Mathematical modeling of echinococcosis in humans, dogs and sheep.

by

Birhan Getachew Bitew

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Supervisor: *Prof. Justin Manango W. Munganga*
Co-supervisor: *Dr. Adamu Shitu Hassan*

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Declaration-I

Name : *Getachew Bitew Birhan*

Student number : *65101472*

Degree : *Doctor of Phylosophy in Applied Mathematics*

Title of the thesis : *Mathematical modeling of echinococcosis in humans, dogs and sheep.*

I declare that the work contained in this thesis is my own original work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references. And, it has not previously, in its entirety or in part, been submitted at any university for a degree.

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Getachew Bitew Birhan — Date

Declaration-II: Publications

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Getachew Bitew Birhan

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Date

Dedication

I dedicate this thesis work to my mother Alemnesh Semahagn and my sisters Mulunesh Bitew, Melkam Bitew and Banchiamlak Bitew.

Acknowledgments

First and foremost, I would like to thank the Almighty God, for His blessings throughout my life.

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Abbreviation	Meaning
CE	Cystic Echinococcosis
AE	Alveolar Echinococcosis
WHO	World Health Organization
DFE	Disease Free Equilibrium
EE	Endemic Equilibrium
GAS	Globally Asymptotically Stable
LAS	Locally Asymptotically Stable
ODE	Ordinary Differential Equation
PRCC	Partial Rank Correlation Coefficients

Abstract

In this study, mathematical models for the dynamics of cystic echinococcosis transmission in populations of dogs, sheep, and people are developed and analyzed. The predator-prey interaction in these populations is first considered and analyzed. The primary objective of taking this model into account is to determine sufficient conditions to ensure the existence of stable equilibrium point which represent coexistence of the three populations. A mathematical model for the dynamics of cystic echinococcosis transmission in the absence of controls is then formulated and analyzed. Analytically, the basic reproduction number $\mathcal{R}_0$ and equilibrium points are determined. To examine the dynamics of the disease, stability analysis of the disease free equilibrium and endemic equilibrium is carried out. The results show that the disease-free equilibrium is globally asymptotically stable if $\mathcal{R}_0 \leq 1$, and unstable otherwise. It is further demonstrated that the endemic equilibrium is asymptotically stable if $\mathcal{R}_0 > 1$. To support analytic results numerical simulations are carried out. Sensitivity analyses of the critical parameters are performed. In the result it is shown that the transmission rate of *echinococcus'* eggs from the environment to sheep (β_{es}) is the most influential parameters in the dynamics of cystic echinococcosis.

To this effect, a model for the spread of cystic echinococcosis under interventions that involve vaccination of sheep and cleaning or disinfection of the environment is formulated and studied. The disease-free and endemic equilibrium points of the model are calculated. The control reproduction number $\mathcal{R}_c$ for the deterministic model is derived, and the global dynamics are established by the values of $\mathcal{R}_c$. The disease-free equilibrium is globally asymptotically stable if and only if the control reproduction number $\mathcal{R}_c \leq 1$, and the disease will be wiped out of the populations. For $\mathcal{R}_c > 1$, using Volterra-Lyapunov stable matrices, it is proven that the endemic equilibrium is globally asymptotically stable, and the disease persists. Sensitivity analyses on the control reproduction number $\mathcal{R}_c$ is carried out. It is revealed that the transmission rate from sheep to dog (β_{sd}) is the most influential parameter in the dynamics of cystic echinococcosis. To

illustrate the analytical results and establish the long term behavior of the disease numerical simulations are performed. The impact of control strategies is investigated. It is shown that, whenever vaccination of sheep is carried out solely or in combination with cleaning or disinfection of the environment, transmission of cystic echinococcosis can be controlled. However, with cleaning or disinfecting of the environment alone, the disease persists in the populations.

Furthermore, an optimal control approach is applied to a model of cystic echinococcosis in the populations of sheep, dog and human. The main objective is to reduce or eliminate the disease from the three populations while minimizing the intervention implementation costs. We used Pontryagin's Minimum Principle to solve the optimal control problem. Numerical simulations of the time evolution of infected sheep, dog and human populations are provided to illustrate the effects of optimal and constant controls. It is noticed that optimal control strategy is better than the small amount constant controls in reducing the prevalence of the disease in the populations. While time independent control(s) is(are) administered at maximum amount, it is also noticed that the optimal control strategy is effective as the time-dependent controls. We also calculate the Incremental Cost Effectiveness Ratio(ICER) to investigate the cost effectiveness of these strategies. Our results show that the most cost-effective strategy for cystic echinoccosis control is the combination of vaccination of sheep and cleaning or disinfection of the environment.

Chapter 1

Introduction

1.1 Background

Echinococcosis, which is commonly known as hydatidosis, is zoonotic parasitic disease caused by the larvae of *Echinococcus*. It is a parasitic disease caused by ingesting the eggs of tapeworm genus *Echinococcus* through contaminated environment (typically food or water). The life cycle of the parasite is maintained by intermediate herbivore hosts, such as sheep, goats, cattle, camels, and cervids, as well as by predators that serve as definitive hosts (such as dogs, foxes, canines, felids, or hyenids. [7]. Five species of *Echinococcus* have been identified which infect wide range of domestic and wild animals. However, *Echinococcus granulosus* and *Echinococcus multilocularis* are the most common species that infect human population [25, 32]. *Echinococcus granulosus* causes cystic echinococcosis while *Echinococcus multilocularis* causes a type of echinococcosis known as alveolar echinococcosis. The two types of echinococcosis have wide geographic distribution, high prevalence and great economic impact [25, 32, 46]. Overall economic losses due to this disease are estimated at two billion US$ annually and cystic echinoccoccosis is believed to affect more than one million people worldwide [48].

Cystic echinococcosis (CE) is parasitic disease, also called "cystic hydated disease" caused by the larval stage of small tapeworms (dog tapeworms) known as *Echinococcus granulosus* [25]. The life cycle of the parasite involves two hosts, an intermediate host, commonly sheep, and a definitive host, commonly dogs. In its transmission dynamics, the domestic dog is the principal definitive host. When dogs are fed fresh offal or scavenge infected sheep carcasses containing cysts, they become infected. The cysts develop into adult tapeworms in dogs. Infected dogs shed tapeworm eggs in the feces to the environment. *Echinococcus granulosus* eggs that have been

deposited in the soil can stay viable for up to a year [24, 29, 31]. The intermediate host such as sheep, goats, cattle, camels, and cervids ingests the eggs incidentally while grazing, foraging or drinking. The eggs hatch in the small intestine of the intermediate host, become larvae which penetrate the gut wall, and are carried in the circulatory system to various organs. There the cysts, called hydatid cysts or metacestodes, are formed. The life cycle of the parasite is completed when the cysts are ingested by the definitive host, the larvae (protoscoleces) are released from the cyst into the small intestine, and develop into adult tapeworms that produce eggs which are released into the environment in the feces of the host animal. The most common infection of humans is due to accidental ingestion of *Echinococcus granulosus* eggs passed into the environment with feces from definitive hosts (dogs are the main sources). This occurs by consumption of contaminated food and water or through contact with contaminated soil [48]. Only infected definitive hosts, which release *Echinococcus granulosus* eggs within their feces, are relevant in terms of transmission of the infection/disease to humans. In humans, the cysts of *Echinococcus granulosus* usually developed in organs such as the liver or lungs, so the signs of disease are due to liver or lung deficiency. Rarely, cysts form in bones causing spontaneous fractures, or in the brain causing neurological signs [25]. Figure 1.1 shows the life cycle of *Echinococcus granulosus*.

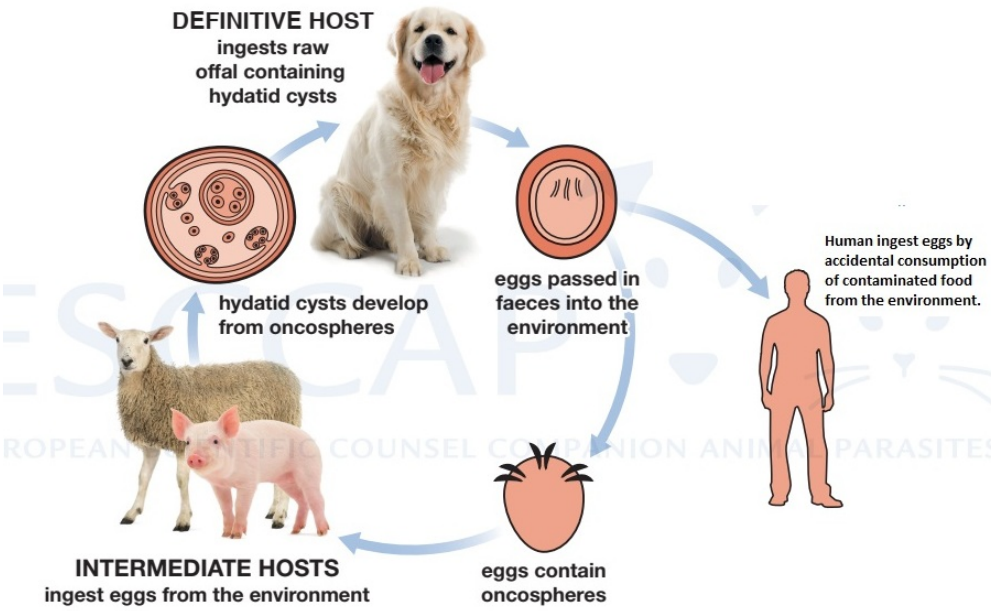

Figure 1.1: Life cycle of *Echinococcus granulosus* [Source: European Scientific Counsel Companion Animal Parasites (ESCCAP)] [58].

The dynamics of *Echinococcus granulosus* transmission depends on number of factors. These include the parasite's biotic potential, activation of the immune system in its hosts over the life cycle, life expectancy, and parasite development time [63]. Transmission of this parasite can be impacted by social and ecological factors such as meat inspection procedures, how dead and injured animals are disposed of, and populations of stray, feral, or sylvatic hosts, to name a few. The prevalence of the parasites within the offal and the frequency of offal feedings both influence the infection pressure within the definitive host. The transmission of the parasite is heavily influenced by the definitive host's immunity as well as the frequency of interaction between the intermediate and definitive hosts (such as in herding dogs and pasture animals being kept in close proximity where dogs can contaminate grazing areas with fecal matter) [1, 2, 6, 45]. When the carrier host dies in the field or is slaughtered for consumption releasing viscera to the environment, the carnivore-omnivore or predator–prey cycle is completed; therefore, the domestic routine of slaughtering game or small animals is the main risk factor for the spread of the disease [37].

Cystic echinococcosis has worldwide geographical distribution. Its prevalence in both animals and humans has been extensively recorded in Australia, some parts of America (especially South America), Central Asia, Northern and Eastern Africa, and the Mediterranean Basin [24, 31, 46]. The disease is typically common in pastoral regions where sheep, cattle, and camelids are prominent and dogs are kept for herding or property guarding in close proximity to house holds. Dogs in such regions are frequently fed offal and for religious and other reasons, their populations might not be curtailed [21].

1.2 Socio-economic consequences of cystic echinoccosis

Cystic echinococcosis affects both human and animal health and has important economic consequences. In humans, it may have various consequences, including direct monetary costs (diagnosis, hospitalization, surgical or percutaneous treatments, therapy, post-treatment care, travel for both patient and family members) as well as indirect costs (suffering and social consequences of disability, loss of working days or "production", abandonment of farming or agricultural activities by affected or at-risk persons). It should be noted that some of the above mentioned consequences are difficult to evaluate from an economic point of view and others can be mainly or exclusively evaluated in social terms. The disease may negatively affect the "quality" of life. In livestock, the following consequences of CE must be considered: reduced

yield and quality of meat, milk and wool; decreased hide value; reduced birth rate and fecundity; delayed performance and growth; condemnation of organs, especially liver and lungs; costs for destruction of infected viscera and dead animals. There are also other possible indirect detrimental consequences, such as bans on export of animals and their products if these are required to be free of CE. In livestock, the importance of the above-mentioned economic consequences will depend, to a large extent, on the typology and general health status of the animals and on the characteristics of the farming or livestock industry. Quantification, standardized evaluation of such losses and exclusion of biasing factors in animal production are very difficult; therefore the available data should be interpreted with caution [5, 13].

The awareness of the socio-economic impact of the disease has stimulated the implementation of control campaigns against CE in certain areas or countries. Education, dog control, dog treatment, detection and disposal of infected viscera, diagnosis (such as mass screening), and therapy in humans, epidemiological surveillance and monitoring, program administration, and evaluation are the main expenses incurred for cystic echinococcosis control programs. It should be noted that some of the expenses sustained for echinococcosis control may simultaneously be beneficial to control programs against other diseases or animal correlated problems (e.g. rabies, tapeworm infections, dog straying, food hygiene). If the control includes vaccination, costs of vaccine and stock vaccination must also be considered. The benefits of control programs may be financial and non-financial (the latter category is difficult to evaluate). The most relevant financial benefits are the following: increase in farm animal production; increase in the quantity and quality of organs suitable for consumption by humans and carnivorous animals; decreased medical costs. The non-financial benefits (in some cases these may be evaluated from an economic point of view) include the following: increase in the average number of healthy years of life, improvement of the physical, psychological and social status of the population, improvement of veterinary and public health services, hygiene and primary health care, reduction in other health or zoo-economic problems such as rabies, food-borne infections, diseases by cestode larvae in farm animals, etc [5, 13].

1.3 Methods of Control of cystic echinococcosis

Infection with *Echinococcus granulosus* has become a major public health issue in several countries and regions, even in places where the prevalence of the disease was previously at low levels. This is due to less implementation of control programs against the disease as a result of

economical problems and lack of resources [31]. Although control programs against human cystic (CE) have been built up and viable control methodologies are accessible in some nations, the parasite has still influenced many countries. Human CE is persisting in many parts of the world with high incidences [25, 31]. The human incidence can exceed 50 per 100,000 person-years in areas of endemicity, and prevalence rates as high as 5% to 10% can be found in some countries [32]. The incidence of human Hydatid disease in any country is closely related to the prevalence of the disease in domestic animals and is highest where there is a large dog population and high sheep production [22]. The average annual death rate from echinococcosis is 0.007 per 10,000 population, which is very low. The main causes of death are either complications of hepatic and pulmonary echinococcosis or echinococcosis of the heart. The complications of liver echinococcosis may develop due to the changes occurring not only in the parasitic cyst, but also in the affected organ or in the patient's body [35]

According to WHO, cystic echinococcosis is a preventable disease. Under the umbrella of One Health, WHO and its partner, the World Organization for Animal Health (OIE) are supporting the development of echinococcosis control programs including animal interventions. Joint meetings are being held regularly and technical support is provided to promote control. WHO assists countries to develop and implement pilot projects leading to the validation of effective cystic echinococcosis control strategies. Working with the veterinary and food safety authorities as well as with other sectors is essential to attain the long-term outcomes of reducing the burden of disease and safeguarding the food value chain [49]. To employ preventive measures, understanding of the transmission dynamics, between dogs and sheep, and from dogs to human is important. It is from this knowledge that effective control strategies can be devised, so that the control strategies can be utilized to reduce the prevalence of the parasite in intermediate and domestic hosts. Understanding of the epidemiology of echinococcosis has been greatly improved, new diagnostic techniques for both humans and animals have been developed, new prevention strategies have emerged with the development of a vaccine against *Echinococcus granulosus* in intermediate hosts [25] . Since sheep has a substantial potential to transmit the parasite, vaccination of sheep with an *Echinococcus granulosus* recombinant antigen (EG95) offers encouraging prospects for prevention and control [9]. The EG95 vaccine against CE has proven to be highly effective, it is currently being produced commercially and is registered in China and Argentina. Trials in Argentina demonstrated the added value of vaccinating sheep, and in China the vaccine is being used extensively [3, 22, 66]. Currently there are no human vaccines against any form of echinococcosis [3]. To reduce the concentration of the parasite and break the

parasite's life cycle, cleaning or sanitization of environment offers a practical preventive technique [50]. Echinococcus eggs can be inactivated by disinfectants such as formalin, chlorine gas, certain freshly-prepared iodine solutions (but not most iodides) or lime can inhibit hatching of the embryo and reduce the number of viable eggs. Food safety precautions such as washing of fruits and vegetables, combined with good hygiene, can reduce exposure to eggs on food. The hands should always be washed after handling pets or farming, gardening or preparing food, and before eating. Water from unsafe sources such as lakes should be boiled or filtered. Meat, particularly the intestinal tract of carnivores, should be thoroughly cooked before eating [28].

1.4 Aim and objectives of the study

The aim of this research is to derive optimal strategies to control cystic echinococcosis in the populations of sheep, dog and human.

1.4.1 Objectives

This research work intends to :

- derive and analyze a mathematical model of the transmission dynamics of cystic echinococcosis, and obtain the equilibrium points and study their stability,
- investigate the degree at which different parameters affects the transmission dynamics of cystic echinococcosis, and
- obtain optimal strategies to eradicate or control cystic echinococcosis.

1.5 Significance of the study

This research work will put forward some controlling strategies, which will help the Ministry of Health, policy makers and some concerned sectors in order to plan and implement the proposed strategies to control the disease. Besides, the results obtained from this research can be used as an input for researchers to extend the research work further.

1.6 Organization of the thesis

This thesis is presented in six chapters. Chapter 1 provides background of the life cycle of the disease, controlling methods of the disease, objectives of the study and significance of the study. Chapter 2 deals with Mathematical preliminaries and review of literature. Basic definitions of important terminology that state properties of solutions of a system of ODE such as existence and uniqueness of solutions and stability are presented. Chapter 3 presents the mathematical model of predator-prey interaction model, and mathematical modeling of cystic echinococcosis without interventions, and mathematical analyses are done. Chapter 4 deals with mathematical model with intervention strategies, and a detail mathematical analysis of the model is done. Chapter 5 presents the optimal control theory of the disease transmission with the proposed controls. Finally, Chapter 6 includes discussion of results, conclusion and recommendations.

Chapter 2

Review of literature and Mathematical Preliminaries

In this chapter we introduce review of literature and some of the preliminary notion of dynamical systems theory that are relevant in this thesis. Basic definitions of important terminology, theorems (propositions) that state fundamental properties of solutions of dynamical system (systems of ODE) like existence, uniqueness of solutions and stability will be presented.

2.1 Review of literature

Mathematical modeling is an important interdisciplinary activity involving biology, epidemiology, ecology and so on. Diseases' dynamics are some of the various aspects of the disciplines studied using mathematical modeling. It has played a significant role in understanding the dynamics of the disease and in developing different control measures [12, 16, 18]. Considered as one of the first compartmental models, Kermack–McKendrick epidemic model was developed in the late 1920s [34]. The model is described as the SIR model for the spread of disease. The model is a good one for many infectious diseases, then, numerous and more complex compartmental mathematical models have been developed. Moreover, the prey–predator interaction between species have been taken into account in mathematical models of disease dynamics by many scholars. The predator-prey interaction between species is an important issue from mathematical as well as ecological point of view. There are considerable and significant efforts to study the population dynamics in predator–prey relationships by using mathematical modeling. Lotka and Volterra initially proposed the predator–prey model [41, 65]. Anderson and May were the first who combined the disease dynamics model with the predator–prey interaction model [1].

A mathematical model of the life cycle of *Echinococcus granulosus* was first developed by Roberts and co-workers and by Harris and co-workers in the 1980s [20]. Over the last 30 years, mathematical models of the transmission dynamics of this disease have also been developed and studied [14, 29, 30, 53, 54, 63, 68]. A survey of *Echinococcus granulosus*, Taenia hydatigena and T. ovis for sheep and goats were undertaken in order to investigate the transmission dynamics of these parasites in northern Jordan. It was found that *Echinococcus granulosus* was in an endemic steady state with no evidence of protective immunity in the intermediate host [47, 62]. Yang et al. [69] used statistical analysis to conclude that a control program, which combined sheep vaccination and dog anthelmintic treatment, could achieve the goal of echinococcosis control in the long term. Moss et al. [39] considered the reinfection of canine echinococcosis to investigate the role of dogs in the spread of *Echinococcus multilocularis* in Tibetan communities of Sichuan Province. The results suggested that dog deworming could be an effective strategy to reduce the endemic in those communities. Craig et al. in [20] pointed out that combining treatment and control measures to control echinococcosis was the most effective potential. Some models have suggested that the use of both livestock vaccination and treatment of dogs could reduce the frequency of anthelmintic treatment of dogs that is required whilst still achieving effective control [57]. However, studies have shown that cystic echinococcosis is often expensive and complicated to treat and may require extensive surgery and/or prolonged drug therapy. Prevention programs focus on other control measures such as improved food inspection, slaughterhouse hygiene, and public education campaigns. Conditions such as poor hygiene and failure to wash contaminated food facilitate the spread of CE infection in the human population. CE transmission from food to humans is common in areas where people usually consume raw vegetables; most are cultivated in open fields where stray dogs roam freely and contaminate the vegetables by dropping feces containing *Echinococcus granulosus* eggs [71].

Although, the aforementioned studies have produced useful insights on the transmission dynamics of cystic echinococcosis. These models lacks the human transmission pathway, predator–prey relationship between the populations, the saturation effect and other intervention strategies. From the fact that cystic echinococcosis is a disease that affect human population, advanced study by inclusion of a human transmission component to the model is essential. Moreover, the predator-prey relationships between species play an important role from ecological and epidemiological point of view. It affect the distribution, abundance, and dynamics of species in ecosystems, and it has a detrimental effect in the dynamics of disease. Mathematical modeling

in ecology helps to determine sufficient conditions for which the interacting populations coexist. However, the predator-prey interaction between sheep, dog and human was not considered in previous mathematical models of cystic echinococcosis. The incidence rate, i.e., the rate of new infection plays an important role in the context of epidemiological modeling. Generally, the incidence rate is assumed to be bilinear in the infected fraction I and the susceptible fraction S. There are many factors that emphasize the need for a modification of the standard bilinear form. It has been suggested by some authors [15, 26] that the disease transmission process may follow the saturation incidence, saturation factor, which is more realistic than the bilinear one, as it includes the behavioral change and crowding effect of the susceptible individual and also prevents unboundeness of the contact rate.

The optimal control theory to find the optimal measures among comprehensive implementation interventions, has been applied to models of infectious diseases [11, 38, 57], including the human alveolar echinococcosis in Hokkaido [33]. Usually, the control of CE remains notoriously difficult, time-consuming and costly, especially in large scale campaign in remote and larger pastoral communities [22]. The prevention and control of CE require substantial financial resources. In order to evaluate the effectiveness of the control programs, the optimal control measures must be carried out in real-world interventions of CE [57].

In this thesis, the predator–prey model which represents the interaction between dog, sheep and human populations is developed and analyzed. Sufficient conditions for which the interacting populations coexist is determined. We formulate and analyze mathematical models for the transmission dynamics of cystic echinococcosis without control, and then with vaccination of sheep and disinfection or cleaning of the environment as control strategies. In these models, we consider the populations of dog as definite host, the populations of sheep and human as intermediate hosts and the concentration of parasites in the environment as the source of infection for intermediate hosts. Due to the fact that sufficient number (saturation) of parasite in the environment is required to produce infection in intermediate hosts, saturation effect in the models is incorporated. We find equilibrium solutions and derive the basic and control reproduction numbers using next generation method. Matrix-theoretic method is used to prove the global stability of disease free equilibrium, and the Volterra–Lyapunov matrix theory approach is used to prove the global stability of endemic equilibrium. Sensitivity analysis is done to determine the most sensitive parameters. For this purpose, data from the literature and assumed (estimated) values are used. Numerical simulations are used to illustrate our results.

Although an analysis of the time-optimal application of outbreak controls is of clear practical value, surprisingly little attention has been given in the models of cystic echinococcosis. In this study, an optimal control problem is formulated by incorporating vaccination of sheep and cleaning or disinfection of the environment as intervention strategies. Optimal control theory is applied to suggest the most effective mitigation strategy to minimize the number of individuals who become infected in the course of an infection while efficiently balancing the two controls applied to the models over a finite time period. The detailed qualitative optimal control analysis of the resulting model is carried out and the necessary conditions for optimal control is given using Pontryagin's Maximum Principle, in order to determine optimal strategies for controlling the spread of the disease. The cost-effectiveness analysis of the control strategies is further considered, in order to ascertain the most cost-effectiveness of strategies.

2.2 Mathematical Preliminaries

Definition 2.2.1 *[61] Let X be a real vector space. A norm on X is a map $||.|| : X \to [0, \infty)$ satisfying the following requirements:*

(i) $||0|| = 0$, $||x|| > 0$ *for all* $x \in X \backslash \{0\}$

(ii) $||\lambda x|| = |\lambda| ||x||$ *for all* $\lambda \in \mathbb{R}$ *and* $x \in X$,

(iii) $||x + y|| \leq ||x|| + ||y||$ *for all* $x, y \in X$.

The pair $(X, ||.||)$ is called a normed vector space.

Remark 2.2.2 *The $p-norm$ of $x = (x_1, x_2, \cdots, x_n)$ is defined as*

$$||x||_p = \left(|x_1|^2 + |x_2|^2 + \cdots + |x_n|^2\right)^p$$

Definition 2.2.3 *[61] The function $f : \mathbb{R}^n \to \mathbb{R}^n$ is differentiable at $x_0 \in \mathbb{R}^n$ if there is a linear transformation $Df(x_0) \in L(\mathbb{R}^n)$ that satisfies* $\lim_{||h|| \to 0} \dfrac{||f(x_0 + h) - f(x_0) - Df(x_0)||}{||h||} = 0.$

The linear transformation $Df(x_0)$ is called the derivative of f at x_0.

Definition 2.2.4 *[61] Suppose that $f : E \to \mathbb{R}^n$ is differentiable on E, then $f \in C^1(E)$ if the partial derivative $Df : E \to L(\mathbb{R}^n)$, is continuous on E .*

Theorem 2.2.5 *[61] Suppose that E is an open subset of $\mathbb{R}^n$ and that $f : E \to \mathbb{R}^n$. Then $f \in C^1(E)$ if the partial derivatives $\dfrac{\partial f_i}{\partial x_j}, i, j = 1, 2, \cdots n$, exist and are continuous on E.*

2.3 Dynamical system

A system of differential equations is a collection of n interrelated differential equations of the form

$$\dot{x}(t) = f(t, x), \tag{2.3.1}$$

where $f(t, x(t)) = \begin{pmatrix} f_1(t, x_1, \cdots, x_n) \\ f_2(t, x_1, \cdots, x_n) \\ \cdot \\ \cdot \\ \cdot \\ f_n(t, x_1, \cdots, x_n) \end{pmatrix}$.

An initial condition or initial value for a solution $x : S \to \mathbb{R}^n$ is a specification of the form $x(t_0) = x_0$ where $t_0 \in S$ and $x_0 \in \mathbb{R}^n$.

Definition 2.3.1 *[17] Let $I \subseteq [a, \infty)$ be a time interval. A solution to* (2.3.1) *on I with initial value $x(0) = x_0$ is a mapping $\psi : I \to \mathbb{R}^n$ which is continuously differentiable on I, and satisfies*

(i) $\frac{d}{dt}\psi(t) = f(t, x)$ *for all* $t \in I$,

(ii) $\psi(t_0) = x_0$.

An autonomous differential equation is a system of ordinary differential equations which does not depend on the independent variable. An initial valued autonomous system is an equation of the following form:

$$\dot{x} = f(x), \quad x(t_0) = x_0 \tag{2.3.2}$$

where $f : \mathbb{R}^n \to \mathbb{R}^n$.

2.4 Existence and Uniqueness Theorem

The main problem in differential equations is to find the solution of any initial value problem; that is, to determine the solution of the system that satisfies the initial condition $x(t_0) = x_0$ for each $x_0 \in \mathbb{R}^n$. Unfortunately, nonlinear differential equations may have no solutions satisfying certain initial conditions. To ensure existence and uniqueness of solutions, certain conditions must be imposed on the function f.

Definition 2.4.1 *[61] Let E be an open subset of $\mathbb{R}^n$. A function $f : E \to \mathbb{R}^n$ is said to be Lipschitz continuous on E if there is a positive constant K such that for all $x, y \in E$, $||f(x) - f(y)|| \leq K||x - y||$.*

Remark 2.4.2 *One effective way to check if a function satisfies a Lipschitz condition is to check if it is continuously differentiable. A continuously differentiable function is locally Lipschitz, hence every IVP problem with $f \in C^1(E)$ possesses a unique maximal solution. Moreover, if the domain E is convex, then a continuously differentiable function f is globally Lipschitz if and only if its partial derivatives $\frac{\partial f_i}{\partial x_j}, i, j = 1, 2, \cdots n$, are globally bounded.*

Theorem 2.4.3 *[55] (The Existence and Uniqueness Theorem)*
If f is Lipschitz in a ball around the initial condition $x(t_0) = x_0$, then there exists a $\delta > 0$ such that the IVP (2.3.2) has unique solution over $[t_0, t_0 + \delta]$.

We are interested in the IVPs of form (2.3.2) whose solutions are defined on an interval I containing the interval (t_0, ∞), i.e., IVPs with solutions defined globally in time. There are various results ensuring this fact, and we first present one that is straightforward to understand but still covers many interesting situations. This is done using the growth condition presented in the following theorem.

Theorem 2.4.4 *[17] Assume that $f : (a, \infty) \times \mathbb{R}^n \to \mathbb{R}^n$ is continuously differentiable, i.e., its partial derivatives of first order are continuous functions, and there exist non- negative continuous mappings $h, k : (a, \infty) \to \mathbb{R}$ such that*

$$||f(t, x)|| \leq h(t)||x|| + k(t), \text{ for all } (t, x) \in (a, \infty) \times \mathbb{R}^n.$$

Then, there exists a unique solution to (2.3.1) which is defined globally in time.

