**KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, KUMASI**

# MATHEMATICAL MODELS FOR THE STUDY OF BURULI ULCER DYNAMICS IN GHANA

BY

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# DECLARATION

I hereby declare that this submission is my own work towards the award of the PhD degree and that, to the best of my knowledge, it contains no material previously published by another person nor material which had been accepted for the award of any other degree of the university, except where due acknowledgement had been made in the text.

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# DEDICATION

This thesis is dedicated to my late Mother Madam Adwoa Nyarko and my family.

# Abstract

*Mycobacterium ulcerans* (MU) is known to cause Buruli ulcer (BU). The association between the ulcer and environmental exposure has been fairly documented, however, the epidemiology of the ulcer is not well understood. The hypothesised transmission involves humans being bitten by the water bugs that prey on mollusks, snails and young fishes. In this thesis, deterministic, optimal control and age dependent models were developed for the study of the dynamics of the disease. The models equilibria are determined and conditions for the existence of the equilibria established. The transmission dynamics of BU model of the Susceptible, Infected and Recovered (SIR) type showed that the infected humans increased as long as there are enough infected water bugs to sustain the epidemic. Sensitivity analysis showed that the BU epidemic is highly influenced by the shedding of MU into the environment. The model SIR is found to fit reasonably well to data from Ashanti region of Ghana and projections on the future of the BU epidemic are also made. Again, a deterministic of the model Susceptible,Infected, under Treatment and Recovered (SITR) type with saturation treatment is formulated. The suggestion that giving the patients timely treatment, improving the cure efficiency and decreasing the infective coefficient are all valid methods for the control of disease. It was also found that increasing the density of *Mycobacterium ulcerans* in the environment led to an increase in the number of infected water bugs. Furthermore, model was modified to incorporate treatment and preventive measures. The SIR model was analysed without treatment and preventive measures and investigated its stability at both disease free and endemic steady states. Furthermore, treatment and preventive measures were incorporated (mass treatment, spaying of insecticides and provision of mass education) and investigated the effects of different control strategies on the spread of Buruli ulcer. Further, we used optimal control methods

to determine the necessary conditions for the optimality of the disease eradication or control. The best strategies in fighting Buruli ulcer disease was determined and obtained that a combination of all the three strategies are the most effective way to manage BU disease. On the age model SIR dynamics, a representation from the method of characteristics and fixed point theory was applied to determine the existence and uniqueness of solutions to the nonlinear system of the age model. The simulations revealed an increase in recovered humans and this is attributed to antibiotic treatment and few people getting recovered naturally. It was found that there is a peak for MU spread, which subsequently reduces as more susceptible get awareness of the disease in both two and three dimensional plots.

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# CHAPTER 1

# INTRODUCTION

## 1.1 Background of the Study

One mysterious tropical disease whose epidemiology is yet to be unravelled is Buruli ulcer (BU) (Duker et al., 2006). Buruli ulcer, also known as Bairnsdale ulcer is a chronic, indolent, and necrotizing disease of the skin tissue caused by Mycobacterium ulcerans (MU). The disease usually begins as a painless nodule or papule and may progress to massive skin ulceration (WHO, 2012). The large number of cases and the complications associated with the disease as well as its long-term socio-economic impact could have a substantial effect on the national economy (Chauty et al., 2007). BU is a poorly understood disease that has emerged dramatically since the 1980s. The disease is mostly found in rural areas located near wetlands and slow-moving rivers, especially areas prone to flooding and that are often associated with rapid environmental change (Merrit et al., 2010). Unlike leprosy and tuberculosis, caused by the organism belonging to the same family as BU, which are characterized by person-to person transmission, inoculation of Mycobacterium ulcerans into the subcutaneous tissues likely occurs through environmental contact, although the mode of transmission is still not entirely clear (Merrit et al., 2010). The agent produces a potent toxin known as mycolactone, which destroys cells in the subcutaneous tissues leading to the development of large skin ulcers (Noeske et al., 2004).

The incubation period, the time between infection with Mycobacterium ulcerans and clinical presentation of Buruli ulcer, is usually under three months (Johnson et al., 2005). It affects any part of the body, but predominantly affects the limbs (Asiedu et al., 2000). About 70% of cases are in people under 15 years of age

(Asiedu et al., 2000). The clinical features of Buruli ulcer have been clearly defined by the World Health Organization (Marston et al., 1995). It starts as a localized swelling in the skin that is typically painless and firm. It is referred to as a papule when the skin swelling is less than one centimetre in diameter, and a nodule when it is one to two centimetres in diameter, attached and under the skin (subcutaneous). It is called a plaque when the ulcer has irregular edges and is more than two centimetres in diameter (Amofah et al., 2002) and may later develop into ulcers. The ulcers typically have undermined edges, which make the real size of the ulcer difficult to estimate visually. The base of the ulcer is filled with dead (necrotic) tissue. Ulcers may remain small and heal without treatment, or may spread rapidly over large areas. Healing is slow, taking an average of four to six months and often follows a course with shrinking of lesions followed by a further extension. Healing results in scars which are usually depressed and star shaped (Amofah et al., 2002). Death due to Buruli ulcer is rare. The disease may however, result in joint deformities (contractures) from excessive scarring, making movement at joints difficult. Loss of or severe damage to vital organs such as eyes, breast, or genitalia may occur.

Despite the advances in medical sciences, extensive public education and research on the treatment and control of the disease, the World Health Organization reports that incidence of Buruli ulcer disease in Africa has not seen significant reduction over the years (Bonyah et al., 2013). This calls for a more urgent and rigorous research to uncover the epidemiology of the disease of which mathematical modelling offers a way.

