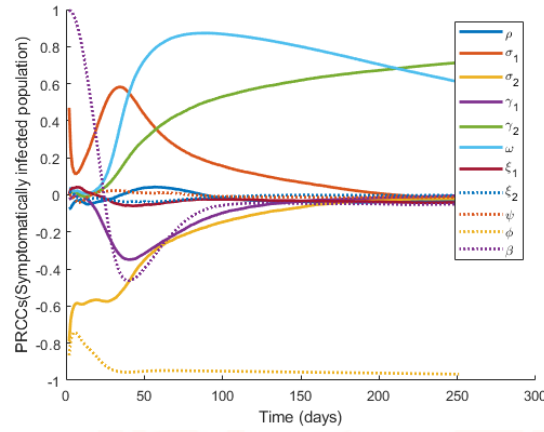


Figure 3.6: Sensitivity analysis PRCCs of symptomatically infected class.

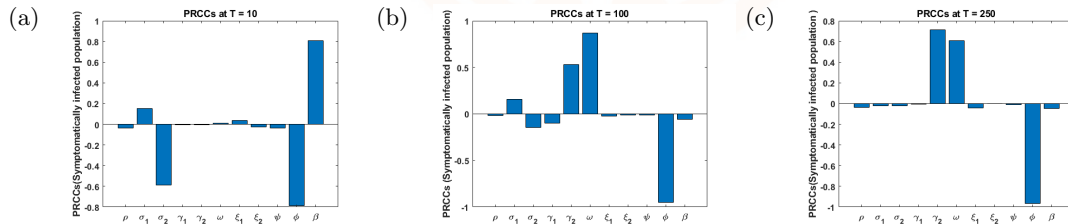


Figure 3.7: PRCCs of symptomatically infected class at T = 10 days, T = 100 days, and T = 250 days.

3.3.4 Numerical simulations

In this subsection, the aim is to examine the effect of some selected parameters, the selected parameters were contact rate(β) and shedding rate (ξ_1). We varied the values of contact rate and shedding rate (ξ_1) for the infected population. The two parameters were also combined to investigate their combined effect on the disease burden. To examine the effect of contact rate(β) and shedding rate (ξ_1), we kept other parameters constant and varied values of β and ξ_1 . We computed their percentage changes, and obtained plots corresponding to the varied values of β and ξ_1 showing their effect on the infected population.

Effect of varrying contact rate, β

People tend to eat raw or uncooked food that may be contaminated with the pathogen, or wade in contaminated waters. This can be reduced by avoiding consuming raw or undercooked meat from animals that serve as hosts for *Gnathostoma*, and if it is likely that people will come into contact with contaminated water, they should wear gum boots, gloves or wash their hands frequently with clean water and soap. People should not swim or wade in *Gnathostoma* infested waters if the disease is to be contained. These precautions can reduce contact rate. To vary contact rate(β), our baseline was 0.05 and it was reduced by 50% and 98%. That is our selected values were $\beta = [0.05, 0.025, 0.001]$. We computed their percentage changes, and obtained plots corresponding to the varied values of β showing their effect on infected population. When carrying out the simulations, the two scenarios were considered, namely, (1) a case when controls are implemented right at the start of the outbreak, (see Figure (3.8a)), and (2) after some time when the disease has progressed (see Figure (3.8b)). We observed that when decreasing the value of contact rate the infected population also decreases. This shows that contact rate β is reduced the infection can be contained. For the baseline value, we observe that infected population increases and decreases after reaching the peak. We also observe that when controls are implemented near peak the infection disappears around 100 days. Implementing controls near the peak makes *Gnathostomiasis* disappears faster.

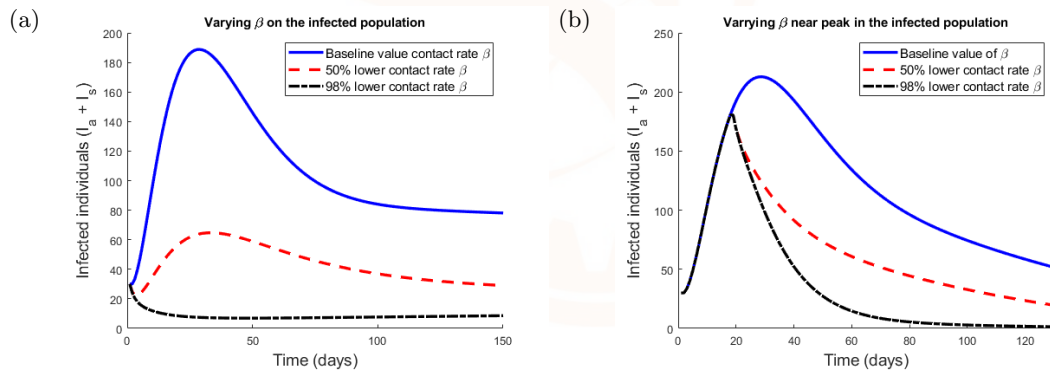


Figure 3.8: Effect of changing contact rate(β) on infected population: control at the beginning of the *Gnathostomiasis* epidemic in Figure (3.8a) and in Figure (3.8b) controls are implemented after several days

Effect of varrying shedding rate, ξ_1

Depending on the pathogen and the environment, pathogens transmitted through the environment may survive for some days outside the host. Pathogen can be shed through faeces and urine, so this can contaminate the environment and increase the chances of people being infected. To reduce shedding rate ξ_1 , people can be educated or made aware of the disease and how shedding rate can increase the disease burden. To check the effect of shedding rate (ξ_1), we vary it. Our baseline was 0.12445 and it was reduced by 20% and 60%. That is our selected values were $\xi_1 = [0.12445, 0.09956, 0.04978]$. We computed their percentage changes, obtained plots corresponding to the varied values of ξ_1 showing their effect on infected population. When carrying out the simulations, the two scenarios were considered, namely, (1) a case when controls

are implemented right at the start of the outbreak, (see Figure (3.9a)), and (2) after some time when the disease has progressed (see Figure (3.9b)). For the baseline value, we observe that infected population increases and decreases after reaching the peak. Although in both cases displayed in Figure (3.9) the disease is not contained, the disease burden is higher when controls are implemented later on the outbreak than at the beginning.

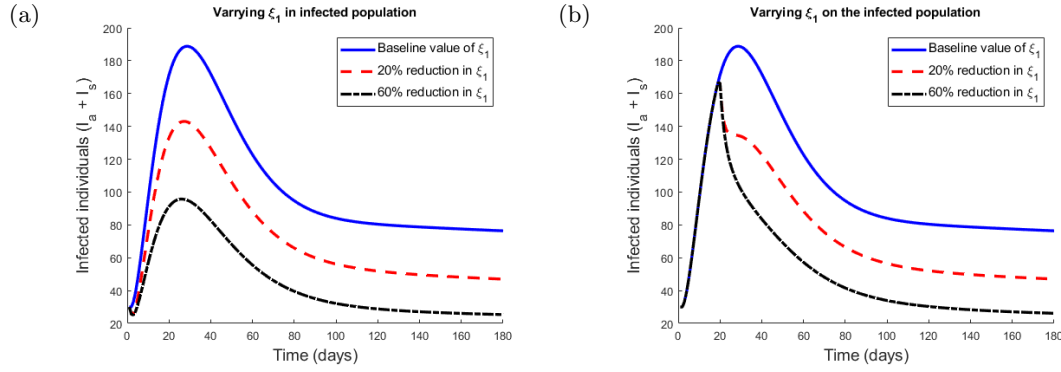


Figure 3.9: Effect of varying shedding rate(ξ_1) on infected population.

Effect of varying contact rate (β) and shedding rate(ξ_1) on infected population

On examining the effect of combining the parameters, the selected values for β were $\beta = [0.05, 0.025, 0.001]$ and for ξ_1 , selected values were $\xi_1 = [0.12445, 0.09956, 0.04978]$. When two parameters are combined, we observe that the disease can be contained in less than 100 days. We also observe that they reach peak values faster. When both controls are implemented, the infection disappears faster than when one control is implemented. This shows that all the controls should be implemented to contain the infection.

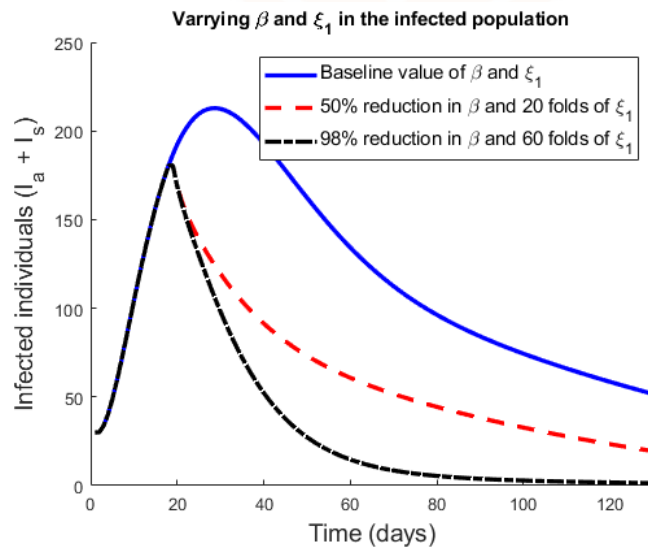


Figure 3.10: Effect of varying contact rate (β) and shedding rate(ξ_1) on infected population.