Another condition that also ensures the existence of solutions defined globally in time is the so-called dissipativity condition. This condition is used for autonomous version.

Theorem 2.4.5 *[17] Assume that $f : \mathbb{R}^n \to \mathbb{R}^n$ is continuously differentiable, and and there exist two constants α and β with $\beta > 0$ such that $f(x).x \leq \alpha||x||^2 + \beta$. Then, there exists a unique solution to (2.3.2) which is defined globally in time.*

2.5 Equilibrium points, and stability

Definition 2.5.1 *[60] A point $x = x^*$ is an equilibrium point of the system* (2.3.2) *if $f(x^*) = 0$ for all $t \in \mathbb{R}$.*

An equilibrium point is also referred to as steady-state solution or critical point.

Definition 2.5.2 *[60] The equilibrium point $x = x^*$ of* (2.3.2) *is*

(a) *stable, if for each $\epsilon > 0$ there is $\delta = \delta(\epsilon) > 0$ such that $||x(t_0) - x^*|| < \delta \implies ||x(t) - x^*|| < \epsilon, \forall t > t_0 \geq 0$,*

(b) *asymptotically stable if is stable and there exist a $\delta > 0$ such that $||x(t_0) - x^*|| < \delta \implies \lim_{t\to\infty} ||x(t) - x^*|| = 0$,*

(c) *globally-asymptotically stable if it is stable and $\lim_{t\to\infty} ||x(t_0) - x^*|| = 0$ for all $x(t_0) \in \mathbb{R}^n$,*

(d) *unstable if it is not stable.*

Definition 2.5.3 *[17] A continuous function $V : U \subseteq \mathbb{R}^n \to \mathbb{R}$*

(a) *is positive definite around $x = 0$ if $V(0) = 0$, and $V(x) > 0$, for all $x \in U\backslash\{0\}$.*

(b) *is positive semi-definite around $x = 0$ if $V(0) = 0$, and $V(x) \geq 0$, for all $x \in U\backslash\{0\}$.*

(c) *is negative definite or negative semi-definite if $-V$ is positive definite or positive semi-definite, respectively.*

2.5.1 Lyapunov stability and LaSalle's Invariance Principle

Definition 2.5.4 *[17] A function $V : U \subseteq \mathbb{R}^n \to \mathbb{R}$ is said to be a Liapunov function for* (2.3.2) *if*

- *V is positive definite, and*
- *$\dot{V}(x) < 0$, for all $x \in U\backslash\{0\}$*

The following theorem provide sufficient conditions for the stability of the equilibrium point of (2.3.2).

Theorem 2.5.5 *[17] (Lyapunov's stability theorem) Let $V : U \subseteq \mathbb{R}^n \to \mathbb{R}$ be continuously differentiable function with $\dot{V}$ along the trajectories of the system* (2.3.2).

1. *If V is positive definite and $\dot{V}$ is negative semi-definite, then the equilibrium point is stable.*

2. *If V is positive definite and $\dot{V}$ is negative definite, then the equilibrium point is asymptotically stable.*

Theorem 2.5.6 *[36] Let $x = \mathbf{0}$ be an equilibrium point for (2.3.2). Let $V : U \subseteq \mathbb{R}^n \to \mathbb{R}$ be continuously differentiable function such that*

(i) *V is a Lyapunov function and*

(ii) *V is radially unbounded, that is, $||x|| \to \infty \implies V(x) \to \infty$*

then $x = \mathbf{0}$ is globally asymptotically stable.

Some times an equilibrium point can be asymptotically stable even if $\dot{V}$ is not negative definite. In fact if we can find a Lyapunov function whose derivative along the trajectories of the system is only negative semi-definite, but we can further establish that no trajectory can stay at point where $\dot{V} = 0$, then the equilibrium is asymptotically stable. This is the idea of LaSalle's invariance principle. Before stating the principle, we introduce the definitions of $\omega - limit$ set and invariant set, which are important to state the LaSalle's invariance principle.

Let $\phi(t, x_0)$ be the autonomous dynamical system generated by the solutions of IVP (2.3.2).

Definition 2.5.7 *[17] A set E is said to be $\omega - limit$ set of $\phi(t, x_0)$ if for every $x \in E$, there exist a strictly increasing sequence of times $\{t_n\}$ such that $\phi(t_n, x_0) \to x$ as $t_n \to \infty$.*

Definition 2.5.8 *[17] A set $M \subseteq \mathbb{R}^n$ is said to be (positively) invariant set with respect to (2.3.2) if $\forall x \in M$, we have $\phi(t, x) \in M$, $\forall t \geq 0$.*

Theorem 2.5.9 *[36](LaSalle's invariance theorem) Let $\Omega \in D$ is a compact (i.e. closed and bounded) positively invariant set with respect to (2.3.2). Let $V : D \to \mathbb{R}$ be continuously differentiable function such that $\dot{V}(t) \leq 0$ in Ω. Let E be a set of all points in Ω, where $\dot{V}(0) = 0$. Let M be the largest invariant set in E. Then every solution starting in Ω approaches M as $t \to \infty$.*

2.5.2 Local stability

Linearization is a key concept when examining the equilibrium stability of a system of differential equations [36]. In order to linearize the system (2.3.1) we need to first compute the Jacobian matrix for the system. If a system consists of n functions of n variables, i.e $f_1(x_1, \cdots, x_n)$, $f_2(x_1, \cdots, x_n)$,$\cdots$, $f_n(x_1, \cdots, x_n)$, then the Jacobian matrix, J , is a matrix of the partial derivative of each function with respect to each variable: $J = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \vdots & & \vdots \\ \frac{\partial f_n}{\partial x_1} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix}$.

The matrix J provides a linear approximation of a system at any given point, and when evaluated at an equilibrium point P. $J(P)$ also encodes information above the nonlinear system. It is necessary to evaluate a Jacobian matrix at P and examine its corresponding eigenvalues, since analysis of the eigenvalues of the Jacobian matrix evaluated at a equilibrium gives insight into the stability properties of that equilibrium.

Theorem 2.5.10 *[36] Let $f : \mathbb{R}^n \to \mathbb{R}^n$ be C^1 and $x^* \in \mathbb{R}^n$ be a fixed point of (2.3.2). Let $Df(x^*)$ be the linearization of f and $\lambda_1, \lambda_2, \cdots, \lambda_n$ be its eigenvalues. x^* is*

(i) *asymptotically stable if $Re(\lambda_i) < 0$ for all $i = 1, 2, \cdots, n$,*

(ii) *unstable if $Re(\lambda_i) > 0$ for some i.*

If the eigenvalues all have real parts zero, then further analysis is necessary.

It is possible to determine the signs of the eigenvalues of the Jacobian using a theorem of Routh and Hurwitz. This is presented below.

Theorem 2.5.11 *[51] (Routh-Hurwitz Criteria for a Characteristic Polynomial). Given the polynomial $P_n(x) = x^n + a_1x^{n-1} + a_2x^{n-2} + \cdots + a_{n-1}x + a_n$ where each a_i is a constant real coefficient, define the n Hurwitz matrices using the coefficients a_i :*

$$H_1 = \begin{pmatrix} a_1 \end{pmatrix},\ H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix},\ H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix} \cdots\ H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & . & . & 0 \\ a_3 & a_2 & a_1 & 1 & . & . & 0 \\ a_5 & a_4 & a_3 & a_2 & . & . & 0 \\ . & . & . & . & . & . & . \\ . & . & . & . & . & . & . \\ . & . & . & . & . & . & . \\ 0 & 0 & 0 & . & . & . & a_n \end{pmatrix}$$

All of the roots of $P_n(x)$ are negative or have negative real part if and only if the determinants of all the Hurwitz matrices are positive.

Corollary 2.5.12 *[51] All of the roots of $P_3(x)$ are negative or have negative real part if and only if $a_1 > 0$, $a_1 a_2 > a_3$, and $a_3 > 0$.*

2.6 The basic reproduction number

The basic reproduction number, $\mathcal{R}_0$, is defined as the expected number of secondary cases produced by a single (typical) infection in a completely susceptible population. It is a threshold parameter, intended to quantify the spread of disease by estimating the average number of secondary infections in a wholly susceptible population, giving an indication of the invasion strength of an epidemic. If $\mathcal{R}_0 < 1$ then on average an infected individual produces less than one new infected individual over the course of its infectious period, and the infection cannot grow. Conversely, if $\mathcal{R}_0 > 1$, then each infected individual produces, on average, at least one new infection, and the disease can invade the population. A more general basic reproduction number can be defined as the number of new infections produced by a typical infective individual in a population at a DFE. One way to calculate the basic reproduction number uses the next generation approach is presented in [23, 64] below.

In compartmental models for infectious disease transmission, individuals are categorized into compartments. Let $x = (x_1, x_2, \cdots, x_n)$ with each $x_i \geq 0$, be the number of individuals in each compartment. In this case, the first m compartments correspond to infected individuals. In order to compute $\mathcal{R}_0$, it is important to distinguish new infections from all other changes in population. Let $\mathcal{F}_i(x)$ be the rate of appearance of new infections in compartment i, $\mathcal{V}_i^+(x)$ be the rate of transfer of individuals into compartment i by all other means, and $\mathcal{V}_i^-(x)$ be the rate

of transfer of individuals out of compartment i. It is assumed that each function is continuously differentiable at least twice in each variable. The disease transmission model consists of non-negative initial conditions together with the following system of equations:

$$\dot{x}_i = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \qquad i = 1, 2, \cdots n \tag{2.6.1}$$

where $\mathcal{V}_i(x) = \mathcal{V}_i^+(x) - \mathcal{V}_i^-(x)$ and the functions satisfy assumptions **(A1)**–**(A5)** described below. Since each function represents a directed transfer of individuals, they are all non-negative. Thus,

(A1) if $x \geq 0$, then $\mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0$ for all $i = 1, 2, \cdots n$.

If a compartment is empty, then there can be no transfer of individuals out of the compartment by death, infection, nor any other means. Thus,

(A2) if $x_i = 0$ then $\mathcal{V}_i^- = 0$. In particular, if $x \in X_s$, where $X_s = \{x \geq 0 | x_i = 0, i = 1, 2, \cdots m\}$ is the set of all disease free states, then $\mathcal{V}_i^- = 0$ for $i = 1, 2, \cdots m$.

The next condition arises from the simple fact that the incidence of infection for uninfected compartments is zero.

(A3) $\mathcal{F}_i = 0$ if $i > m$.

To ensure that the disease free subspace is invariant, we assume that if the population is free of disease then the population will remain free of disease. That is, there is no (density independent) immigration of infectives. This condition is stated as follows:

(A4) If $x \in X_s$ then $\mathcal{F}_i = 0$ and $\mathcal{V}_i^+ = 0$ for $i = 1, 2, \cdots m$.

The remaining condition is based on the derivatives of f near a DFE. For our purposes, we define a DFE of (2.6.1) to be a (locally asymptotically) stable equilibrium solution of the disease free model. Consider a population near the DFE x_0. If the population remains near the DFE (i.e., if the introduction of a few infective individuals does not result in an epidemic) then the population will return to the DFE according to the linearized system

$$\dot{x} = Df(x_0)(x - x_0) \tag{2.6.2}$$

where $Df(x_0)$ is the derivative $\dfrac{\partial f_i}{\partial x_j}$ evaluated at the DFE x_0, (i.e, the Jacobian matrix). We restrict our attention to systems in which the DFE is stable in the absence of new infection. That is,

(A5) If $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts. The conditions listed above allow us to partition the matrix $Df(x_0)$ as shown by the following lemma.

Lemma 2.6.1 *[23, 64] If x_0 is a DFE of (2.6.1) and $f_i(x)$ satisfies* **(A1)**–**(A5)** *then the derivatives $D\mathcal{F}(x_0)$ and $D\mathcal{V}(x_0)$ are partitioned as $D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}$, $D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}$, where F and V are the $m \times m$ matrices defined by $F = \left[\frac{\mathcal{F}_i}{x_j}(x_0)\right]$ and $V = \left[\frac{\mathcal{V}_i}{x_j}(x_0)\right]$ with $1 \leq i,\ j \leq m$.*
Further, F is non-negative, V is a non-singular M-matrix and all eigenvalues of J_4 have positive real part.

The next generation matrix is $K = FV^{-1}$, whose (i, k) entry represent the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k. The (j, k) entry of V^{-1} is the average length of time this individual spends in compartment j during its lifetime, assuming that the population remains near the DFE and barring reinfection, and the (i, j) entry of F is the rate at which infected individuals in compartment j produce new infections in compartment i. Thus, the basic reproduction number is defined as the spectral radius of K [23, 64], given by

$$\mathcal{R}_0 = \rho(FV^{-1}) \tag{2.6.3}$$

The DFE, x_0, is locally asymptotically stable if all the eigenvalues of the matrix $Df(x_0)$ have negative real parts and unstable if any eigenvalue of $Df(x_0)$ has a positive real part. By Lemma 2.6.1, the eigenvalues of $Df(x_0)$ can be partitioned into two sets corresponding to the infected and uninfected compartments, $F - V$ and those of J_4. The stability of the DFE is determined by the eigenvalues of $F - V$. The following theorem states that $\mathcal{R}_0$ is a threshold parameter for the stability of the DFE.

Theorem 2.6.2 *[23, 64] Consider the disease transmission model given by (2.6.1) with $f(x)$ satisfying conditions* **(A1)**–**(A5)**. *If x_0 is a DFE of the model, then x_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0$ is defined by (2.6.3).*

Global stability of DFE: *A matrix-theoretic method*

This method based on Perron eigenvector is used to prove the GAS of DFE. We use this approach to systematically construct a Lyapunov function. Following the steps used in [23, 64], set

$$f(x, y) = (F - V)x - \mathcal{F}(x, y) + \mathcal{V}(x, y) \tag{2.6.4}$$

Then the compartmental disease transmission model is given by

$$\dot{x} = \mathcal{V}(x, y) - \mathcal{F}(x, y), y' = g(x, y) \tag{2.6.5}$$

with $g = (g_1, \cdots g_m)^T$, $x = (x_1, \cdots x_n)^T \in \mathbb{R}^n$ and $y = (y_1, \cdots y_m)^T \in \mathbb{R}^m$ represent the populations in disease compartments and non disease compartments, respectively; $\mathcal{F} = (\mathcal{F}_1, \cdots \mathcal{F}_1)^T$ and $\mathcal{V} = (\mathcal{V}_1, \cdots \mathcal{V}_1)^T$ where $\mathcal{F}_i$ represents the rate of new infections in i^{th} disease compartment; and $\mathcal{V}_i$ represents the transition terms in i^{th} disease compartment. The disease compartmental model can be written as

$$\dot{x} = (F - V)x - f(x, y) \tag{2.6.6}$$

Theorem 2.6.3 *[59] Let F, V satisfy conditions* **(A1)**–**(A5)** *and $f(x, y)$ be defined as in* (2.6.4). *If $f(x, y) \geq 0$ in $\Gamma \in \mathbb{R}^{n+m}_+$, $F \geq 0$, $V^{-1} \geq 0$, $\mathcal{R}_0 \leq 1$ and then the function $W^T V^{-1} x$ is a Lyapunov function for model* (2.6.5) *in* Γ.

Theorem 2.6.4 *[59] Let F, V satisfy conditions* **(A1)**–**(A5)** *and $f(x, y)$ be defined as in* (2.6.4), *$\Gamma \in \mathbb{R}^{n+m}_+$ be compact such that $(0, y_0) \in \Gamma$ and Γ is positively invariant with respect to* (2.6.5). *Suppose that $f(x, y) \geq 0$ with $f(x, y_0) = 0$ in Γ, $F \geq 0$, $V^{-1} \geq 0$ and $V^{-1}F$ is irreducible. Assume that the disease-free system $\dot{y} = g(0, y)$ has a unique equilibrium $y = y_0 > 0$ that is GAS in $\mathbb{R}^m_+$. Then the following results hold for* (2.6.5).

1. *If $\mathcal{R}_0 \leq 1$, then the DFE, P_0 is GAS in Γ,*
2. *If $\mathcal{R}_0 > 1$, then P_0 is unstable and system* (2.6.5) *is uniformly persistent and there exists at least one EE.*

Global stability of EE: *Volterra–Lyapunov matrix theory*

The study of the endemic global stability is not only mathematically important, but also essential in predicting the evolution of the disease in the long run so that prevention and intervention strategies can be effectively designed. The method of Lyapunov functions are widely used to prove the global stability of Endemic equilibrium point. However, it is often difficult to construct such Lyapunov function and no general method is available. The general form of Lyapunov functions used in mathematical biology is given by $D = \sum_{i=1}^{n} c_i(x_i - x_i^* - x_i^* \ln \frac{x_i}{x_i^*})$. When applied to a disease models, suitable coefficients c_i have to be determined such that the derivative of D along solutions

of the model is non positive, and such a determination becomes very challenging for models with higher dimensions. We incorporated the Volterra-Lyapunov matrix theory into Lyapunov functions, which under certain conditions eliminates the need of determining the coefficients. We apply the method of Lyapunov functions combined with the Volterra-Lyapunov matrix properties which lead to the proof of the global stabiltiy of the endemic equilibrium (EE). Below we introduce necessary concepts and notations that will facilitate our global stability analysis, as presented in [40, 70].

Definition 2.6.5 *[56] Let A is a symmetric matrix. A is*

(a) *positive definite if the quadratic form $x^TAx > 0$ for all $x = (x_1, x_2, \cdots, x_n) \neq 0$.*

(b) *negative definite if the quadratic form $x^TAx < 0$ for all $x = (x_1, x_2, \cdots, x_n) \neq 0$.*

Notation: We write a matrix $A > 0 (< 0)$ if A is symmetric positive (negative) definite. The following fundamental result on matrix stability was originally proved by Lyapunov.

Lemma 2.6.6 *[40] Let A be an $n \times n$ real matrix. Then all the eigenvalues of A have negative (positive) real parts if and only if there exists a matrix $H > 0$ such that $HA + A^TH^T < 0 (> 0)$.*

Definition 2.6.7 *[40] We say a non-singular $n \times n$ matrix A is Volterra–Lyapunov stable if there exists a positive diagonal $n \times n$ matrix M such that $MA + A^TM^T < 0$.*

The following lemma determines all 2×2 Volterra–Lyapunov stable matrices.

Lemma 2.6.8 *[40] Let $D = \begin{pmatrix} d_{11} & d_{12} \\ d_{21} & d_{22} \end{pmatrix}$ be a 2×2 matrix. Then D is Volterra–Lyapunov stable if and only if $d_{11} < 0$, $d_{22} < 0$, and $det(D) = d_{11}d_{22} - d_{12}d_{21} > 0$.*

The characterization of Volterra–Lyapunov stable matrices of higher dimensions, however, is much more difficult. We need the following definition.

Definition 2.6.9 *[40] We say a non-singular $n \times n$ matrix A is diagonally stable (or positive stable) if there exists a positive diagonal $n \times n$ matrix M such that $MA + A^TM^T > 0$.*

From Definitions 2.6.7 and 2.6.9, it is clear that a matrix A is Volterra–Lyapunov stable if and only if its negative matrix, $-A$, is diagonally stable.

Lemma 2.6.10 *[40] Let $D = (d_{ij})$ be a non singular $n \times n$ matrix ($n \geq 2$) and $M = diag(m_1, m_2, \cdots m_n)$ be a positive diagonal $n \times n$ matrix. Let $E = D^{-1}$. Then, if $d_{nn} > 0$, $\tilde{M}\tilde{D} + (\tilde{M}\tilde{D})^T > 0$ and $\tilde{M}\tilde{E} + (\tilde{M}\tilde{E})^T > 0$, it is possible to choose $m_n > 0$ such that $MD + D^TM^T > 0$*

2.7 Bernoulli Equation

A first-order order differential equation (ODE) is said to be linear if it can be brought into the form $y' + p(x)y = r(x)$ [76]. If it cannot be brought into this form, the differential is called nonlinear. The general solution of the linear equation $y' + p(x)y = r(x)$, is $y(x) = e^{-h}\left(\int e^h r(x)dx + c\right)$, where $h = \int p(x)dx$.

Numerous applications can be modeled by ordinary differential equations (ODEs) that are nonlinear but can be transformed to linear ODEs [76]. One of the most useful ones of these is the Bernoulli equation:

$$y' + p(x)y = g(x)y^a$$

where a any real number. If $a = 0$ or $a = 1$, the resulting equation is linear. Otherwise it is nonlinear. To find the solutions to non linear equations, we substitute $u(x) = [y(x)]^{1-a}$, so that we get the linear ODE

$$u' + (1-a)pu = (1-a)g(x),$$

which has a solution $u(x) = e^{-(1-a)p}\left(\int e^{(1-a)p}(1-a)g(x)dx + c\right)$.

2.8 Optimal control theory

Optimal control theory is a modern extension of the calculus of variations to find an optimal path or value that gives either maximum or minimum points of functions. An optimal control problem contains state variables, control(s) and an objective function(s). Optimal control theory is applied to suggest the most effective mitigation strategy to minimize the number of individuals who become infected in the course of an infection while efficiently balancing the controls applied to the models with various cost scenarios. The formulation of optimal control problem mainly involves three parts; state variables, controls and objective functional. In general, an optimal control problem can be formed by a system of equations where state variables are described by

$$\frac{dx}{dt} = g(x(t), u(t), t)), \tag{2.8.1}$$

where $x(t) = (x_1(t), x_2(t), \cdots, x_n(t))^T$ denotes a vector of state variables $u(t) = (u_1(t), u_2(t), \cdots, u_m(t))^T$ is a vector of control variables, g is a $n \times 1$ vector field. The

objective functional is in the form

$$J(\phi, u) = \phi(t) + \int_0^T L(x(t), u(t), t)dt, \tag{2.8.2}$$

where a real valued function L is called the running cost, and $\phi(t)$ is called the terminal cost. Generally, an optimal control problem aims to find the optimal control, $u(t)$ so that the functional $J(\phi, u)$ is minimized or maximized. The solution method involves defining an ancillary function known as the control Hamiltonian

$$H = L(x(t), u(t), t) + \lambda(t)g(x(t), u(t), t)),$$

which combines the objective function and the state equations much like a Lagrangian in a static optimization problem, only that the multipliers $\lambda(t)$, referred to as costate variables, are functions of time rather than constants. To achieve this goal, we need to use Pontryagin's Maximum/Minimum principle and some numerical methods [44, 52]. The Pontryagin's Maximum principle is described below.

Theorem 2.8.1 *[52] If $u^*(t)$ and $x^*(t)$ are optimal for our problem as described above, then there exists a piecewise differentiable adjoint variable, $\lambda(t)$ such that $H(t, x^*, u(t), \lambda(t)) \leq H(t, x^*, u^*(t), \lambda(t))$ for all controls u at each time t, where the Hamiltonian H is*

$$H = L(x(t), u(t), t) + \lambda(t)g(x(t), u(t), t)),$$

and

$$\lambda'(t) = \frac{\partial(H(t, x^*, u(t), \lambda(t)))}{\partial(x)}$$

$$\lambda(T) = 0, \ \textit{where } t_0 \leq t \leq T.$$

After formulating the Hamiltonian and applying the theorem above, our optimal control problem now includes two systems of differential equations that need to be solved. The first system is from the original state equations and the second one is the system of adjoint equations. One necessary

condition for the optimality is that at u^*:

$$\frac{\partial H}{\partial u} = 0$$

Due to the presence of both initial conditions (for the state equations) and final time conditions (for the adjoint equations), and the fact that most models of our interest are nonlinear, the optimal control system has to be solved numerically. We will use the Forward-Backward Sweep Method to conduct the numerical simulation. The steps are described as follows:

Assume that $u = u(t, x, \lambda)$ can be found explicitly from the optimality condition.

Step 1 Make an initial guess for u (usually 0) on the entire domain.

step 2 Using the initial condition $x(0) = a$ and the values for u, solve x forward in time over the domain.

Step 3 Using the transversality condition $\lambda(T) = b$ (usually 0) and the values for u and x, solve λ backward in time.

Step 4 Update u by the new x and λ values. We use the optimality condition to update control u at this step.

Step 5 Check convergence. If values in this iteration and the last one are negligibly close, output the current values as solutions; otherwise, return to Step 2.

Chapter 3

Mathematical modeling of echinococcosis in humans, dogs and sheep without intervention

In this chapter, the transmission dynamics of echinococcosis in the humans, dogs and sheep populations without intervention modeled and analyzed. A compartmental nonlinear deterministic mathematical model for the disease outbreak is used. Mathematical analysis of the model will be carried out to study the disease dynamics over time and this is used as a tool for the development of control strategies.

3.1 A mathematical model of cystic echinococcosis without any intervention

3.1.1 Predator–Prey model

A deterministic mathematical model to represent the population dynamics of sheep, dog and human population in an ecological situation is used. We assume that sheep are the main food source for human and dogs. In the absence of the two populations, the sheep population N_s initially grows exponentially at a per-capita growth rate $r_s = b_s - \mu_s$, where b_s and μ_s are the birth rate and death rate of sheep respectively. However, due to lack of availability of food for sheep the growth of sheep is self-limiting by the carrying capacity of the environment K_s. The dog population, N_d grows at a rate proportional to the number of encounters between sheep population (N_s), and dog population (N_d). The growth rate of dog population due to consumption of sheep

only is $\omega N_s N_d$, where ω denotes the conversion efficiency of consumed sheep into dog reproduction rate. Without sheep as the source of food, the dog population (N_d) grows at a per-capita growth rate $r_d = b_d - \mu_d$, where b_d and μ_d are the birth rate and the natural death rate of dog respectively. The growth of dog population never exceeds the carrying capacity of the environment K_d. Sheep are the main food source for human. In the absence of sheep, it is assumed that there exists some alternative food source for growth of human population. With sheep as source of food, human population (N_h) grows at a rate $\theta N_s N_h$, where θ denotes the conversion efficiency of consumed sheep into human reproduction rate. In the absence of sheep as source of food, human population N_h grows exponentially at a per-capita growth rate $r_h = b_h - \mu_h$, where b_h and μ_h are the birth rate and death rate of human respectively. Human population eventually increase up to the carrying capacity of the environment K_h. The rate of consumption of sheep by dog and human are represented by a and c respectively. Furthermore, the sheep, dog and human populations die naturally at rates represented by μ_s, μ_d and μ_h respectively. Hence, the predator-prey interaction between the sheep, dog and human populations is represented by a system of nonlinear ordinary differential equations:

$$\frac{dN_s}{dt} = r_s\left(1 - \frac{N_s}{K_s}\right)N_s - aN_sN_d - cN_hN_s \tag{3.1.1}$$

$$\frac{dN_d}{dt} = r_d\left(1 - \frac{N_d}{K_d}\right)N_d + \omega N_sN_d \tag{3.1.2}$$

$$\frac{dN_h}{dt} = r_h\left(1 - \frac{N_h}{K_h}\right)N_h + \theta N_sN_h, \tag{3.1.3}$$

with initial conditions $N_s(0) \geq 0$, $N_d(0) \geq 0$, $N_h(0) \geq 0$, where $r_s > 0$, $a > 0$, $\omega > 0$, $c > 0$, $\mu_s > 0$, $\mu_d > 0$, $\mu_h > 0$, $\theta > 0$ and $r_h > 0$.

Theorem 3.1.1 *The region*
$\Omega = \left\{(N_s, N_d, N_h) \in \mathbb{R}^3_+ : 0 \leq N_s(t) \leq K_s, N_d(t) \leq K_d + \frac{\omega K_d K_s}{r_d}, N_h(t) \leq K_h + \frac{\theta K_h K_s}{r_h}\right\}$ *is positively invariant for model* (3.1.1)-(3.1.3).

Proof. We show the existence and uniqueness of solutions, positivity and boundedness of the solution of model (3.1.1)-(3.1.3), since the state variables N_s, N_d and N_h represent population densities. The positivity of these variables is to conform the reality for biological populations, while boundedness of the solution to conform with the natural restriction to growth due to limited resources.

Existence and Uniqueness of solutions: The system (3.1.1)-(3.1.3) with initial conditions

can be expressed as : $\frac{dx}{dt} = f(x), x(0) = x_0$, where $x = (N_s, N_d, N_h)^T$ is a vector in $\mathbb{R}^3_+$, and $f(x) = (f_1(x), f_2(x), f_3(x))^T$ is the vector field in $\mathbb{R}^3_+$ such that $f_1(x) = r_s\left(1 - \frac{N_s}{K_s}\right)N_s - aN_sN_d - cN_hN_s$, $f_2(x) = r_d\left(1 - \frac{N_d}{K_d}\right)N_d + \omega N_sN_d$, and $f_3(x) = r_h\left(1 - \frac{N_h}{K_h}\right)N_h + \theta N_sN_h$. Using standard theorem of the dynamical system [60], $f(x)$ is the Lipschitz continuous. Hence, a unique solution of (3.1.1)-(3.1.3) exists in some open ball containing $x(0)$. To show that this is a global solution, it suffices to verify that the dissipative condition of Theorem 2.4.5 is satisfied. Before proving this theorem is satisfied, we first prove positivity and boundedness of the solutions as follows.