## 1.2 Statement of Problem

Statistics from the World Health Organization indicates that globally 5,076 Buruli ulcer cases had been recorded as at the end of 2012 alone with Africa being the worst affected region (WHO, 2012). Ghana is the second most endemic

country with 1,048 Buruli ulcer cases after Cote d'Ivoire with 2,670 Buruli Ulcer cases (WHO, 2012). This by implication means that Ghana and Cote d'Ivoire contributed 73 percent of the world incidence. The Ghana Ministry of Health 2012 annual report shows the Ashanti Region accounted for over 60% of all cases. Buruli ulcer was first brought to public attention in Ghana in 1993 when severe cases were reported from the Amansie West district of Ashanti Region in August that same year (MOH). Specifically the most affected town was Tontokorom, although earlier cases had been reported from the Densu and Afram plains, Baylay (1971) and Van der werf et al. (1989). In Ghana, a national survey conducted in 1999 found 6000 cases and showed that Buruli Ulcer is in all 10 regions. Since then cases have come from many districts. In 2003, 739 cases were reported. For the first half of 2004, 562 new cases were reported. Today, 30 districts regularly report on the disease to the National Control Program (Ministry of Health, 2001). There are uncertainties about the epidemiology of the disease. There are knowledge gaps about where the bacterium lives in the environment and how the mycobacterium enters the human body, although it is clear the bacterium is unable to do so by itself. The high rate of re-occurrence has fuelled the mystery of how it enters the body. Despite these uncertainties, it is greatly acknowledged that the application of mathematical models offers a vigorous weapon for understanding the disease epidemiological processes. This is in line with the great successes showed by combining empirical and theoretical work in the field of biomedical science. Researchers have come to realise the potential significance of mathematical models in epidemiological studies. This is the purpose of this research.

The disease is known to affect impoverished inhabitants in the rural areas. Since the treatment cost of BU is high, these rural folks scarcely go to the hospitals for treatment but rather go for traditional treatment (Amofah et al., 1993). In addition to the high cost of surgical treatment, fear of surgery and concerns about the resulting scars and possible amputations may also prevail. The impact of the

disease on the few health facilities in the affected areas is enormous. The long hospital stay, often more than three months per patient, represents a huge loss in productivity for adult patients and family caregivers, and loss of educational opportunities for children. The prolonged hospitalizations also create a huge burden on the resources of the hospitals. The long-term care for those disabled, most of whom are children aged around 15 years (Asiedu et al.,1998).

It is against this background that this research is carried out to ascertain and investigate the wide spread of Buruli ulcer disease in humans and recommend strategies to manage/control the disease.

## 1.3 Research Objectives

The main objective of this work is to study the dynamics of Buruli ulcer disease. In particular, to put up a constructive mathematical models incorporating important macro-epidemiological parameters influencing the spread of the epidemic and possible control strategies. The objectives of the study are;

1. To develop SIR model, which takes into account the human population, water bugs as vector and fish as potential reservoirs of Mycobacterium ulcerans.

2. To develop SITR model that investigate the possible impact of the challenges associated with the treatment and management of the BU.

3. To use optimal control to examine the costs and effectiveness of the control measures and determine the most cost effective control measure(s).

4. To develop an age-structured BU model and provide a theoretical and numerical analysis of the model.

## 1.4 Methodology

We present mathematical models that examine epidemiology of Buruli ulcer through human beings bitten by water bag (vector) and direct contact with environment using deterministic approach. Again we formulate two of such models of Susceptible- Infected- Recovered (SIR) and Susceptible-Infected-under Treatment-Recovered (SITR). We further incorporate saturation treatment function on the SITR model to study resources distribution in Ghana Health Service (GHS) for BU patients. Then we incorporate three optimal controls on the SIR type deterministic to determine the optimal way to reduce the spread of BU. In addition, we formulate an age structured Buruli ulcer model to capture age factor on the spread of BU disease of SIR- type and provide both analytical and numerical solutions for all the models using matlab software. Finally data from Ashanti Region of Ghana on BU from 2003 to 2012 is fitted to SIR deterministic model.

## 1.5 Significance of the Study

The study will help medical health practitioners to understand BU transmission dynamics better . The outcomes of this work will provide a broader framework for policy makers in Ghana to formulate the right policies on the ecological systems. The study will further, provide insight into health facilities resource distribution for BU patients under treatment. Finally it will add more knowledge to the existing literature on BU and provide a platform for researchers to extend the frontiers of knowledge on the disease.

## 1.6 Organization of the Thesis

The thesis is organized as follows: Chapter 1 describes the background of the research including the objectives. Chapter 2 is devoted to the literature review

on Buruli ulcer and spatial modeling of the disease as well as applications of optimal control methods in epidemiological models. Chapter 3 is concerned with the construction and analysis an SIR model as well as the formulation and establishment of the basic properties of the model. The steady states are determined and analyzed for their stability in this chapter. Also, the parameter estimation and sensitivity analysis and the numerical results on the behaviour of the model are also examined. The development and analysis of an SITR model and the formulation and establishment of the basic properties of the model is captured in Chapter 4. Chapter 5, mass treatment and preventive measures such as mass education and insecticides are incorporated into the SIR model. Chapter 6 is also devoted to the development and analysis of the SIR model with time and age considered. The chapter also presents the system of differential equations along with initial and boundary conditions that form the disease model. Finally, Chapter 7 captures the summary and conclusions of the study.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Introduction

This chapter presents reviewed literature on the Buruli ulcer. It focuses on the history, epidemiology of the disease and BU situation in Ghana. The clinical manifestation and the treatment options available are also captured. Finally, It is followed with mathematical modeling of BU disease.

## 2.2 History and epidemiology

Mycobacterium ulcerans is caused by the environmental pathogen and mainly affects the skin. It is considered as the third most common mycobacterial disease, after tuberculosis and leprosy that occur in immuno-competent individuals (Asiedu et al., 2000). In historical perspective, the disease was first noticed in 1897 by Sir Robert Cook, a British physician working in Uganda and later by Kleinschmidt in northeast Congo during the 1920s (Asiedu et al., 2000; Meyers et al., 1994).