Investigating the influence of consuming contaminated food

In this subsubsection, we investigate the influence of consuming food contaminated with the pathogen on the disease burden. For this part, we focus only on the numerical simulations to investigate the dynamics of the disease. We add the new term to the force of infection, now the force of infection

$$\lambda_1 = \beta \frac{W}{K + W} + \beta_1 \frac{I_a}{K + I_a}. \quad (3.41)$$

Now the model system changes to

$$\frac{dS}{dt} = \pi + \omega R - \lambda_1 S - \mu S, \quad (3.42a)$$

$$\frac{dE}{dt} = \lambda_1 S - Q_1 E, \quad (3.42b)$$

$$\frac{dI_a}{dt} = \rho \epsilon E - Q_2 I_a + \sigma_2 I_s \quad (3.42c)$$

$$\frac{dI_s}{dt} = (1 - \rho) \epsilon E + \sigma_1 I_a - Q_3 I_s, \quad (3.42d)$$

$$\frac{dH}{dt} = \phi I_s - Q_4 H, \quad (3.42e)$$

$$\frac{dR}{dt} = \gamma_2 H + \gamma_1 I_a - Q_5 R, \quad (3.42f)$$

$$\frac{dW}{dt} = \xi_1 I_a + \xi_2 I_s - \varphi W, \quad (3.42g)$$

We investigate the influence of consuming food contaminated with the pathogen by letting our β_1 be zero and on the side β_1 not equal to zero.

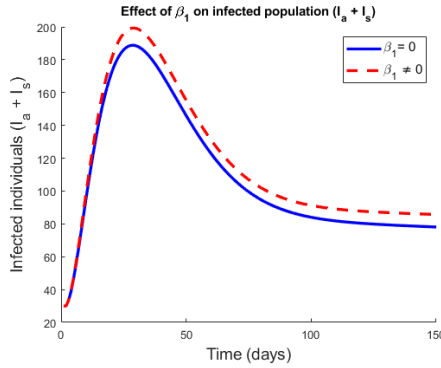


Figure 3.11: Effect of β_1 on infected population

From Figure 3.11, we observe that when $\beta_1 \neq 0$ the infected population is larger than when $\beta_1 = 0$. This implies that eating raw or undercooked food contaminated with the pathogen has a potential of worsening the disease when ignored. Eating raw or uncooked fishes should be avoided to lessen the changes of being infected with Gnathostomiasis. In addition, we note that ignoring some important aspects in the model framework can lead to underestimation of the burden of the disease. This could also negatively influence resource allocation to curtailing the spread of the disease.

3.4 Conclusion

Using a set of ordinary differential equations, we developed and analyzed a model for the transmission dynamics of Gnathostomiasis. We explored the model properties such as positivity and boundedness of solutions. Reproduction number ($\mathcal{R}_0$) was calculated and employed to determine out the local stability of the disease-free equilibrium as well as the existence of the endemic equilibrium. We found that the endemic equilibrium is unique for $\mathcal{R}_0 > 1$. We also proved that the disease-free equilibrium is globally asymptotically stable when $\mathcal{R}_0 < 1$. Sensitivity analysis and numerical simulations of the model were performed. We found that contact rate (β) was observed as a parameter that has the highest potential of worsening the disease when increased, followed by shedding rates ξ_1 and ξ_2 . We also observed that hospitalisation rate ϕ , φ which is the rate of decay of the pathogen and recovery rate (γ_1) are some of the parameters that, when maximised, have the ability to contain the disease. Due to small magnitude of PRCC, ω was predicted to have very little effect on the reproduction number. Some parameters were varried to check their effect on the infected population. We observed that we need to minimize the contact rate β and shedding rate to contain the disease. We also observed that when controls are implemented at the same time, the disease can be contained in a shorter time compared to a case when controls are implemented in a piecemeal approach.



4. Optimal Control

In this Chapter, we build an optimal control problem by incorporating several intervention measures as control variables in the Gnathostomiasis model system (3.3). We explore the effect of implementing controls on the susceptible population, asymptotically and symptomatically infected population.

4.1 Gnathostomiasis model with controls

The surgical removal of the larva is one of the recommended treatments for Gnathostomiasis. However, this is only useful when the worms are in an accessible subcutaneous tissue. Infected people can also be treated with Albendazole or Ivermectin. The following interventions are used in our model system as a Gnathostomiasis control strategy:

- reducing the contact rate,
- effective medical treatment for infected individuals and
- efforts made to reduce Gnathostomiasis from the environment.

In order to manage the dynamics of the disease, these interventions are applied as control parameters. x represents reducing the contact rate and y accounts for effective medical care for infected individuals. The third control, z accounts for efforts made to reduce Gnathostomiasis from the pathogen infested environment.

1. **Reducing contact rate:** Avoiding consuming raw or undercooked hosts, and if it is likely that people will come into contact with contaminated water, they should wear gum boots, gloves or wash their hands frequently with clean water and soap. People should not swim or wade in potentially infested freshwaters. These precautions can reduce the chances of getting infected. In the model system (3.3) the term λ will be multiplied by $(1 - x)$, where x is the control for reducing contact rate.
2. **Effective medical treatment for infected individuals:** All healthcare professionals should put the needs of their patients first in order to achieve high levels of patient satisfaction, and the recovery rates. Patients can be treated with Albendazole or Ivermectin to accelerate the recovery process. We introduce our control in the model system, so it becomes $-yH$.
3. **Efforts made to reduce Gnathostomiasis from the environment:** Disinfecting contaminated waters and enhanced hygiene practices may reduce or stop the spread of the disease. In the model system (3.3) the term φ will be replaced by $\varphi + z$, where z accounts for efforts made to reduce Gnathostomiasis from the environment by accelerating its decay.

Now, the model system (3.3) can be rebuilt as follows using the control parameters mentioned above:

$$\frac{dS}{dt} = \pi + \omega_1 R - (1-x)\lambda S - \mu S, \quad (4.1a)$$

$$\frac{dE}{dt} = (1-x)\lambda S - Q_1 E, \quad (4.1b)$$

$$\frac{dI_a}{dt} = \rho \epsilon E - Q_2 I_a + \sigma_2 I_s, \quad (4.1c)$$

$$\frac{dI_s}{dt} = (1-\rho)\epsilon E + \sigma_1 I_a - Q_3 I_s, \quad (4.1d)$$

$$\frac{dH}{dt} = \phi I_s - (\gamma_2 + \delta_2 + \mu + y)H, \quad (4.1e)$$

$$\frac{dR}{dt} = (\gamma_2 + y)H + \gamma_1 I_a - Q_5 R, \quad (4.1f)$$

$$\frac{dW}{dt} = \xi_1 I_a + \xi_2 I_s - (\varphi + z)W, \quad (4.1g)$$

where

$$\begin{cases} Q_1 = \epsilon + \mu, \\ Q_2 = \mu + \sigma_1 + \gamma_1, \\ Q_3 = \delta_1 + \mu + \sigma_2 + \phi, \\ Q_4 = \gamma_2 + \delta_2 + \mu, \\ Q_5 = \mu + \omega_1, \end{cases} \quad (4.2)$$

In an epidemiological model, the general steps for optimal control process are as follows [40]: (1) determining the model-appropriate permissible controls; (2) setting up the objective function with controls; (3) constructing the Hamiltonian; (4) evaluating costate variables (adjoint functions); and (5) identifying the threshold controls that minimize the Hamiltonian.

The objective function for our minimisation problem is given by

$$\mathcal{F}(x, y, z) = \int_0^T (aI_s + bI_a + ux^2 + vy^2 + mz^2) dt. \quad (4.3)$$

The coefficients a, b, u, v , and m in the objective cost functional that correspond to the costs over a finite time T , aI_s , and bI_a show the cost related to minimizing the infection. The relative cost weights for the corresponding control measures are u, v , and m . We assume that the costs of control is non-linear, so we use a quadratic term. The fundamental goal of investigating control measures is to reduce the number of infected while also lowering the cost of putting controls in place. In this case, we look for optimal controls x^*, y^* and z^* such that

$$\mathcal{F}(x, y, z) = \min_{x, y, z} \{ \mathcal{J}(x, y, z) | x, y, z \in \mathcal{U} \}, \quad (4.4)$$

where

$$\mathcal{U} := \{ (x, y, z) \mid x, y, z : [0, T] \rightarrow [0, 1], \forall x, y, z \}. \quad (4.5)$$

To determine the integral in (4.3), we employ the Hamiltonian constructed for the model system of equations with the required adjoint functions. Let λ_S , λ_E , λ_{I_a} , λ_{I_s} , λ_H , λ_R , and λ_W be the adjoint functions associated with the evolution of the corresponding state variables. The right side of the equation describing the evolution of each state variable is multiplied by each of the adjoint functions to obtain

$$\begin{aligned}\mathcal{H} = & aI_s + bI_a + ux^2 + vy^2 + mz^2 + \lambda_S [\pi + \omega_1 R - (1-x)\lambda_S - \mu S] \\ & + \lambda_E [(1-x)\lambda_S - Q_1 E] + \lambda_{I_a} [\rho \epsilon E - Q_2 I_a + \sigma_2 I_s] \\ & + \lambda_{I_s} [(1-\rho)\epsilon E + \sigma_1 I_a - Q_3 I_s] + \lambda_H [-(\gamma_2 + \delta_2 + \mu + y)H + \phi I_s] \\ & + \lambda_W [\xi_1 I_a + \xi_2 I_s - (\varphi + z)W] + \lambda_R [(\gamma_2 + y)H + \gamma_1 I_a - Q_5 R].\end{aligned}\quad (4.6)$$

Theorem 6. For the controls x^* , y^* and z^* for (4.1), according to Lenhart 2007 [49] we define f^* as the state space at equilibrium, and $\lambda_{(\cdot)}$ as positive semidefinite piecewise differentiable functions for every $t \in [0, T]$. Assume for any $t \in [0, T]$

$$\begin{aligned}0 &= \mathcal{H}_x(t, f^*, x^*, y^*, z^*, \lambda(t)) \\ &= \mathcal{H}_y(t, f^*, x^*, y^*, z^*, \lambda(t)) \\ &= \mathcal{H}_z(t, f^*, x^*, y^*, z^*, \lambda(t)),\end{aligned}\quad (4.7)$$

then the following holds for optimal controls x^* , y^* and z^*

$$\mathcal{H}(t, f^*, x^*, y^*, z^*, \lambda(t)) \leq \mathcal{H}(t, f^*, x, y, z, \lambda(t)). \quad (4.8)$$