Positivity and boundedness of solutions:
Equation (3.1.1) is a Bernoulli type [76]. Thus, the integral solution of equation (3.1.1) is given by

$$N_s(t) = \frac{K_sN_s(0)e^{\int_0^t(r_s - aN_d - cN_h)d\tau}}{K_s + r_sN_s(0)\int_0^t e^{\int_0^\tau(r_s - aN_d - cN_h)dz}d\tau}.$$

Since $N_s(0) \geq 0$, we have $N_s(t) \geq 0$ for all $t > 0$.
Equation (3.1.2) is a Bernoulli type [76], whose integral solution is given by

$$N_d(t) = \frac{K_dN_d(0)e^{\int_0^t(r_d + \omega N_s)d\tau}}{K_d + r_dN_d(0)\int_0^t e^{\int_0^\tau(r_d + \omega N_s)dz}d\tau}.$$

Thus, $N_d(0) \geq 0$ implies that $N_d(t) \geq 0$ for all $t > 0$. In similar manner, an integral solution of (3.1.3) is given by

$$N_h(t) = \frac{K_hN_h(0)e^{\int_0^t(r_h + \theta N_s)d\tau}}{K_h + r_hN_h(0)\int_0^t e^{\int_0^\tau(r_h + \theta N_s)dz}d\tau}.$$

Since $N_h(0) \geq 0$, we obtain $N_h(t) \geq 0$ for $t > 0$. Therefore, the solution $(N_s(t), N_d(t), N_h(t))$ of the model (3.1.1)-(3.1.3) is non negative for all $t \geq 0$.

Boundedness of the solution is proved as follows.

From 3.1.1, we have

$$\frac{dN_s}{dt} = r_s\left(1 - \frac{N_s}{K_s}\right)N_s - aN_sN_d - cN_hN_s \leq r_s\left(1 - \frac{N_s}{K_s}\right)N_s,$$

In this case, $\lim_{t\to\infty} \sup N_s(t) = K_s$. Hence, $N_s(t) \leq K_s$.

From 3.1.2, we have

$$\begin{aligned}
\frac{dN_d}{dt} &= r_d\left(1-\frac{N_d}{K_d}\right)N_d + \omega N_s N_d \\
&\leq r_d\left(1-\frac{N_d}{K_d}\right)N_d + \omega K_d N_d, \\
&:= (r_d+\omega K_s)N_d - \frac{r_d}{K_d}N_d^2 \\
&:= -(r_d+\omega K_s)N_d - \frac{r_d}{K_d}\left(N_d^2 - \frac{2K_d(r_d+\omega K_s)}{r_d}N_d + \frac{K_d^2(r_d+\omega K_s)^2}{r_d^2}\right) + \frac{K_d(r_d+\omega K_s)^2}{r_d} \\
&:= -(r_d+\omega K_s)N_d - \frac{r_d}{K_d}\left(N_d - \frac{K_d(r_d+\omega K_s)}{r_d}\right)^2 + \frac{K_d(r_d+\omega K_s)^2}{r_d}
\end{aligned}$$

This gives us

$$\frac{dN_d}{dt} + \psi N_d \leq \eta$$

where $\psi = r_d + \omega K_s$ and $\eta = \frac{K_d}{r_d}(r_d+\omega K_s)^2$. From the solution of the corresponding differential equation, we have $N_d(t) \leq \frac{\eta}{\psi} - \left(N_d(0) - \frac{\eta}{\psi}\right)e^{-\psi t}$. As $t \to \infty$, it is clear that $N_d(t) \to \frac{\eta}{\psi}$. Therefore, $N_d(t) \leq K_d + \frac{\omega K_d K_s}{r_d}$.

In similar ways, $N_h(t) \leq K_h + \frac{\theta K_h K_s}{r_h}$. This proves that all solutions of the system are uniformly bounded.

Now we prove the dissipative condition is satisfied as follows.

$$\begin{aligned}
f(x).x =& (f_1, f_2, f_3).(N_s, N_d, N_h) \\
=& r_s\left(1-\frac{N_s}{K_s}\right)N_s^2 - aN_s^2N_d - cN_hN_s^2 + r_d\left(1-\frac{N_d}{K_d}\right)N_d^2 + \omega N_s N_d^2 \\
&+ r_h\left(1-\frac{N_h}{K_h}\right)N_h^2 + \theta N_s N_h^2 \\
&\leq r_s N_s^2 + r_d N_d^2 + r_h N_h^2 + \omega N_s N_d^2 + \theta N_s N_h^2 \\
&\leq r_s N_s^2 + r_h N_h^2 + \omega K_s {K_d}^2 + \theta K_s K_h^2 \leq \alpha||x||^2 + \beta
\end{aligned}$$

where $\alpha = r_s + r_d + r_h$ and $\beta = \omega K_s {K_d}^2 + \theta K_s K_h^2$. In this case $x = (N_s, N_d, N_h)^T$ is a vector $\mathbb{R}^3_+$. Hence, condition of Theorem 2.4.5 is satisfied and hence a unique solution x which is globally defined in time exists. ■

Equilibrium Points

Our next result concerns the existence of equilibrium points of the system (3.1.1)-(3.1.3) that are biologically feasible, and determine the conditions for the existence of the equilibrium of the system in the feasible region. At equilibrium, equations of model (3.1.1)-(3.1.3) are

$$r_s\left(1 - \frac{N_s}{K_s}\right)N_s - aN_sN_d - cN_hN_s = 0 \tag{3.1.4}$$

$$r_d\left(1 - \frac{N_d}{K_d}\right)N_d + \omega N_sN_d = 0 \tag{3.1.5}$$

$$r_h\left(1 - \frac{N_h}{K_h}\right)N_h + \theta N_sN_h = 0 \tag{3.1.6}$$

Equilibrium points are:

1. The trivial fixed point $E_0 = (0, 0, 0)$, which represents the extinction of the three populations.

2. $E_1 = (K_s, 0, 0)$,

3. $E_2 = (0, 0, K_h)$,

4. $E_3 = (0, K_d, 0)$,

5. $E_4 = (0, K_d, K_h)$,

6. $E_5 = (\bar{N}_s, \bar{N}_d, \bar{N}_h) = \left(\dfrac{r_dK_s(r_s - aK_d)}{r_sr_d + a\omega K_sK_d}, \dfrac{r_sK_d(r_d + \omega K_s)}{r_sr_d + a\omega K_sK_d}, 0\right)$, where $r_s > aK_d$. This represents the extinction of humans.

7. $E_6 = (\widehat{N}_s, \widehat{N}_d, \widehat{N}_h) = \left(\dfrac{r_hK_s(r_s - cK_h)}{r_sr_h + c\theta K_sK_h}, 0, \dfrac{r_sK_h(r_h + \theta K_s)}{r_sr_h + c\theta K_sK_h}\right)$, where $r_s > cK_h$. This represents the extinction of dog.

8. Equilibrium point of the coexistence:

$$E_7 = (N_s^*, N_d^*, N_h^*),$$

with $N_s^* = \dfrac{-r_d r_h K_s(aK_d + cK_h - r_s)}{A^*}$, if $r_s \geq aK_d + cK_h$,
$N_d^* = \dfrac{K_d(r_s r_d r_h + \omega r_s r_h K_s + c\theta r_d K_s K_h - c\omega r_h K_s K_h)}{A^*}$ if $r_s r_d r_h + \omega r_s r_h K_s + c\theta r_d K_s K_h > c\omega r_h K_s K_h$,
$N_h^* = \dfrac{K_h(r_s r_d r_h + \theta r_s r_d K_s + a\omega r_h K_s K_d - a\theta r_d K_s K_d)}{A^*}$ if $r_s r_d r_h + \theta r_s r_d K_s + a\omega r_h K_s K_d > a\theta r_d K_s K_d$
where $A^* = r_s r_d r_h + c\theta r_d K_s K_h + a\omega r_h K_s K_d$.

3.1.2 Stability of equilibrium points

Since we are working with a first order nonlinear system of differential equations, we can analyze the local stability of our model at its equilibrium points by linearizing the system using the Jacobian matrix as stated in section 2.5.2. The Jacobian matrix for the system (3.1.1)-(3.1.3) is

$$J = \begin{pmatrix} r_s - \dfrac{2r_s N_s}{K_s} - aN_d - cN_h & -aN_s & -cN_s \\ \omega N_d & r_d - \dfrac{2r_d N_d}{K_d} + \omega N_s & 0 \\ \theta N_h & 0 & r_h - \dfrac{2r_h N_h}{K_h} + \theta N_s \end{pmatrix}$$

The eigenvalues of the Jacobian are determined from the characteristic equation

$$\chi(J) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0,$$

where $a_1 = -Tr(J)$, $a_2 = M_{11} + M_{22} + M_{33}$ and $a_3 = -det(J)$; where M_{11}, M_{22} and M_{33} are the minors of the entries a_{11}, a_{22} and a_{33} for the Jacobian $J = (a_{ij})_3$.

The conditions for local stability of the equilibrium points are discussed as follows.

1. At equilibrium point E_0, the Jacobian matrix is $J(E_0) = \begin{pmatrix} r_s & 0 & 0 \\ 0 & r_d & 0 \\ 0 & 0 & r_h \end{pmatrix}$. The eigenvalues of $J(E_0)$ are $\lambda_1 = r_s$, $\lambda_2 = r_d$ and $\lambda_3 = r_h$. Hence, E_0 is unstable since the eigenvalues $\lambda_1 = r_s > 0$, $\lambda_2 = r_d > 0$ and $\lambda_3 = r_h > 0$ are positive.

2. At equilibrium point E_1, the Jacobian matrix is

$$J(E_1) = \begin{pmatrix} -r_s & -aK_s & -cK_s \\ 0 & r_d + \omega K_s & 0 \\ 0 & 0 & \theta K_s + r_h \end{pmatrix}$$

The eigenvalues of $J(E_1)$ are $\lambda_1 = -r_s$, $\lambda_2 = r_d + \omega K_s > 0$ and $\lambda_3 = \theta K_s + r_h > 0$. Thus, E_1 is unstable because the eigenvalues $\lambda_2 > 0$ and $\lambda_3 > 0$.

3. At equilibrium point E_2, the Jacobian matrix is $J(E_2) = \begin{pmatrix} r_s - cK_h & 0 & 0 \\ 0 & r_d & 0 \\ \theta K_h & 0 & -r_h \end{pmatrix}$. The eigenvalues of $J(E_2)$ are $\lambda_1 = r_s - cK_h$, $\lambda_2 = r_d$ and $\lambda_3 = -r_h$. Hence, E_2 is unstable.

4. At equilibrium point E_3, the Jacobian matrix is

$$J(E_3) = \begin{pmatrix} r_s - aK_d & 0 & 0 \\ \omega K_d & -r_d & 0 \\ 0 & 0 & r_h \end{pmatrix}.$$

The eigenvalues of $J(E_3)$ are $\lambda_1 = r_s - aK_d$, $\lambda_2 = -r_d$ and $\lambda_3 = r_h$. Hence, E_3 is unstable.

5. At equilibrium point E_4, the Jacobian matrix is

$$J(E_4) = \begin{pmatrix} r_s - aK_d - cK_h & 0 & 0 \\ \omega K_d & -r_d & 0 \\ \theta K_h & 0 & -r_h \end{pmatrix}$$

One of the eigenvalue of $J(E_4)$ is $\lambda_1 = r_s - aK_d - cK_h$, and the other two are determined from the quadratic equation

$$\lambda^2 + (r_d + r_h)\lambda + r_d r_h = 0$$

Hence, E_4 is stable if $r_s < aK_d + cK_h$. Otherwise, it is unstable.

6. At equilibrium point E_5, the Jacobian matrix is

$$J(E_5) = \begin{pmatrix} r_s - \dfrac{2r_s\bar{N}_s}{K_s} - a\bar{N}_d & -a\bar{N}_s & -c\bar{N}_s \\ \omega\bar{N}_d & r_d - \dfrac{2r_d\bar{N}_d}{K_d} + \omega\bar{N}_s & 0 \\ 0 & 0 & r_h + \theta\bar{N}_s \end{pmatrix}$$

One of the eigenvalue of $J(E_5)$ is $\lambda_1 = r_h + \theta\bar{N}_s$, the remaining two are obtained from

$$\begin{vmatrix} r_s - \dfrac{2r_s\bar{N}_s}{K_s} - a\bar{N}_d - c\bar{N}_h - \lambda & -a\bar{N}_s \\ \omega\bar{N}_d & r_d - \dfrac{2r_d\bar{N}_d}{K_d} + \omega\bar{N}_s - \lambda \end{vmatrix} = 0$$

which has the characteristic polynomial

$$\lambda^2 + \left(\frac{r_s}{K_s}\bar{N}_s + \frac{r_d}{K_d}\bar{N}_d\right)\lambda + \left(\frac{r_s r_d}{K_s K_d} + a\omega\right)\bar{N}_s\bar{N}_d = 0$$

Hence, E_5 is unstable because $\lambda_1 = r_h + \theta\bar{N}_s > 0$.

7. At equilibrium point E_6, the Jacobian matrix is

$$J(E_6) = \begin{pmatrix} r_s - \dfrac{2r_s\widehat{N_s}}{K_s} - c\widehat{N_h} & -a\widehat{N_s} & -c\widehat{N_s} \\ 0 & r_d + \omega\widehat{N_s} & 0 \\ \theta\widehat{N_h} & 0 & r_h - \dfrac{2r_h\widehat{N_h}}{K_h} + \theta\widehat{N_s} \end{pmatrix}$$

One of the eigenvalue of $J(E_6)$ is $\lambda_1 = r_d + \omega\widehat{N_s}$, the other two are obtained from the quadratic equation

$$\lambda^2 + \left(\frac{r_s}{K_s}\widehat{N_s} + \frac{r_h}{K_h}\widehat{N_h}\right)\lambda + \left(\frac{r_s r_h}{K_s K_h} + c\theta\right)\widehat{N_s}\widehat{N_h} = 0$$

Hence, E_6 is unstable because $\lambda_1 > 0$.

8. At equilibrium point E_7, the Jacobian matrix is

$$J(E_7) = \begin{pmatrix} r_s - \frac{2r_sN_s^*}{K_s} - aN_d^* - cN_h^* & -aN_s^* & -cN_s^* \\ \omega N_d^* & r_d - \frac{2r_dN_d^*}{K_d} + \omega N_s^* & 0 \\ \theta N_h^* & 0 & r_h - \frac{2r_hN_h^*}{K_h} + \theta N_s^* \end{pmatrix}$$

The characteristic equation of the matrix is given by: $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$, where $a_1 = -tr(J(E_7)) = r_s - \frac{2r_sN_s^*}{K_s} - aN_d^* - cN_h^* + r_d - \frac{2r_dN_d^*}{K_d} + \omega N_s^* + r_h - \frac{2r_hN_h^*}{K_h} + \theta N_s^*$, $a_2 = M_{11} + M_{22} + M_{33}$ (sum of the second order principal minors), and $a_3 = -det(J(E_7))$. By the necessary and sufficient conditions of Routh-Hurtwitz criteria, E_7 is asymptotically stable when the following conditions are satisfied: $a_1 > 0$, $a_3 = -det(J(E_7)) > 0$ and $a_1a_2 - a_3 > 0$.

Stability of equilibrium point E_7

Since the transmission dynamics of the cystic echinococcosis involves the dog, sheep and human populations, we are mainly concerned in equilibrium point of the coexistence. The detail analysis of the local stability conditions of the equilibrium points were presented above, and the conditions for local and global stability of the equilibrium point E_7 are presented in the following Theorem.

Theorem 3.1.2 *1. E_7 is locally asymptotically stable if $r_s \geq \frac{2r_sN_s^*}{K_s} + aN_s^* + cN_h^*$, $r_d \geq \frac{2r_dN_d^*}{K_d} - \omega N_s^*$, $r_h \geq \frac{2r_hN_h^*}{K_h} - \theta N_s^*$.*

2. The equilibrium point E_7 is globally asymptotically stable in $Int.\mathbb{R}^3_+$.

Proof. The method of Lyapunov function is used to prove global stability of E_7. To study the global stability of the co-existence equilibrium point, we construct a Lyapunov function for a predator-prey model (3.1.1)-(3.1.3) (Theorem 2.5.6). For an equilibrium point $E_7 = (N_s^*, N_d^*, N_h^*)$, let us define a function

$$V(N_s, N_d, N_h) = N_s - N_s^* - N_s^* \ln \frac{N_s}{N_s^*} + \frac{a}{\omega}\left\{N_d - N_d^* - N_d^* \ln \frac{N_d}{N_d^*}\right\} + \frac{c}{\theta}\left\{N_h - N_h^* - N_h^* \ln \frac{N_h}{N_h^*}\right\}.$$

(i) $V(E_7) = N_s^* - N_s^* - N_s^* \ln \frac{N_s^*}{N_s^*} + \frac{a}{\omega}\left\{N_d^* - N_d^* - N_d^* \ln \frac{N_d^*}{N_d^*}\right\} + \frac{c}{\theta}\left\{N_h^* - N_h^* - N_h^* \ln \frac{N_h^*}{N_h^*}\right\} = 0,$

The time derivative of V is

$$\begin{aligned} V'(N_s,N_d,N_h) &= (\bigtriangledown V(N_s,N_d,N_h))^T V(N_s,N_d,N_h) = \frac{\partial V}{\partial N_s}\frac{dN_s}{dt} + \frac{\partial V}{\partial N_d}\frac{dN_d}{dt} + \frac{\partial V}{\partial N_h}\frac{dN_h}{dt} \\ &= \left(\frac{N_s - N_s^*}{N_s}\right)\frac{dN_s}{dt} + \frac{a}{\omega}\left(\frac{N_d - N_d^*}{N_d}\right)\frac{dN_d}{dt} + \frac{c}{\theta}\left(\frac{N_h - N_h^*}{N_h}\right)\frac{dN_h}{dt} \\ &= -\left(\frac{r_s}{K_s}(N_s - N_s^*)^2 + \frac{ar_d}{\omega K_d}(N_d - N_d^*)^2 + \frac{cr_h}{\theta K_h}(N_h - N_h^*)^2\right). \end{aligned}$$

In particular, if $N_s = N_s^*$, $N_d = N_d^*$ and $N_h = N_h^*$, we have $V' = -\left(\frac{r_s}{K_s}(N_s^* - N_s^*)^2 + \frac{cr_h}{\theta K_h}(N_h^* - N_h^*)^2\right) = 0$. This indicates that $V'(E_7) = 0$. But if $(N_s, N_d, N_h) \neq E_7$, it is clear that $V' < 0$. Therefore, $\frac{dV}{dt}$ is negative definite.

In order to verify that $V(N_s, N_d, N_h) > 0$ for all $(N_s, N_d, N_h) \neq E_7$, it suffices to show that $V(E_7)$ is a minimum(global minimum). In this case we apply the second order partial test for three variables. The Hessian matrix $H(E_7) = \begin{pmatrix} \frac{1}{(N_s^*)^2} & 0 & 0 \\ 0 & \frac{a}{\omega(N_d^*)^2} & 0 \\ 0 & 0 & \frac{c}{\theta(N_d^*)^2} \end{pmatrix}$ with $D_1 = \frac{1}{(N_s^*)^2} > 0$, $D_2 = \begin{vmatrix} \frac{1}{(N_s^*)^2} & 0 \\ 0 & \frac{a}{\omega(N_d^*)^2} \end{vmatrix} > 0$ and $D_3 = |H(E_7)| > 0$. This indicates that $V(E_7)$ is the local minimum. Moreover, V is a convex function on a convex set. Therefore, $V(E_7)$ is minimum, and consequently $V(N_s, N_d, N_h) > 0$ for all $(N_s, N_d, N_h) \neq E_7$.

(ii) From result in (i), we can see that $V'(N_s, N_d, N_h) < 0$ whenever $(N_s, N_d, N_h) \neq E_7$.

(iii) Clearly $V(N_s, N_d, N_h) \to \infty$ if $||(N_s, N_d, N_h)|| = \sqrt{N_s^2 + N_d^2 + N_h^2} \to \infty$

Thus, V is a Lyapunov function. Therefore, the equilibrium point $E_7 = (N_s^*, N_d^*, N_h^*)$ is globally asymptotically stable. ■

3.2 Modeling the transmission dynamics of Cyst Echinococcosis

In Section 3.1.1, sufficient conditions to ensure the existence of stable equilibrium point which represent coexistence of the three populations in the predator-prey interaction model are derived. The intuition is to study the dynamics of cystic echinococcosis on an environment where the three populations coexist in the area. At any time t the existing total dog, human and sheep populations in the area are denoted by $N_d(t)$, $N_h(t)$ and $N_s(t)$ respectively. To describe the dynamics of echinococcosis compartmental framework is used. In human population there are four classes: the Susceptible (S_h), the Exposed (E_h), the Infectious (I_h) and the Removed (R_h) classes. The dog population has three classes: the Susceptible (S_d), the Exposed (E_d), and the Infectious (I_d) classes. The sheep population has also three classes: the Susceptible (S_s), the Exposed (E_s), and the Infectious (I_s) classes. The dog, human and sheep populations are recruited to the susceptible population at constant rates denoted by Λ_d, Λ_h and Λ_s respectively. In the dynamics of the disease transmission, susceptible sheep are infected by ingesting parasite eggs in the feces of infected definitive hosts (dogs), while humans are infected by accidentally ingesting *Echinococcus granulosus'* eggs from the environment (typically food or water). The concentration of *Echinococcus granulosus'* eggs in the environment is denoted by B. The incorporation of the saturation is relevant since for the disease to be spread from environment to sheep, there must be a sufficient number (saturation) of parasite eggs in the environment that can cause infection. Rate of infection of susceptible sheep is $\frac{\beta_{es}B}{\chi_s + B}$, where β_{es} denotes the rate of ingestion of *Echinococcus'* egg from the environment by sheep and χ_s is the half-saturation constant of parasite in the environment sufficient to infect sheep. Rate of infection of susceptible humans is $\frac{\beta_{eh}B}{\chi_h + B}$, where β_{eh} denotes the rate of ingestion of *Echinococcus'* egg from the environment by human, and χ_h is the half-saturation constant of parasite in the environment sufficient to infect human. Susceptible dogs are infected by preying on the infected sheep. The disease transmission rate from sheep to dogs is denoted by β_{sd}. The rates at which exposed dog, sheep and human progress to infectious classes are denoted by γ_d, γ_s and γ_h respectively. Infected human population could recover from the disease naturally, at rate α_h, where as sheep and dogs cannot recover once they are infected. We assume that there is no *Echinococcus* induced death. However, dogs, sheep and humans die naturally at rates μ_d, μ_s and μ_h respectively. The concentration of *Echinococcus granulosus'* eggs in the environment is increased by shedding of a parasite from infected dog at rate δ and decreased by the natural death rate of *Echinococcus granulosus'* eggs at rate μ_e. The variables and parameters of the model are summarized in Table 3.1 and Table 3.2.

Table 3.1: Definitions of Variables

Variables	**Definitions**
S_h, E_h, I_h and R_h	Number of Susceptible, Exposed, Infected and Removed humans respectively.
S_d, E_d, and I_d	Number of Susceptible, Exposed and Infected dogs respectively.
S_s, E_s, and I_s	Number of Susceptible, Exposed and Infected sheep respectively.
B	The concentration of *Echinococcus granulosus'* eggs in the environment.
N_d^*, N_s^*, and N_h^*	Total number of dog, sheep and human respectively.

Table 3.2: Descriptions of parameters

Parameters	**Descriptions**
Λ_d, Λ_h, Λ_s	recruitment rate of dog, human and sheep respectively.
μ_d	Natural death rate of dog
μ_h	Natural death rate of human
μ_s	Natural death rate of sheep
μ_e	Natural death rate of *Echinococcus granulosus'* eggs.
γ_d, γ_s and γ_h	The rates at which exposed dog, sheep and human progress to infective classes respectively.
β_{sd}	The transmission rate from sheep to dogs.
β_{es}	Transmission rate of *Echinococcus'* eggs from the environment to sheep.
β_{eh}	Transmission rate of *Echinococcus'* eggs from the environment to human.
δ	Eggs contamination rate of the environment by infected dogs.
χ_h	The concentration of *Echinococcus granulosus'* eggs at which half of all contacts with human produce infection.
χ_s	The concentration of *Echinococcus granulosus'* eggs at which half of all contacts with sheep produce infection.
α_h	Human recovery rate.

The Flow Chart for the transmission dynamics of the disease is shown in Figure 4.1. It demonstrates the interactions between the three populations and the transition of individuals from one compartment to another. The solid arrows show progression of individuals from one compartment to another. The broken line from I_s to the line between S_d and E_d tells us that dogs become infected when they feed on organs of an infected sheep. The broken lines from B to the line between E_s and S_s, and from B to the line between E_h and S_h express the fact that sheep and humans are infected by accidentally ingesting an egg of *Echinococcus granulosus*.

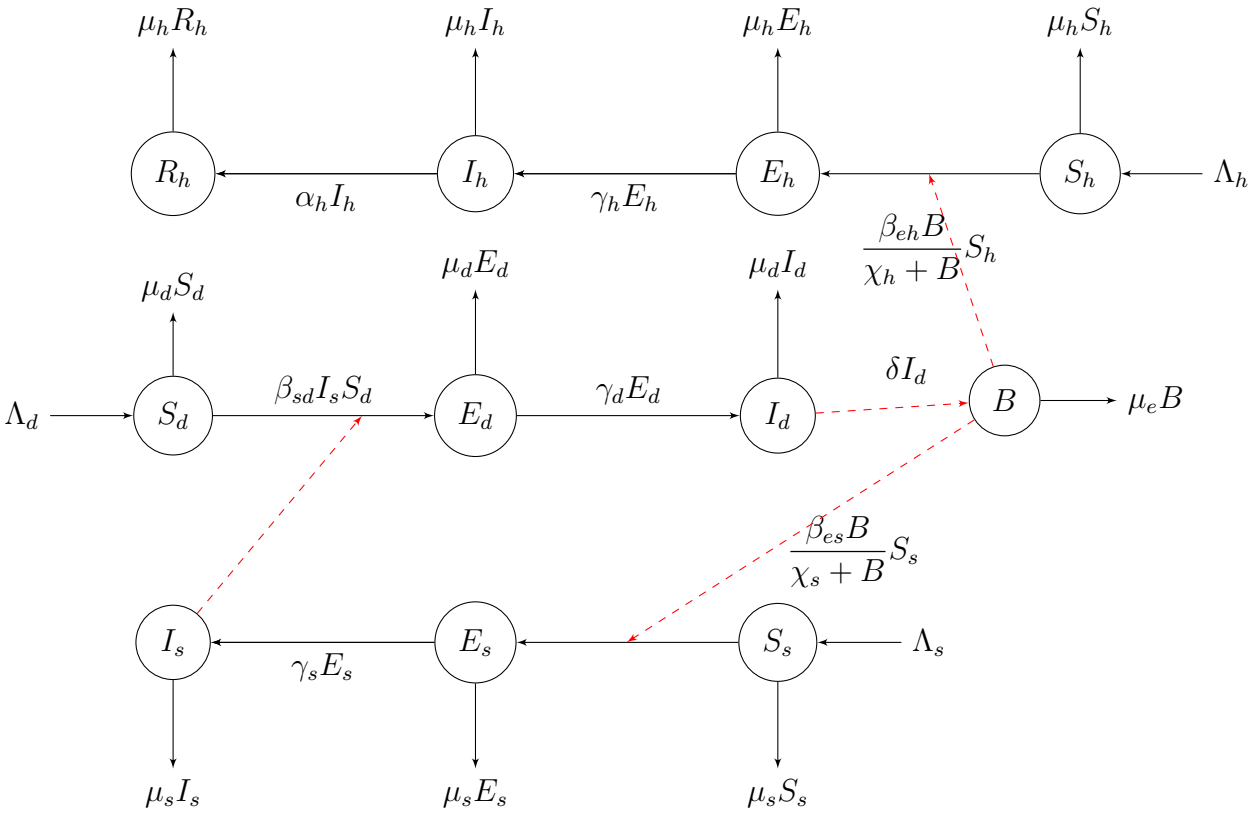

Figure 3.1: The flow diagram for cyst echinococcosis transmission dynamics.

Based on these assumptions and using the transitions among different classes of disease stages given in Figure 4.1, the transmission dynamics of cyst echinococcosis in the populations of dog, human and sheep is represented by the following system of ordinary differential equations.

$$\frac{dS_d}{dt} = \Lambda_d - \beta_{sd} I_s S_d - \mu_d S_d \tag{3.2.1}$$
$$\frac{dE_d}{dt} = \beta_{sd} I_s S_d - \tilde{\gamma_d} E_d \tag{3.2.2}$$
$$\frac{dI_d}{dt} = \gamma_d E_d - \mu_d I_d \tag{3.2.3}$$
$$\frac{dB}{dt} = \delta I_d - \mu_e B \tag{3.2.4}$$
$$\frac{dS_h}{dt} = \Lambda_h - \frac{\beta_{eh} B}{\chi_h + B} S_h - \mu_h S_h \tag{3.2.5}$$
$$\frac{dE_h}{dt} = \frac{\beta_{eh} B}{\chi_h + B} S_h - \tilde{\gamma_h} E_h \tag{3.2.6}$$
$$\frac{dI_h}{dt} = \gamma_h E_h - \tilde{q_h} I_h \tag{3.2.7}$$
$$\frac{dR_h}{dt} = \alpha_h I_h - \mu_h R_h \tag{3.2.8}$$
$$\frac{dS_s}{dt} = \Lambda_s - \frac{\beta_{es} B}{\chi_s + B} S_s - \mu_s S_s \tag{3.2.9}$$
$$\frac{dE_s}{dt} = \frac{\beta_{es} B}{\chi_s + B} S_s - \tilde{\gamma_s} E_s \tag{3.2.10}$$
$$\frac{dI_s}{dt} = \gamma_s E_s - \mu_s I_s \tag{3.2.11}$$

subject to initial conditions $S_d(0) \geq 0$, $E_d(0) \geq 0$, $I_d(0) \geq 0$, $B(0) \geq 0$, $S_h(0) \geq 0$, $E_h(0) \geq 0$, $I_h(0) \geq 0$, $R_h(0) \geq 0$, $S_s(0) \geq 0$, $E_s(0) \geq 0$, and $I_s(0) \geq 0$, where $\tilde{\gamma_d} = \mu_d + \gamma_d$, $\tilde{\gamma_h} = \mu_h + \gamma_h$, $\tilde{q_h} = \mu_h + \alpha_h$ and $\tilde{\gamma_s} = \mu_s + \gamma_s$

3.3 Well-posedness of the Model

In this section we prove model (3.2.1)-(3.2.11) is epidemiologically and mathematically well posed in a set or not.