The first vivid definitive of cases and the etiologic agent was published in 1948 by Professor Peter MacCallum and his colleagues in Australia (MacCallum, 1948). From the 1960s through the 1970s new dimension of endemic foci were observed in many tropical countries including Uganda, the Democratic Republic of the Congo, and Papua New Guinea. In this respect, some of the reports were by Oye and Ballion, Janssens and Meyers et al. who made an assertion that, traumatic lesions might be involved in the transmission of M. ulcerans. At the end of 1974, more than four hundred cases had been observed in Zaire (Meyers

et al.,1984; Clancey et al., 1962).

In the 1960s, many patients in refugee camps in an area near the Nile River in Uganda, called Buruli, got ulcers which were caused by M. ulcerans ( Clancey et al., 1962). The disease has since become to be known as Buruli ulcer. The global consequence of BU is not well explained, because of lack of sufficient and efficient data collection system in most endemic countries (Johnson et al., 2005).

It is now established that BU is endemic in at least thirty-two tropical countries of Africa, Western Pacific, Asia, the Indian Ocean and Latin America (Figure 2.1) (Johnson et al., 2005). The worst unfortunate region is within countries lying along the Gulf of Guinea in West Africa, where BU has overtaken leprosy as the second most common mycobacterial disease, after tuberculosis. Cases have been noticed in all the countries with Ghana, Ivory-Coast, Togo, Cameroon and Benin reporting the highest number of cases (Aguiar et al.,1997; Oluwasanmi et al.,1976). For instance, the prevalence of BU in some of the villages in Benin and Cameroon are higher than that of tuberculosis and can affect more than 20% of the inhabitants. In Ivory-Coast, more than 15,000 (Kanga et al., 2001) cases were detected from 1978 to 1999 while nearly 2,000 cases were observed within a 4-year period in one single hospital in Benin (Debacker et al., 2004). Very few cases have been noticed in non-endemic areas particularly, Europe and North America. Even though, BU has effect on all age groups in both sexes, it has been observed to affect mainly children 15 years of age and below in Africa (Kanga et al., 2001). Most of the lesions are seen around the legs, feet, arms and hands

In an international meeting in July 1998 in Cote d'Ivoire, the Yamoussoukro Declaration on Buruli Ulcer was established, making assertion that little is known as far as this disease is concerned, and invite the international community to make contribution to support the control and research activities (van der Werf et al., 1989).

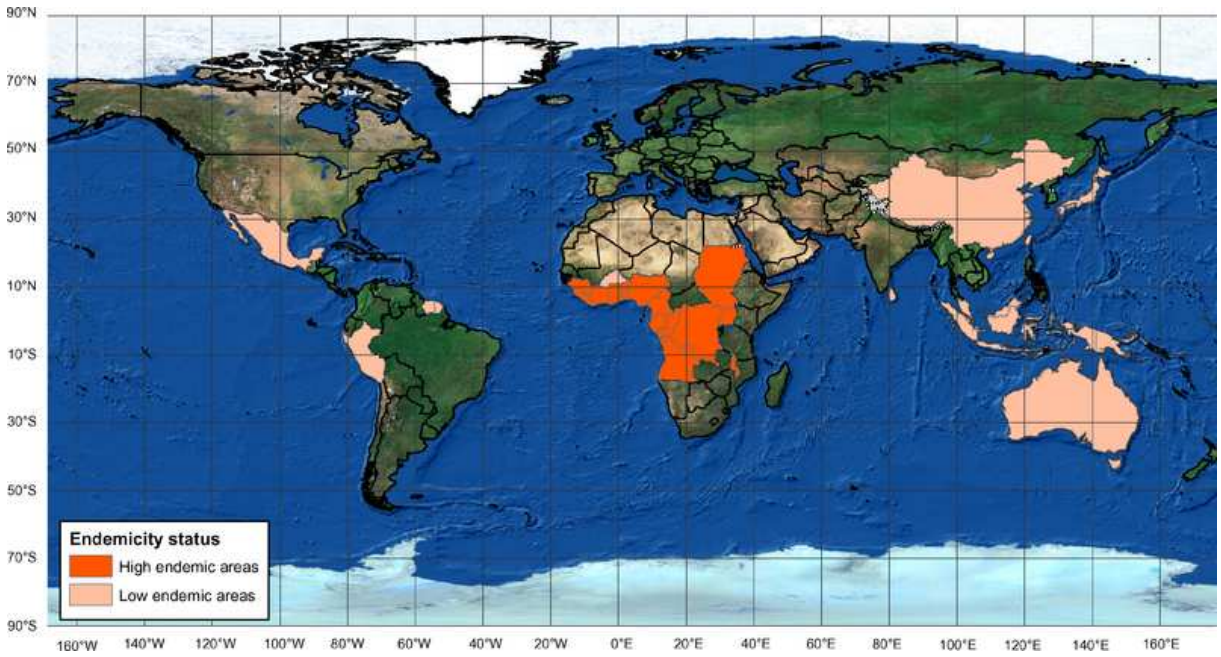



Figure 2.1: Spatial Distribution of Buruli ulcer in the World. (Source: Johnson et al., 2005)

## 2.3 Buruli ulcer in Ghana

The first documentation made on a Buruli ulcer patient in Ghana occurred on a patient from Amasaman at the Korle-Bu Teaching Hospital (Bayley et al., 1971). The occurrence of other cases along the Densu River in the area was well thought - out as a possibility. Around 1989, van der Werf et al. came out with a publication with a series of 96 cases in the Afram valley at Agogo, in the Ashanti Akim North District in the Ashanti Region (van der Werf et al., 1989). Amofa et al., 1993 also accounted for a major endemic concentrate in the Amansie West district in the same region (Amofah et al., 1993). Ever since then, there have been a number recorded cases of scattered endemic foci in most parts of the country, especially in the Ashanti Region. At the moment, the disease account for a significant proportion of all disease cases registered in some endemic district health facilities. BU is impacting negatively on all the parts of the country. It was previously noticed that the disease exists only in areas around swampy vegetation and tropical rain forest in the country. However, a national survey that was carried out in 1999 established that the disease could be