To determine the differential equations for the related adjoint functions, we differentiate the Hamiltonian with respect to each of the state variables to obtain

$$\begin{aligned}\frac{d\lambda_S}{dt} &= [(1-x)\lambda](\lambda_S - \lambda_E) + \mu\lambda_S, \\ \frac{d\lambda_E}{dt} &= \epsilon(\lambda_E - \lambda_{I_a}) + \mu\lambda_E, \\ \frac{d\lambda_{I_a}}{dt} &= \sigma_1(\lambda_{I_a} - \lambda_{I_s}) + \gamma_1(\lambda_{I_a} - \lambda_R) + \mu\lambda_{I_a} - b - \lambda_W\xi_1 \\ \frac{d\lambda_{I_s}}{dt} &= \sigma_2(\lambda_{I_s} - \lambda_{I_a}) + \phi(\lambda_{I_s} - \lambda_H) - a + \lambda_{I_a}\delta_1 - \lambda_W\xi_2 + \lambda_{I_s}(\mu + \sigma_2), \\ \frac{d\lambda_H}{dt} &= y(\lambda_H - \lambda_R) + \lambda_H(\gamma_1 + \delta_2 + \mu) - \lambda_R\gamma_2, \\ \frac{d\lambda_W}{dt} &= \lambda_W(\mu + z), \\ \frac{d\lambda_R}{dt} &= \omega(\lambda_R - \lambda_S) + \mu\lambda_R,\end{aligned}\quad (4.9)$$

with transversality conditions

$$\lambda_i(T) = 0, \quad \text{where } \lambda_i = \lambda_S, \lambda_E, \lambda_{I_a}, \lambda_{I_s}, \lambda_R, \lambda_H, \lambda_W. \quad (4.10)$$

For the transversality condition above (4.10), the following hold

$$\begin{aligned}\frac{d\lambda_S}{dt} &= -\frac{\partial \mathcal{H}}{\partial S}, \\ &\vdots \\ \frac{d\lambda_R}{dt} &= -\frac{\partial \mathcal{H}}{\partial R}.\end{aligned}\tag{4.11}$$

Our optimal controls are

$$\begin{aligned}x^*(t) &= \max(0, \min(\bar{x}(t), 1)), \\ y^*(t) &= \max(0, \min(\bar{y}(t), 1)), \\ z^*(t) &= \max(0, \min(\bar{z}(t), 1)).\end{aligned}\tag{4.12}$$

According to [50] the standard control arguments for controls are as follows

$$x^* = \begin{cases} 0 & \text{if } \bar{x} \leq 0, \\ \bar{x} & \text{if } 0 < \bar{x} < 1, \\ 1 & \text{if } \bar{x} \geq 1. \end{cases}\tag{4.13}$$

The upper bound x^* shows that reducing the contact rate is probable to reduce the transmission of the infection. The bound for the control associated with effective medical intervention is given by,

$$y^* = \begin{cases} 0 & \text{if } \bar{y} \leq 0, \\ \bar{y} & \text{if } 0 < \bar{y} < 1, \\ 1 & \text{if } \bar{y} \geq 1. \end{cases}\tag{4.14}$$

The value $y^* = 1$ assumes perfectly effective medical care for infected individuals. Having effective medical care can reduce the infected even though individuals may become susceptible again. The Ivermectin drug takes about 18 hours to leave or decay from the bloodstream but it stays in the intestines for about 12 days [51]. The upper bound ($y^* = 1$) for this control may not be attainable.

$$z^* = \begin{cases} 0 & \text{if } \bar{z} \leq 0, \\ \bar{z} & \text{if } 0 < \bar{z} < 1, \\ 1 & \text{if } \bar{z} \geq 1. \end{cases}\tag{4.15}$$

The upper bound z^* consists of disinfecting contaminated waters and reducing the shedding rate to the environment to reduce the infection in the environment. The Hamiltonian was differentiated with respect to each control to get

$$\begin{aligned}\frac{\partial \mathcal{H}}{\partial x} &= 2ux + \lambda S(\lambda_S - \lambda_E), \\ \frac{\partial \mathcal{H}}{\partial y} &= 2vy + H(\lambda_R - \lambda_H), \\ \frac{\partial \mathcal{H}}{\partial z} &= 2mz - \lambda_W W.\end{aligned}\tag{4.16}$$

The controls characterizations, $\bar{x}$, $\bar{y}$, and $\bar{z}$, of the optimal controls x^* , y^* , and z^* are obtained by equating the right side of the system of equations (4.16) to zero, that is $\frac{\partial \mathcal{H}}{\partial x} = \frac{\partial \mathcal{H}}{\partial y} = \frac{\partial \mathcal{H}}{\partial z} = 0$, and simplify to obtain

$$\begin{aligned}\bar{x} &= \frac{(\lambda_E - \lambda_S)\lambda S}{2u}, \\ \bar{y} &= \frac{H(\lambda_H - \lambda_R)}{2v}, \\ \bar{z} &= \frac{\lambda_H W}{2m}.\end{aligned}\tag{4.17}$$

From equation (4.17), we observed that the control characterisations are inversely proportional to the associated costs of implementing the controls.

4.2 Numerical Results

In this section we solve the numerical optimal control problem using the forward and backward sweep method described by Lenhart and Workman [49]. The fourth-order Runge-Kutta method in Matlab is used to numerically integrate the model system of equations. The numerical simulations were carried out to check the importance of optimal control strategies such as reducing the contact rate, implementation of effective medication and all other efforts that can curtail disease spread. We give the results based on how controls affected susceptible, asymptotically infected and symptomatically infected population.

When all the controls are implemented, we observed that the susceptible population remained high. In the absence of controls, we observed that there was high number of infected population. After the implementation of controls, asymptotically infected and symptomatically infected population decreased. This demonstrates the significance of control in curtailing the disease.

Figure (4.2) show the profiles of the controls explored in the model. All the controls reduce the risk of the susceptible population getting the infection and reducing the infected population.

When there are no controls in place for Gnathostomiasis, the susceptible population experiences a sudden decrease. This indicates that without any interventions or preventive measures, the

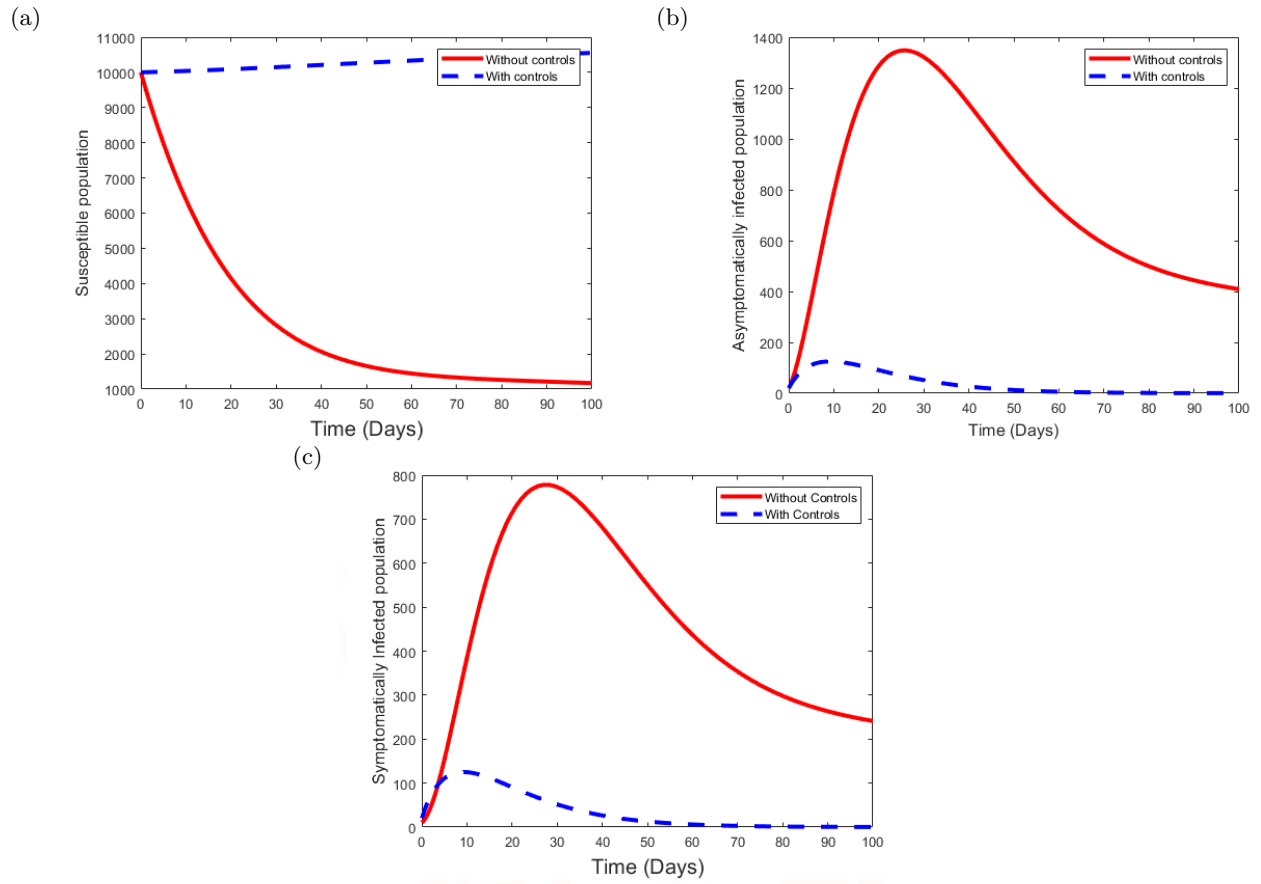


Figure 4.1: The asymptotically infected and symptomatically infected and susceptible population in presence of controls and in absence of controls