Theorem 3.3.1 *The region* $\mathbb{D} = \mathbb{D}_1 \times \mathbb{D}_2 \times \mathbb{D}_3 \times \mathbb{D}_4 \subset \mathbb{R}^3 \times \mathbb{R}^4 \times \mathbb{R}^3 \times \mathbb{R}$, *where*

$$\mathbb{D}_1 = \left\{ (S_d, E_d, I_d) \subset \mathbb{R}^3_+ : S_d + E_d + I_d = \frac{\Lambda_d}{\mu_d} \right\},$$
$$\mathbb{D}_2 = \left\{ (S_h, E_h, I_h, R_h) \subset \mathbb{R}^4_+ : S_h + E_h + I_h + R_h = \frac{\Lambda_h}{\mu_h} \right\},$$

$\mathbb{D}_3 = \left\{(S_s, E_s, I_s) \subset \mathbb{R}^3_+ : S_s + E_s + I_s = \frac{\Lambda_s}{\mu_s}\right\}$ *and* $\mathbb{D}_4 = \left\{B \subset \mathbb{R}_+ : B \leq \frac{\delta\Lambda_d}{\mu_e\mu_d}\right\}$ *is positively invariant for model* (3.2.1)-(3.2.11).

Proof. Existence and Uniqueness of solutions:

The model (3.2.1)-(3.2.11) with initial conditions can be expressed as :

$$\frac{dx}{dt} = f(x), x(0) = x_0$$

where $x = (S_d, E_d, I_d, B, S_h, E_h, I_h, R_h, S_s, E_s, I_s)^T$ is a vector in $\mathbb{R}^{11}_+$, and
$f(x) = (f_1(x), f_2(x), \cdots, f_{11}(x))^T$ is the vector field in $\mathbb{R}^{11}_+$ such that $f_1(x)$, $f_2(x)$, $\cdots$, $f_{11}(x)$ are right sides of the model (3.2.1)-(3.2.11). Using standard theorem of the dynamical system [60], $f(x)$ is Lipschitz continuous. Hence, a unique solution of (3.2.1)-(3.2.11) exists in some open ball containing $x(0)$. To show that this is a global solution, it suffices to verify that the dissipative condition of Theorem 2.4.5 is satisfied. Before proving this theorem is satisfied, we first prove positivity and boundedness of the solutions as follows.

Positivity and boundedness of solutions

Since the model deals with the human, sheep and dog populations, we need to show that the state variables remain positive at all times.
Suppose that $(S_d(t), E_d(t), I_d(t), B(t), S_h(t), E_h(t), I_h(t), R_h(t), S_s(t), E_s(t), I_s(t))$ be the solution of the model (3.2.1)-(3.2.11) defined for all $t \geq 0$.

From equations (3.2.1), (3.2.5) and (3.2.9) we respectively obtain

$$\frac{dS_d}{dt} > -\left(\beta_{sd}I_s + \mu_d\right)S_d \Rightarrow S_d(t) > S_d(0)e^{-\int_0^t(\beta_{sd}I_s+\mu_d)d\tau} > 0,$$

$$\frac{dS_h}{d\tau} > -\left(\mu_h + \frac{\beta_{eh}B}{\chi_h + B}\right)S_h \Rightarrow S_h(t) > S_h(0)e^{-\int_0^t\left(\mu_h+\frac{\beta_{eh}B}{\chi_h+B}\right)d\tau} > 0,$$

$$\frac{dS_s}{dt} > -\left(\mu_s + \frac{\beta_{es}B}{\chi_s + B}\right)S_s \Rightarrow S_s(t) > S_s(0)e^{-\int_0^t\left(\mu_s+\frac{\beta_{es}B}{\chi_s+B}\right)d\tau} > 0.$$

Thus, the variables $S_d(t)$, $S_h(t)$ and $S_s(t)$ are positive for all $t \geq 0$.

We prove the remaining variables are positive by a method of contradiction. Suppose that the conclusion is not true. Then, there exists $t_1 \in [0, r)$ for some $r > 0$ such that

$$e(t_1) = \min\{(E_d(t_1), I_d(t_1), B(t_1), E_h(t_1), I_h(t_1), R_h(t_1), E_s(t_1), I_s(t_1))\} = 0.$$

If $e(t_1) = E_d(t_1)$, then from (3.2.2) and since $S_d(t) > 0$ for $t > 0$, we obtain $\frac{dE_d}{dt} > -\tilde{\gamma}_d E_d$ for all $t \in [0, t_1)$. It then follows that

$$0 = E_d(t_1) > E_d(0)e^{\int_0^{t_1} -\tilde{\gamma}_d dt} > 0,$$

which leads to a contradiction.

If $e(t_1) = I_d(t_1)$, then from (3.2.3) we have $\frac{dI_d}{dt} > -\mu_d I_d$ for all $t \in [0, t_1)$. Thus,

$$0 = I_d(t_1) > I_d(0)e^{\int_0^{t_1} -\mu_d dt} > 0,$$

which leads to a contradiction.

If $e(t_1) = B(t_1)$, then from (3.2.4), we have $\frac{dB}{dt} > -\mu_e B$ for all $t \in [0, t_1)$. Thus,

$$0 = B(t_1) > B(0)e^{\int_0^{t_1} -\mu_e dt} > 0,$$

which also leads to a contradiction.

Similar contradictions can be obtained if $e(t_1) = E_h(t_1)$, $e(t_1) = I_h(t_1)$, $e(t_1) = R_h(t_1)$, $e(t_1) = E_s(t_1)$ or $e(t_1) = I_s(t_1)$.

From continuity of the functions (the state variables), any of the variables can never be negative. Therefore, the solution of (3.2.1)-(3.2.11) is positive for all $t \geq 0$.

Secondly, we prove boundedness of the solutions as follows.

From equations (3.2.1)-(3.2.3), we have

$$\frac{dN_d}{dt} = \Lambda_d - \mu_d N_d,$$

The solution of the differential equation results in $N_d(t) = N_d(0)e^{-\mu_d t} + \frac{\Lambda_d}{\mu_d}(1 - e^{-\mu_d t})$, which shows that $\lim_{t\to\infty} \sup N_d(t) = \frac{\Lambda_d}{\mu_d}$. Hence, $S_d(t)$, $E_d(t)$, and $I_d(t)$ are bounded.

From equations (3.2.5)-(3.2.8), we have

$$\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h,$$

The solution of the differential equation results in $N_h(t) = N_h(0)e^{-\mu_d t} + \frac{\Lambda_h}{\mu_h}(1 - e^{-\mu_h t})$, which shows that $\lim_{t\to\infty} \sup N_h(t) = \frac{\Lambda_h}{\mu_h}$. Hence, $S_h(t)$, $E_h(t)$ $R_h(t)$, and $I_h(t)$ are bounded.

From equations (3.2.9)-(3.2.11), we have $\frac{dN_s}{dt} = \Lambda_s - \mu_s N_s$, The solution of the differential equation results in $N_s(t) = N_s(0)e^{-\mu_s t} + \frac{\Lambda_s}{\mu_s}(1 - e^{-\mu_s t})$, which shows that $\lim_{t\to\infty} \sup N_s(t) = \frac{\Lambda_s}{\mu_s}$. Hence, $S_s(t)$, $E_s(t)$ and $I_s(t)$ are bounded. Finally, from equation (3.2.4) of the model, and since $I_d(t) \leq N_d(t) \leq \frac{\Lambda_d}{\mu_d}$, we have

$$B(t) \leq e^{-\int_0^t \mu_e d\tau}\left(\int_0^t \delta \frac{\Lambda_d}{\mu_d} e^{-\int_0^\tau \mu_e ds} d\tau\right) := \frac{\delta\Lambda_d}{\mu_e\mu_d} - \frac{\delta\Lambda_d}{\mu_e\mu_d}e^{-\mu_e t} \leq \frac{\delta\Lambda_d}{\mu_e\mu_d}.$$

Now we prove the dissipative condition is satisfied as follows.

$$\begin{aligned}
f(x).x &= (f_1, f_2, \cdots f_{11}).(S_d(t), E_d(t), I_d(t), B(t), S_h(t), E_h(t), I_h(t), R_h(t), S_s(t), E_s(t), I_s(t)) \\
&\leq \Lambda_d S_d + \beta_{sd} I_s S_d E_d + \gamma_d E_d^2 + \delta I_d + \Lambda_h S_h + \frac{\beta_{eh} B}{\chi_h + B} S_h E_h + \gamma_h E_h I_h + \alpha_h I_h R_h + \Lambda_s S_s \\
&+ \frac{\beta_{es} B}{\chi_s + B} S_s E_s + \gamma_s E_s I_s \\
&\leq \Lambda_d S_d + \Lambda_h S_h + \Lambda_s S_s + \frac{\beta_{sd}\Lambda_s}{\mu_s}\left(\frac{\Lambda_d}{\mu_d}\right)^2 + \gamma_d\left(\frac{\Lambda_d}{\mu_d}\right)^2 + \frac{\delta\Lambda_d}{\mu_d} + \beta_{eh}\left(\frac{\Lambda_h}{\mu_h}\right)^2 + \gamma_h\left(\frac{\Lambda_h}{\mu_h}\right)^2 \\
&+ \alpha_h\left(\frac{\Lambda_h}{\mu_h}\right)^2 + \beta_{es}\left(\frac{\Lambda_s}{\mu_s}\right)^2 \\
&\leq (\Lambda_d + \Lambda_h + \Lambda_s)(S_d + S_h + S_s) + \frac{\beta_{sd}\Lambda_s}{\mu_s}\left(\frac{\Lambda_d}{\mu_d}\right)^2 + \gamma_d\left(\frac{\Lambda_d}{\mu_d}\right)^2 + \frac{\delta\Lambda_d}{\mu_d} + \beta_{eh}\left(\frac{\Lambda_h}{\mu_h}\right)^2 \\
&+ \gamma_h\left(\frac{\Lambda_h}{\mu_h}\right)^2 + \alpha_h\left(\frac{\Lambda_h}{\mu_h}\right)^2 + \beta_{es}\left(\frac{\Lambda_s}{\mu_s}\right)^2 \leq a||x||^2 + b
\end{aligned}$$

where $a = \Lambda_d + \Lambda_h + \Lambda_s$, and

$$b = \frac{\beta_{sd}\Lambda_s}{\mu_s}\left(\frac{\Lambda_d}{\mu_d}\right)^2 + \gamma_d\left(\frac{\Lambda_d}{\mu_d}\right)^2 + \frac{\delta\Lambda_d}{\mu_d} + \beta_{eh}\left(\frac{\Lambda_h}{\mu_h}\right)^2 + \gamma_h\left(\frac{\Lambda_h}{\mu_h}\right)^2 + \alpha_h\left(\frac{\Lambda_h}{\mu_h}\right)^2 + \beta_{es}\left(\frac{\Lambda_s}{\mu_s}\right)^2.$$

Hence, condition of Theorem 2.4.5 is satisfied and hence a unique solution x which is globally defined in time exists. ■

3.4 Existence and stability of Equilibria

The equilibrium point(s) of the system (3.2.1)-(3.2.11) are found by solving the system:

$$\Lambda_d - \beta_{sd}I_sS_d - \mu_dS_d = 0 \tag{3.4.1}$$
$$\beta_{sd}I_sS_d - \tilde{\gamma_d}E_d = 0 \tag{3.4.2}$$
$$\gamma_dE_d - \mu_dI_d = 0 \tag{3.4.3}$$
$$\delta I_d - \mu_eB = 0 \tag{3.4.4}$$
$$\Lambda_h - \frac{\beta_{eh}B}{\chi_h + B}S_h - \mu_hS_h = 0 \tag{3.4.5}$$
$$\frac{\beta_{eh}B}{\chi_h + B}S_h - \tilde{\gamma_h}E_h = 0 \tag{3.4.6}$$
$$\gamma_hE_h - \tilde{q_h}I_h = 0 \tag{3.4.7}$$
$$\alpha_hI_h - \mu_hR_h = 0 \tag{3.4.8}$$
$$\Lambda_s - \frac{\beta_{es}B}{\chi_s + B}S_s - \mu_sS_s = 0 \tag{3.4.9}$$
$$\frac{\beta_{es}B}{\chi_s + B}S_s - \tilde{\gamma_s}E_s = 0 \tag{3.4.10}$$
$$\gamma_sE_s - \mu_sI_s = 0 \tag{3.4.11}$$

From equations (3.4.3) and (3.4.4), we respectively have

$$I_d = \frac{\mu_eB}{\delta} \quad \text{and } E_d = \frac{\mu_d\mu_eB}{\delta\gamma_d} \tag{3.4.12}$$

From equations (3.4.1), (3.4.2) and using (3.4.12) we have

$$S_d = \frac{\Lambda_d}{\mu_d} - \frac{\mu_e\tilde{\gamma_d}B}{\delta\gamma_d} \tag{3.4.13}$$

Substituting (3.4.13) in (3.4.1) yields

$$I_s = \frac{1}{\beta_{sd}}\left(\frac{\mu_e\mu_d^2\tilde{\gamma_d}B}{\delta\gamma_d\Lambda_d - \mu_e\mu_d\tilde{\gamma_d}B}\right) \tag{3.4.14}$$

Similarly, from equations (3.4.9)-(3.4.11), we obtain

$$I_s = \frac{\gamma_s\beta_{es}\Lambda_s B}{\mu_s\tilde{\gamma_s}[\mu_s\chi_s + (\mu_s + B_{es})B]} \tag{3.4.15}$$

By equating (3.4.14) and (3.4.15), we then obtain a quadratic equation

$$B^2[\mu_e\tilde{\gamma_d}(\mu_s\mu_d^2\tilde{\gamma_s}(\mu_s + \beta_{es}) + \mu_d\gamma_s\beta_{es}\beta_{sd}\Lambda_s)] - B[\delta\gamma_d\gamma_s\beta_{es}\beta_{sd}\Lambda_s\Lambda_d - \mu_e\chi_s\mu_s^2\mu_d^2\tilde{\gamma_d}\tilde{\gamma_s}] = 0 \tag{3.4.16}$$

Thus, we have two roots

$$B = 0 \text{ and } B = \frac{\delta\gamma_d\gamma_s\beta_{es}\beta_{sd}\Lambda_s\Lambda_d - \mu_e\chi_s\mu_s^2\mu_d^2\tilde{\gamma_d}\tilde{\gamma_s}}{\mu_e\tilde{\gamma_d}(\mu_s\mu_d^2\tilde{\gamma_s}(\mu_s + \beta_{es}) + \mu_d\gamma_s\beta_{es}\beta_{sd}\Lambda_s)} \tag{3.4.17}$$

All the remaining state variables S_h, E_h, I_h, R_h, S_s and E_s obtained from equations (3.4.5)-(3.4.10) are expressed in terms of B, where $B \geq 0$. Thus, the results of the possible equilibrium points of the above cases are presented in sections 3.4.1 and 3.4.3.

3.4.1 Disease-Free Equilibrium (DFE)

From algebraic computation when $B = 0$, the system (3.2.1)-(3.2.11) has the DFE

$$X_0 = (\frac{\Lambda_d}{\mu_d}, 0, 0, 0, \frac{\Lambda_h}{\mu_h}, 0, 0, 0, \frac{\Lambda_s}{\mu_s}, 0, 0).$$

The basic reproductive number is one of the fundamental concepts in mathematical biology. We determine the basic reproduction number using the Next Generation Matrix (NGM) approach [64]. According to the concepts of the next generation matrix and reproduction number presented in 2.6, we define

$$\mathcal{F} = \begin{pmatrix} \beta_{sd} I_s S_d \\ 0 \\ 0 \\ \dfrac{\beta_{eh} B}{\chi_h + B} S_h \\ 0 \\ \dfrac{\beta_{es} B}{\chi_s + B} S_s \\ 0 \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} \tilde{\gamma_d} E_d \\ \mu_d I_d - \gamma_d E_d \\ \mu_e B - \delta I_d \\ \tilde{\gamma_h} E_h \\ \tilde{q_h} I_h - \gamma_h E_h \\ \tilde{\gamma_s} E_s \\ \mu_s I_s - \gamma_s E_s \end{pmatrix}. \text{ The Jacobian matrix of the infection subsystem at } X_0 \text{ can be decomposed as } F - V, \text{ where } F \text{ is a matrix of transmission rates given by}$$

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \beta_{sd} \dfrac{\Lambda_d}{\mu_d} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \dfrac{\beta_{eh} \Lambda_h}{\chi_h \mu_h} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \dfrac{\beta_{es} \Lambda_s}{\chi_s \mu_s} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \tag{3.4.18}$$

and V is a matrix of transition rates given by

$$V = \begin{pmatrix} \tilde{\gamma_d} & 0 & 0 & 0 & 0 & 0 & 0 \\ -\gamma_d & \mu_d & 0 & 0 & 0 & 0 & 0 \\ 0 & -\delta & \mu_e & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \tilde{\gamma_h} & 0 & 0 & 0 \\ 0 & 0 & 0 & -\gamma_h & \tilde{q_h} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \tilde{\gamma_s} & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma_s & \mu_s \end{pmatrix}. \tag{3.4.19}$$

Thus,

$$V^{-1} = \begin{pmatrix} \frac{1}{\tilde{\gamma}_d} & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\gamma_d}{\mu_d\tilde{\gamma}_d} & \frac{1}{\mu_d} & 0 & 0 & 0 & 0 & 0 \\ \frac{\delta\gamma_d}{\mu_e\mu_d\tilde{\gamma}_d} & \frac{\delta}{\mu_e\mu_d} & \frac{1}{\mu_e} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\tilde{\gamma}_h} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\gamma_h}{\tilde{\gamma}_h\tilde{q}_h} & \frac{1}{\tilde{q}_h} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{\tilde{\gamma}_s} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\gamma_s}{\mu_s\tilde{\gamma}_s} & \frac{1}{\mu_s} \end{pmatrix},$$

and the next generation matrix is

$$FV^{-1} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\gamma_s\beta_{sd}\Lambda_d}{\mu_s\mu_d\tilde{\gamma}_s} & \frac{\beta_{sd}\Lambda_d}{\mu_d\mu_s} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\delta r_d\beta_{eh}\Lambda_h}{\chi_h\mu_d\mu_h\mu_e\tilde{\gamma}_d} & \frac{\delta\beta_{eh}\Lambda_h}{\chi_h\mu_d\mu_h\mu_e} & \frac{\beta_{eh}\Lambda_h}{\chi_h\mu_h\mu_e} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\delta r_d\beta_{es}\Lambda_s}{\chi_s\mu_d\mu_s\mu_e\tilde{\gamma}_d} & \frac{\delta\beta_{es}\Lambda_s}{\chi_s\mu_s\mu_d\mu_e} & \frac{\beta_{es}\Lambda_s}{\chi_s\mu_s\mu_e} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

The basic reproduction number is the spectral radius. Thus,

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\frac{\gamma_s\beta_{es}\Lambda_s}{\chi_s\mu_e}\frac{\beta_{sd}}{\mu_s^2\tilde{\gamma}_s}\frac{\delta\gamma_d\Lambda_d}{\mu_d^2\tilde{\gamma}_d}}. \tag{3.4.20}$$

We write as $\mathcal{R}_0 = \sqrt{R_dR_sR_e}$, where $R_d = \frac{\beta_{sd}\gamma_d\Lambda_d}{\mu_d^2\tilde{\gamma}_d}$ corresponds to the number of dog that one infectious sheep causes the disease over its expected infection period in a completely susceptible dog population, $R_s = \frac{\gamma_s\beta_{es}\Lambda_s}{\mu_s^2\tilde{\gamma}_s}$ corresponds to the number of sheep that an infectious dog induce the disease over its expected infection period in a completely susceptible sheep population, and $R_e = \frac{\delta}{\mu_e\chi_s}$ corresponds to the contribution of environment to sheep population as a result of one infectious dog subject during its infectious period.

3.4.2 Stability of the DFE

Theorem 3.4.1 *If $\mathcal{R}_0 < 1$, then the disease free equilibrium X_0 is globally asymptotically stable in $\mathbb{D}$. If $\mathcal{R}_0 > 1$, then the DFE is unstable, the system is persistent and there is at least one equilibrium in the interior of $\mathbb{D}$.*

Proof. We use a matrix-theoretic method as explained in Section 2.6.

The disease compartments of model (3.2.1)-(3.2.11) can be written as $x' = (F - V)x - f(x, y)$ where $x = (E_d, I_d, B, E_h, I_h, E_s, I_s)^T$, $y = (S_d, S_h, R_h, S_s)^T$, F and V are matrices given in (4.3.3) and (3.4.19), and

$$f(x,y) = \begin{pmatrix} \beta_{sd} I_s (\frac{\Lambda_d}{\mu_d} - S_d) \\ 0 \\ 0 \\ \frac{\beta_{eh} B}{\chi_h}(\frac{\Lambda_h}{\mu_h} - \frac{\chi_h S_h}{B + \chi_h}) \\ 0 \\ \frac{\beta_{es} B}{\chi_s}(\frac{\Lambda_s}{\mu_s} - \frac{\chi_s S_s}{B + \chi_s}) \\ 0 \end{pmatrix} \geq 0,$$

since $S_d \leq \frac{\Lambda_d}{\mu_d}$, $S_h \leq \frac{\Lambda_h}{\mu_h}$, $\chi_h \leq \chi_h + B$, $S_s \leq \frac{\Lambda_s}{\mu_s}$, and $\chi_s \leq \chi_s + B$. Matrices F and V^{-1} are entry wise non negative with

$$V^{-1}F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{sd}\Lambda_d}{\mu_d \tilde{\gamma_d}} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\gamma_d \beta_{sd} \Lambda_d}{\mu_d^2 \tilde{\gamma_d}} \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{\delta \gamma_d \beta_{sd} \Lambda_d}{\mu_e \mu_d^2 \tilde{\gamma_d}} \\ 0 & 0 & \frac{\beta_{eh}\Lambda_h}{\mu_h \chi_h \tilde{\gamma_h}} & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\gamma_h \beta_{eh} \Lambda_h}{\mu_h \chi_h \tilde{\gamma_h} \tilde{q_h}} & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\beta_{es}\Lambda_s}{\mu_s \chi_s \tilde{\gamma_s}} & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\gamma_s \beta_{es} \Lambda_s}{\mu_s^2 \chi_s \tilde{\gamma_s}} & 0 & 0 & 0 & 0 \end{pmatrix}$$

Since $V^{-1}F$ is a reducible matrix [8], the condition of Theorem 2.6.4 fails. Instead, to establish the global stability of the DFE, we construct a Lyapunov function by using Theorem 2.6.3. Let $W^T = (w_1, w_2, w_3, w_4, w_5, w_6, w_7)$ be the left eigenvector of $V^{-1}F$ corresponding to the eigenvalue $\mathcal{R}_0$. Thus,

$$W^T V^{-1} F = \mathcal{R}_0 W.$$

As a result, we found that $W = \left(0, 0, 1, 0, 0, 0, 0, \frac{\delta\gamma_d\beta_{sd}\Lambda_d}{\mu_d^2\mu_e\tilde{\gamma_d}\mathcal{R}_0}\right)$ is the left eigenvector of $V^{-1}F$ corresponding to the eigenvalue $\mathcal{R}_0$. Thus, by Theorem 2.6.3,

$$Q = W^T V^{-1} x = \frac{\delta\gamma_d E_d}{\mu_d\mu_e\tilde{\gamma_d}} + \frac{\delta I_d}{\mu_d\mu_e} + \frac{B}{\mu_e} + \left(\frac{\gamma_s}{\mu_s\tilde{\gamma_s}}E_s + \frac{I_s}{\mu_s}\right)\frac{\delta\gamma_d\beta_{sd}\Lambda_d}{\mu_e\tilde{\gamma_d}\mu_d^2\mathcal{R}_0},$$

is a Lyapunov function for the model (3.2.1)-(3.2.11). Then differentiating along the solutions of the system (3.2.1)-(3.2.11) gives

$$Q' = (\mathcal{R}_0 - 1)\left(\frac{\delta\gamma_d\beta_{sd}I_s\Lambda_d}{\mu_d^2\mu_e\tilde{\gamma_d}\mathcal{R}_0} + B\right) - \left(\frac{\delta\gamma_d\beta_{sd}I_s}{\mu_d\mu_e\tilde{\gamma_d}}(\frac{\Lambda_d}{\mu_d} - S_d) + \frac{\gamma_s\gamma_d\beta_{es}\beta_{sd}B\Lambda_d}{\mu_s\mu_e\mu_d^2\chi_s\tilde{\gamma_d}\mathcal{R}_0}(\frac{\Lambda_s}{\mu_s} - \frac{S_s\chi_s}{B+\chi_s})\right). \quad (3.4.21)$$

Since $S_d \leq \frac{\Lambda_d}{\mu_d}$, $S_s \leq \frac{\Lambda_s}{\mu_s}$ and $\chi_s \leq \chi_s + B$, $Q' \leq 0$ if $\mathcal{R}_0 < 1$. Furthermore, $Q' = 0$ implies that

Case 1. $B = 0$ and $I_s = 0$. Thus, using the results obtained in Section 3.4, we have $E_d = 0$, $I_d = 0$, $E_h = 0$, $I_h = 0$, $R_h = 0$, $E_s = 0$, $S_d = \frac{\Lambda_d}{\mu_d}$, $S_h = \frac{\Lambda_h}{\mu_h}$, and $S_s = \frac{\Lambda_s}{\mu_s}$.

Case 2. $\mathcal{R}_0 = 1$, $S_d = \frac{\Lambda_d}{\mu_d}$ and $S_s = \frac{(\chi_s + B)\Lambda_s}{\mu_s\chi_s}$. Thus, using the results obtained in Section 3.4, we also have $E_d = 0$, $I_d = 0$, $E_h = 0$, $I_h = 0$, $R_h = 0$, $E_s = 0$, $S_d = \frac{\Lambda_d}{\mu_d}$, $S_h = \frac{\Lambda_h}{\mu_h}$, and $S_s = \frac{\Lambda_s}{\mu_s}$.