found in all ten administrative regions of the country. Again, a national survey

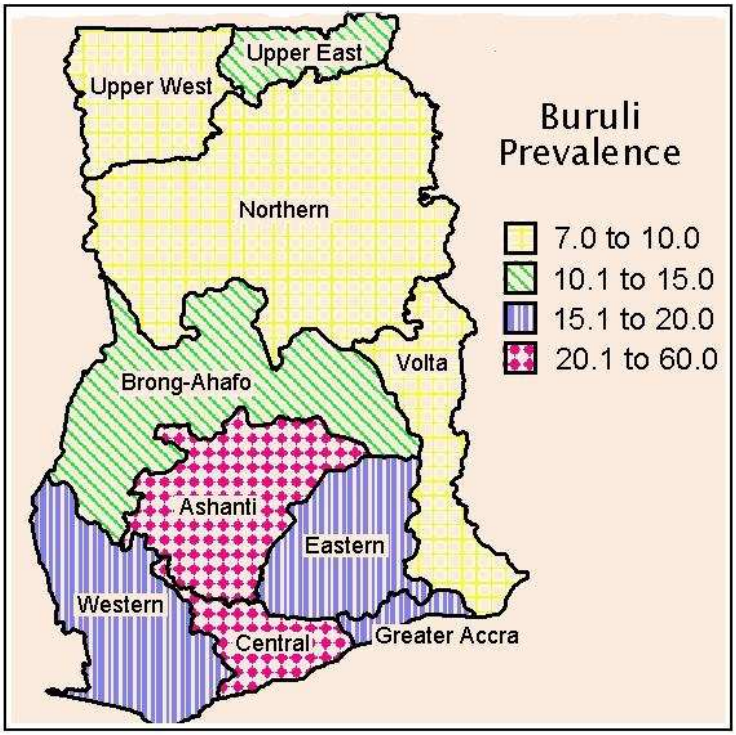



Figure 2.2: Spatial Distribution of Buruli ulcer in Ghana. (Source: Amofah et al., 1993)

conducted, over 6000 BU cases were identified across the country (Amofah et al., 2002). The total prevalence of BU in Ghana was estimated to be 20.7 per 100,000 populations indicating that it is the second most prevalent mycobacterial disease after tuberculosis. Programmes and policies have been put in place to control the disease in Ghana among them is offering of free treatment to BU patients and training of health workers to enhance diagnosis. However, diagnosis is usually began late based on socio-cultural beliefs of the people in addition to distance to treatment centres (Stienstra et al., 2002). Diagnosis of BU is usually made on the basis of clinical case definition without laboratory confirmation.

## 2.4 Clinical Presentation

*Mycobacterium ulcerans* may get into contact with the skin by traumatic inoculation and that some biting insects may be involved (Meyers et al., 1974). After entry into the skin, the organism lives in the subcutaneous tissues and the overlaying skin, where it multiplies.The incubation period is extraordinarily variable, and has been approximated to range from 2 weeks to 3 years, with an average of 2 to 3 months. The disease starts typically as a painless nodule under the skin at the site of the trauma. In some areas, the first materialization is a papule rather than the firm, painless nodule. When some few weeks have passed, the nodule gradually spreads and erodes through the skin surface, creating a well-demarcated ulcer with a necrotic slough in the base and widely undermined edges (WHO 2001, Portaels et al., 2000). This form of disease state is known as localised. Analysis of a large number of cases by Meyers and colleagues concluded that in some cases, infections spread rapidly and bypass the localized nodular-ulcerative stage. This disseminated form results in oedematous plaques that, if cured, move into ragged ulcers. As like the other steps in pathogenesis, the mode of spread is not clear. M. ulcerans may spread to large vast distant through the lymphatic and haematogenous pathway. Severe osteomyelitis is frequent and this may bring about amputation and other disabilities (Pszolla et al., 2003).

## 2.5 Treatment

### 2.5.1 Surgery

Currently, the appropriate method of treating patients with BU is the surgical excision of infected tissue followed by skin grafting. This procedure being cumbersome and the price is very high, costing around 780 US dollar per treatment as reported in Ghana (Asiedu et al., 1998), however, has different degree of success which has to do with a number of factors including the experience

of the clinician. The fact is that, there are no approved guidelines as to the extent of excision of lesions, therefore the surgeon has to make decision on a very good healthy and infected tissue. Recurrence rates between 4 and 5 percent have been noticed in different studies (Agbenorku , 2011).

Interestingly, not all patients in rural endemic areas have access to health institutions that provide surgical services (Etuaful et al., 2005). Therefore, patients first try to under take self treatment within their communities or seeking treatment from local health providers with herbal preparations (Stienstra et al., 2002). These individuals may later develop very extensive lesions that require long post-operative care and restorative physiotherapy, which increases the cost of treatment. Some of them even end up with amputations and with different degrees of disability. A study conducted by Martson et al .,1995 revealed that almost 30% of persons with healed lesions had developed chronic functional disabilities, such as loss of eyes and limbs. Large ulcers or extensive edematous lesions generally need excision followed by skin grafting (Agbenorku , 2011). Ulceration that extends to the eyelid and base of the nose are treated by four surgical excisions, daily wound dressings and skin grafts.

Ulcers closer to the eye cannot have entire excision. They are dressed over long periods with standard saline or 2% acetic acid lotions and the excised ulcers are grafted owing to the difficulty in achieving good hemostasis (Agbenorku et al., 2013). Sharp debridement can also be applied to treat BU of the face that has good healthy edges with hypertrophic granulation and the wound is covered with split-thickness skin grafts or local transposition flaps after meticulous hemostasis and dressed with Vaseline gauze and tie-over dressing (Agbenorku , 2011). The eyes must also be confined during the day with hats and glasses, and an eye shield at night to decrease dryness from contact, and to protect the eye from dust and other foreign objects. Frequent exercise to close the eye helps lubricate the cornea, strengthen weakened muscles and maintain full movement for eye closure. Gentle massage over the scar area softens it, stretches it and limits spread of adhesions to

nearby structures, which can otherwise limit movement (Herbinger et al., 2009). Interventions to put off disability should initiate before excision and go on after excision and skin grafting in order to stop soft tissue contractures. Avoidance of disability and rehabilitation are only feasible with the active participation of those pretentious by BU, their families, the community, and the health-care team (Agbenorku et al., 2012).