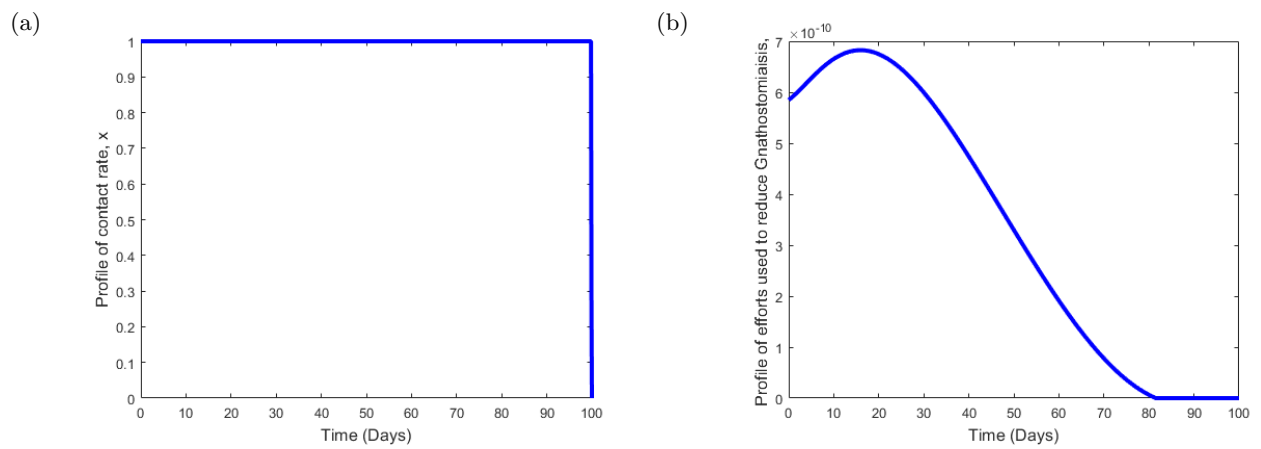


Figure 4.2: Profiles of contact rate, great medical care and efforts to reduce Gnathostomiasis

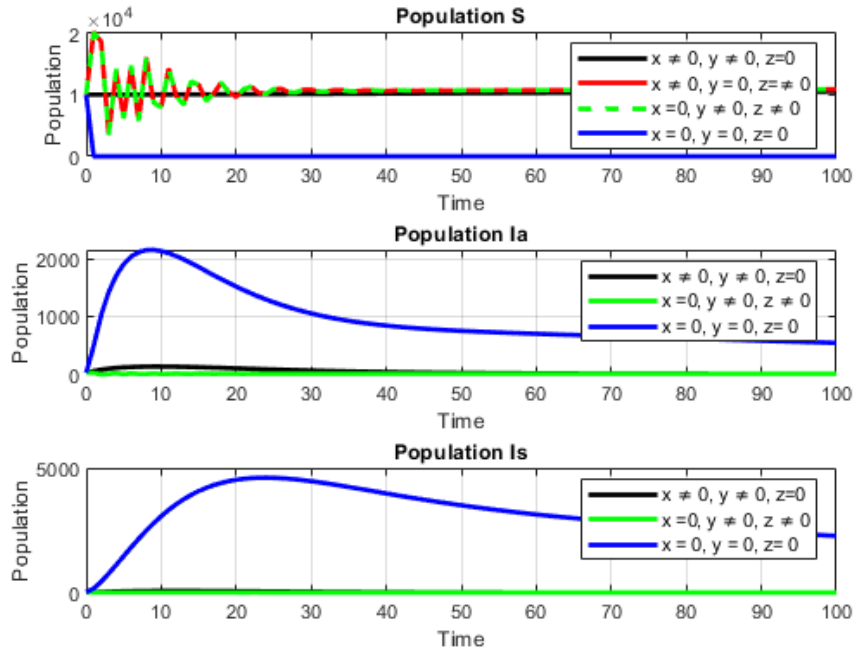


Figure 4.3: Effect of varying controls susceptible population and infected population

disease can spread rapidly within the population. When controls are implemented to manage Gnathostomiasis, there is a subsequent increase in the population. This suggests that the controls are effective in reducing the transmission or incidence of the disease. After some time the population becomes constant. This implies that the disease reaches a certain equilibrium or stability within the population. It could be that the remaining susceptible individuals have built immunity or that the disease has reached a level where it is no longer spreading rapidly.

When there are no controls in place, the symptomatically asymptotically infected population increases and reaches a peak. This indicates that without any interventions, the disease spreads within the population, leading to a significant number of individuals becoming infected. The disease continues to persist within the population, possibly due to ongoing transmission or the presence of reservoirs for the infection. When controls are implemented, there is a very small increase in the infected population, which immediately goes to zero. This pattern suggests that the implemented controls are highly effective in preventing further transmission of the disease. The small increase could be due to residual cases or a lag in the implementation of controls. However, the fact that the infected population quickly drops to zero indicates successful containment of the disease. From this, we can conclude that effective medical treatment for infected individuals and efforts made to reduce Gnathostomiasis from the environment are the most effective controls.

4.3 Conclusion

We introduced an optimal control model for Gnathostomiasis, which is a reduced version of the model employed in Chapter 3. The goal is to examine the effects of employing control strategies

to curtail the infection. We introduced three controls, the first one which accounts for reducing contact rate, the other one is effective medical care for the infected individuals. The last one accounts for efforts made to reduce Gnathostomiasis from the environment through mitigation measures as disinfecting contaminated waters. We implemented the objective cost function with the aim of reducing the infected population and the accompanying costs. We deduced from the numerical results that when all the controls are in place, the susceptible population increased. It was noted that the infected population was significant without controls. Controls were put in place, and the population's symptomatic and asymptomatic infections declined. This illustrates how important control implementation is.



5. Conclusion

Gnathostomiasis is a food-borne parasitic disease, it is usually consumed or ingested in contaminated raw fish, which is one of the main risk factors. Chapter 1 provides an introduction of Gnathostomiasis. Chapter 2 contains a review the literature and gave the tools used. Relevant mathematical preliminaries and definitions are also given. In the third chapter (3), using a system of differential equations, we developed and analyzed a model for the transmission dynamics of Gnathostomiasis. Since the model being analysed studies the change in the number of organisms, we made ensure that the model is well posed and that the solutions are always non-negative and bounded. We explored possible interventions such as positivity and boundedness of solutions. According to the results, all of the state variables were non-negative for all $t \geq 0$ and since all the populations were also non-negative and the domain of biological significance was shown to be bounded, then the model is well posed and and it is appropriate to analyze the model on the domain provided. We next determined the disease-free equilibrium and computed the basic reproduction number ($\mathcal{R}_0$). The basic reproduction number, R_0 of the model was obtained by employing the next generation method described in [41, 42]. We used the same approach that was used in [41] and adopting the same matrix notations for new terms and transfer terms. $\mathcal{R}_0$ was simplified as the sum of the components of the reproduction number representing the contribution of environment, human to human due to I_a and I_s and human and environment. Basic reproduction number ($\mathcal{R}_0$) was used to find out the local stability of the disease-free equilibrium along with the existence of the endemic equilibrium. To find the disease-free equilibrium's local stability, we considered a Jacobian matrix and evaluated it at the disease-free equilibrium. We considered stability by finding the Jacobian's eigenvalues at disease-free equilibrium. All the eigenvalues were negative, then we deduced that the disease-free equilibrium is locally asymptotically stable when $\mathcal{R}_0 < 1$ and unstable otherwise. We found that the endemic equilibrium is unique for $\mathcal{R}_0 > 1$. We went on to prove that the disease-free equilibrium is globally asymptotically stable when $\mathcal{R}_0 < 1$. To prove the global stability of the disease-free equilibrium, we differentiated our Lyapunov function and substituted the relevant terms. We observed that $\frac{dV}{dt} < 0$ when $\mathcal{R}_0 < 1$, and the disease-free equilibrium E_0 is stable and $\frac{dV}{dt} = 0$ when $E = 0$ or when $\mathcal{R}_0 = 1$. Using the LaSalle invariance principle [43], this indicated that equilibrium E_0 is globally stable when $\mathcal{R}_0 < 1$. Sensitivity analysis and numerical results were executed. In this work we performed sensitivity analysis using Latin Hypercube Sampling scheme (LHS). With 1000 simulations each run, the partial rank correlation coefficients (PRCCs) were calculated using MATLAB, and the tornado plot and box plot were also produced. The PRCCs calculated ranged from -1 and 1 . To determine which parameters are vital, we computed p -values for each one. From the box plot, the median was approximately 0.998 , that is our $\mathcal{R}_0$. We also found that contact rate (β) was observed as a parameter that has the high potential of worsening the disease when increased, followed by shedding rates ξ_1 and ξ_2 . We also observed that hospitalisation rate ϕ , φ which is the rate of decay of the pathogen and recovery rate γ_1 are some of the parameters that, when maximised, have the ability to contain

the Gnathostomiasis disease. A decrease in the number of infected individuals is due to increase in recovery rates. Due to small magnitude of PRCC, ω have very little effect on the reproduction number. Some parameters were varied to check their effect on the infected population. We observed that we need to minimize the contact rate β and shedding rate to contain the disease. We also discovered that when controls are implemented at the same time, the disease clear in a shorter time and the controls measure should be implemented immediately when the outbreak is detected. For investigating the influence of consuming food contaminated with the pathogen, we extended our force of infection. We investigated the influence of consuming food contaminated with the pathogen by letting our β_1 be zero and on the side β_1 not equal to zero. We observed that when $\beta_1 \neq 0$ the infected population is larger than when $\beta_1 = 0$. This implies that if this aspect is not considered there is likelihood of underestimating the number of cases.

In Chapter 4, we introduced an optimal control model for Gnathostomiasis, which is a reduced version of the model employed in Chapter 3. Introduced three controls, the first one accounts for reducing contact rate, the other one is great medical care for the infected individuals and the last one accounts for efforts made to reduce Gnathostomiasis from the environment such as disinfecting contaminated waters. The goal is to examine the effects of employing control strategies to lessen the infection. We employed an objective/cost functional to minimize the number of infected individuals as well as minimising the cost of implementing the controls. Since the controls are non-linear, we chose a quadratic objective function. We solved the numerical optimal control problem using forward and backward sweep method by Lenhart and Workman [49]. The fourth-order Runge-Kutta method in MATLAB was used to numerically integrate the model system of equations. The numerical simulations were carried out to check the importance of optimal control strategies such as reducing the contact rate, great medical care and all other efforts that can reduce Gnathostomiasis. We gave the results based on how controls affected susceptible, asymptotically infected and symptomatically infected population. When all the controls are implemented, we observed that susceptible population was increased. In the absence of controls, observed that there was high number of infected population. After the implementation of controls, asymptotically infected and symptomatically infected population decreased. This demonstrates the significance of control implementation.