Hence, the largest invariant set with respect to (3.2.1)-(3.2.11) where $Q' = 0$ in $int(\mathbb{D})$ is the singleton $\{X_0\}$. Therefore, by Lasalle's invariance principle as stated in Theorem 2.5.1, the disease free equilibrium X_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$. Furthermore, from (3.4.21), if $\mathcal{R}_0 > 1$ then $Q' = (\mathcal{R}_0 - 1)W^T x = (\mathcal{R}_0 - 1)\left(\frac{\delta\gamma_d\beta_{sd}I_s\Lambda_d}{\mu_d^2\mu_e\tilde{\gamma_d}\mathcal{R}_0} + B\right) > 0$ in $\mathbb{D}$ provided $B > 0$ and $(S_d, S_s) = (\frac{\Lambda_d}{\mu_d}, \frac{\Lambda_s}{\mu_s})$. By continuity $Q' > 0$ in a neighborhood of X_0. Thus, the disease

free equilibrium X_0 is unstable, and using Theorem 2.6.4, the system (3.2.1)-(3.2.11) is uniformly persistent and hence imply there is at least one endemic equilibrium in the interior of $\mathbb{D}$. ■

3.4.3 Existence and stability of the Endemic Equilibrium (EE)

From the result in (3.4.17), an endemic equilibrium is obtained when $B > 0$. Thus, the endemic equilibrium point of the system in terms of the reproduction number $\mathcal{R}_0$ is given by

$$X_E = (S_d^*, E_d^*, I_d^*, B^*, S_h^*, E_h^*, I_h^*, R_h^*, S_s^*, E_s^*, I_s^*),$$

where

$$I_d^* = \frac{\mu_e B^*}{\delta} \tag{3.4.22}$$

$$E_d^* = \frac{\mu_e \mu_d B^*}{\delta \gamma_d} \tag{3.4.23}$$

$$S_d^* = \frac{\Lambda_d}{\mu_d} - \frac{\mu_e \tilde{\gamma}_d B^*}{\delta \gamma_d} \tag{3.4.24}$$

$$S_h^* = \frac{(\chi_h + B^*)\Lambda_h}{\mu_h(\chi_h + B^*) + \beta_{eh} B^*} \tag{3.4.25}$$

$$E_h^* = \frac{\beta_{eh}\Lambda_h B^*}{\tilde{\gamma}_h(\mu_h(\chi_h + B^*) + \beta_{eh} B^*)} \tag{3.4.26}$$

$$I_h^* = \frac{\gamma_h \beta_{eh}\Lambda_h B^*}{\tilde{q}_h\tilde{\gamma}_h(\mu_h(\chi_h + B^*) + \beta_{eh} B^*)} \tag{3.4.27}$$

$$R_h^* = \frac{\gamma_h \alpha_h \beta_{eh}\Lambda_h B^*}{\mu_h \tilde{q}_h\tilde{\gamma}_h(\mu_h(\chi_h + B^*) + \beta_{eh} B^*)} \tag{3.4.28}$$

$$S_s^* = \frac{\Lambda_s(\chi_s + B^*)}{\mu_s(\chi_s + B^*) + \beta_{es} B^*} \tag{3.4.29}$$

$$E_s^* = \frac{\Lambda_s \beta_{es} B^*}{\tilde{\gamma}_s(\mu_s(\chi_s + B^*) + \beta_{es} B^*)} \tag{3.4.30}$$

$$I_s^* = \frac{\gamma_s \beta_{es}\Lambda_s B^*}{\mu_s\tilde{\gamma}_s(\mu_s(\chi_s + B^*) + \beta_{es} B^*)} \tag{3.4.31}$$

$$B^* = \frac{\chi_s \tilde{\gamma}_s \mu_d \mu_s^2}{\mu_s \mu_d \tilde{\gamma}_s(\mu_s + \beta_{es}) + \gamma_s \beta_{sd}\beta_{es}\Lambda_s}(\mathcal{R}_0^2 - 1) \tag{3.4.32}$$

Theorem 3.4.2 *If $\mathcal{R}_0 > 1$, then an endemic equilibrium $X_E = (S_d^*, E_d^*, I_d^*, B^*, S_h^*, E_h^*, I_h^*, R_h^*, S_s^*, E_s^*, I_s^*)$ defined by equations* (3.4.22) - (3.4.32) *is globally asymptotically stable.*

Proof. To prove the global asymptotic stability of the endemic equilibria, we use the method of Lyapunov functions combined with the theory of Volterra–Lyapunov stable matrices. To do this, we define a Lyapunov function :

$$\begin{aligned} V =& w_1(S_d - S_d^*)^2 + w_2(E_d - E_d^*)^2 + w_3(I_d - I_d^*)^2 + w_4(B - B^*)^2 \\ &+ \frac{1}{2}(S_h - S_h^* + E_h - E_h^* + I_h - I_h^* + R_h - R_h^*)^2 + \frac{1}{2}(S_s - S_s^* + E_s - E_s^* + I_s - I_s^*)^2. \end{aligned}$$

Thus,

$$\begin{aligned} \frac{dV}{dt} =& 2w_1(S_d - S_d^*)\left(\frac{dS_d}{dt}\right) + 2w_2(E_d - E_d^*)\left(\frac{dE_d}{dt}\right) + 2w_3(I_d - I_d^*)\left(\frac{dI_d}{dt}\right) + 2w_4(B - B^*)\left(\frac{dB}{dt}\right) \\ &+ (S_s - S_s^* + E_s - E_s^* + I_s - I_s^*)\left(\frac{d}{dt}(S_s + E_s + I_s)\right) \\ &+ (S_h - S_h^* + E_h - E_h^* + I_h - I_h^* + R_h - R_h^*)\left(\frac{d}{dt}(S_h + E_h + I_h + R_h)\right). \end{aligned}$$

The time derivative of $V(t)$ along the solutions of model equations (3.2.1)-(3.2.11), we obtain

$$\begin{aligned} \frac{dV}{dt} =& Y(WA + A^T W^T)Y^T - \mu_s(S_s - S_s^* + E_s - E_s^* + I_s - I_s^*)^2 \\ &- \mu_h(S_h - S_h^* + E_h - E_h^* + I_h - I_h^* + R_h - R_h^*)^2, \end{aligned}$$

where $Y = (S_d - S_d^*, E_d - E_d^*, I_d - I_d^*, B - B^*)$, $W = diag(w_1, w_2, w_3, w_4)$ and

$$A = \begin{pmatrix} -\beta_{sd} I_s - \mu_d & 0 & 0 & 0 \\ \beta_{sd} I_s & -\tilde{\gamma_d} & 0 & 0 \\ 0 & \gamma_d & -\mu_d & 0 \\ 0 & 0 & \delta & -\mu_e \end{pmatrix}.$$

Obviously, the second and third terms of $\frac{dV}{dt}$ are negative. To show the global stability of endemic equilibrium X_E, it suffices to show that A is Volterra-Lyapunov stable in $\mathbb{D}\backslash\{X_E\}$. For this purpose, we show that matrix $\tilde{A}$ is Volterra-Lyapunov stable, and matrix $U = \widetilde{A^{-1}}$ is Volterra-Lyapunov stable (or $-\widetilde{A^{-1}}$ is diagonally stable).

Condition 1: To show $\tilde{A}$ is Volterra-Lyapunov stable, we consider

$$D = -\tilde{A} = \begin{pmatrix} \beta_{sd}I_s + \mu_d & 0 & 0 \\ -\beta_{sd}I_s & \tilde{\gamma_d} & 0 \\ 0 & -\gamma_d & \mu_d \end{pmatrix}.$$

The matrix $\tilde{D}$ is obtained by deleting its 3^{rd} row and 3^{rd} column,

$$-\widetilde{D} = \begin{pmatrix} -\beta_{sd}I_s - \mu_d & 0 \\ \beta_{sd}I_s & -\tilde{\gamma_d} \end{pmatrix}.$$

Clearly $a_{11} = -\beta_{sd}I_s - \mu_d < 0$, $a_{22} = -\tilde{\gamma_d}$ and $det(-\widetilde{D}) > 0$. Based on Lemma 2.6.8, $-\widetilde{D}$ is Volterra-Lyapunov stable.

Moreover, we obtain

$$-\widetilde{D^{-1}} = \begin{pmatrix} -\dfrac{1}{\beta_{sd}I_s + \mu_d} & 0 \\ -\dfrac{\beta_{sd}I_s}{\tilde{\gamma_d}(\mu_d + \beta_{sd}I_s)} & -\dfrac{1}{\tilde{\gamma_d}} \end{pmatrix}.$$

Clearly, the diagonal elements $-\dfrac{1}{\beta_{sd}I_s + \mu_d} < 0$, $-\dfrac{1}{\tilde{\gamma_d}} < 0$ and $det(-\widetilde{D^{-1}}) > 0$. Thus, based on Lemma 2.6.8, $-\widetilde{D^{-1}}$ is Volterra-Lyapunov stable.

Therefore, $D = -\tilde{A}$ is diagonally stable, and hence $\tilde{A}$ is Volterra-Lyapunov stable.

Condition 2: To show $\widetilde{A^{-1}}$ is Volterra-Lyapunov stable, we consider

$$E = -\widetilde{A^{-1}} = \begin{pmatrix} \dfrac{1}{\beta_{sd}I_s + \mu_d} & 0 & 0 \\ \dfrac{\beta_{sd}I_s}{\tilde{\gamma_d}(\mu_d + \beta_{sd}I_s)} & \dfrac{1}{\tilde{\gamma_d}} & 0 \\ \dfrac{\beta_{sd}I_s\gamma_d}{\tilde{\gamma_d}\mu_d(\mu_d + \beta_{sd}I_s)} & \dfrac{\gamma_d}{\tilde{\gamma_d}\mu_d} & \dfrac{1}{\mu_d} \end{pmatrix}, \text{ and we have}$$

$$-\tilde{E} = \begin{pmatrix} -\dfrac{1}{\beta_{sd}I_s + \mu_d} & 0 \\ -\dfrac{\beta_{sd}I_s}{\tilde{\gamma_d}(\mu_d + \beta_{sd}I_s)} & -\dfrac{1}{\tilde{\gamma_d}} \end{pmatrix}.$$

Using Lemma 2.6.8, it is easy to observe that $-\tilde{E}$ is Volterra-Lyapunov stable.

Moreover, we have $-\widetilde{E^{-1}} = \begin{pmatrix} -\beta_{sd}I_s - \mu_d & 0 \\ \beta_{sd}I_s & -\tilde{\gamma}_d \end{pmatrix}$.

Based on Lemma 2.6.8, we can also observe that $-\widetilde{E^{-1}}$ is also Volterra-Lyapunov stable.

Therefore, $\widetilde{A^{-1}}$ is Volterra-Lyapunov stable.

Based on Lemma 2.6.10, there exists a diagonal matrix $W = diag\{w_1, w_2, w_3, w_4\}$ such that $W(-A) + (-A)^T W^T > 0$ or $WA + A^T W^T < 0$. This shows that A is Volterra-Lyapunov stable.

Therefore, $\frac{dV}{dt} < 0$, and by LaSalle's invariance principle (Theorem 2.5.1), X_E is globally asymptotically stable in the interior of $\mathbb{D}$, and is unique provided that $\mathcal{R}_0 > 1$. ■

3.5 Numerical simulations of the model

3.5.1 *Elasticity indices*

Our study in previous sections illustrated that the quantity of $\mathcal{R}_0$ plays a significant role in dynamics of cystic echinococcosis. In this section, we perform a sensitivity analysis of the basic reproduction number $\mathcal{R}_0$ to determine the most influential parameters in the dynamics of the disease. For this purpose, some important data are taken from the literature. and some parameter values are computed, and assumed (estimated) values are also used, as given in Table 3.3. According to World Health Organization, from 2000-2019 GC, the global life expectancy of human is 66.8-73.4 [68] . Using mean value of 70.1, the death rate of human is taken to be $\mu_h = \frac{1}{70.1 \times 365} = 0.00004$. The incubation period of cystic echinococcosis in human is $20 - 30$ years. Using the mean value of 25 years, we found that $\gamma_h = \frac{1}{25 \times 365} = 0.0001$. The life expectancy of dog is $10 - 13$ [74, 75]. Using mean value of 11.5, the death rate of dog is taken to be $\mu_d = \frac{1}{11.5 \times 365} = 0.00024$. The life expectancy of sheep is $10 - 12$ [73]. Using mean value of 11, the death rate of dog is taken to be $\mu_s = \frac{1}{11 \times 365} = 0.00025$. The parasite's eggs which are shed from dogs can survive for long periods in the environment and remain viable up to a year [63]. This results in $\mu_e = \frac{1}{365} = 0.003$. It was reported in [37] that latent period of human is 5-15 years, with this value we obtain $\gamma_h = \frac{1}{14 \times 365} = 0.00019$. Some realistically feasible assumed (estimated) parameter values (specially for transition and transmission rates) are also used based on range of data reported in [4, 5, 37, 63]. The intention for this work is not validating

the model results of the real situation obtained in a particular study, but for illustrative purposes only, and the result will be used to suggest possible intervention strategies.

Table 3.3: Parameters, Baseline values and Sources

Parameters	Baseline values(with *unit*)	Range	Sources
μ_d	$0.00024/day$		[74, 75]
β_{sd}	$0.00001/day$		Assumed
γ_d	$0.001/day$	$[\frac{1}{3\times 365}, \frac{1}{1\times 365}]$	Assumed
μ_h	$0.00004/day$		[68]
β_{eh}	$0.00001/day$	$[1\times 10^{-5}, 5\times 10^{-5}]$	Assumed
γ_h	$0.00019/day$		[67]
α_h	$0.00001/day$	$[\frac{1}{25\times 365}, \frac{1}{2\times 365}]$	Assumed
μ_s	$0.00025/day$		[73]
β_{es}	$0.00005/day$	$[0.000001, 0.1]$	Assumed
μ_e	$0.003/day$		[63]
γ_s	$0.001/day$	$[\frac{1}{3\times 365}, \frac{1}{1\times 365}]$	[4]
δ	$0.00014 cells/ml.day$		[63]
χ_h	$120 cells/ml$		Assumed
χ_s	$100 cells/ml$		Assumed

To determine the parameter that contributes most to the disease transmission, we perform local sensitivity analysis by calculating the normalized sensitivity index (elasticity index) as introduced in [19, 43]. The normalized forward sensitivity index (elasticity index) of a variable ($\mathcal{R}_0$) with respect to a parameter p is the ratio of the relative change in the variable to the relative change in the parameter, given by

$$\Upsilon_p^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0}$$

Table 3.4: Elasticity indices of $\mathcal{R}_0$ relative to some model parameters

Parameters	$\Upsilon_p^{R_0} = \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0}$	Baseline value	**Range**	**Elasticity index**
β_{es}	$\frac{1}{2}$	0.00005	$0.000005 - 0.0001$	0.5
β_{sd}	$\frac{1}{2}$	0.000001	$0.0000001 - 0.000002$	0.5
δ	$\frac{1}{2}$	0.000014	$0.0000014 - 0.000028$	0.5
χ_s	$-\frac{1}{2}$	100	$60 - 140$	-0.5
γ_s	$\frac{\mu_s}{2(\mu_s + \gamma_s)}$	0.0001	$0.00001 - 0.0002$	0.1
γ_d	$\frac{\mu_d}{2(\mu_d + \gamma_d)}$	0.0001	$0.0001 - 0.0002$	0.1

Table 3.4 gives the elasticity indices of $\mathcal{R}_0$ with respect to key parameters of model (3.2.1)-(3.2.11) at the baseline values indicated in Table 3.3 and arranged in descending order of magnitudes. The sign of the elasticity index tells whether $\mathcal{R}_0$ increases (positive sign) or decreases (negative sign) with the parameter; whereas the magnitude determines the relative importance of the parameter. From the magnitude of elasticity index, we can notice that four parameters $(\beta_{es}, \beta_{sd}, \delta, \chi_s)$ have equal and the greatest influence for the transmission of the disease, followed by γ_s and γ_d.

3.5.2 *Global sensitivity analysis*

From the local sensitivity analysis, we observed that it is difficult to differentiate explicitly the most influential parameter(s) of the model. In order to determine which parameter(s) among the six is (are) most influential in the dynamics of the disease, global sensitivity analysis is done. We employed the technique of Latin Hypercube Sampling (LHS) to test the sensitivity of the model to each input parameter, as described and implemented in [42], and Partial Rank Correlation

Coefficients (PRCCs) to measure the relative degree of sensitivity of the outcome variable to each parameter, regardless of whether the parameter has a positive or negative influence on the outcome variable. This is done computationally by sampling parameters from a uniformly distributed range using Latin Hy- percube Sampling (LHS). Latin Hypercube Sampling is a statistical sampling method that evaluates sensitivity of an outcome variable to all input variables. To examine the dependence of $\mathcal{R}_0$ on parameter variations, we determine the PRCC values by considering a range of parameters as given in Table 3.4. The parameters were sampled 1000 times for 1000 runs. Figure 3.2 show the plots of 1000 runs output and PRCCs plotted for 6 parameters. The parameter with PRCC value far away from zero indicates the more strongly the parameter influence $\mathcal{R}_0$. The negative sign for PRCCs indicates inverse proportionality.

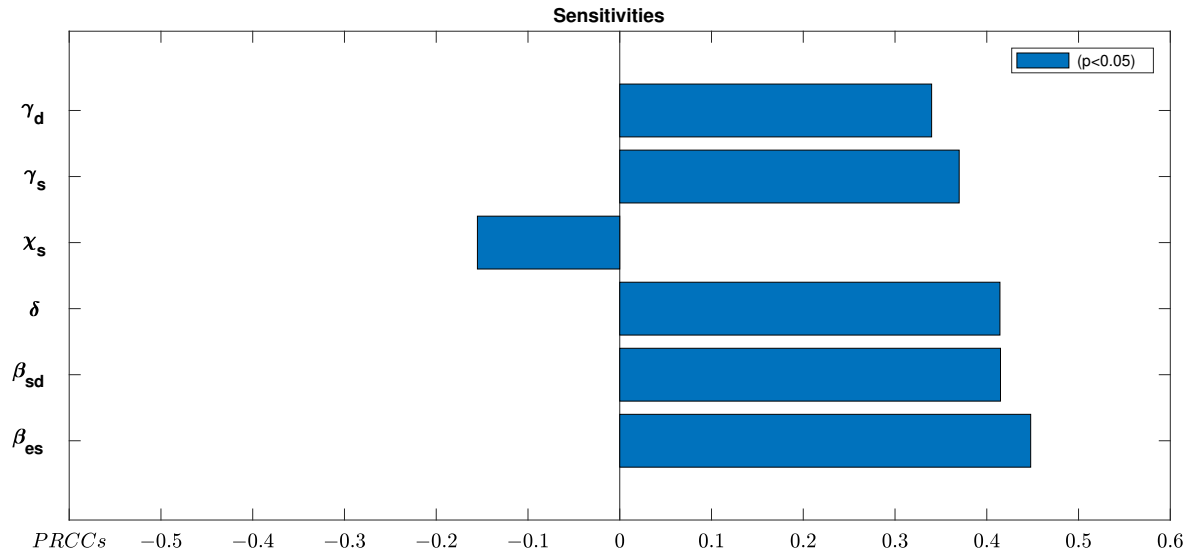

Figure 3.2: Global sensitivity analysis displaying the partial rank correlation coefficients(PRCC) of $\mathcal{R}_0$.

From Figure 3.2 , it is observed that the transmission rate of Echinococcus' eggs from environment to sheep (β_{es}), followed by transmission rate from sheep to dog (β_{sd}), and eggs contamination rate of the environment by infected dogs (δ) are the most influential parameters among the six parameters in the disease dynamics.

3.5.3 *Numerical simulations*

In this section, numerical simulations to gain insight into some of quantitative features of the model (3.2.1)-(3.2.11) are presented.

Simulations are carried out using the baseline parameter values given in Table 3.4, and this results in a reproductive number $\mathcal{R}_0 = 2.56 > 1$. The total populations of dog, human and sheep are assumed to be $\Lambda_d = 3$, $\Lambda_h = 2$, $\Lambda_s = 4$ respectively. The time evolution of human, sheep and dog populations is depicted in Figure 3.3. It can be noticed that all the compartments of the dog, human and sheep populations converge asymptotically to their respective endemic equilibrium points irrespective of different initial conditions. This shows the global stability of the endemic equilibrium as proved in Theorem 3.4.2.

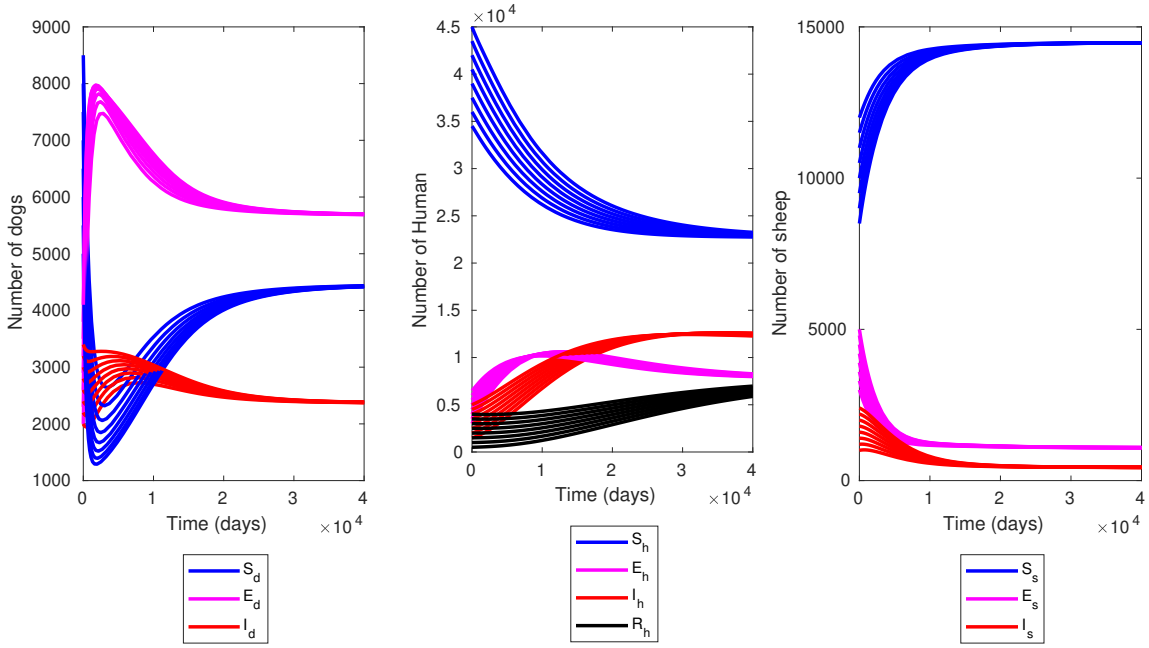

Figure 3.3: Time evolution of the dog, sheep and human populations with baseline parameter values as in Table 3.4, using different initial conditions gives $\mathcal{R}_0 = 2.56$, and with approximate equilibrium values $S_d^* = 4449$, $E_d^* = 5683$, $I_d^* = 2368$, $S_h^* = 22742$, $E_h^* = 7788$, $I_h^* = 11624$, $R_h^* = 7846$, $S_s^* = 14480$, $E_s^* = 1086$, $I_s^* = 434, B = 111$.

By reducing $\beta_{es} = 0.00005$ to $\beta_{es} = 0.00005/10$, we get $\mathcal{R}_0 = 0.80 < 1$. From the Numerical simulation with different initial conditions in Figure 3.4 depicts that all disease compartments E_d^*, I_d^*, B^*, E_h^*, I_h^*, R_h^*, E_s^* and I_s^* converge asymptotically to zero, while the non infected compartments S_d^*, S_h^* and S_s^* converge to $\frac{\Lambda_d}{\mu_d} = 12,500$, $\frac{\Lambda_h}{\mu_h} = 50,000$ and $\frac{\Lambda_s}{\mu_s} = 16,000$ respectively. This shows

the global stability of the disease free equilibrium as proved in Theorem 3.4.1.

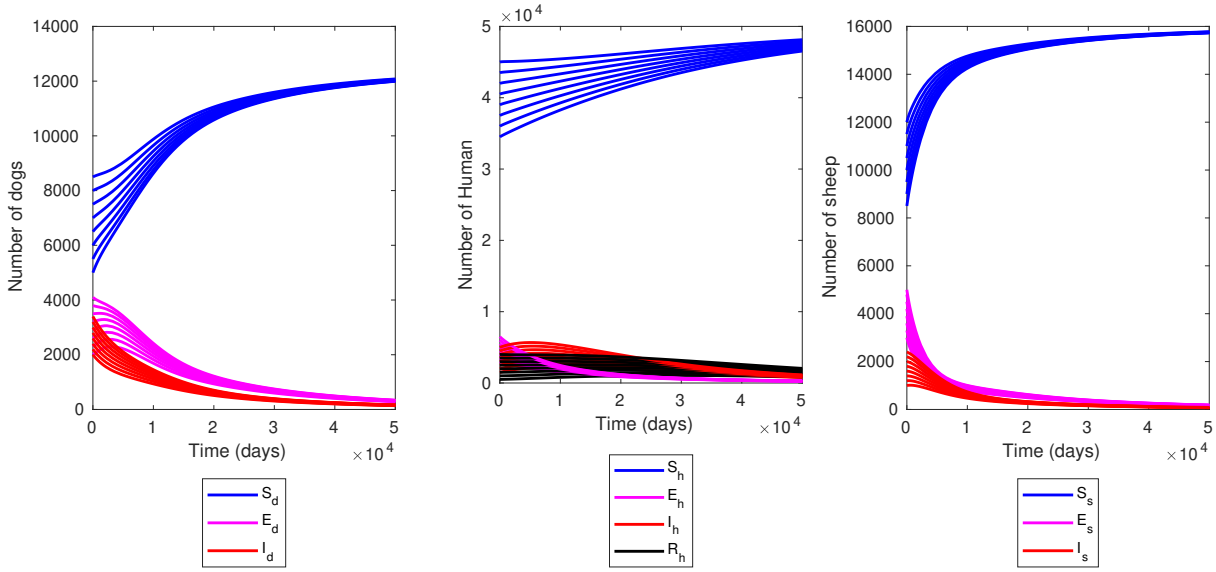

Figure 3.4: Time evolution of the dog, sheep and human populations with baseline parameter values as in Table 3.4, using different initial conditions,except for $\beta es = 0.00005/10$, which gives $\mathcal{R}_0 = 0.80$.

3.5.4 *Control strategies*

The global sensitivity analysis presented in section 3.5.2 depicts that cyst echinococcosis can be controlled by reducing the transmission rate of echinococcus' eggs from environment to sheep (β_{es}). In this section, we illustrate the effect of the transmission rate of *echinococcus granulosus'* eggs from environment to sheep (β_{es}).

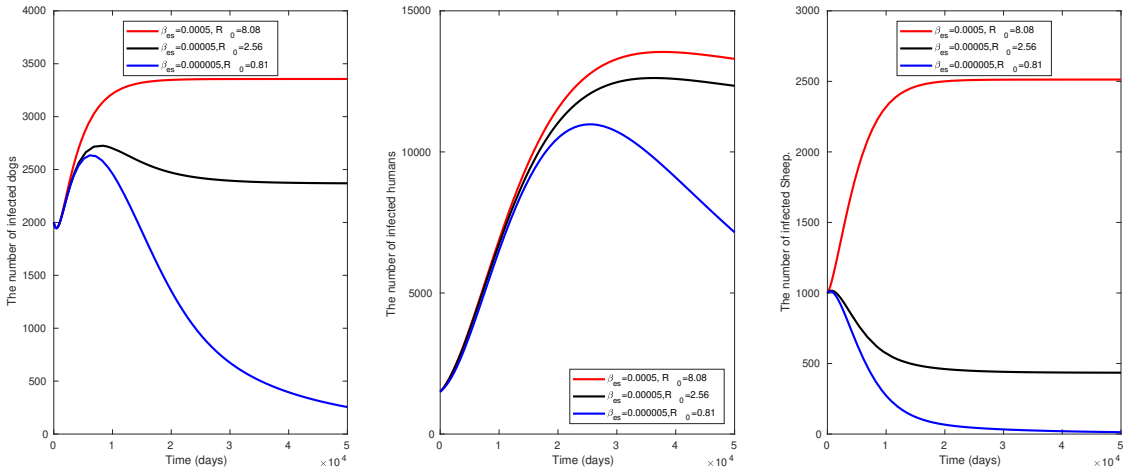

Figure 3.5: The numerical simulations displaying effects of controlling strategies on cumulative number of infectious dog, human and sheep populations, using parameter values in Table 3.4, with varying values of β_{es}.

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The effect of the transmission rate of *Echinococcus granulosus'* eggs from environment to sheep (β_{es}) using baseline parameter values in Table 3.4, and when β_{es} varied from 0.0005 to 0.000005, is displayed in Figure 3.5. As a result the infectious sheep, dog and human populations are respectively reduced from 2513 to 0 , 3356 to 0, and 12495 to 0, where the basic reproductive number is also reduced from $\mathcal{R}_0 = 8.08$ to $\mathcal{R}_0 = 0.808$. The result shows that increasing the transmission rate of *Echinococcus granulosus'* eggs from environment to sheep (β_{es}) will intensify the transmission of the disease. Thus, to control the disease transmission, we suggest that it is important to plan an intervention strategy to decrease the transmission rate of *Echinococcus granulosus'* eggs from environment to sheep (β_{es}).

Chapter 4

A mathematical model of echinococcosis with intervention

In this chapter, a mathematical model of the dynamics of CE with vaccination of sheep and cleaning or disinfection of the environment is formulated and analyzed. This is a valuable tool to develop best ways of controlling the disease transmission, including comparisons of different possible approaches. The use of mathematical models to evaluate these interventions proceeds by first constructing a mathematical model that describes the transmission of the infection. The mathematical model of cyst echinococcosis with the proposed interventions is presented and studied in the following sections.

4.1 Model formulation

In this section, the mathematical model presented in 3.1 is extended by incorporating vaccination of sheep and cleaning or disinfection of the environment. However, due to the presence of vaccination of sheep, the sheep population has four classes: the Susceptible (S_s), the Exposed (E_s), the Infectious (I_s), and the Vaccinated (V_s) classes. We introduced vaccination to the susceptible sheep population at a rate ν, so that the population of susceptible sheep is reduced through vaccination and moved to vaccinated V_s class. We assume that sheep that are vaccinated will progress to vaccinated class, but vaccination is not lifelong. The sheep population may lose of vaccine-induced immunity and move back to susceptible class at a rate ρ, i.e $\tau = \frac{1}{\rho}$ is the average duration of vaccine protection. Since the EG95 vaccine against CE has proven to be highly effective [66], the efficacy of sheep vaccination is assumed to be 100%. The concentration of *Echinococcus granulosus'* eggs is increased by shedding of a parasite from infected dog at rate δ and

decreased by the natural death rate of *Echinococcus granulosus'* eggs at rate μ_e and disinfection or cleaning of environment at rate μ. All other assumptions and the variables stated in Section 3.1 including the total populations is valid for this model too.