### 2.5.2 Drug Treatment

The Global Buruli Ulcer Initiative (GBUI) of the World Health Organization has in recent times recommended the preliminary use of conservative treatment mainly when lesions are positioned on the face, breast, and genitalia. The recommended approach for treatment of such patients is a combination of specific antibiotics with or without surgery and to follow proper Prevention of Disability (POD) program assiduously (WHO, 2004). The Anti-microbacterial treatment agents have disappointed particularly at the advanced stage of the disease. Observations of human trials have not been very encouraging; while clofazimine (Revill et al., 1973) and cotrimoxazole (Fehr et al., 1994) were observed not to be effective and a combination of dapsone and rifampin was found to have limited efficacy for ulcers (Espey et al., 2002).

Again, M. ulcerans are susceptible to rifampicin, some aminoglycosides, macrolides and quinolones in vitro (Portaels et al., 1998; Thangaraj et al., 2000). The lack of success with regard to these drugs to effectively inhibit M. ulcerans spread in humans has been hypothesised to be the fact that the inability of the drugs to penetrate the necrotic lesions (Sizaire et al., 2006). The results from mice model studies show that a combination of rifampicin with either streptomycin or amikacin have serious bactericidal activity (Dega et al., 2000; Dega et al., 2002). Treatment of mouse footpad with a combination of rifampicin and amikacin for 12 weeks reduced progressively, the number of viable counts decreased and treated mice did not relapse after 17 weeks. A

clinical trial conducted by Etuaful and colleagues revealed that a minimum of 4 weeks treatment with rifampin and streptomycin put together, brings down the growth of M. ulcerans in pre-ulcerative lesions, as affirmed by at least one of the following; direct Acid Fast Bacilli (AFB) staining, Polymerase Chain Reaction (PCR) and culture (Etuaful et al., 2005). However, they could not validate that this combination could substitute surgery and suggested it to be employed as an adjunct to surgery. Based on this successful report and other observations made, recent WHO guidelines have been established that needed an eight weeks course of treatment with rifampicin and streptomycin (Sizaire et al., 2006). The first clinical experience shows that this treatment brings about healing without subsequent surgery in about 50% of cases.

## 2.6 Some Evidence of Transmission of Buruli ulcer disease

Presently the exact mode of transmission of M. ulcerans is still not elucidated. But Buruli ulcer affects humans in scattered foci and endemic foci are normally associated with wetlands with hot and humid climates (van der Werf, et al., 2005). In Uganda, for instance, hundreds of cases cropped up among refugee populations camping near to the Nile River and the incidence of cases reduced when the refugees were taken out of the area (Clancey et al., 1962). Large number of cases have also being noticed in areas where the environment has been disturbed; examples include, flooding, damming of rivers, introduction of rice swamp fields and irrigation systems (Asiedu et al., 2000). In Nigeria, the rise in incidence happened when a small stream was dammed to create an artificial lake (Oluwasanmi et al., 1976). Similarly, in Philip Island, the formation of a small swamp brought about the increased cases, which went down when the irrigation was improved (Veitch et al., 1997).

M. ulcerans is an environmental mycobacterium and the engagement of aquatic

species in endemic areas as either environmental reservoirs and/or vectors for transmission appears possibly. M. ulcerans has been observed in aquatic bugs (Marsollier et al., 2002), mollusc (Marsollier et al., 2004), fish (Eddyani et al., 2004) and biofilms on vegetation (Marsollier et al., 2002). These have been ascertained mainly applying Polymerase Chain Reaction as a result of detection of IS2404 DNA sequence (Ross et al., 1997), which now appears not to be very particular for M. ulcerans (Mve-Obiang et al., 2005). It is known that only two pure cultures of M. ulcerans have been ascertained from environmental sources so far (Sizaire et al., 2006). In respect to a laboratory experimental model made, an aquatic insect was able to infect the tail of laboratory mice through biting (Marsollier et al., 2003). That is infected insects may gather M. ulcerans in their salivary glands and pass on to man through biting. This hypothesis is gained more weight by the detection of M. ulcerans in the salivary gland of an aquatic insect, Naucoris spp (Marsollier et al., 2005).

The extent of man to man transmission is not verified but evidence of developing BU after a human bite is known and rare (Debacker et al., 2003). There is no available properly tailored measure for prevention of BU due to the insufficient knowledge on transmission and the insufficient of an effective vaccine against BU. A study performed in Ivory-Coast however showed that covering of the exposed body sites by wearing of long trousers in endemic communities is protective (Brauer et al., 2008). Again the M. bovis BCG vaccines appears to give some degree of protection, especially against systemic infections (Portael et al., 2002).

## 2.7 Previous applications of Mathematics and Statistics to the study of Buruli ulcer disease

Duker et al., (2006) conducted a study at Amansie West District of Ghana and observed that settlements near artisanal mining activities tend to have higher BU incidence because artisanal mining contributes to the release of arsenic into

natural drainage used as potable water and for irrigation of farmlands where food crops are grown for consumption. The authors again concluded that High BU prevalence rate was found to occur in arsenic-enriched domains suggesting that arsenic-enriched domains maybe a factor for the development of BU.In 2012, Sekyere investigated the spread of BU in the same geographical space and also deduced that the disease is more profound in the areas where artisanal mining is increasing. A study carried out by Bonyah et al., (2013) using area to point kriging to examine the spread of BU within both Ashanti and Brong Ahafo region concluded that the disease is more common in places where environment has been degraded. Another study conducted by Bonyah et al., (2013) in Amansie West using Poisson kriging observed that arsenic consumption influence the spread of BU.