One drawback is that since Gnathostomiasis disease is uncommon, it is difficult to access data in hospitals, which results in the estimation of some parameters that may have an impact on accuracy. For further research, we advise using information gathered from various health institutes for additional study on this topic.

After modeling the transmission dynamics of Gnathostomiasis and conducting an analysis of optimal control measures, I would like to provide the following recommendations to stakeholders:

- Enhance Public Awareness: Implement an extensive public awareness campaign to educate the population about the transmission dynamics, symptoms, and prevention strategies of Gnathostomiasis. This can include media campaigns, educational materials in schools and healthcare facilities, and community outreach programs.
- Vector Control: Focus on comprehensive vector control measures to minimize the risk of

transmission. This can involve initiatives such as regular cleaning and removal of stagnant water sources, implementing proper waste disposal systems, and conducting vector surveillance programs to identify high-risk areas.

- **Veterinary and Animal Control:** Collaborate with veterinary authorities and animal control agencies to address the role of animals, particularly fish and crustaceans, in the transmission cycle. Implement regulations and guidelines to ensure safe handling, processing, and cooking of animal products to reduce the risk of infection.



A. Chapter three codes

A.1 Section title

A.1.1 Matlab Code for the Tornado Plot, Box Plot and Monte Carlo simulations for parameters with the greatest PRCC magnitude respectively in Figure (3.2a), Figure (3.2b) and Figure (3.3).

```
1 clear ;
2
3
4 LHS; % call the LHS program
5 b = size(latin_output);
6 c = length(latin_output);
7
8
9 num = b(2);
10
11 % delcare initial parameters
12
13 rank_outcome = zeros(1000,1);
14 rank = zeros(1000,10);
15 outcome = zeros(1000,100);
16 parameters = zeros(1000,10);
17 CC = zeros(10, 10);
18 lengthofmatrix = b(2);
19
20
21 [parameters, outcome] = read_in_data(N, num, latin_output);
22 [rank_outcome] = create_outcome_rank(N, num, outcome);
23 [rank, ranks] = create_rank_matrix(N, num, parameters, rank,
    rank_outcome);
24 [CC] = make_c_matrix(N, num, rank);
25 RCCMatrix = [CC];
26 Prcclist = RCCMatrix(:,12)
27
28
29 set(0,'defaulttextinterpreter','tex');
30 fig11 = figure(11);
31 barh(CC(1:length(CC)-1,length(CC)));
```

```

32
33 set(gca, 'YTick', 1:11);
34 [hx, hy] = format_ticks(gca, ...
35     {'$-0.6$', '$-0.4$', '$-0.2$', '$0$', '$0.2$', '$0.4$', '$0.6$'}, ...
36     {'$\rho$', '$\sigma_1$', '$\sigma_2$', '$\gamma_1$', '$\gamma_2$', '$\omega_1$', '$\xi_1$', '$\xi_2$', '$\varphi$', '$\phi$', '$\beta_1$'}, ...
37     -0.6:0.2:0.6, [], 0, 0, [], ...
38     'FontSize', 14, 'FontWeight', 'Bold');

1 % I have to run LHS first, then define a new matrix C to be para.
2 n= 2;
3 Pi = 4; % estimated total population of the Hubei Province
4 mu = 1/(66.1*365); % the estimated life expectancy of the province is
    76.79 years
5 N0 = 50000; %mu*Pi;
6 K = 5000;
7 delta1 = 0.0625;
8 delta2 = 0.056;
9 epsilon = 0.075;
10
11
12 for i=1:1000;
13     rho(i)=para(i,1);
14 %     epsilon(i)=para(i,2);
15     sigma1(i)=para(i,2);
16     sigma2(i)=para(i,3);
17     gamma1(i)=para(i,4);
18     gamma2(i)=para(i,5);
19     omega1(i)=para(i,6);
20     xi1(i) = para(i,7);
21     xi2(i) = para(i,8);
22     varphi(i) = para(i,9);
23     phi(i) = para(i,10);
24     beta1(i) = para(i,11);
25
26
27 Q1(i) = epsilon + mu;
28 Q2(i) = mu+sigma1(i)+ gamma1(i);
29 Q3(i) = mu+delta1 + sigma2(i) + phi(i);
30 Q4(i) = mu+gamma2(i) + delta2;
31 Q5(i) = omega1(i) + mu;
32 Phi1(i) = ((sigma1(i).*sigma2(i))./(Q2(i).*Q3(i)));

```

```

33
34 % R01(i) = ((beta1(i).*epsilon.*xi1(i)).*rho(i))./(K*varphi(i).*Q1(i)
    ).*Q2(i).*(1-Phi1(i)));
35 % R02(i) = (beta1(i).*epsilon.*(xi2(i).*((1-rho(i)).*Q2(i) + rho(i)
    ).*Q1(i))))./(K*varphi(i).*Q1(i).*Q2(i).*Q3(i).*(1 - Phi1(i)));
36 % R_C(i) = R01(i) + R02(i);
37 R01(i) = (beta1(i).*epsilon.*pi.*rho(i).*(Q3(i).*xi1(i) + xi2(i).*
    sigma1(i)))./(mu.*K*varphi(i).*Q1(i).*Q2(i).*Q3(i).*(1 - Phi1(i)
    )));
38 R02(i) = (beta1(i).*pi.*epsilon.*(1-rho(i)).*(xi2(i).*Q2(i) + xi2(i)
    ).*sigma1(i)))./(mu.*K*varphi(i).*Q1(i).*Q2(i).*Q3(i).*(1 -
    Phi1(i)));
39 R_C(i) = R01(i) + R02(i);
40 end
41
42 v=0;
43 figure(1)
44 beta1;
45 Repnum = log(R_C);
46 pbeta1 = polyfit(beta1,Repnum,1)
47 R0beta1yfit = polyval(pbeta1,beta1);
48 plot(beta1,Repnum,'.')
49 hold on
50 plot(beta1,R0beta1yfit,'LineWidth',2)
51 xlabel('Transmission rate, \beta','FontSize',14)
52 ylabel('log(R_0)','FontSize',14)
53
54
55 figure(2)
56 xi1;
57 Repnum = log(R_C);
58 pxi1 = polyfit(xi1,Repnum,1)
59 R0xi1yfit = polyval(pxi1,xi1);
60 plot(xi1,Repnum,'.')
61 hold on
62 plot(xi1,R0xi1yfit,'LineWidth',2)
63 xlabel('Shedding rate by asymptotically infected individuals, \xi_1',
    'FontSize',14)
64 ylabel('log(R_0)','FontSize',14)
65
66 figure(3)
67 xi2;

```

```
68 Repnum = log(R_C);
69 pxi2 = polyfit(xi2,Repnum,1)
70 R0xi2yfit = polyval(pxi2,xi2);
71 plot(xi2,Repnum, 'r')
72 hold on
73 plot(xi2,R0xi2yfit, 'LineWidth',2)
74 xlabel('Shedding rate by symptomatically infected individuals, \xi_2',
       'FontSize',14)
75 ylabel('log(R_0)', 'FontSize',14)
76
77 figure(4)
78 phi;
79 Repnum = log(R_C);
80 pphi = polyfit(phi,Repnum,1)
81 R0phiyfit = polyval(pphi,phi);
82 plot(phi,Repnum, 'r')
83 hold on
84 plot(phi,R0phiyfit, 'LineWidth',2)
85 xlabel('Hospitalisation rate, \phi', 'FontSize',14)
86 ylabel('log(R_0)', 'FontSize',14)
87
88
89 figure(9)
90 boxplot(R_C)
91 axis([0.5 1.5 0 4])
92 ylabel('Reproduction number, {R}_{0}', 'FontSize',15)
93 xlabel('Column number', 'FontSize',12)
```