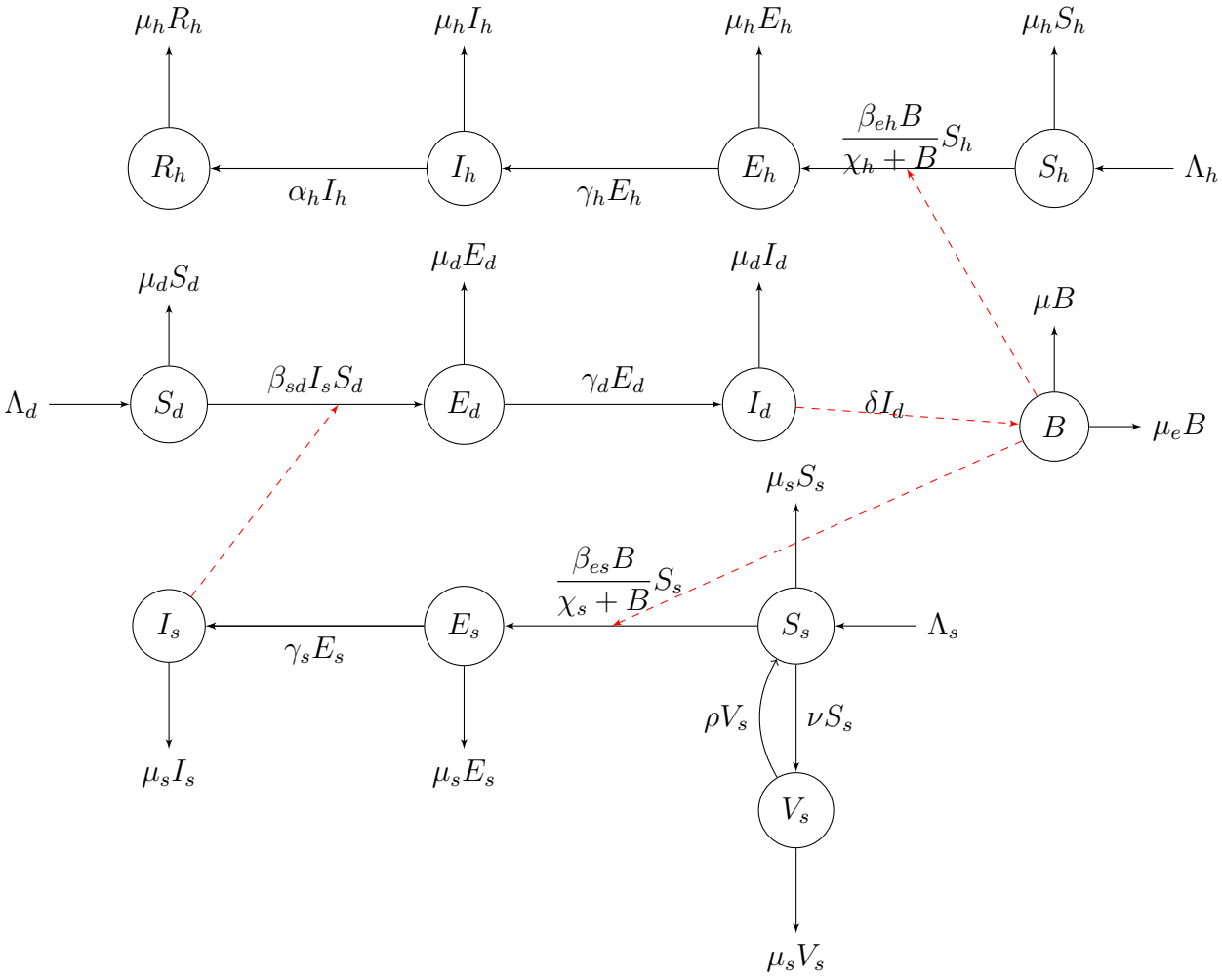

Figure 4.1: The flow diagram for cyst echinococcosis transmission dynamics with controls.

The transmission dynamics of the disease in the three populations is expressed by the following system of first order differential equations:

$$\frac{dS_d}{dt} = \Lambda_d - \beta_{sd} I_s S_d - \mu_d S_d, \tag{4.1.1}$$
$$\frac{dE_d}{dt} = \beta_{sd} I_s S_d - (\mu_d + \gamma_d) E_d, \tag{4.1.2}$$
$$\frac{dI_d}{dt} = \gamma_d E_d - \mu_d I_d, \tag{4.1.3}$$
$$\frac{dB}{dt} = \delta I_d - (\mu_e + \mu) B, \tag{4.1.4}$$
$$\frac{dS_h}{dt} = \Lambda_h - \frac{\beta_{eh} B}{\chi_h + B} S_h - \mu_h S_h, \tag{4.1.5}$$
$$\frac{dE_h}{dt} = \frac{\beta_{eh} B}{\chi_h + B} S_h - (\mu_h + \gamma_h) E_h, \tag{4.1.6}$$
$$\frac{dI_h}{dt} = \gamma_h E_h - (\mu_h + \alpha_h) I_h, \tag{4.1.7}$$
$$\frac{dR_h}{dt} = \alpha_h I_h - \mu_h R_h, \tag{4.1.8}$$
$$\frac{dS_s}{dt} = \Lambda_s + \rho V_s - \frac{\beta_{es} B}{\chi_s + B} S_s - \nu S_s - \mu_s S_s \tag{4.1.9}$$
$$\frac{dV_s}{dt} = \nu S_s - \rho V_s - \mu_s V s, \tag{4.1.10}$$
$$\frac{dE_s}{dt} = \frac{\beta_{es} B}{\chi_s + B} S_s - (\mu_s + \gamma_s) E_s, \tag{4.1.11}$$
$$\frac{dI_s}{dt} = \gamma_s E_s - \mu_s I_s, \tag{4.1.12}$$

with initial conditions $S_d(0) \geq 0$, $E_d(0) \geq 0$, $I_d(0) \geq 0$, $B(0) \geq 0$, $S_h(0) \geq 0$, $E_h(0) \geq 0$, $I_h(0) \geq 0$, $R_h(0) \geq 0$, $S_s(0) \geq 0$, $E_s(0) \geq 0$, $I_s(0) \geq 0$ and $V_s(0) \geq 0$.

For convenience, we make the following substitutions: $\tilde{\gamma_d} = \mu_d + \gamma_d$, $\tilde{\gamma_h} = \mu_h + \gamma_h$, $\tilde{q_h} = \mu_h + \alpha_h$ and $\tilde{\gamma_s} = \mu_s + \gamma_s$. Thus, we can rewrite the system (4.1.1)-(4.1.12) with initial conditions as

$$\frac{dX}{dt} = g(t, X(t)), X(0) = X_0 \tag{4.1.13}$$

where $X(t) = (S_d, E_d, I_d, B, S_h, E_h, I_h, R_h, S_s, V_s, E_s, I_s)^T$, $g : \mathbb{R}_+ \times \mathbb{R}_+^{12} \to \mathbb{R}_+^{12}$ defined by

$$g(t, X(t)) = \begin{pmatrix} \Lambda_d - \beta_{sd} I_s S_d - \mu_d S_d \\ \beta_{sd} I_s S_d - \tilde{\gamma_d} E_d \\ \gamma_d E_d - \mu_d I_d \\ \delta I_d - (\mu_e + \mu) B \\ \Lambda_h - \dfrac{\beta_{eh} B}{\chi_h + B} S_h - \mu_h S_h \\ \dfrac{\beta_{eh} B}{\chi_h + B} S_h - \tilde{\gamma_h} E_h \\ \gamma_h E_h - \tilde{q_h} I_h \\ \alpha_h I_h - \mu_h R_h \\ \Lambda_s + \rho V_s - \dfrac{\beta_{es} B}{\chi_s + B} S_s - \nu S_s - \mu_s S_s \\ \nu S_s - \rho V_s - \mu_s V s \\ \dfrac{\beta_{es} B}{\chi_s + B} S_s - \tilde{\gamma_s} E_s \\ \gamma_s E_s - \mu_s I_s \end{pmatrix}$$

4.2 Well-posedness of the Model

Before we proceed with the mathematical analysis, we need to show that the model (4.1.1)-(4.1.12) (alternatively model (4.1.13)) is well-posed epidemiologically and mathematically in a feasible domain.

Theorem 4.2.1 *The region* $\mathbb{D} = \mathbb{D}_1 \times \mathbb{D}_2 \times \mathbb{D}_3 \times \mathbb{D}_4$, *where*
$\mathbb{D}_1 = \left\{ (S_d, E_d, I_d) \subset \mathbb{R}_+^3 : S_d + E_d + I_d = \dfrac{\Lambda_d}{\mu_d} \right\}$,
$\mathbb{D}_2 = \left\{ (S_h, E_h, I_h, R_h) \subset \mathbb{R}_+^4 : S_h + E_h + I_h + R_h = \dfrac{\Lambda_h}{\mu_h} \right\}$,
$\mathbb{D}_3 = \left\{ (S_s, E_s, I_s) \subset \mathbb{R}_+^3 : S_s + E_s + I_s + V_s = \dfrac{\Lambda_s}{\mu_s} \right\}$ *and* $\mathbb{D}_4 = \left\{ B \subset \mathbb{R}_+ : B \leq \dfrac{\delta \Lambda_d}{\mu_d(\mu_e + \mu)} \right\}$ *is positively invariant for model* (4.1.1)-(4.1.12).

Proof. The proof of this theorem follows similar ways as the proof of Theorem 3.3.1. ■

4.3 Existence and stability of Equilibria

The equilibrium point(s) of the system (4.1.1)-(4.1.12) are obtained by equating the right hand sides zero. Following similar algebraic computations as Section 3.4, we found a quadratic equation

in B. Thus,

$$dB^2 - eB = 0, \tag{4.3.1}$$

where

$$d = \tilde{\gamma_d}(\mu_e + \mu)[\mu_s\mu_d^2\tilde{\gamma_s}(\beta_{es}(\rho + \mu_s) + \mu_s(\rho + \mu_s + \nu)) + \gamma_s\beta_{es}\beta_{sd}(\rho + \mu_s)\Lambda_s]$$

and

$$e = \delta\gamma_d\gamma_s(\rho + \mu_s)\beta_{es}\beta_{sd}\Lambda_s\Lambda_d - (\mu_e + \mu)\mu_s^2\chi_s\mu_d^2\tilde{\gamma_d}\tilde{\gamma_s}(\rho + \mu_s + \nu).$$

Thus, we have two roots

$$B = 0, \text{ and}$$

$$B = \frac{\delta\delta\gamma_d\gamma_s(\rho + \mu_s)\beta_{es}\beta_{sd}\Lambda_s\Lambda_d - (\mu_e + \mu)\mu_s^2\chi_s\mu_d^2\tilde{\gamma_d}\tilde{\gamma_s}(\rho + \mu_s + \nu)}{\tilde{\gamma_d}(\mu_e + \mu)[\mu_s\mu_d^2\tilde{\gamma_s}(\beta_{es}(\rho + \mu_s) + \mu_s(\rho + \mu_s + \nu)) + \gamma_s\beta_{es}\beta_{sd}(\rho + \mu_s)\Lambda_s]}. \tag{4.3.2}$$

The results presented in sections 4.3.1 and 4.3.4 follow from these two roots.

4.3.1 Disease-Free Equilibrium (DFE)

From algebraic computation when $B = 0$, the system (4.1.13) has the DFE given by

$$\begin{aligned} X^0 &= (S_d^0, E_d^0, I_d^0, B^0, S_h^0, E_h^0, I_h^0, R_h^0, S_s^0, E_s^0, I_s^0, V_s^0) \\ &= \left(\frac{\Lambda_d}{\mu_d}, 0, 0, 0, \frac{\Lambda_h}{\mu_h}, 0, 0, 0, \frac{(\rho + \mu_s)\Lambda_s}{\mu_s(\rho + \mu_s + \nu)}, 0, 0, \frac{\nu\Lambda_s}{\mu_s(\rho + \mu_s + \nu)}\right). \end{aligned}$$

4.3.2 The Control Reproduction Number

Due to the presence of controls in the model (4.1.13), the term "the control reproduction number" is used. The control reproduction number, denoted by $\mathcal{R}_c$ represents the average number of secondary infections caused by an infectious individual over the course of infectious period in a totally susceptible population under specified controls. We derive the control reproduction number $\mathcal{R}_c$ by using the Next Generation Matrix (NGM) approach [23, 64] on the system (4.1.13). According to the concepts of the next generation matrix and reproduction number presented in Section 2.6, we define

$$\mathcal{F} = \begin{pmatrix} \beta_{sd} I_s S_d \\ 0 \\ 0 \\ \dfrac{\beta_{eh} B}{\chi_h + B} S_h \\ 0 \\ \dfrac{\beta_{es} B}{\chi_s + B} S_s \\ 0 \end{pmatrix} \text{ and } \mathcal{V} = \begin{pmatrix} \tilde{\gamma_d} E_d \\ \mu_d I_d - \gamma_d E_d \\ (\mu_e + \mu) B - \delta I_d \\ \tilde{\gamma_h} E_h \\ \tilde{q_h} I_h - \gamma_h E_h \\ \tilde{\gamma_s} E_s \\ \mu_s I_s - \gamma_s E_s \end{pmatrix},$$

The Jacobian matrix of the infection subsystem at X^0 can be decomposed as $F - V$, where F is a matrix of transmission rates given by

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \beta_{sd}\dfrac{\Lambda_d}{\mu_d} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \dfrac{\beta_{eh}\Lambda_h}{\mu_h \chi_h} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \dfrac{\beta_{es}(\rho + \mu_s)\Lambda_s}{\mu_s \chi_s (\rho + \mu_s + \nu)} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \tag{4.3.3}$$

and V is a matrix of transition rates given by

$$V = \begin{pmatrix} \tilde{\gamma_d} & 0 & 0 & 0 & 0 & 0 & 0 \\ -\gamma_d & \mu_d & 0 & 0 & 0 & 0 & 0 \\ 0 & -\delta & \mu_e + \mu & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \tilde{\gamma_h} & 0 & 0 & 0 \\ 0 & 0 & 0 & -\gamma_h & \tilde{q_h} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \tilde{\gamma_s} & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma_s & \mu_s \end{pmatrix}. \tag{4.3.4}$$

Thus,

$$V^{-1} = \begin{pmatrix} \frac{1}{\tilde{\gamma}_d} & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\gamma_d}{\mu_d\tilde{\gamma}_d} & \frac{1}{\mu_d} & 0 & 0 & 0 & 0 & 0 \\ \frac{\delta\gamma_d}{(\mu_e+\mu)\mu_d\tilde{\gamma}_d} & \frac{\delta}{(\mu_e+\mu)\mu_d} & \frac{1}{\mu_e+\mu} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{\tilde{\gamma}_h} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\gamma_h}{\tilde{\gamma}_h\tilde{q}_h} & \frac{1}{\tilde{q}_h} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{\tilde{\gamma}_s} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\gamma_s}{\mu_s\tilde{\gamma}_s} & \frac{1}{\mu_s} \end{pmatrix},$$

and the next generation matrix is

$$FV^{-1} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\gamma_s\beta_{sd}\Lambda_d}{\mu_s^2\tilde{\gamma}_s} & \frac{\beta_{sd}\Lambda_d}{\mu_s^2} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\delta r_d\beta_{eh}\Lambda_h}{\chi_h\mu_h\mu_d\tilde{\gamma}_d(\mu_e+\mu)} & \frac{\delta\beta_{eh}\Lambda_h}{\chi_h\mu_d\mu_h(\mu_e+\mu)} & \frac{\beta_{eh}\Lambda_h}{\chi_h\mu_h(\mu_e+\mu)} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\phi\delta\gamma_d\beta_{es}\Lambda_s}{\chi_s\mu_s\mu_d\tilde{\gamma}_d(\mu_e+\mu)} & \frac{\phi\delta\beta_{es}\Lambda_s}{\chi_s\mu_s\mu_d(\mu_e+\mu)} & \frac{\phi\beta_{es}\Lambda_s}{\chi_s\mu_s(\mu_e+\mu)} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

where $\phi = \dfrac{\rho+\mu_s}{\rho+\mu_s+\nu}$.

Thus, the control reproduction number is given by

$$\mathcal{R}_c = \rho(FV^{-1}) = \sqrt{\phi\frac{\gamma_s\beta_{es}\Lambda_s}{\chi_s(\mu_e+\mu)}\frac{\beta_{sd}}{\mu_s^2\tilde{\gamma}_s}\frac{\delta\gamma_d\Lambda_d}{\mu_d^2\tilde{\gamma}_d}} = \sqrt{\frac{\phi\mu_e}{\mu_e+\mu}}\mathcal{R}_0,$$

where $\mathcal{R}_0 = \sqrt{\dfrac{\gamma_s\beta_{es}K_s}{\chi_s\mu_e}\dfrac{\beta_{sd}}{\mu_s^2\tilde{\gamma}_s}\dfrac{\delta\gamma_dK_d}{\mu_d^2\tilde{\gamma}_d}}$ is the basic reproduction number as derived in (3.4.20), which represents the average number of secondary infections caused by an infectious individual over the course of infectious period in a totally susceptible population without vaccination and disinfection or cleaning of the environment. Here, we can notice that $\mathcal{R}_c < \mathcal{R}_0$.

4.3.3 Stability of the DFE

Theorem 4.3.1 *If $\mathcal{R}_c < 1$, then the disease free equilibrium X^0 is globally asymptotically stable in $\mathbb{D}$. If $\mathcal{R}_c > 1$, then the DFE is unstable, the system is persistent and there is at least one equilibrium in the interior of $\mathbb{D}$.*

Proof. To prove the global stability of the disease free equilibrium X^0, we use a matrix-theoretic method as explained in Section 2.6. Similar to Theorem 3.4.1, we prove the global stability of the DFE by constructing a Lyapunov function by using Theorem 2.6.3. As a result, we found that

$$Q = W^T V^{-1} x = \frac{\delta\gamma_d E_d}{\mu_d(\mu_e+\mu)\tilde{\gamma_d}} + \frac{\delta I_d}{\mu_d(\mu_e+\mu)} + \frac{B}{(\mu_e+\mu)} + \left(\frac{\gamma_s}{\mu_s\tilde{\gamma_s}}E_s + \frac{I_s}{\mu_s}\right)\frac{\delta\gamma_d\beta_{sd}\Lambda_d}{\mu_d^2(\mu_e+\mu)\tilde{\gamma_d}\mathcal{R}_c},$$

is a Lyapunov function for model (4.1.1)-(4.1.12). Then differentiating along the solutions of the system (3.2.1)-(3.2.11) gives

$$Q' = (\mathcal{R}_c - 1)\left(\frac{\delta\gamma_d\beta_{sd}I_s\Lambda_d}{\mu_d^2(\mu_e+\mu)\tilde{\gamma_d}\mathcal{R}_c} + B\right) - \left(\frac{\delta\gamma_d\beta_{sd}I_s}{\mu_d(\mu_e+\mu)\tilde{\gamma_d}}\left(\frac{\Lambda_d}{\mu_d} - S_d\right) + \frac{\gamma_s\gamma_d\beta_{es}\beta_{sd}B\Lambda_d}{\mu_s(\mu_e+\mu)\chi_s\mu_d^2\tilde{\gamma_d}\mathcal{R}_c}\left(S_s^0 - \frac{S_s\chi_s}{B+\chi_s}\right)\right).$$

Since $S_d \leq \dfrac{\Lambda_d}{\mu_d}$, $S_s \leq S_s^0$ and $\chi_s \leq \chi_s + B$, $Q' < 0$ if $\mathcal{R}_c < 1$. $Q' = 0$ implies that

Case 1. $B = 0$ and $I_s = 0$. Thus, using the results obtained in Section 3.4, we have $E_d = 0$, $I_d = 0$, $E_h = 0$, $I_h = 0$, $R_h = 0$, $E_s = 0$, $S_d = \dfrac{\Lambda_d}{\mu_d}$, $S_h = \dfrac{\Lambda_h}{\mu_h}$, and $S_s = \dfrac{\Lambda_s}{\mu_s}$.

Case 2. $\mathcal{R}_c = 1$, $S_d = \dfrac{\Lambda_d}{\mu_d}$ and $S_s = \dfrac{(\chi_s + B)S_s^0}{\chi_s}$. Since $S_s \leq S_s^0$, we have $S_s = S_s^0$ and $B = 0$. Thus, using the results obtained in Section 3.4, we also have $E_d = 0$, $I_d = 0$, $E_h = 0$, $I_h = 0$, $R_h = 0$, $E_s = 0$, $S_d = \dfrac{\Lambda_d}{\mu_d}$, $S_h = \dfrac{\Lambda_h}{\mu_h}$, $V_s = V_s^0$ and $S_s = S_s^0$.

Hence, the largest invariant set of the model where $Q' = 0$ in $int(\mathbb{D})$ is the singleton $\{X^0\}$. Therefore, as stated in Theorem 2.5.1 by Lasalle's invariance principle, the disease free equilibrium X^0 is globally asymptotically stable if $\mathcal{R}_c < 1$.

For $\mathcal{R}_c > 1$, then $Q' = (\mathcal{R}_c - 1)W^T x = (\mathcal{R}_c - 1)\left(\dfrac{\delta\gamma_d\beta_{sd}I_s\Lambda_d}{\mu_d^2(\mu_e+\mu)\tilde{\gamma_d}\mathcal{R}_c} + B\right) > 0$ in $\mathbb{D}$ provided $B > 0$ and $(S_d, S_s) = (S_d^0, S_s^0)$, where $S_d^0 = \dfrac{\Lambda_d}{\mu_d}$ and $S_s^0 = \dfrac{(\rho+\mu_s)\Lambda_s}{\mu_s(\rho+\mu_s+\nu)}$. By continuity $Q' > 0$ in a neighborhood of X^0. Thus, the disease free equilibrium X^0 is unstable , and using Theorem 2.6.4, the system (4.1.13) is uniformly persistent and hence imply there is at least one endemic equilibrium in the interior of $\mathbb{D}$. ■

4.3.4 Existence and stability of the Endemic Equilibrium (EE)

From (4.3.2), it follows that the model (4.1.13) admits an endemic equilibrium. Thus, the endemic equilibrium point of the system in terms of the control reproduction number $\mathcal{R}_c$ is given by

$$X_E = (S_d^*, E_d^*, I_d^*, B^*, S_h^*, E_h^*, I_h^*, R_h^*, S_s^*, E_s^*, I_s^*, V_s^*),$$

where

$$I_d^* = \frac{(\mu_e + \mu)B^*}{\delta} \tag{4.3.5}$$

$$E_d^* == \frac{\mu_d(\mu_e + \mu)B^*}{\delta\gamma_d} \tag{4.3.6}$$

$$S_d^* = \frac{\Lambda_d}{\mu_d} - \frac{(\mu_e + \mu)\tilde{\gamma_d}B}{\delta\gamma_d} \tag{4.3.7}$$

$$S_h^* = \frac{(\chi_h + B^*)\Lambda_h}{\mu_h(\chi_h + B^*) + \beta_{eh}B^*} \tag{4.3.8}$$

$$E_h^* = \frac{\beta_{eh}\Lambda_h B^*}{\tilde{\gamma_h}(\mu_h(\chi_h + B^*) + \beta_{eh}B^*)} \tag{4.3.9}$$

$$I_h^* = \frac{\gamma_h\beta_{eh}\Lambda_h B^*}{\tilde{q_h}\tilde{\gamma_h}(\mu_h(\chi_h + B^*) + \beta_{eh}B^*)} \tag{4.3.10}$$

$$R_h^* = \frac{\gamma_h\alpha_h\beta_{eh}\Lambda_h B^*}{\mu_h\tilde{q_h}\tilde{\gamma_h}(\mu_h(\chi_h + B^*) + \beta_{eh}B^*)} \tag{4.3.11}$$

$$S_s^* = \frac{(\rho + \mu_s)(\chi_s + B^*)\Lambda_s}{(\beta_{es}(\rho + \mu_s) + \mu_s(\rho + \mu_s + \nu))B^* + \mu_s\chi_s(\rho + \mu_s + \nu)} \tag{4.3.12}$$

$$E_s^* = \frac{\beta_{es}(\rho + \mu_s)\Lambda_s B^*}{\tilde{\gamma_s}[(\beta_{es}(\rho + \mu_s) + \mu_s(\rho + \mu_s + \nu))B^* + \mu_s\chi_s(\rho + \mu_s + \nu)]} \tag{4.3.13}$$

$$I_s^* = \frac{\gamma_s\beta_{es}(\rho + \mu_s)\Lambda_s B^*}{\mu_s\tilde{\gamma_s}[(\beta_{es}(\rho + \mu_s) + \mu_s(\rho + \mu_s + \nu))B^* + \mu_s\chi_s(\rho + \mu_s + \nu)]} \tag{4.3.14}$$

$$V_s^* = \frac{\nu(\chi_s + B^*)\Lambda_s}{(\beta_{es}(\rho + \mu_s) + \mu_s(\rho + \mu_s + \nu))B^* + \mu_s\chi_s(\rho + \mu_s + \nu)} \tag{4.3.15}$$

$$B^* = \frac{\chi_s\tilde{\gamma_s}\mu_d\mu_s^2(\rho + \mu_s + \nu)}{\mu_s\mu_d\tilde{\gamma_s}[\beta_{es}(\rho + \mu_s) + \mu_s(\rho + \mu_s + \nu)] + \gamma_s\beta_{es}\beta_{sd}(\rho + \mu_s)\Lambda_s}(\mathcal{R}_c^2 - 1) \tag{4.3.16}$$

It can be noted that the endemic equilibrium point reduces to disease free equilibrium point for $\mathcal{R}_c = 1$.

Theorem 4.3.2 *If $\mathcal{R}_c > 1$, then an endemic equilibrium $X_E = (S_d^*, E_d^*, I_d^*, B^*, S_h^*, E_h^*, I_h^*, R_h^*, S_s^*, E_s^*, I_s^*, V_s^*)$ defined by equations* (4.3.5) - (4.3.16) *is globally asymptotically stable.*

Proof. The method of Lyapunov functions combined with the theory of Volterra–Lyapunov stable matrices is used to prove the global asymptotic stability of the endemic equilibria. To do this, we define a Lyapunov function :

$$\begin{aligned} L =& w_1(S_d - S_d^*)^2 + w_2(E_d - E_d^*)^2 + w_3(I_d - I_d^*)^2 + w_4(B - B^*)^2 + \frac{1}{2}(S_h - S_h^* + E_h - E_h^* \\ &+ I_h - I_h^* + R_h - R_h^*)^2 + \frac{1}{2}(S_s - S_s^* + E_s - E_s^* + I_s - I_s^* + V_s - V_s^*)^2. \end{aligned}$$

Thus,

$$\begin{aligned} \frac{dL}{dt} =& 2w_1(S_d - S_d^*)\left(\frac{dS_d}{dt}\right) + 2w_2(E_d - E_d^*)\left(\frac{dE_d}{dt}\right) + 2w_3(I_d - I_d^*)\left(\frac{dI_d}{dt}\right) + 2w_4(B - B^*)\left(\frac{dB}{dt}\right) \\ &+ (S_s - S_s^* + E_s - E_s^* + I_s - I_s^* + V_s - V_s^*)\left(\frac{d}{dt}(S_s + E_s + I_s + V_s)\right) \\ &+ (S_h - S_h^* + E_h - E_h^* + I_h - I_h^* + R_h - R_h^*)\left(\frac{d}{dt}(S_h + E_h + I_h + R_h)\right). \end{aligned}$$

The time derivative of $L(t)$ along the solutions of model equations (4.1.1)-(4.1.12), we obtain

$$\begin{aligned} \frac{dL}{dt} =& Y(WA + A^T W^T)Y^T - \mu_s(S_s - S_s^* + E_s - E_s^* + I_s - I_s^* + V_s - V_s^*)^2 \\ &- \mu_h(S_h - S_h^* + E_h - E_h^* + I_h - I_h^* + R_h - R_h^*)^2, \end{aligned}$$

where $Y = (S_d - S_d^*, E_d - E_d^*, I_d - I_d^*, B - B^*)$, $W = diag(w_1, w_2, w_3, w_4)$ and

$$A = \begin{pmatrix} -\beta_{sd} I_s - \mu_d & 0 & 0 & 0 \\ \beta_{sd} I_s & -\tilde{\gamma_d} & 0 & 0 \\ 0 & \gamma_d & -\mu_d & 0 \\ 0 & 0 & \delta & -\mu_e - \mu \end{pmatrix}.$$

Obviously, the second and third terms of $\frac{dL}{dt}$ are negative. To show the global stability of endemic equilibrium X_E, it suffice to show that A is Volterra-Lyapunov stable in $\mathbb{D}/\{X_E\}$. For this purpose, we show that matrix $\tilde{A}$ is Volterra-Lyapunov stable, and matrix $U = \widetilde{A^{-1}}$ is Volterra-Lyapunov stable (or $-\widetilde{A^{-1}}$ is diagonally stable).

Condition 1: To show $\tilde{A}$ is Volterra-Lyapunov stable, we consider

$$D = -\tilde{A} = \begin{pmatrix} \beta_{sd}I_s + \mu_d & 0 & 0 \\ -\beta_{sd}I_s & \tilde{\gamma_d} & 0 \\ 0 & -\gamma_d & \mu_d \end{pmatrix}.$$

The matrix $\tilde{D}$ is obtained by deleting its 3^{rd} row and 3^{rd} column, and results in

$$-\widetilde{D} = \begin{pmatrix} -\beta_{sd}I_s - \mu_d & 0 \\ \beta_{sd}I_s & -\tilde{\gamma_d} \end{pmatrix}.$$

Clearly $a_{11} = -\beta_{sd}I_s - \mu_d < 0$, $a_{22} = -\tilde{\gamma_d}$ and $det(-\widetilde{D}) > 0$. Based on Lemma 2.6.8, $-\widetilde{D}$ is Volterra-Lyapunov stable.

Moreover, we obtain $-\widetilde{D^{-1}} = \begin{pmatrix} -\dfrac{1}{\beta_{sd}I_s + \mu_d} & 0 \\ -\dfrac{\beta_{sd}I_s}{\tilde{\gamma_d}(\mu_d + \beta_{sd}I_s)} & -\dfrac{1}{\tilde{\gamma_d}} \end{pmatrix}$.
Clearly, the diagonal elements $-\dfrac{1}{\beta_{sd}I_s + \mu_d} < 0$, $-\dfrac{1}{\tilde{\gamma_d}} < 0$ and $det(-\widetilde{D^{-1}}) > 0$. Thus, based on Lemma 2.6.8, $-\widetilde{D^{-1}}$ is Volterra-Lyapunov stable.

Therefore, $D = -\tilde{A}$ is diagonally stable, and hence $\tilde{A}$ is Volterra-Lyapunov stable.