Aidoo and Bonsu, (2007) proposed a mathematical model of the SIR- type in an endeavour to explain the role of aquatic insects and arsenic in the spread of Buruli ulcer disease. The authors considered arsenic environment as a reservoir for *Mycobacterium ulcerans* and water bug (vector) for BU disease. In their model they proposed that BU is a micro parasitic disease in which host parasite interaction basically occurs within isolated communities. Again it was assumed that the host population is of fixed size containing susceptible individuals who are not yet infected with MU and therefore lead to SIR model.

The model equations describing the proportion of humans infected by MU and the corresponding proportion of water-bugs according to them are given by:

$$\begin{aligned} \frac{dx}{dt} &= maby(1-x) - rx \\ \frac{dy}{dt} &= a_1 x(1-y) - (\mu - \alpha)y \end{aligned}$$

High BU prevalence rate was found to occur in arsenic-enriched domains suggesting that arsenic-enriched domains are a factor for the development of

Table 2.1: Description of parameters used in the model.

| Symbol | Description |
|---|---|
| $m$ | Density of water bugs (Number of water bugs per human host) |
| $a$ | bite frequency ( biting rate of human by single water-bug |
| $a_1$ | Rate of ingestion of MU by water bugs |
| $b$ | Proportion of infected bites on humans that produce infection |
| $\alpha$ | Relative concentration as As in water |
| $\mu$ | Mortality rate of water-bugs |
| $x$ | Proportion of humans infected by MU |
| $y$ | Proportion of water-bugs infected by MU |
| $r$ | Death rate of humans |

BU. BU prevalence, however, is higher along arsenic-enriched drainage than in arsenic-enriched farmlands. However, their model was not comprehensive enough to capture other many important dynamics of BU including entire environment, small fish as MU reservoir. It is a contention in this work that more broad based mathematical models are proposed to study the dynamics of the BU. We thus provide, in addition to the work by Aidoo, ground breaking models on the disease.

## 2.8 Mathematical tools

### 2.8.1 Definitions and Notations and Proposition

For the definitions, propositions and lemmas given in this subsection, we closely follow work in (Lawson, 2003). Let $U$ be an open set of $\mathbb{R}^n$ . A function $f : U \to \mathbb{R}^n$ is said to be a $C^r$ map for $0 \leqslant r \leqslant \infty$ if all partial derivatives up through order $r$ exist for all points of $U$ and are continuous. In the extreme case $C^0$ means that $f$ is continuous and $C^\infty$ means that all partial derivatives of all order exist and are continuous on $U$.

**Definition 2.8.1** *(Lawson , 2003) A function $f : U \to \mathbb{R}^n$ is a $C^r$ map if $f_i := \pi_i f$ is $C^r$ for $i = 1, 2...n$ where $\pi_i : \mathbb{R}^n \to \mathbb{R}$ is the $i^{th}$ projection map by*

$$\pi_i(x_i, ..., x_n) = x_i$$

Let $x_i \rightarrow f(x_i)$ be map from an open subset $D_1 \subset \mathbb{R}^n$ to$\mathbb{R}^n$ such that each solution $x(t)$ to be system of differential equations

$$\overset{*}{x_i} = |f(x_i) \tag{2.1}$$

is uniquely determined by its initial conditions $x_i(0) = x_{i0}$, and denote the solution by $x_i(t, x_0)$. Let the nonlinear system 2.1 have a linear form which is given by

$$\dot{x_i} = Ax \tag{2.2}$$

with $A = D\ f(x_0)$.

**Proposition 2.8.1** *Let $U$ be a non- empty open subset of $\mathbb{R}^n$ and let $f : U \rightarrow \mathbb{R}^n$ be a $C^1$ map. Then $f$ is differentiable at all $x \in U$ and*

$$Df = Jf := \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ & & \cdot & \cdot \\ \cdot & \cdot & & \\ & & \cdot & \cdot \\ \cdot & \cdot & & \\ & & \cdot & \cdot \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{bmatrix}$$

Undoubtedly, $Df(x) = Jf(x) : \mathbb{R}^n \rightarrow \mathbb{R}^n$ where the entries of the Jacobian matrix are evaluated at $x = (x_i, ..., x_n)$ . Let also $x^* \in$ E be an equilibrium point of 2.1

**Definition 2.8.2** *A point $x^* \subset \mathbb{R}^n$ is an equilibrium point of 2.1 if $f(x^*) = 0$. $x^*$ is called a hyperbolic equilibrium point of 2.1 if non of the eigenvalues of the matrix $Df(x^*)$ 2.1 has a zero real part.*

**Definition 2.8.3** *$x^*$ is said to be locally stable or simply stable if, for each neighbourhood $U$ of $x^*$ , there exists a neighbourhood $V$ of $x^*$ such that $x(t, v) \subset U$ for all and for all $v \in V$ and for all $t > 0$.*

In other words, if $x^*$ is a stable equilibrium point of 2.1 no eigenvalue of $Df(x^*)$ has a positive real part. In this case the solutions starting at nearby initial conditions, remain close to $x^*$. More correctly, $x^*$ is stable if and only if for any $\varepsilon > 0$ , there exists a corresponding number $\delta(\varepsilon) > 0$ such that

$$\|x(t_0) - x^*\| < \delta(\varepsilon) \rightarrow \|x(t) - x^*\| < \varepsilon$$

for all $t > t_0$ We use the linearisation method to prove local stability of the system. On the other, hand if the equilibrium point of $Df(x^*)$ is nonhyperbolic, then the linearisation process does not give enough information about the stability of the equilibrium point. We then apply the lyapunov function as described below.
Let the function $V$ be a continuous function defined as$V : \mathbb{R}^n \rightarrow \mathbb{R}$ . If $V$ satisfies the hypotheses in 2.8.2, then it is a Lyapunov function

**Theorem 2.8.2** *Let* E *be an open subset of* $\mathbb{R}^n$ *containing* $x^*$ . *Suppose that* $f \in C^1(\mathrm{E})$ *and that* $f(x^*) = 0$ . *Suppose further that there exists a real valued function* $V \in C^1(\mathrm{E})$ *satisfying* $V(x^*) = 0$ *and* $V(x) > 0$ *if* $x \neq x^*$. *Then*

- $\dot{V}(x) \leqslant 0$ *for all* $x \in \mathrm{E}$, $x^*$ *is stable;*
- $\dot{V}(x) < 0$ *for all* $x \in \mathrm{E}\backslash\{x^*\}$, $x^*$ *is asymptotically stable;*
- $\dot{V}(x) > 0$ *for some* $x \in \mathrm{E}\backslash\{x^*\}$, $x^*$ *is unstable.*

A lyapunov function is demanding to construct, but once one is constructed and satisfies the first two conditions of Theorem 2.8.2, then the associated steady state of the dynamical system is stable. In addition, lyapunov like functions have been applied to prove persistence and permanence of the population in both epidemiological and ecological models. An instance of this application to prove persistence of solution is illustrated with the model in the next chapter.