A.1.2 Matlab Code for sensitivity analysis for the full model

```
1
2 clear all;
3 close all;
4
5 %% Sample size N
6 runs=1000;
7
8 %% LHS MATRIX %%
9 Parameter_settings_LHS;
10
11
12 rho_LHS=LHS_Call(0, rho, 1, 0 ,runs, 'unif'); % baseline = 10
13 % epsilon_LHS=LHS_Call(0.06, epsilon, 0.08, 0 ,runs, 'unif'); %
    baseline = 10
14 sigma1_LHS=LHS_Call(0.01667, sigma1, 0.165, 0 ,runs, 'unif'); %
    baseline = 10
15 sigma2_LHS=LHS_Call(0.01667, sigma2, 0.165, 0 ,runs, 'unif'); %
    baseline = 10
16 % delta1_LHS=LHS_Call(0, delta1, 1, 0 ,runs, 'unif'); % baseline = 10
17 % delta2_LHS=LHS_Call(0.08, delta2, 0.25, 0 ,runs, 'unif'); % baseline
    = 10
18 gamma1_LHS=LHS_Call(0.0167, gamma1, 0.067, 0 ,runs, 'unif'); %
    baseline = 10
19 gamma2_LHS=LHS_Call(0.033, gamma2, 0.11, 0 ,runs, 'unif'); % baseline
    = 10
20 omega_LHS=LHS_Call(0.00274, omega, 0.033, 0 ,runs, 'unif'); % baseline
    = 10
21 xi1_LHS=LHS_Call(0.017, xi1, 0.63, 0 ,runs, 'unif'); % baseline = 10
22 xi2_LHS=LHS_Call(0.0167, xi2, 0.63, 0 ,runs, 'unif'); % baseline = 10
23 varphi_LHS=LHS_Call(0.000228, varphi, 0.000274, 0 ,runs, 'unif'); %
    baseline = 10
24 phi_LHS=LHS_Call(0.0033, phi, 0.2, 0 ,runs, 'unif'); % baseline = 10
25 beta_LHS=LHS_Call(0.01, beta, 1, 0 ,runs, 'unif'); % baseline = 10
26
27
28
29
30 %% LHS MATRIX and PARAMETER LABELS
31 LHSmatrix=[rho_LHS sigma1_LHS sigma2_LHS gamma1_LHS gamma2_LHS
    omega_LHS xi1_LHS xi2_LHS varphi_LHS phi_LHS beta_LHS ];
32
```

```

33 for x=1:runs %Run solution x times choosing different values
34     f=@ODELHS;
35     x
36     LHSmatrix(x,:)
37     [t,y]=ode15s(@(t,y)f(t,y,LHSmatrix,x,runs),tspan,y0,[]);
38     A=[t y]; % [time y]
39 );
40
41 %% Save only the outputs at the time points of interest [
    time_points]:
42 %% MORE EFFICIENT
43 T_lhs(:,x)=A(time_points+1,1);
44 S_lhs(:,x)=A(time_points+1,2);
45 E_lhs(:,x)=A(time_points+1,3);
46 Ia_lhs(:,x)=A(time_points+1,4);
47 Is_lhs(:,x)=A(time_points+1,5);
48 H_lhs(:,x)=A(time_points+1,6);
49 R_lhs(:,x)=A(time_points+1,7);
50 W_lhs(:,x)=A(time_points+1,8);
51 end
52 %% Save the workspace
53 save Model_LHS.mat;
54 % CALCULATE PRCC
55 [prcc3 sign sign_label]=PRCC(LHSmatrix,Ia_lhs,1:length(time_points),
    PRCC_var,0.05);
56 prcc3(10,:) '
57 prcc3(100,:) '
58 prcc3(250,:) '
59
60 [prcc4 sign sign_label]=PRCC(LHSmatrix,Is_lhs,1:length(time_points),
    PRCC_var,0.05);
61 prcc4(10,:) '
62 prcc4(100,:) '
63 prcc4(250,:) '
64
65
66 figure(1)
67 bar(prcc3(10,:));
68 set(gca,'XTickLabel',PRCC_var,'XTick',[1:11],'FontSize',12,'
    FontWeight','Bold'),title('PRCCs at T = 10');
69 ylabel('PRCCs(Asymptotically infected population)')
70

```

```

71 figure(5)
72 bar(prcc4(10,:));
73 set(gca,'XTickLabel',PRCC_var,'XTick',[1:11],'FontSize',12,'
    FontWeight','Bold'),title('PRCCs at T = 10');
74 ylabel('PRCCs(Symptomatically infected population)')
75
76 figure(2)
77 bar(prcc3(100,:));
78 set(gca,'XTickLabel',PRCC_var,'XTick',[1:11],'FontSize',12,'
    FontWeight','Bold'),title('PRCCs at T = 100');
79 ylabel('PRCCs (Asymptomatically infected population)')
80
81 figure(6)
82 bar(prcc4(100,:));
83 set(gca,'XTickLabel',PRCC_var,'XTick',[1:11],'FontSize',12,'
    FontWeight','Bold'),title('PRCCs at T = 100');
84 ylabel('PRCCs (Symptomatically infected population)')
85
86
87 figure(3)
88 bar(prcc3(250,:));
89 set(gca,'XTickLabel',PRCC_var,'XTick',[1:11],'FontSize',12,'
    FontWeight','Bold'),title('PRCCs at T = 250');
90 ylabel('PRCCs (Asymptomatically infected population)')
91
92 figure(7)
93 bar(prcc4(250,:));
94 set(gca,'XTickLabel',PRCC_var,'XTick',[1:11],'FontSize',12,'
    FontWeight','Bold'),title('PRCCs at T = 250');
95 ylabel('PRCCs(Symptomatically infected population)')
96
97 figure(4)
98
99 set(gca,'linestyleorder',{ '-',':','-','—','*','+' },'nextplot','add
    ')
100 plot(prcc3,'linewidth',2)
101 legend('\rho','\sigma_1','\sigma_2','\gamma_1','\gamma_2','\omega',
    '\xi_1','\xi_2','\psi','\phi','\beta');
102 % set(h1,'Interpreter','latex')
103 xlabel('Time (days)'), ylabel('PRCCs(Asymptomatically infected
    population)')
104

```

```

105     figure(8)
106     set(gca,'linestyleorder',{ '-',':', '-.','—','*','+' },'nextplot','add
        ')
107     plot(prcc4,'linewidth',2)
108     legend('\rho','\sigma_1','\sigma_2','\gamma_1','\gamma_2','\omega',
        '\xi_1','\xi_2','\psi','\phi','\beta');
109     % set(h1,'Interpreter','latex')
110     xlabel('Time (days)'), ylabel('PRCCs(Symptomatically infected
        population)')

```



A.1.3 Matlab Code for effect of varrying β

```
1 function GnathostomiasissolutionBeta1Varying
2
3
4 format long % specifying higher precision
5 % tforward = Istart:0.01:Iend; % t mesh for the solution of the
    differential equation
6 tmeasure1 = [1:1:500];
7 %tmeasure = [1:100:(LL*100+1)]'; % selects the points in the solution
8 tmeasure = [1:1:1000]'; % selects the points in the solution
9 %tmeasure1 = [100:1:250];
10 tmeasure2 = [251:1:550];
11 tmeasureF = [100:550];
12
13 h0 = 0.35;
14
15 mu = 1/(66.1*365);
16 N0 = 100000; %mu*Pi; % estimated total population of Namibia
17 K = 50000;
18 % Initialize states (A guess is fine)
19 x1(1)= 4;% Pi
20 x1(2)= 0.0625;% delta1
21 x1(3)= 0.056;% delta2
22 x1(4)= 0.2;% rho
23 x1(5) = 0.09;% epsilon
24 x1(6)= 0.155;% sigma1
25 x1(7)= 0.155;% sigma2
26 x1(8)= 0.055;% gamma1
27 x1(9)= 0.05;% gamma2
28 x1(10)= 0.0153;% omega1
29 x1(11)= 0.12445;% xi1
30 x1(12)= 0.13315;% xi2
31 x1(13)= 0.000249;% varphi
32 x1(14)= 0.1;% phi
33 x1(15) = 0.05;%beta
34
35 % Changed parameters with new beta
36 x2(1)= 4;% Pi
37 x2(2)= 0.32;% delta1
38 x2(3)= 0.12;% delta2
39 x2(4)= 0.2;% rho
40 x2(5) = 0.075;% epsilon
```

```

41 x2(6)= 0.155;% sigma1
42 x2(7)= 0.155;% sigma2
43 x2(8)= 0.055;% gamma1
44 x2(9)= 0.05;% gamma2
45 x2(10)= 0.0153;% omega1
46 x2(11)= 0.12445;% xi1
47 x2(12)= 0.13315;% xi2
48 x2(13)= 0.000249% varphi
49 x2(14)= 0.1% phi
50 x2(15) = 0.025;%beta1
51
52 x3(1)= 4;% Pi
53 x3(2)= 0.32;% delta1
54 x3(3)= 0.12;% delta2
55 x3(4)= 0.8;% rho
56 x3(5) = 0.075;% epsilon
57 x3(6)= 0.155;% sigma1
58 x3(7)= 0.155;% sigma2
59 x3(8)= 0.055;% gamma1
60 x3(9)= 0.05;% gamma2
61 x3(10)= 0.0153;% omega1
62 x3(11)= 0.12445;% xi1
63 x3(12)= 0.13315;% xi2
64 x3(13)= 0.000249;% varphi
65 x3(14)= 0.1;% phi
66 x3(15) = 0.001;%beta1
67
68 % initial values
69
70 S0 = 1000;
71 E0 = 20;
72 Ia0 = 10;
73 Is0 = 20;
74 H0 = 0;
75 R0 = 0;
76 W0 = 50000;
77
78 INITIAL0=[S0, E0, Ia0, Is0, H0, R0, W0];
79
80
81 %First ODES
82 [T1, Y1] = ode45(@(t,y)(gnathostomiasis(t,y,x1)),tmeasure1,INITIAL0);

```

```

83 [T1, Y2] = ode45(@(t,y)(gnathostomiasis(t,y,x2)),tmeasure1,INITIAL0);
84 [T1, Y3] = ode45(@(t,y)(gnathostomiasis(t,y,x3)),tmeasure1,INITIAL0);
85
86 T = T1
87
88 YYInfecB = Y1(:,3)+Y1(:,4);
89
90
91 YYInfecB1 = Y2(:,3)+Y2(:,4);
92 %%
93 YYInfecB12 = Y3(:,3)+Y3(:,4);
94
95 figure(2)
96 hold on
97 %plot(tdata,qdataF,'r.','LineWidth',2.5); %% ,tdata,dData,'c:',tdata,
    ModelDeath,'k-'
98 plot(T,YYInfecB,'b-','LineWidth',2.5); %
99 plot(T,YYInfecB1,'r—','LineWidth',2.5); %
100 plot(T,YYInfecB12,'k-','LineWidth',2.5); %
101
102 legend('Baseline value contact rate \beta','50% lower contact rate \
    beta','98% lower contact rate \beta','fontsize', 11) %,
103 xlabel('Time (days)','fontsize', 14); % plotting final fit
104 ylabel('Infected individuals (I_a + I_s)','fontsize', 14);
105 title('Varying \beta on the infected population')
106 xlim([0 150])
107 %title('New case fit with Ro');
108 %hold off
109
110 %nReproduction number
111 x = x1;
112 Pi=x(1);% Pi
113 delta1= x(2)% delta1
114 delta2= x(3)% delta2
115 rho = x(4)% rho
116 epsilon = x(5) % epsilon
117 sigma1= x(6)% sigma1
118 sigma2 = x(7)% sigma2
119 gamma1 =x(8)% gamma1
120 gamma2 = x(9)% gamma2
121 omega1 = x(10)% omega1
122 xi1 = x(11)% xi1