Condition 2: To show $\widetilde{A^{-1}}$ is Volterra-Lyapunov stable, we consider

$$E = -\widetilde{A^{-1}} = \begin{pmatrix} \dfrac{1}{\beta_{sd}I_s + \mu_d} & 0 & 0 \\ \dfrac{\beta_{sd}I_s}{\tilde{\gamma_d}(\mu_d + \beta_{sd}I_s)} & \dfrac{1}{\tilde{\gamma_d}} & 0 \\ \dfrac{\beta_{sd}I_s\gamma_d}{\tilde{\gamma_d}\mu_d(\mu_d + \beta_{sd}I_s)} & \dfrac{\gamma_d}{\tilde{\gamma_d}\mu_d} & \dfrac{1}{\mu_d} \end{pmatrix}.$$

This results in

$$-\tilde{E} = \begin{pmatrix} -\dfrac{1}{\beta_{sd}I_s + \mu_d} & 0 \\ -\dfrac{\beta_{sd}I_s}{\tilde{\gamma_d}(\mu_d + \beta_{sd}I_s)} & -\dfrac{1}{\tilde{\gamma_d}} \end{pmatrix}.$$

Using Lemma 2.6.8, it is easy to observe that $-\tilde{E}$ is Volterra-Lyapunov stable.

Moreover, we have $-\widetilde{E^{-1}} = \begin{pmatrix} -\beta_{sd}I_s - \mu_d & 0 \\ \beta_{sd}I_s & -\tilde{\gamma}_d \end{pmatrix}$. Based on Lemma 2.6.8, we can also observe that $-\widetilde{E^{-1}}$ is also Volterra-Lyapunov stable.

Therefore, $\widetilde{A^{-1}}$ is Volterra-Lyapunov stable.

Based on Lemma 2.6.10, there exist a diagonal matrix $W = diag\{w_1, w_2, w_3, w_4\}$ such that $W(-A) + (-A)^T W^T > 0$ or $WA + A^T W^T < 0$, which indicates that A is Volterra-Lyapunov stable. Therefore, $\dfrac{dL}{dt} < 0$, and by LaSalle's invariance principle (Theorem 2.5.1), X_E is globally asymptotically stable in the interior of $\mathbb{D}$, and is unique provided that $\mathcal{R}_c > 1$. ■

4.4 Numerical simulation of the model

4.4.1 *Elasticity indices*

To identify the most important parameter(s) in the dynamics of the disease, we carried out sensitivity analysis as done in Section 3.5.1. The normalized forward sensitivity index (elasticity index) of a variable ($\mathcal{R}_c$) with respect to a parameter p is the ratio of the relative change in the variable to the relative change in the parameter, given by

$$\Upsilon_p^{\mathcal{R}_c} = \frac{\partial \mathcal{R}_c}{\partial p} \times \frac{p}{\mathcal{R}_c}.$$

The intention for this work is not also to validate the model results of the real situation obtained in a particular study, but for illustrative purposes only. For this purpose, we use data as given in Table 4.1, and with sensitivity analysis, we can get insight into the appropriate intervention strategies to prevent and control the spread of the disease.

Table 4.1: Parameters, Baseline values and Sources

Parameters	**Baseline values** ($Unit$)	**Sources**
μ_d	$0.00024/day$	[74, 75]
β_{sd}	$0.00001/day$	Assumed
γ_d	$0.001/day$	Assumed
μ_h	$0.00004/day$	[68]
β_{eh}	$0.00001/day$	Assumed
γ_h	$0.00019/day$	[67]
α_h	$0.00001/day$	Assumed
μ_s	$0.00025/day$	[73]
β_{es}	$0.00001/day$	Assumed
μ_e	$0.003/day$	[63]
γ_s	$0.001/day$	[4]
δ	$0.00014 cells/ml.day$	[63]
χ_h	$120 cells/ml$	Assumed
χ_s	$100 cells/ml$	Assumed
ν	$0.005/day$	Assumed
ρ	$0.001/day$	Assumed
μ	$0.001/day$	Assumed

Sensitivity indices of the control reproduction number $\mathcal{R}_c$ with respect to the model parameters are determined and presented in Table below.

Table 4.2: Elasticity indices of $\mathcal{R}_c$ relative to some model parameters

Parameters	$\Upsilon_p^{R_c} = \frac{\partial \mathcal{R}_c}{\partial p} \times \frac{p}{\mathcal{R}_c}$	Baseline value	**Range**	**Elasticity index**
β_{es}	$\frac{1}{2}$	0.00001	$0.000005 - 0.0001$	0.5
β_{sd}	$\frac{1}{2}$	0.000001	$0.0000001 - 0.000002$	0.5
δ	$\frac{1}{2}$	0.001	$0.0001 - 0.002$	0.5
χ_s	$-\frac{1}{2}$	100	$60 - 140$	-0.5
ν	$-\frac{\nu}{2(\rho+\nu+\mu_s)}$	0.005	$0.0005 - 0.01$	-0.48
ρ	$\frac{\rho\nu}{2(\rho+\mu_s)(\rho+\nu+\mu_s)}$	0.001	$0.0001 - 0.002$	0.39
μ	$-\frac{\mu}{2(\mu_e+\mu)}$	0.001	$0.0001 - 0.002$	-0.38
γ_s	$\frac{\mu_s}{2(\mu_s+\gamma_s)}$	0.001	$0.0001 - 0.002$	0.1
γ_d	$\frac{\mu_d}{2(\mu_d+\gamma_d)}$	0.001	$0.0001 - 0.002$	0.1

Table 4.2 gives the elasticity indices of $\mathcal{R}_c$ with respect to key parameters of model (4.1.1)-(4.1.12) at the baseline values indicated in Table 4.1 and arranged in descending order of magnitudes. The sign of the elasticity index tells whether $\mathcal{R}_c$ increases (positive sign) or decreases (negative sign) with the parameter; whereas the magnitude determines the relative importance of the parameter. From the magnitude of elasticity index, we can notice that four

parameters $(\beta_{es}, \beta_{sd}, \delta, \chi_s)$ have equal and the greatest influence for the transmission of the disease, whereas γ_s and γ_d have the least influence.

4.4.2 *Global sensitivity analysis*

In order to determine which parameter(s) among the eight is (are) most influential in the dynamics of the disease, global sensitivity analysis is done. To examine the dependence of $\mathcal{R}_c$ on parameter variations, we determine the PRCC values by considering a range of parameters as given in Table 4.2 , with sample size 1000. The result is depicted in Figure 4.2.

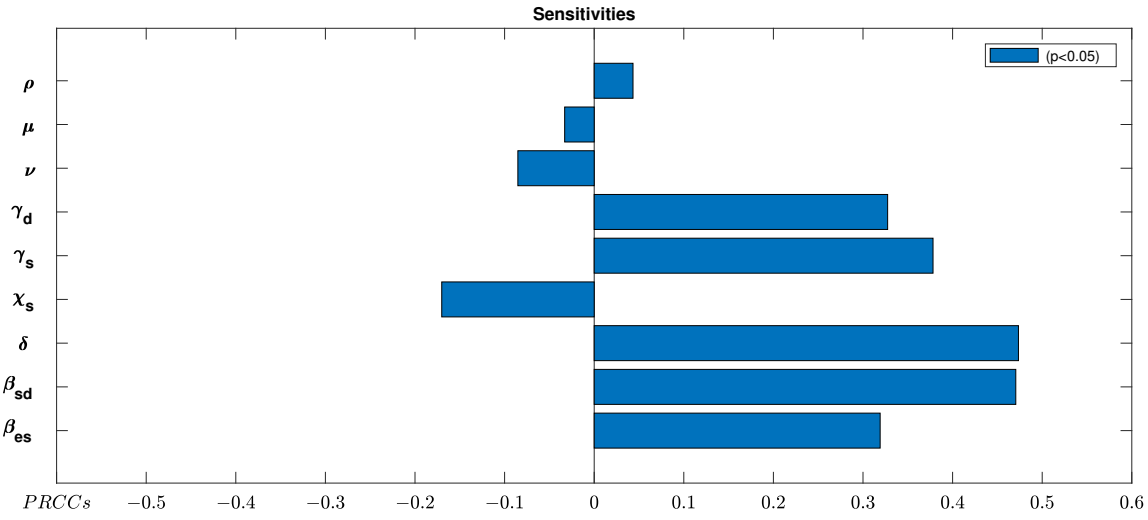

Figure 4.2: Global sensitivity analysis displaying the partial rank correlation coefficients(PRCC) of control reproduction number $\mathcal{R}_c$.

From Figure 4.2, it is observed that the transmission rate from sheep to dog (β_{sd}) and parasite eggs contamination rate of the environment by infected dogs (δ) are the most influential parameters among the eight parameters in the disease dynamics. On the other hand, μ is the least sensitive parameter for the dynamics of the disease.

4.4.3 *Numerical simulations*

In this section, we carry out numerical simulations for mathematical model of cystic echinococcosis in the populations of sheep, dogs and humans. We use the total populations $\Lambda_d = 8$, $\Lambda_h = 2$, $\Lambda_s = 10$, and parameter values given in Table 4.1. This yields a control reproduction number $\mathcal{R}_c = 0.58 < 1$. Using different initial conditions, the time evolution of human, sheep and dog populations for model (4.1.13) is displayed in Figure 4.4. We can notice that all disease compartments E_d^*, I_d^*, B^*, E_h^*, I_h^*, R_h^*, E_s^* and I_s^* converge asymptotically to zero, while the non infected compartments S_d^*, S_h^* and $S_s^* + V_s^*$ converge to $\dfrac{\Lambda_d}{\mu_d} = 12,500$, $\dfrac{\Lambda_h}{\mu_h} = 50,000$ and $\dfrac{\Lambda_s}{\mu_s} = 16,000$ respectively. This asserts the global stability of the disease free equilibrium as proved in Theorem 4.3.1.

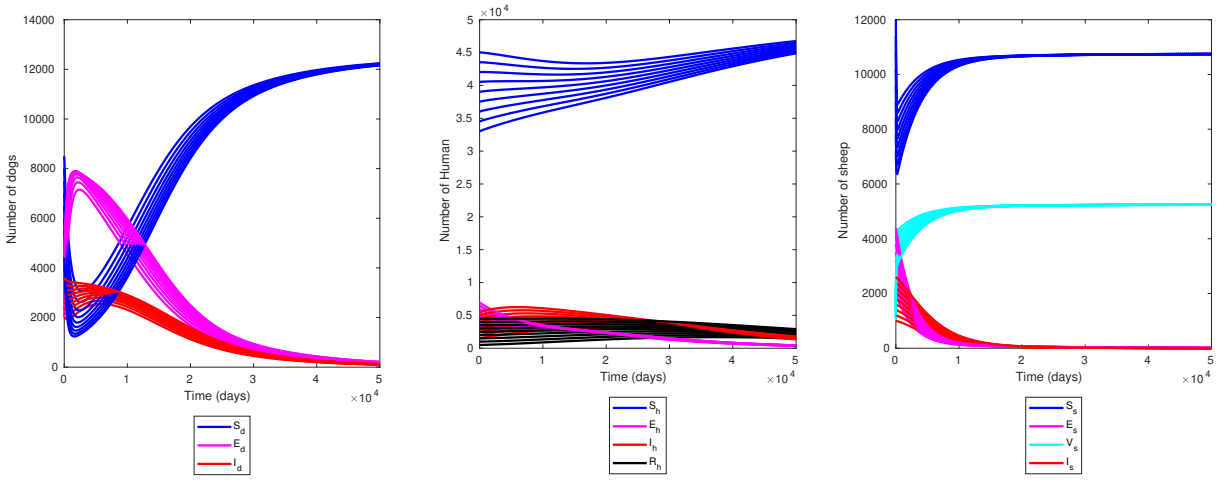

Figure 4.3: Time evolution of the dog, sheep and human populations with baseline parameter values as in Table 4.1, using different initial conditions which gives $\mathcal{R}_c = 0.58$.

Figures 4.4 shows that the time evolution of human, sheep and dog populations for model (4.1.13) with parameter values given in Table 4.1 by increasing $\beta_{sd} = 0.0000001$ to $\beta_{sd} = 0.000001$. In this case, the control reproductive number is $\mathcal{R}_c = 1.82 > 1$, and depict the global stability of the endemic equilibrium as proved in Theorem 4.3.2. It can be noticed that all the compartments of the dog, human and sheep populations converge asymptotically to their respective endemic equilibrium points irrespective of any value for the initial conditions.

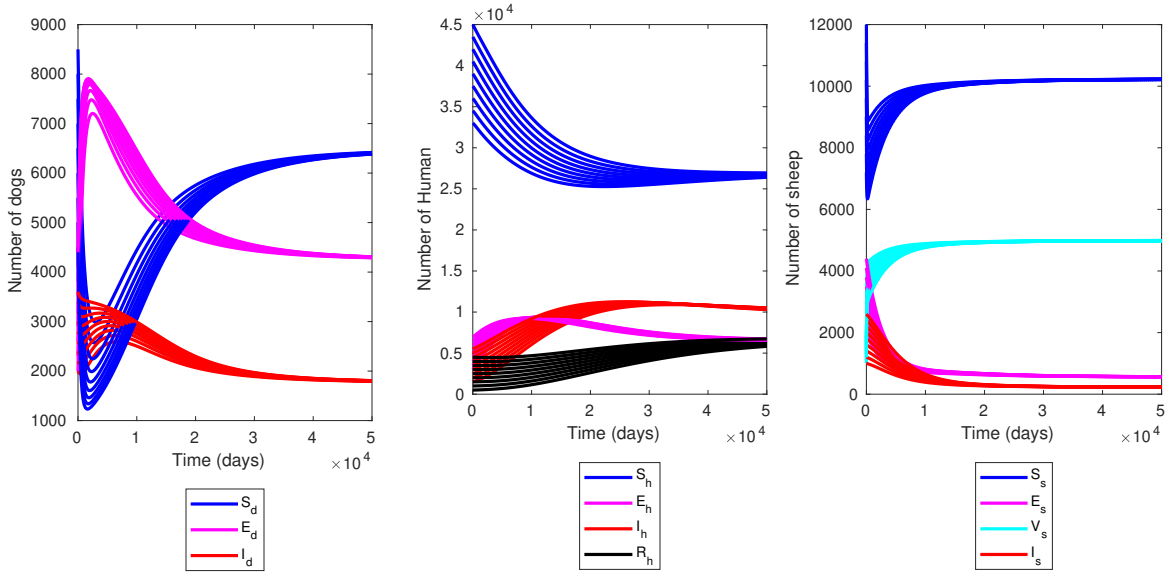

Figure 4.4: Time evolution of the dog, sheep and human populations with baseline parameter values as in Table 4.1, using different initial conditions, except for $\beta_{sd} = 0.000001$ which gives $\mathcal{R}_c = 1.82$, and with approximate equilibrium values $S_d^* = 6467$, $E_d^* = 4259$, $I_d^* = 1774$, $S_h^* = 26989$, $E_h^* = 6575$, $I_h^* = 9813$, $R_h^* = 6624$, $S_s^* = 10227$, $E_s^* = 560$, $I_s^* = 224$, $V_s^* = 5023$.

In the case of endemicity, the prevalence rate of human is

$$\frac{\text{Number of new cases of disease during specified period}}{\text{average population size} \times \text{duration of follow up}} = \frac{9813}{50000 \times 1} \times 100\%$$
$$= 19.6\%$$

The prevalence rate resulted in the numerical simulation is higher than the WHO published data, since the WHO report showed that the human prevalence rate is $5\% - 10\%$ (as indicated in [32]). This result has shown 9.6%. discrepancy from maximum WHO published data.

4.4.4 Effects of Control Strategies on $\mathcal{R}_c$

The numerical simulations are performed to illustrate the effect of vaccination of sheep and cleaning or disinfecting the environment in the dynamics of the disease transmission in the populations of sheep, dogs and humans while they are used alone or simultaneously.

The effect of vaccination of sheep using baseline parameter values in Table 4.1 except for $\mu = 0$, and when ν is varied from 0.005 to 0.5, is displayed in Figure 4.5. As a result the infectious sheep, dog and human populations are respectively reduced from 635 to 0 , 2668 to 0, and 8293 to 0, where the control reproduction number is also reduced from $\mathcal{R}_c = 2.93$ to $\mathcal{R}_c = 0.51$. This result shows that increasing the rate of vaccination of sheep (ν) reduces the time evolution of infected human, sheep and dog populations. The effect of disinfection or cleaning the environment using baseline parameter values in Table 4.1 except for $\nu = 0$, and when μ is varied from 0.1 to 0.001, is displayed in Figure 4.6. As a result the infectious sheep, dog and human populations are respectively reduced from 452 to 0 , 1640 to 0, and 5136 to 0, where the control reproduction number is also reduced from $\mathcal{R}_c = 2.65$ to $\mathcal{R}_c = 0.58$. This result shows that increasing the rate of disinfection or cleaning the environment (μ) has very less effect to eradicate the disease transmission in human, sheep and dog populations.

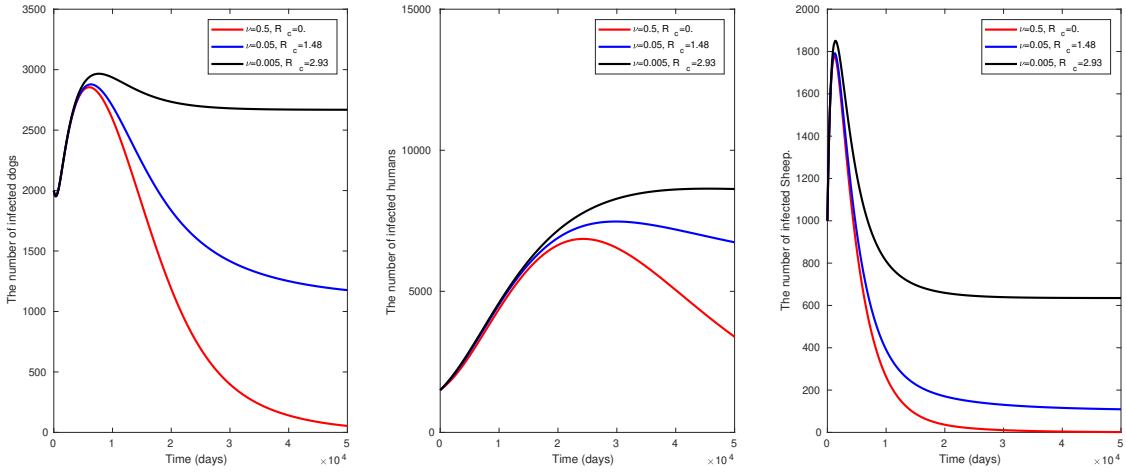

Figure 4.5: The numerical simulations displaying effects of vaccination of sheep only on the number of infectious dog, human and sheep populations, using parameter values in Table 4.1, with varying values of ν ($\mu = 0$).

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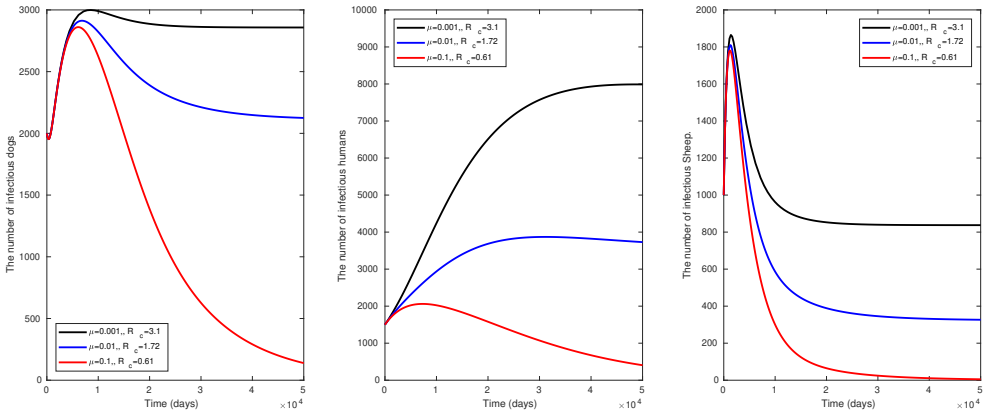

Figure 4.6: The numerical simulations displaying effects of disinfection or cleaning the environment only on the number of infectious dog, human and sheep populations, using parameter values in Table 4.1, with varying values of μ ($\nu = 0$).

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Numerical simulation is also performed to illustrate the effect of vaccination of sheep and disinfection or cleaning the environment when the two control strategies are administered simultaneously, as displayed in Figure 4.7. The number of infectious sheep, dog and human populations are respectively reduced from 544 to 0, 2551 to 0, and 7416 to 0, where the control reproduction number is also reduced from $\mathcal{R}_c = 2.54$ to $\mathcal{R}_c = 0.09$. One can observe that these combined effects allow to reduce the size of infected individuals. Thus, increasing the vaccination rate of sheep alone or a simultaneous increase of the vaccination rate of sheep and rate of cleaning or disinfecting the environment is an effective control measure of cyst echinococcosis.

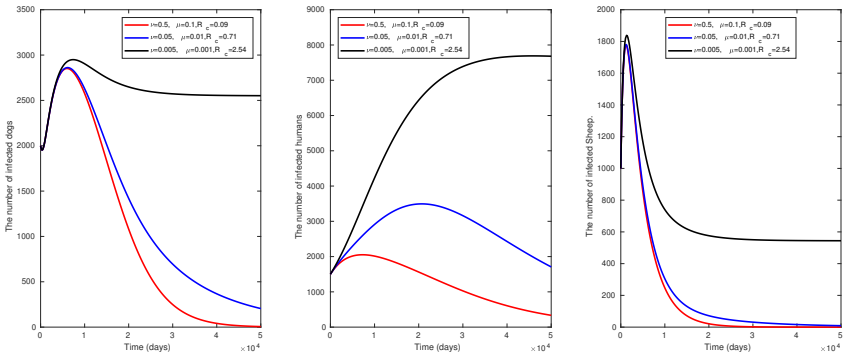

Figure 4.7: The numerical simulations displaying effects of combining controlling strategies on the number of infectious dog, human and sheep populations, using parameter values in Table 4.1.

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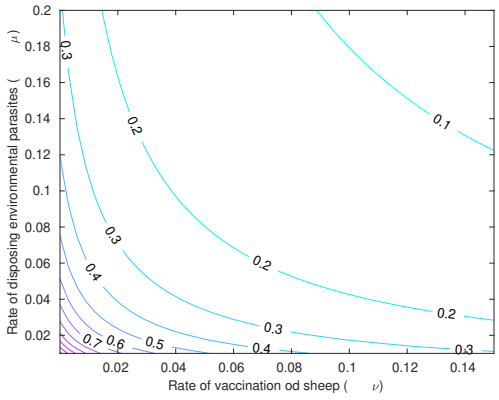
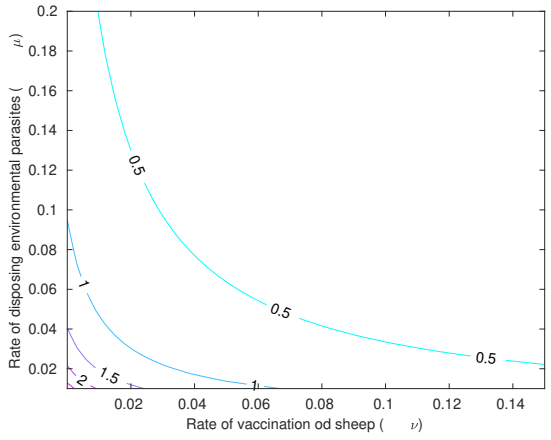
Furthermore, we assess the impact of combined control strategies using contour plots of $\mathcal{R}_c$ as function of the control strategies, and with varying rate of transmission from sheep to dog (β_{sd}), we estimate the least values of the two control parameters which will ensure the disease eradication in the populations.

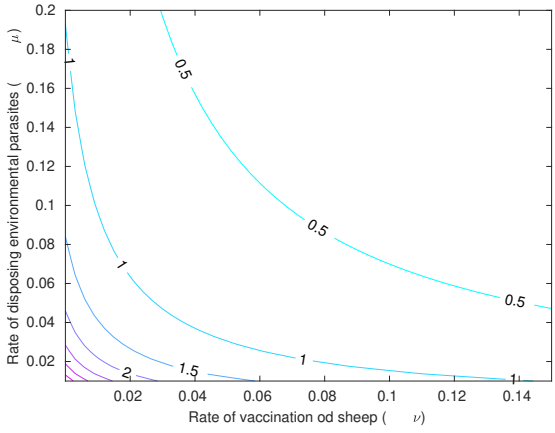
Figure 4.8(a) shows contour curves of $\mathcal{R}_c$ as a function of ν and μ using baseline parameter values in Table 3.1. The figure depicts that the disease will be eliminated if the controls $\nu \in [0, 0.2]$ and $\mu \in [0, 0.14]$. Contour plots of $\mathcal{R}_c$ as function of the control strategies, for rate of transmission from sheep to dog ($\beta_{sd} = 0.000005$) is displayed in Figure 4.8(b). The least values of ν and μ that will ensure parasites eradication are estimated to be $\nu = 0.06$ and $\mu = 0.1$ or $\nu = 0$ and $\mu = 0.1$ so that $\mathcal{R}_c = 98$. In this case, the combined control strategies has effect in the disease transmission with range of $\mathcal{R}_c \in [0.37, 0.98]$ and mean 0.675. Contour plots of $\mathcal{R}_c$ as function of the control strategies, for rate of transmission from sheep to dog ($\beta_{sd} = 0.000005$) is displayed in Figure 4.8(c). The least values of ν and μ that will ensure parasites eradication are estimated to be $\nu = 0.14$ and $\mu = 0.19$ or $\nu = 0$ and $\mu = 0.19$ so that $\mathcal{R}_c = 1$.. In this case, the combined control strategies have effect in the disease transmission with range of $\mathcal{R}_c \in [0.26, 1]$ and mean 0.63. These results have shown that a remarkable increase in the control reproduction number is observed with an increase rate of transmission from sheep to dog (β_{sd}). Hence, to ensure the eradication of parasites, we must introduce the least values of the controls that can bring the value $\mathcal{R}_c < 1$ with respect to the rate of transmission from sheep to dog (β_{sd}).



(a)



(b)



(c)

Figure 4.8: Contour curves of $\mathcal{R}_c$ as a function of ν and μ using different rate of transmission from sheep to dog (β_{sd}) with (a) parameter values in Table 4.1, (b) $\beta_{sd} = 0.000005$, (c) $\beta_{sd} = 0.00001$

Chapter 5

Optimal control of a mathematical model of Echinococcosis in humans, dogs and sheep.

The mathematical model (4.1.1)-(4.1.12) presented in Chapter 4 is considered. From numerical simulations performed in 4.4.4, it was found that vaccination of sheep when carried out solely or in combination with cleaning or disinfection of the environment is an effective control method for the disease. In this study, the impact of time dependent intervention strategies will be investigated. The effectiveness of optimal control(s) in comparison to constant control(s) is also explored. All assumptions stated in Chapter 4, including the total populations is valid for this model too.

5.1 Optimal Control of the model

In this section, we perform optimal control study on model (4.1.1)-(4.1.12) to explore the most effective mitigation strategy which will minimize the number of sheep, dogs and human who become infected in the course of infection while efficiently balancing vaccination of sheep and cleaning or disinfection of the environment when applied to the models with various cost scenarios. The optimal control model for the disease is formulated by considering the following controls:

1. Sanitation control, $\mu(t)$ which measures the efforts to prevent susceptible sheep and human from contracting the disease. This include drinking clean water, personal hygiene, avoiding eating raw food, and intensive cleanliness of the environment which help to break the parasite transmission cycle,

2. Vaccination of sheep, which is administered at rate $\nu(t)$.

The objective functional is given by

$$J(\nu,\mu)=\int_0^T \left(w_1 I_d + w_2 I_h + w_3 I_s + B_1\nu(t)^2 + B_2\mu(t)^2\right) dt, \tag{5.1.1}$$

where w_1, w_2 and w_3 are positive balancing coefficients corresponding to state variables I_d, I_h and I_s respectively. The terms w_1, w_2 and w_3 represent the weights associated with infectious dog (I_d), infectious human (I_h) and infectious sheep (I_s) respectively. The coefficients B_1 and B_2 represent the weights on the cost associated with vaccination of sheep and cleaning or disinfection of environment respectively. We consider the system on a time interval $[0,T]$ for some $T>0$. The controls are defined as

$$\Gamma=\{(\nu,\mu)\mid 0\leq\nu(t)\leq\nu_{max}, 0\leq\mu(t)\leq\mu_{max}\},$$

where ν_{max} and μ_{max} denote the upper bounds for the effort of vaccination and sanitation respectively. A successful control strategy is one that reduces the number of infected individuals while minimising the costs $J(\nu,\mu)$ associated with these efforts. Thus, our goal is to find a pair of controls (ν^*,μ^*), such that

$$J(\nu^*,\mu^*)=\min_{(\nu,\mu)\in\Gamma} J(\nu,\mu),$$

This minimise the number of infected individuals from the populations while keeping the cost of controls low.

5.2 Existence of the Optimal Control

The existence of optimal control follows from Fleming and Rischel [27] due to convexity of the integrand of the objective functional J in (5.1.1) over a convex and closed control set Γ, and system (4.1.1)-(4.1.12) satisfies the Lipschitz property with respect to the state variables since the state solutions are bounded. The basic framework of an optimal control problem is to prove the existence of an optimal control and then characterize it. Pontryagin's Maximum Principle is used to establish necessary conditions that must be satisfied by an optimal control solution [52]. The existence of an optimal control pair as well as the necessary conditions that the optimal control solutions of system (4.1.1)-(4.1.12) satisfy are shown below. This principle introduces adjoint functions that allow the state system (4.1.1)-(4.1.12) to be attached to the objective functional, that is, it converts the system (4.1.1)-(4.1.12) into the problem of minimizing the Hamiltonian

$H(t)$ given by:

$$H(t) = w_1 I_d + w_2 I_h + w_3 I_s + B_1 \nu^2 + B_2 \mu^2 + \lambda g(t, X(t)), \tag{5.2.1}$$

where $\lambda = (\lambda_1, \lambda_2, \cdots, \lambda_n)$ is a row matrix (vector) of adjoint functions (variables) or co-state variables. In the following theorem, we present the adjoint system and control characterisation.