### 2.8.2 Sensitivity Analysis

The parameter values and assumptions of any model are subject to variation and error. It is a technique for systematically varying parameters in a model to determine the effects of such changes. Sensitivity analysis as the assessment of the impact of changes input values on a model output. Sensitivity analysis assists to build confidence in the model by studying the uncertainty associated with parameters in the model. This is because many parameters in the system dynamics models characterize quantities that are very difficult or even impossible to measure accurately in the real world. It helps the modeller to comprehend dynamics of the system under study. In general, modellers carry out sensitivity analysis so as to establish which input parameters contribute the most to output variability. It also facilitates model development, verification and validation. In a given independent variable will impact on a specific dependent variable when the variable is a differentiable function of the parameter and its sensitivity index may be expressed using partial derivatives (Saltelli et al., 2004).

**Definition 2.8.4** *The sensitivity index of a variable z, that depends on differentiability on a parameter v, is defined as:*

$$\varepsilon_v^z = \frac{\partial z}{\partial v} \times \frac{v}{z}$$

Therefore sensitivity indices of $R_0$ with respect to a parameter $v$ can be defined as;

$$\varepsilon_v^{R_0} = \frac{\partial R_0}{\partial v} \times \frac{v}{R_0}$$

Sensitivity analysis provides valid tools for characterizing the uncertainty of parameters with respect to a model, in other words how uncertainties impact on a model. It is vital, because good modeling practice demand that modeling provides an evaluation of the confidence in the model. It also offers the importance, the strength and relevance of the inputs in determining the variation in the output of the model (Saltelli et al., 2004).

### 2.8.3 Optimal control method

Optimal control theory has been a powerful mathematical technique obtained from the calculus of variation and is very important in decision making with respect to complex situations, such as biological, finance, economics, ecology and many more. The behavour of a dynamical system is explained by the state variable(s). The assumption is that there is a way to control the state variable(s) $x$ say, by acting upon it with a suitable control. Thus the dynamics of the system (state $x$ ) depends on the control $u$. The ultimate goal is to adjust control $u$ to minimize or maximize a given objective functional, $J(u(t), x(t), t)$ that attains the desired goal and the required cost to achieving it. The optimal solution is then achieved when the most desired goal is determined with least cost. The functional depends on the control and the state variables. There are a number of different methods for computing the optimal control for specific model. Pontryagins Maximum Principle for instance, allows the calculation of the optimal control for an ordinary differential equations model system with given constraints. In (Lenhart et al., 2007: Morton et al., 1991), other powerful optimal control techniques have been established for partial differential equations and difference equations.

### 2.8.4 The general optimal control

The optimal control problems of the form is considered
$J(x(t), u(t), t) = \min \left\{ \phi(t_f, x(t_f) + \int_0^{t_f} g(t, x(t), u(t))dt) \right\}$. Here, $t \in \Re$ denotes the independent variable, called time, for T $= [0, \infty)$
where

$$x(t) = [x_1(t), x_2(t), ..., x_n(t)]^T \in \Re^n$$

a $n$ vector of state variables $x_i(t)$. These explain the state of the system at any

point in time, and

$$u(t) = [u_1(t), u_2(t), ..., u_m(t)]^T \in \Re^m$$

is a $m$ - vector of control variables at any point in time. These are the choice variables in the optimization problem. The dynamics of the state variables are ordered by the set of first order ordinary differential equations which have been described $(1 \leq i \leq n)$:

$$\frac{dx_i}{dt} = f_i(t, x(t), u(t)); x_0 = x(0), 0 \leq i \leq n$$

The functions:

$$f_i : \mathrm{T} \times \Re^n \times \Re^m \to \Re$$

,

$$g_i : \mathrm{T} \times \Re^n \times \Re^m \to \Re$$

and

$$\phi : \mathrm{T} \times \Re^n \to \Re$$

are continuously differentiable given each component of $x$ and $u$ ( where relevant), and piecewise continuous with respect to $t$. In the case where $f_1$ does not depend explicitly on $t$, the system is called autonomous. These functions $u(t)$ then belong to a certain class of admissible functions.

**Definition 2.8.5** *A piecewise continuous control $u(.)$ , defined on some time interval $t_0 \leq t \leq t_f$ , with range in the control region $U$ ,*

$$u(t) \in U, \qquad \forall t \in [t_0, t_f],$$

*is said to be an admissible control.*

### 2.8.5 Pontryagins Maximum Principle

This principle stipulates that the optimization problem $J(u(t), x(t), t)$ can be solved using Hamiltonian function $H$ over one period. That is, the principle converts the maximization/minimization of the objective functional, $J$ , coupled with the state variable into maximizing/minimizing pointwise the Hamiltonian with respect to the control

**Theorem 2.8.3** *Following Lenhert et al., (2007) in order that* $u^*(t)$ *and* $x^*(t)$ *be optimal for problem, it is necessary that there exist a piecewise differential adjoint variable* $\lambda(t)$*, where for all* $0 \leq t \leq \mathrm{T}$ *we have* $\lambda(t) \neq 0$ *such that for every* $0 \leq t \leq \mathrm{T}$

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t))$$

*for all controls at each time* $t$*, where the Hamiltonian* $H$ *is*

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

*and*

$$\frac{\lambda(t)}{dt} = \frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}$$

$$\lambda(t_f) = 0$$

Necessary conditions

If $u^*(t)$ and $x^*(t)$ are optimal, then the following condition hold:

$$\frac{\lambda(t)}{dt} = \frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}$$

$$\lambda(t_f) = 0,$$

$$\frac{\partial H(t, x*(t), u^*(t), \lambda(t))}{\partial u} = 0$$

Sufficient conditions

If all the functions $f_i$ and $g$ are jointly convex with respect to $x$ and $u$ and if $\lambda_i(t) \geq 0$ for $i$ all $t$ and all then jointly with the stated necessary conditions, we have a set of sufficient conditions for optimality.