```

```

123 xi2 = x(12)% xi2
124 varphi =x(13);% varphi
125 phi = x(14)% phi
126 beta1 = x(15) %beta1
127
128 Q1 = epsilon + mu
129 Q2 = mu + sigma1 + gamma1
130 Q3 = delta1 + mu + sigma2 + phi
131 Q4 = gamma2 + delta2 + mu
132 Q5 = mu + omegal
133
134 R01 = ((beta1*epsilon*xi1)*rho)/(K*varphi*Q1*Q2*(1-((sigma1*sigma2)/(
    Q2*(delta1 + mu + sigma2 + phi)))));
135 R02 = (beta1*epsilon*(xi2*((1-epsilon)*Q2 + rho*Q1)))/(K*varphi*Q1*Q2
    *(delta1 + mu + sigma2 + phi)*(1 - ((sigma1*sigma2)/(Q2*(delta1 +
    mu + sigma2 + phi)))));
136 R0 = R01 + R02
137 end

```

B. Optimal Control Codes

Matlab Code for asymptotically infected and symptomatically infected and susceptible population in presence of controls and in absence of controls for Figure (??)

```
1
2 function y = optimalcontrolnew(Pi,mu,delta1,delta2,K,rho,epsilon,
    signal,sigma2,gamma1,gamma2,omega1,xi1,xi2,varphi,phi,beta1,a,b,u,
    v,m,S10,E10,Ia10,Is10,H10,R10,W10,tfinal);
3 test =-1;
4 delta = 0.001;
5 tfinal = 100;
6 M = 1000;
7 S10 = 10000; E10 = 500; Ia10 = 20; Is10 = 10; H10 =0; R10 = 0; W10 =
    50000;
8 Pi = 4;
9 mu = 1/(66.1*365); delta1 = 0.0625; delta2 = 0.056;
10 K = 5000; rho = 0.8; epsilon = 0.09;
11 signal = 0.155; sigma2 = 0.155; gamma1 = 0.055;
12 gamma2 = 0.05; omega1 = 0.0153; xi1 = 0.12445;
13 xi2 = 0.13315; varphi = 0.000249; phi = 0.1;
14 beta1 = 0.05;
15 a = 100;
16 b= 200;
17 X = 80;
18 Y = 50;
19 Z = 50;
20
21 t = linspace(0,tfinal,M+1);
22 h = tfinal/M;
23 h2 = h/2;
24
25 S= zeros(1,M+1);
26 E= zeros(1,M+1);
27 Ia= zeros(1,M+1);
28 Is= zeros(1,M+1);
29 H= zeros(1,M+1);
30 R= zeros(1,M+1);
31 W= zeros(1,M+1);
```

```

32
33 S(1)=S10;
34 E(1)=E10;
35 Ia(1)=Ia10;
36 Is(1)=Is10;
37 H(1)=H10;
38 R(1)=R10;
39 W(1)=W10;
40
41
42 lambdaS= zeros(1,M+1);
43 lambdaE= zeros(1,M+1);
44 lambdaIa= zeros(1,M+1);
45 lambdaIs= zeros(1,M+1);
46 lambdaH= zeros(1,M+1);
47 lambdaR= zeros(1,M+1);
48 lambdaW= zeros(1,M+1);
49 % setup the admissible controls list
50 u= zeros(1,M+1);
51 v=zeros(1,M+1);
52 m=zeros(1,M+1);
53 while (test <0)
54
55   oldu = u;
56   oldv = v;
57   oldm = m;
58   oldS = S;
59   oldE = E;
60   oldIa = Ia;
61   oldIs = Is;
62   oldH = H;
63   oldR = R;
64   oldW = W;
65   oldlambdaS = lambdaS;
66   oldlambdaE = lambdaE;
67   oldlambdaIa = lambdaIa;
68   oldlambdaIs = lambdaIs;
69   oldlambdaH = lambdaH;
70   oldlambdaR = lambdaR;
71   oldlambdaW = lambdaW;
72   for i=1:M
73

```

```

74     M11 = Pi + omegal*R(i) -(1-u(i)).*(beta1*(W(i)./(W(i)+K)))
      .*S(i) - mu*S(i);
75     M12 = (1-u(i)).*(beta1*(W(i)./(W(i)+K))).*S(i) - (epsilon +
      mu)*E(i) ;
76     M13 = rho*epsilon*E(i) - (mu + sigma1 +gamma1)*Ia(i) +
      sigma2*Is(i);
77     M14 = (1- rho)*epsilon*E(i) + sigma1*Ia(i) -(delta1 + mu +
      sigma2 + phi)*Is(i);
78     M15 = phi*Is(i)-(gamma2 + delta2 + mu + v(i)).*H(i);
79     M16 = (gamma2 + v(i)).*H(i) + gamma1*Ia(i) -(mu + omegal)*R
      (i);
80     M17 = xi1*Ia(i) + xi2*Is(i) -(varphi + m(i)).*W(i);
81
82
83     M21 = Pi + omegal*(R(i)+h2*M16) -(1-0.5*(u(i)+u(i+1))).*(
      beta1*(W(i)./(W(i)+K))).*(S(i)+h2*M11) - mu*(S(i)+h2*M11
      );
84     M22 = (1-0.5*(u(i) + u(i+1))).*(beta1*(W(i)./(W(i)+K))).*(S
      (i)+h2*M11) - (epsilon + mu)*(E(i)+h2*M12) ;
85     M23 = rho*epsilon*(E(i)+h2*M12) - (mu + sigma1 +gamma1)*(
      Ia(i)+ h2*M13) + sigma2*(Is(i)+ h2*M14);
86     M24 = (1- rho)*epsilon*(E(i)+h2*M12) + sigma1*(Ia(i)+ h2*
      M13) -(delta1 + mu + sigma2 + phi)*(Is(i)+ h2*M14);
87     M25 = phi*(Is(i)+ h2*M14)-(gamma2 + delta2 + mu + 0.5*(v(i)
      +v(i+1))).*(H(i)+h2*M15);
88     M26 = (gamma2 + 0.5*(v(i)+v(i+1))).*(H(i)+h2*M15) + gamma1
      *(Ia(i)+ h2*M13) -(mu + omegal)*(R(i)+h2*M16);
89     M27 = xi1*(Ia(i)+ h2*M13) + xi2*(Is(i)+ h2*M14) -(varphi
      + 0.5*(m(i)+m(i+1))).*(W(i)+h2*M17);
90
91
92     M31 = Pi + omegal*(R(i)+h2*M26) -(1-0.5*(u(i)+u(i+1))).*(
      beta1*(W(i)./(W(i)+K))).*(S(i)+h2*M21) - mu*(S(i)+h2*M21
      );
93     M32 = (1-0.5*(u(i) + u(i+1))).*(beta1*(W(i)./(W(i)+K))).*(S
      (i)+h2*M21) - (epsilon + mu)*(E(i)+h2*M22) ;
94     M33 = rho*epsilon*(E(i)+h2*M22) - (mu + sigma1 +gamma1)*(
      Ia(i)+ h2*M23) + sigma2*(Is(i)+ h2*M24);
95     M34 = (1- rho)*epsilon*(E(i)+h2*M22) + sigma1*(Ia(i)+ h2*
      M23) -(delta1 + mu + sigma2 + phi)*(Is(i)+ h2*M24);
96     M35 = phi*(Is(i)+ h2*M24)-(gamma2 + delta2 + mu + 0.5*(v(i)
      +v(i+1))).*(H(i)+h2*M25);

```

```

97     M36 = (gamma2 + 0.5*(v(i)+v(i+1))).*(H(i)+h2*M25) + gamma1
          *(Ia(i)+ h2*M23) -(mu + omega1)*(R(i)+h2*M26);
98     M37 = xil*(Ia(i)+ h2*M23) + xi2*(Is(i)+ h2*M24) -(varphi
          + 0.5*(m(i)+m(i+1))).*(W(i)+h2*M27);
99
100    M41 = Pi + omega1*(R(i)+h*M36) -(1-u(i+1)).*(beta1*(W(i)./(
          W(i)+K))).*(S(i)+h*M31) - mu*(S(i)+h*M31);
101    M42 = (1-u(i+1)).*(beta1*(W(i)./(W(i)+K))).*(S(i)+h*M31) -
          (epsilon + mu)*(E(i)+h*M32);
102    M43 = rho*epsilon*(E(i)+h*M32) - (mu + sigma1 +gamma1)*(Ia
          (i)+ h*M33) + sigma2*(Is(i)+ h*M34);
103    M44 = (1- rho)*epsilon*(E(i)+h*M32) + sigma1*(Ia(i)+ h*M33
          ) -(delta1 + mu + sigma2 + phi)*(Is(i)+ h*M34);
104    M45 = phi*(Is(i)+ h*M34)-(gamma2 + delta2 + mu + v(i+1)).*(
          H(i)+h*M35);
105    M46 = (gamma2 + v(i+1)).*(H(i)+h*M35) + gamma1*(Ia(i)+ h*
          M33) -(mu + omega1)*(R(i)+h*M36);
106    M47 = xil*(Ia(i)+ h*M33) + xi2*(Is(i)+ h*M34) -(varphi +
          m(i+1)).*(W(i)+h*M37);
107
108
109
110    S(i+1) = S(i) +(h/6)*(M11+2*M21+2*M31 +M41);
111    E(i+1) = E(i) +(h/6)*(M12+2*M22+2*M32 +M42);
112    Ia(i+1)= Ia(i) +(h/6)*(M13+2*M23+2*M33 +M43);
113    Is(i+1)= Is(i) +(h/6)*(M14+2*M24+2*M34 +M44);
114    H(i+1) = H(i) +(h/6)*(M15+2*M25+2*M35 +M45);
115    R(i+1) = R(i) +(h/6)*(M16+2*M26+2*M36 +M46);
116    W(i+1) = W(i) +(h/6)*(M17+2*M27+2*M37 +M47);
117
118    end
119    for i=1:M
120        j= M+2-i;
121
122
123
124    M11 = (1-u(j)).*(beta1*(W(j)./(W(j)+K))).*(lambdaS(j)-
          lambdaE(j))+ mu*lambdaS(j);
125    M12 = epsilon*(lambdaE(j)- lambdaIa(j))+ mu*lambdaE(j);
126    M13 = sigma1*(lambdaIa(j)- lambdaIs(j)) + gamma1*(lambdaIa(
          j)- lambdaR(j)) + mu*lambdaIa(j) - b -xil*lambdaW(j);
127    M14 = sigma2*(lambdaIs(j)- lambdaIa(j)) + phi*(lambdaIs(j)-