Theorem 5.2.1 *There exists* $(\nu^*, \mu^*) \in \Gamma$ *such that the objective functional in* (5.1.1) *is minimized.*

Proof. To achieve the optimal control, the adjoint functions must satisfy $\frac{d\lambda_i}{dt} = -\frac{\partial H}{\partial X}$. Thus, we obtain the adjoint system

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_d} = \lambda_1 \mu_d + (\lambda_1 - \lambda_2)\beta_{sd} I_s, \tag{5.2.2}$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial E_d} = \lambda_2 \tilde{\gamma_d} - \lambda_3 \gamma_d, \tag{5.2.3}$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I_d} = \lambda_3 \mu_d - \lambda_4 \delta - w_1, \tag{5.2.4}$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial B} = \lambda_4(\mu_e + \mu) + (\lambda_5 - \lambda_6)\frac{\beta_{eh}\chi_h S_h}{(\chi_h + B)^2} + (\lambda_9 - \lambda_{11})\frac{\beta_{es}\chi_s S_s}{(\chi_s + B)^2}, \tag{5.2.5}$$

$$\frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial S_h} = \lambda_5 \mu_h + (\lambda_5 - \lambda_6)\frac{\beta_{eh} B}{\chi_h + B}, \tag{5.2.6}$$

$$\frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial E_h} = \lambda_6 \tilde{\gamma_h} - \lambda_7 \gamma_h, \tag{5.2.7}$$

$$\frac{d\lambda_7}{dt} = -\frac{\partial H}{\partial I_h} = \lambda_7 \tilde{q_h} - \lambda_8 \alpha_h - w_2, \tag{5.2.8}$$

$$\frac{d\lambda_8}{dt} = -\frac{\partial H}{\partial R_h} = \lambda_8 \mu_h, \tag{5.2.9}$$

$$\frac{d\lambda_9}{dt} = -\frac{\partial H}{\partial S_s} = \lambda_9 \mu_s + (\lambda_9 - \lambda_{11})\frac{\beta_{es} B}{\chi_s + B} + (\lambda_9 - \lambda_{10})\nu, \tag{5.2.10}$$

$$\frac{d\lambda_{10}}{dt} = -\frac{\partial H}{\partial V_s} = (\lambda_{10} - \lambda_9)\rho, \tag{5.2.11}$$

$$\frac{d\lambda_{11}}{dt} = -\frac{\partial H}{\partial E_s} = \lambda_{11} \tilde{\gamma_s} - \lambda_{12} \gamma_s, \tag{5.2.12}$$

$$\frac{d\lambda_{12}}{dt} = -\frac{\partial H}{\partial I_s} = \lambda_{12} \mu_s + (\lambda_1 - \lambda_2)\beta_{sd} S_d - w_3, \tag{5.2.13}$$

with transversality conditions (or final time conditions) $\lambda(t_f) = 0$.

The characterization of the optimal controls $\nu^*(t)$ and $\mu^*(t)$ are based on the conditions $\frac{\partial H}{\partial \nu} = 0$

and $\frac{\partial H}{\partial \mu} = 0$ respectively, subject to the constraints $0 \leq \nu \leq \nu_{max}$ and $0 \leq \mu \leq \mu_{max}$. This gives us

$$2B_1\nu + (\lambda_{10} - \lambda_9)S_s = 0, \tag{5.2.14}$$

$$2B_2\mu - \lambda_4 B = 0. \tag{5.2.15}$$

Solving for the controls in (5.2.14) and (5.2.15), we get $\tilde{\nu} = \frac{(\lambda_9 - \lambda_{10})S_s}{2B_1}$, $\tilde{\mu} = \frac{\lambda_4 B}{2B_2}$. By applying the standard arguments and the bounds for the controls, we obtain the characterization of the optimal control

$$\nu^* = \max\{0, \min(\tilde{\nu}), \nu_{max}\} \tag{5.2.16}$$

$$\mu^* = \max\{0, \min(\tilde{\mu}), \mu_{max}\} \tag{5.2.17}$$

■

5.3 Numerical results

In this section, we present some numerical results of the proposed optimal control problem. We use an iterative scheme to solve the optimality system. Starting with a guess for the adjoint variables, the state equations are solved forward in time over the simulated time using fourth order Runge-Kutta scheme. Then these state values are used to solve the adjoint equations backward by a backward fourth order Runge-Kutta scheme. Finally, we update the controls by using the previous controls and the value from the characterizations (5.2.16)-(5.2.17), and the iterations continue until convergence.

To illustrate the results of the foregoing analysis, we have simulated system (4.1.1)-(4.1.12) using the parameters in Table 3.1.

The simulations are carried out using the following initial values: $S_d = 7500$, $E_d = 2500$, $I_d = 2500$, $B = 10$, $S_h = 34000$, $E_h = 6500$, $I_h = 9000$, $R_h = 1000$, $S_s = 7000$, $E_s = 4800$, $V_s = 1700$ and $I_s = 3200$. The total populations of dog (N_d), sheep (N_s) and human (N_h) are respectively 12,500, 16,000 and 50,000 respectively. Furthermore, taking lack of resources and misuse of controls in to account, we take $\Gamma = \{(\nu, \mu) \mid 0 \leq \nu(t) \leq 0.7, 0 \leq \mu(t) \leq 0.7\}$, with $T = 2000$ (days). The cost coefficients corresponding to state variables are set to be $w_1 = 20$,

$w_2 = 20$, and $w_3 = 20$. These weight parameters determine the importance of variables in the objective functional. Assuming that both controls have equal significance, the quadratic cost coefficient corresponding to control measures are arbitrary chosen to be $B_1 = 3.2$ and $B_2 = 3.2$ (dimensionless). Simulations of the populations of infected sheep, dog and human with optimal control and constant control are compared. For this purpose, optimal strategies with the following three scenarios are considered.

Strategy A: Cleaning or disinfection of the environment alone.

Strategy B: Vaccination of sheep alone.

Strategy C: Combination of vaccination of sheep and cleaning or disinfection of the environment.

Strategy A: Cleaning or disinfection of the environment alone

Simulations (a)-(c)in Figure 5.1 illustrate the time evolution of infected dogs (I_d), infected sheep (I_s) and infected humans (I_h), in the presence of vaccination of sheep alone, that is, with optimal cleaning or disinfection of the environment alone, $0 \leq \mu(t) \leq 0.7$ and $\nu = 0$. In order to see the effect of optimal cleaning or disinfection of the environment alone and compare with the time independent rate, we consider time independent rates of cleaning or disinfection of the environment alone $\mu = 0$, $\mu = 0.005$ and $\mu = 0.6$. The number of human and the number of infectious sheep due to the time-independent (constant) rate, μ is less than the number of infectious human and infectious sheep resulted from the optimal control. However, the number of infectious dogs corresponding to the optimal control do not show a significant reduction while compared to the number of infected dogs resulted from the time-independent (constant) rate μ. The total number of infections in dog, human and sheep populations without control are respectively 2277, 8949 and 5204, whereas in the presence of this optimal strategy a total of 2 infected dogs, 20 infected humans, and 138 infected sheep are averted. The cost functions corresponding to cleaning or disinfection of the environment is as shown in the Fig. 5.1(d). The figure depicts that the associated costs of implementing the strategy increases until 970 days then decreases in the rest time horizon. Simulation result of Figure 5.1(e) shows the optimal path of the controls. In this case, the control measure ν start at the highest bound at the beginning and remains there till the final time. The associated total costs of implementing this strategy is $J = 3.25 \times 10^3$.

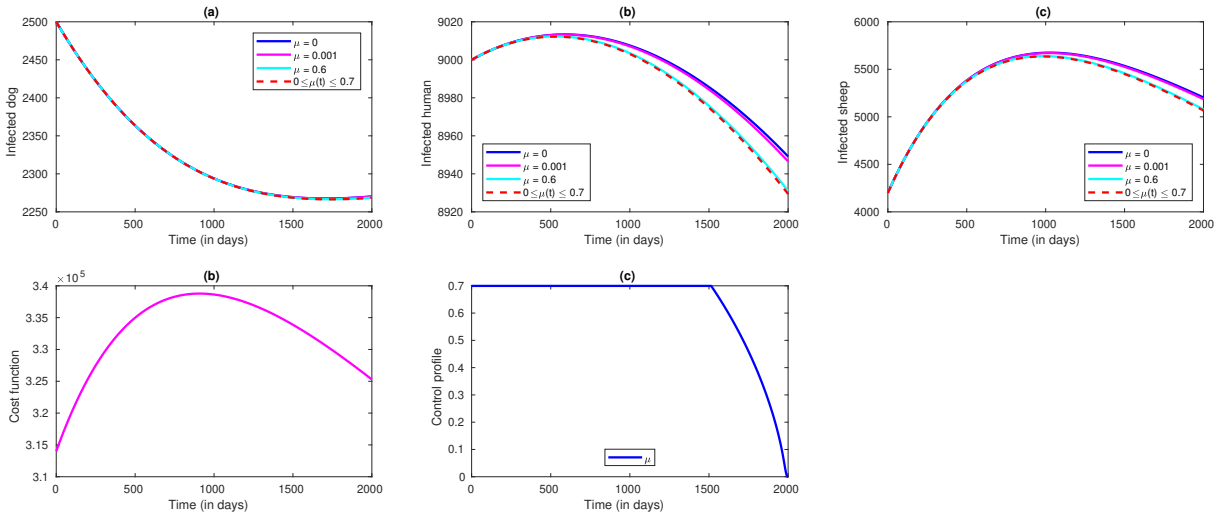


Figure 5.1: The time evolution of the number of infected individuals with optimal and constant rate of cleaning or disinfection of the environment alone (μ)), the cost and the control profile of vaccination of sheep, $\mu(t)$.

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Strategy B: Vaccination of sheep alone

In order to see the effect of optimal vaccination of sheep, and compare with the time independent rate, we consider the time-independent (constant) rate of vaccination of sheep, $\nu = 0$, $\nu = 0.005$ and $\nu = 0.6$. The results in (a)-(c) in Figure 5.2 show that, the number of infectious individuals in the three populations corresponding to the optimal control are less than the number of infectious individuals resulted from the time-independent (constant) rate of vaccination of sheep. The total number of infections in dog, human, sheep populations without control are $I_d = 2214$, $Ih = 8953$, and $I_s = 3769$ respectively, whereas in the presence of the optimal strategy a total of 11 infected dog, 3 infected humans and 170 infected sheep are averted. Simulations results of Figure 5.2(e) show the optimal path of the controls. The control measure ν at the upper bound at the beginning and remains there till the final time. The cost functions corresponding to sheep vaccination are as shown in the Fig. 5.2(d). In this case, the figures depict that the associated costs of implementing the strategy increases up to 476 days then it drops in the remaining time horizon. The associated total costs of implementing this strategy is $J = 2.9503 \times 10^5$.

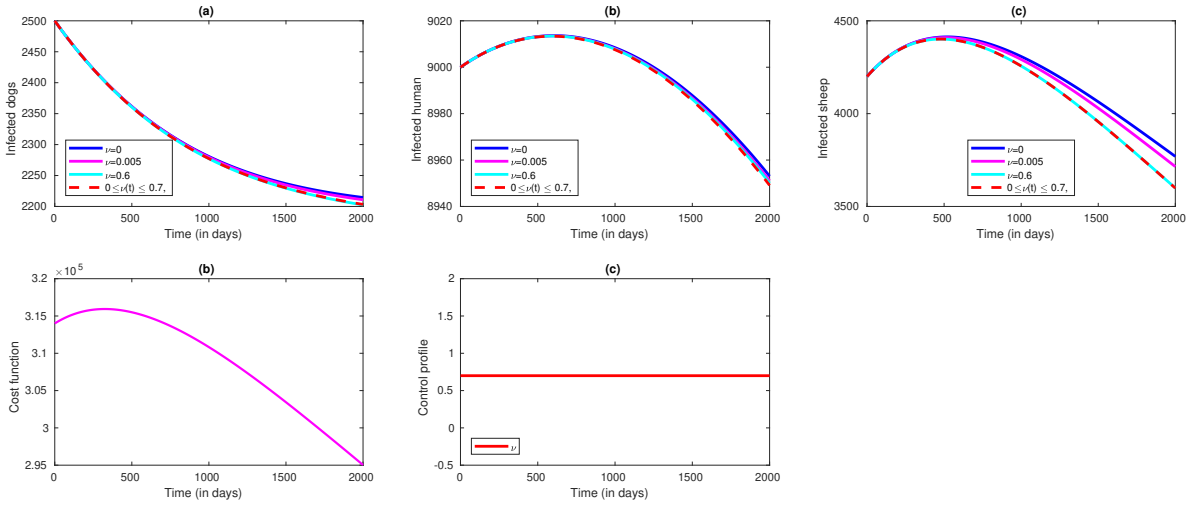

Figure 5.2: The time evolution of the number of infected individuals with optimal and constant rate of vaccination of sheep alone (ν)), the cost and the control profile of vaccination of sheep, $\nu(t)$.

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Strategy C: Combination of vaccination of sheep and cleaning or disinfection of the environment.

Numerical simulations (a)-(c) in Figure 5.3 illustrate the effects of combining the optimal vaccination rate of sheep ν and the optimal rate of cleaning or disinfection of the environment μ, where $0 \leq \nu(t) \leq 0.7$ and $0 \leq \mu(t) \leq 0.7$. The results in Figure 5.3 show that, the number of infectious dogs, human and sheep corresponding to the optimal control are less than the number of infected individuals in the three populations resulted from small amount time-independent (constant) controls. However, it can also be noticed that, the number of infectious dogs, sheep and human populations do not show significant differences while compared to the numbers of infected dos, sheep and human populations obtained with constant controls, $\nu = \mu = 0.7$. The total number of infections in dog, human and sheep populations without control are respectively 2214, 8953 and 3769, whereas in the presence of this optimal strategy a total of 13 infected dogs, 24 infected humans, and 171 infected sheep are averted. Simulations results of Figure 5.3(e) shows the optimal path of the controls. The control measure μ is at upper bound up to 1420 days and eventually drops to the lower bound in the remaining time horizon. But the control measure ν start at the lower bound at the beginning and remains there till the final time. The cost function corresponding to sheep vaccination and cleaning or disinfection of the environment is as shown in the Fig. 5.3(d). The figure depict that the associated costs of implementing the

strategy increases up to 330 days and decrease in the remaining time horizon. The associated total costs of implementing this strategy is $J = 2.946 \times 10^5$.

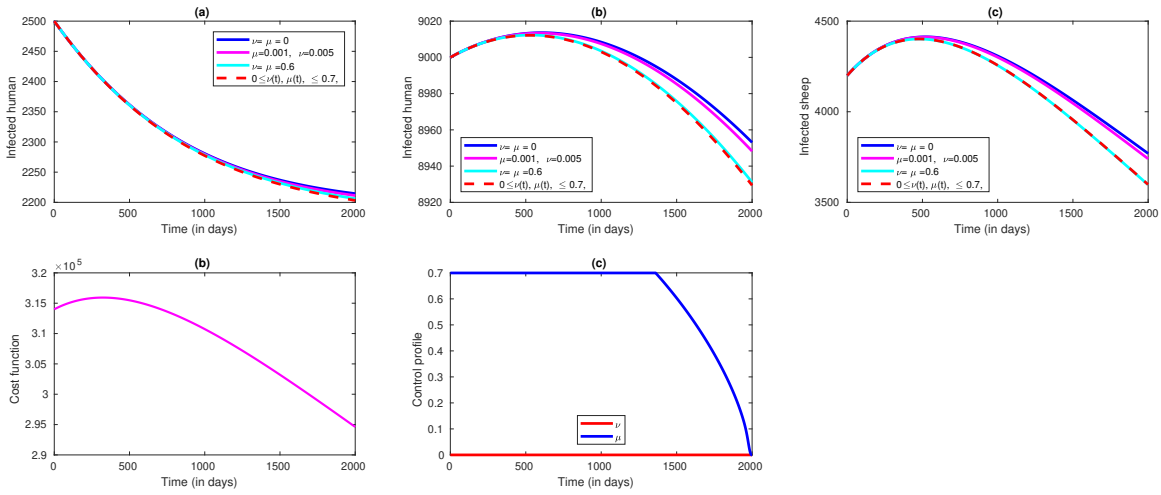

Figure 5.3: The time evolution of the number of infected individuals with optimal and constant optimal controls ($\mu = 0.01, \nu = 0.05$), the cost and the control profile of both interventions, $\nu(t)$ and $\mu(t)$

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From the results of Figures, for a small amount(fraction) of time independent control(s), we can notice that the optimal control strategy is more effective than the time-independent small fraction control(s). However, while time independent control(s) is(are) administered at maximum effort, the optimal control strategy has similar effect as the time-independent control(s). Moreover, combining both optimal controls is more effective in disease management than using the optimal vaccination of sheep alone or optimal disinfection of the environment.

Next, we demonstrate the effect of practicing vaccination of sheep on the number of infected population by keeping cleaning or disinfection of the environment constant. Accordingly, the model is simulated for percentage values $\nu(t) = 1\%$, $\nu(t) = 10\%$ and $\nu(t) = 70\%$, with a constant rate of cleaning or disinfection of the environment $\mu = 0$ and $\mu = 0.01$ in Figure 5.4 and Figure 5.5 respectively.

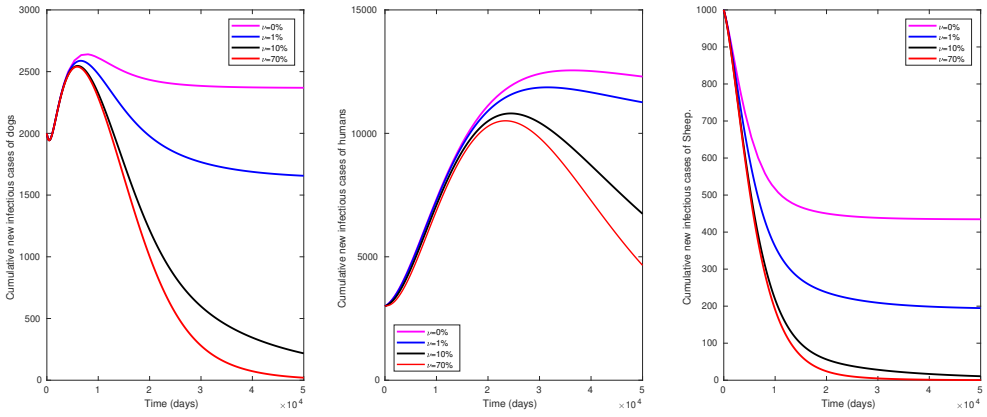

Figure 5.4: Effect of different percentage values of control $\nu(t)$ with $\mu = 0$ on the number of cases.

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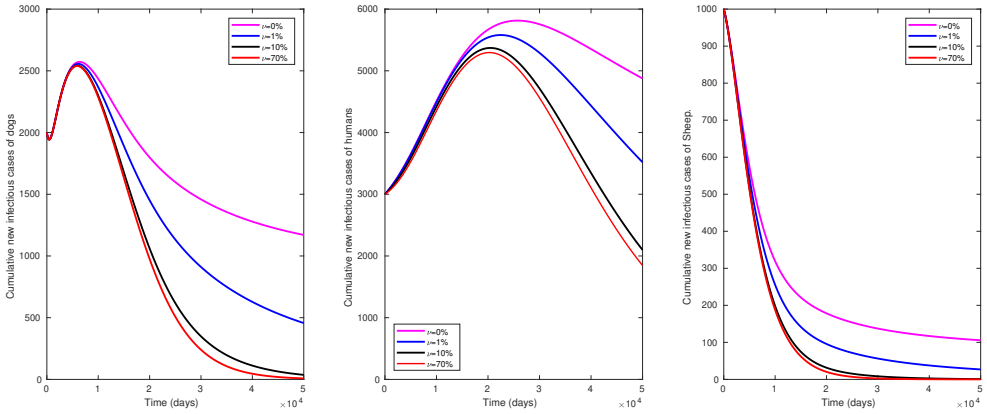

Figure 5.5: Effect of different percentage values of control $\nu(t)$ with $\mu = 0.01$ on the number of cases.

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From Figures 5.4 and 5.5, it can be inferred that, if at least 1% of sheep populations maintained practicing vaccination, then the number of cases in the three populations would have reduced as compared to the results with no vaccination. The figures further reveal that improved results would have been obtained for $\nu = 10\%$ and $\nu = 70\%$ in the the number of cases in the three populations. Figure 5.5 also showed that the number of cases in the three population is significantly reduced when vaccination of sheep is practiced with cleaning or disinfection of the environment.

5.3.1 Cost effectiveness

Controlling and eliminating the spread of infectious diseases in a in community require time and money. Therefore, it is essential to identify and implement cost-effective strategies to prevent the spread the disease. We use the incremental cost-effectiveness ratio (ICER) to do this. The ICER is defined as the cost per health outcome [72], which is given by:

$$ICER = \frac{\text{The difference in costs between strategies}}{\text{Total number of infection averted}}$$

We calculated the number of infections averted by subtracting the number of infections with control from without control. On the other hand, the total cost of each strategy was obtained using the cost function J. To use the ICER method, we first rank the control strategies based on averted human infection, as shown in Table 5.2.

Table 5.1: Cost-effectiveness of the control strategies.

Strategy	**Total human infection averted**	**Total cost ($)**
No Strategy	0	0
Strategy A	6	3.25×10^5
Strategy B	3	2.9503×10^5
Strategy C	24	2.946×10^5

The ICER, is calculated as follows.

$$ICER(A) = \frac{3.25 \times 10^5}{6} = 5.4 \times 10^4$$
$$ICER(B) = \frac{2.9503 \times 10^5 - 3.25 \times 10^5}{3 - 6} = 9.99 \times 10^3$$
$$ICER(C) = \frac{2.946 \times 10^5 - 2.9503 \times 10^5}{24 - 3} = -20.48$$

ICER values for the four strategies indicates that strategy A has greatest ICER value. Due to this reason, Strategy A is excluded, and the analysis continued by comparing ICER values of the remaining strategies. We recalculate ICER as follows.

Table 5.2: Cost-effectiveness of the control strategies.

Strategy	**Total human infection averted**	**Total cost ($)**
No Strategy	0	0
Strategy B	3	2.9503×10^5
Strategy C	24	2.946×10^5

The ICER, is calculated as follows.

$$ICER(B) = \frac{2.9503 \times 10^5}{3} = 9.8 \times 10^4$$
$$ICER(C) = \frac{2.946 \times 10^5 - 2.9503 \times 10^5}{24 - 3} = -20.48$$

The comparison between the two strategies shows that B is more costly than the other C. Thus, B is excluded. Therefore, Strategy C (combination of vaccination of sheep and cleaning or disinfection of the environment) is the most effective strategy to prevent the disease.

Chapter 6

Discussion and Conclusion

6.1 Results and Discussion

In this study, mathematical models with and without intervention strategies were formulated to describe the transmission dynamics of cystic echinococcosis in dogs, sheep and humans. These models are distinct from previous mathematical cystic echinococcosis studies, in which most models do not incorporate human populations [3, 29, 30, 53, 54, 63], predator-prey interaction between the populations, the saturation effect of the parasite in the environment. We introduced a model for the predator–prey interaction of the sheep, dog and human populations in order to ascertain the conditions for the coexistence of these populations. We then determined the equilibrium points, and studied the stability of each of these points. We also formulated a compartmental model for transmission dynamics of cyst echinococcosis without any intervention strategies. We calculated both the Disease Free Equilibrium (DFE) and the Endemic Equilibrium (EE) points of the model. To study the behavior of the disease, the basic reproduction number $\mathcal{R}_0$ was derived. We proved that, when $\mathcal{R}_0 \leq 1$ the DFE is locally asymptotically stable and globally asymptotically stable, which implies the disease dies out, whereas when $\mathcal{R}_0 > 1$, the EE is globally asymptotically stable, which implies that the disease persists in all the populations. To identify which parameter has a great impact in the disease transmission, we performed both local and global sensitivity analyses on the basic reproduction number, from which we noticed that the most sensitive parameter is the transmission rate of *Echinococcus'* eggs from environment to sheep (β_{es}). Furthermore, we observed that the variation of β_{es} has a significant effect on the number of infectious sheep, dog and human populations. Thus, the effective controlling strategy is to decrease the transmission rate of *Echinococcus'* eggs from environment to sheep (β_{es}). We extended the model by incorporating

the vaccination of sheep and cleaning or disinfection of the environment. The model has a Disease Free Equilibrium point (DFE) which is both locally and globally asymptotically stable whenever the control reproduction number $\mathcal{R}_c \leq 1$. We also determined the Endemic Equilibrium points (EE) and proved that it is globally stable whenever the control reproduction number $\mathcal{R}_c > 1$. Moreover, we have performed sensitivity analysis on the control reproduction number with the two control strategies, from which we have noted that the most sensitive parameters are the transmission rate from sheep to dog (β_{sd}) and *Echinococcos'* eggs contamination rate of the environment by infected dogs (δ). Numerical simulations of the model have shown that, whenever the control strategies are carried out solely then vaccination of sheep is the better alternative to eradicate cyst echinococcosis, but when disinfection or cleaning the environment is carried out solely, its effect to eradicate the disease is low. Furthermore, the numerical result obtained in this study is compared with the WHO data.

In order to reduce or eliminate the disease while minimizing the intervention implementation costs, an optimal control model with vaccination of sheep and cleaning or disinfection of the environment is developed and analyzed. The Pontryagin's Maximum Principle is applied in order to determine the necessary conditions for the optimal control of the disease. The effect of constant and time dependent vaccination of sheep and cleaning or disinfection of the environment have not also been examined in the previous studies. It this study their effects are studied. Numerical simulations of two strategies are depicted and discussed. The results of the simulations revealed that the optimal controls are more effective to reduce the disease in the populations of dog, sheep and human than small amount time-independent controls. But the time-independent controls if administered at maximum effort, has also the same effect as the optimal control(s) to reduce the disease in the populations. Carrying out the cost effectiveness analysis using ICER, the most cost-effective strategy to use in the control of cystic echinoccosis disease is determined. Doing this, the differences between the costs and health outcomes of these interventions are compared. The cost effectiveness analysis was carried out using numerical simulations and the result revealed that vaccination of sheep in combination with cleaning or disinfection of the environment is cost-effective strategy. This indicates that administering optimal vaccination of sheep in combination with optimal cleaning or disinfection of the environment is effective strategies to eradicate the outbreak of the disease from the three populations with minimum cost.

6.2 Conclusion

In order to understand the dynamics of the dynamics of cystic echinococcosis in human population, a basic deterministic mathematical model without intervention strategies was first proposed and analyzed. This provided insights into the dynamics of the disease transmission, and helped to formulate intervention strategies. A model which incorporates two control strategies; namely vaccination of sheep and disinfection or cleaning the environment was then proposed and analyzed. The result of the analysis have shown that vaccination of sheep solely or in combination with cleaning or disinfecting of the environment reduce the number of infectious individuals in the three populations. This is distinct from the outcomes seen in [22, 57, 77]. This is because each model uses a different set of intervention techniques. Furthermore, for effective utilization of limited resources, the optimal control measures have played great role during intervention period [22]. The control options would be evaluated on the basis of their effectiveness and cost. Due to this reason, the optimal control measures was carried out in the two interventions of CE. Rong et al in [57] suggest that, the implementation of optimal control strategy can significantly reduce the infections. Improving the cost of health education and domestic dog deworming could not decrease human infections. Due to the difference in intervention strategies, this result do not agree with the result of our study. The analyses of our study have shown that time dependent vaccination of sheep solely or in combination with cleaning or disinfecting of the environment can be carried out for long time span to reduce the disease transmission in the dog, sheep and human populations. Administering time dependent vaccination of sheep solely or in combination with cleaning or disinfecting of the environment with maximum amount is effective strategies to eradicate the outbreak of the disease from the three populations. Due to economic pressure over the government agencies all around the world, the effectiveness and cost-effectiveness of the control strategies needs to be studied [72]. Due to this fact, he cost effective analysis was also carried out. The result of the analyses have shown that combination of vaccination of sheep and cleaning or disinfection of the environment is cost effective strategy to prevent the disease. However, the cost effectiveness analyses were not carried out in the aforementioned studies.

Limitation and extension of the study

One of the limitations of this study is lack of realistic data, thus in this study estimated parameter values were used. For the model to be more realistic and to make possible future predictions, collecting relevant data from the environment is very important. Furthermore, the sensitivity analysis of the model with the two intervention strategies also showed that the most sensitive parameters are the transmission rate from sheep to dog (β_{sd}). This indicates that to eradicate the disease from the three populations the model needs to incorporate other possible intervention strategies that can reduce β_{sd}. We therefore suggest extension of our work by introducing different intervention strategies. It is also understood that models of the dynamics of disease transmission use different scenario to represent the birth/death rates. In this particular study, we have taken a constant birth rate and linear death rate, and other scenarios are needed be considered and studied in the future projects.

KEY TERMS:

Compartmental model; Predator–prey model; Cystic echinococcosis; Equilibrium points; Basic reproduction number; Intervention strategies; Control reproduction number; Locally asymptotically stable; Globally asymptotically stable; Local sensitivity analysis; Global sensitivity analysis; Optimal controls.

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