```

```

lambdaH(j)) -a + delta1*lambdaIa(j) - xi2*lambdaW(j) +
lambdaIs(j)*(mu + sigma2);
128 M15 = v(j).*(lambdaH(j)- lambdaR(j)) + lambdaH(j)*(gamma1 +
delta2 + mu)- gamma2*lambdaR(j);
129 M16 = lambdaW(j)*(mu+m(j));
130 M17 = omega1*(lambdaR(j)- lambdaS(j)) + mu*lambdaR(j);
131
132
133 M21 = [(1-0.5*(u(j)-u(j-1)))*(0.5*((beta1*(W(j))/(W(j)+K))
)-(beta1*(W(j-1))/(W(j-1)+K))))].*((lambdaS(j)-h2*M11)
-(lambdaE(j)-h2*M12))+ mu*(lambdaS(j)-h2*M11);
134 M22 = epsilon*((lambdaE(j)-h2*M12)- (lambdaIa(j)-h2*M13))+
mu*(lambdaE(j)-h2*M12) ;
135 M23 = sigma1*((lambdaIa(j)-h2*M13)- (lambdaIs(j)-h2*M14)) +
gamma1*(lambdaIa(j)-h2*M13)- (lambdaR(j)-h2*M16) + mu*(
lambdaIa(j)-h2*M13) - b -xi1*(lambdaW(j)-h2*M17);
136 M24 = sigma2*((lambdaIs(j)-h2*M14)- (lambdaIa(j)-h2*M13)) +
phi*((lambdaIs(j)-h2*M14)- (lambdaH(j)-h2*M15)) -a +
delta1*(lambdaIa(j)-h2*M13) - xi2*(lambdaW(j)-h2*M17) +
(lambdaIs(j)-h2*M14)*(mu + sigma2);
137 M25 = 0.5*(v(j)-v(j-1)).*((lambdaH(j)-h2*M15)- (lambdaR(j)-
h2*M16)) + (lambdaH(j)-h2*M15)*(gamma1 + delta2 + mu)-
gamma2*(lambdaR(j)-h2*M16);
138 M26 = (lambdaW(j)-h2*M17).*(mu+ 0.5*(m(j)-m(j-1)));
139 M27 = omega1*((lambdaR(j)-h2*M16)- lambdaS(j)) + mu*(
lambdaR(j)-h2*M16);
140
141
142
143 M31 = [(1-0.5*(u(j)-u(j-1)))*(0.5*((beta1*(W(j))/(W(j)+K))
)-(beta1*(W(j-1))/(W(j-1)+K))))].*((lambdaS(j)-h2*M21)
-(lambdaE(j)-h2*M22))+ mu*(lambdaS(j)-h2*M21);
144 M32 = epsilon*((lambdaE(j)-h2*M22)- (lambdaIa(j)-h2*M23))+
mu*(lambdaE(j)-h2*M22) ;
145 M33 = sigma1*((lambdaIa(j)-h2*M23)- (lambdaIs(j)-h2*M24)) +
gamma1*(lambdaIa(j)-h2*M23)- (lambdaR(j)-h2*M26) + mu*(
lambdaIa(j)-h2*M23) - b -xi1*(lambdaW(j)-h2*M27);
146 M34 = sigma2*((lambdaIs(j)-h2*M24)- (lambdaIa(j)-h2*M23)) +
phi*((lambdaIs(j)-h2*M24)- (lambdaH(j)-h2*M25)) -a +
delta1*(lambdaIa(j)-h2*M23) - xi2*(lambdaW(j)-h2*M27) +
(lambdaIs(j)-h2*M24)*(mu + sigma2);
147 M35 = 0.5*(v(j)-v(j-1)).*((lambdaH(j)-h2*M25)- (lambdaR(j)-

```

```

        h2*M26)) + (lambdaH(j)-h2*M25)*(gamma1 + delta2 + mu)-
        gamma2*(lambdaR(j)-h2*M26);
148 M36 = (lambdaW(j)-h2*M27).*(mu+ 0.5*(m(j)-m(j-1)));
149 M37 = omega1*((lambdaR(j)-h2*M26)- lambdaS(j)) + mu*(
        lambdaR(j)-h2*M26);

150
151
152 M41 = ((1-u(j-1)).*(beta1*(W(j-1)./(W(j-1)+K)))).*((lambdaS
        (j)-h*M31)-(lambdaE(j)-h*M32))+ mu*(lambdaS(j)-h*M31);
153 M42 = epsilon*((lambdaE(j)-h*M32)- (lambdaIa(j)-h*M33))+ mu
        *(lambdaE(j)-h*M32);
154 M43 = sigma1*((lambdaIa(j)-h*M33)- (lambdaIs(j)-h*M34)) +
        gamma1*((lambdaIa(j)-h*M33)- (lambdaR(j)-h*M36)) + mu*(
        lambdaIa(j)-h*M33) - b -xi1*(lambdaW(j)-h*M37);
155 M44 = sigma2*((lambdaIs(j)-h*M34)- (lambdaIa(j)-h*M33)) +
        phi*((lambdaIs(j)-h*M34)- (lambdaH(j)-h*M35)) -a +
        delta1*(lambdaIa(j)-h*M33) - xi2*(lambdaW(j)-h*M37) + (
        lambdaIs(j)-h*M34)*(mu + sigma2);
156 M45 = v(j-1).*((lambdaH(j)-h*M35)- (lambdaR(j)-h*M36)) + (
        lambdaH(j)-h*M35)*(gamma1 + delta2 + mu)- gamma2*(
        lambdaR(j)-h*M36);
157 M46 = (lambdaW(j)-h*M37).*(mu+ m(j-1));
158 M47 = omega1*((lambdaR(j)-h*M36)- (lambdaS(j-1)-h*M31)) +
        mu*(lambdaR(j)-h*M36);

159
160
161 lambdaS(j-1)= lambdaS(j)-(h/6)*(M11+2*M21+2*M31+M41);
162 lambdaE(j-1)= lambdaE(j)-(h/6)*(M12+2*M22+2*M32+M42);
163 lambdaIa(j-1)= lambdaIa(j)-(h/6)*(M13+2*M23+2*M33+M43);
164 lambdaIs(j-1)= lambdaIs(j)-(h/6)*(M14+2*M24+2*M34+M44);
165 lambdaH(j-1)= lambdaH(j)-(h/6)*(M15+2*M25+2*M35+M45);
166 lambdaR(j-1)= lambdaR(j)-(h/6)*(M15+2*M25+2*M35+M45);
167 lambdaW(j-1)= lambdaW(j)-(h/6)*(M16+2*M26+2*M36+M46);
168 end
169
170
171 tempu1 = ((lambdaE-lambdaS).*(beta1*(W./(W+K))).*S )./(2*X);
172 u11 = min(1,max(0,tempu1));
173 u = 0.5*(u11 + oldu);
174 tempv1 =((lambdaH-lambdaR).*H)./(2*Y);
175 v1 = min(1,max(0,tempv1));
176 v = 0.5*(v1 + oldv);
    
```

```

177     tempm1 = ((lambdaH).*W)./(2*Z);
178     m1 = min(1,max(0,tempm1));
179     m = 0.5*(m1 + oldm);
180
181     tempu = delta*sum(abs(u)) -sum(abs(ordu-u));
182     tempv = delta*sum(abs(v)) -sum(abs(oldv-v));
183     tempm = delta*sum(abs(m)) -sum(abs(oldm-m));
184     tempS = delta*sum(abs(S)) -sum(abs(oldS-S));
185     tempE = delta*sum(abs(E)) -sum(abs(oldE-E));
186     tempIa = delta*sum(abs(Ia)) -sum(abs(oldIa-Ia));
187     tempIs = delta*sum(abs(Is)) -sum(abs(oldIs-Is));
188     tempH = delta*sum(abs(H)) -sum(abs(oldH-H));
189     tempR = delta*sum(abs(R)) -sum(abs(oldR-R));
190     tempW = delta*sum(abs(W)) -sum(abs(oldW-W));
191     templambdaS= delta*sum(abs(lambdaS)) -sum(abs(oldlambdaS-
        lambdaS));
192     templambdaE= delta*sum(abs(lambdaE)) -sum(abs(oldlambdaE-
        lambdaE));
193     templambdaIa= delta*sum(abs(lambdaIa)) -sum(abs(oldlambdaIa-
        lambdaIa));
194     templambdaIs= delta*sum(abs(lambdaIs)) -sum(abs(oldlambdaIs-
        lambdaIs));
195     templambdaH= delta*sum(abs(lambdaH)) -sum(abs(oldlambdaH-
        lambdaH));
196     templambdaR= delta*sum(abs(lambdaR)) -sum(abs(oldlambdaR-
        lambdaR));
197     templambdaW= delta*sum(abs(lambdaW)) -sum(abs(oldlambdaW-
        lambdaW));
198
199     test = min(tempu,min(tempv,min(tempm,min(tempS,min(tempE,min
        (tempIa,min(tempIs,min(tempH,min(tempR,min(tempW,min(
        templambdaS,...
200         min(templambdaE,min(templambdaIa,min(templambdaIs,min(
        templambdaH,min(templambdaR,min(templambdaW))))))))))
        ))))));
201 end
202
203
204     y(1,:) = t;
205     y(2,:) = S;
206     y(3,:) = E;
207     y(4,:) = Ia;

```

```
208     y(5,:) = Ia;  
209     y(6,:) = H;  
210     y(7,:) = R;  
211     y(8,:) = W;  
212     y(9,:) = u;  
213     y(10,:) = v;  
214     y(11,:) = m;  
215  
216     end
```





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