Here $\lambda(t)$ is the shadow price or co-state variable. This represents the increase of the objective function due to marginal increase of the state variable. At any time the decision maker can apply the control variable to generate direct contributions to the objective function (represented by the term $f(t, x(t), u(t), \lambda(t))$ in the Hamiltonian), or can use the control variable to change the value of the state variable in order to generate contributions to the objective function in the future. These indirect contributions are measured by the term $\lambda(t)g(t, x(t), u(t))$ in the Hamiltonian. In conclusion, the next chapter, we shall develop and analyze an SIR model to elucidate the transmission dynamics of Bruruli ulcer disease, which is a knowledge gab to be filled.

### 2.8.6 Descartes rule of signs

Descartes rule of signs is a method for determining the number of positive or negative real roots of a polynomial. Suppose that $P(x)$ is a polynomial written in descending powers of $x$ such that

$$P(x) = a_n x^n + x_{n-1}x^{n-1} + x_{n-2}x^{n-2} + ... + a_0 \tag{2.3}$$

with coefficients $a_n, a_{n-1}, a_{n-2}, ..., a_0$ all real $\bar{M}$ be the number of sign change between consecutive non zero coefficient $a_n, a_{n-1}, a_{n-2}, ..., a_0$. The Descartes rule of sign says that the number of positive real zeros of $P$ does not exceed the number of sign changes $\bar{M}$ of 2.3. For example consider a polynomial

$$a_3x^3 + a_2x^2 - a_1x + a_0 = 0 \tag{2.4}$$

where $a_i s$ are positive. There are two sign changes in the sequence of coefficients, which shows that polynomial 2.4 has at most two positive real roots. The number of negative roots is the number of changes after substituting the negation of the variable for the variable itself. So for this example, the polynomial becomes

$$-a_3x^3 - a_2x^2 - a_1x^1 + a_0 = 0 \tag{2.5}$$

Since there is one change of sign then there is one negative root. The rule gives us an upper bound number of positive or negative roots of a polynomial but does not tell the exact number of positive or negative real roots. For example if the polynomial has three changes of signs, then it has one or three positive roots. This means that one may not be sure of how many positive roots the polynomial exactly has, that is whether it has one or three.

# CHAPTER 3

# A HOST VECTOR EPIDEMIOLOGICAL MODEL OF BURULI ULCER DISEASE TRANSMISSION DYNAMICS

## 3.1 Introduction

The main concern now is to develop a mathematical model on the transmission of Buruli ulcer to meet the aims and objectives in Section 1.3. In this chapter, the model is formulated and the basic properties are determined. The steady states are determined and analysed for their stability. Parameter estimation and sensitivity analysis are given in this chapter. Numerical results on the behavour of the model are also presented.

## 3.2 The model and its analysis

### 3.2.1 Model formulation

Based on the described transmission dynamics of the Buruli ulcer in Chapter two, a constant human population is considered $N_H(t)$, the vector population of water bugs $N_V(t)$ and the fish population $N_F(t)$ at any time $t$. The total human population is divided into three epidemiological subclasses of those that are

susceptible $S_H(t)$, the infected $I_H(t)$ and the recovered $R_H(t)$.

Total population of vector (water bug) at any time $t$ is divided into two subclasses to susceptible water bugs $S_V(t)$ and those that are infectious and can transmit the buruli ulcer to humans, $I_V(t)$. The total population reservoir of small fish is also divided into two compartments of susceptible fish $S_F(t)$ and infected fish $I_F(t)$. The role of environment is also considered by introducing a compartment $U$, representing the density of *M. ulcerans* in the environment. The following basic assumptions are made:

1. *Mycobacterium ulcerans* are transferred only from vector ( water bug) to the humans.

2. There is homogeneity of human, water bug and fish populations' interactions.

3. Infected humans recover and can be re-infected with *Mycobacterium ulcerans* again. We thus have loss of immunity.

4. Fish are preyed on by the water bugs.

5. Susceptible host (human population) can be infected through biting by an infectious vector (water bug). We represent the effective biting rate that an infectious vector has to susceptible host as $\beta_H$ and the incidence of new infections transmitted by water bugs is expressed by standard incidence rate $\beta_H \frac{S_H I_V}{N_H}$. One can interpret $\beta_H$ as the product of the biting frequency of the water bugs on humans, density of water bugs per human, the probability that a bite will result in an infection and the efficacy of the IEC strategy. In particular we can set $\beta_H = (1-\epsilon)\tau\alpha\beta_H^*$, where $\epsilon \in (0,1)$ is the efficacy of the IEC strategy, $\tau$ the number of water bugs per human host, $\alpha$ the biting frequency (the biting rate of humans by a single water bug) and $\beta_H^*$ the probability that a bite will produce an infection.

6. Susceptible water bugs are infected at a rate $\beta_V \frac{S_V I_F}{N_V}$ through predation of

infected fish and $\eta_v \beta_V \frac{S_V U}{K}$ representing other sources in the environment. Here $\eta_V$ differentiates the infectivity potential of the fish from that of the environment.

7. Since fish prey on infected water bugs, susceptible fish are infected at a rate $\beta_F \frac{S_F I_V}{N_F}$ through predation of infected fish and $\eta_F \beta_F \frac{S_F U}{K}$ representing infection through the environment. Here $\eta_F$ is a modification parameter that models the relative infectivity of fish from that of the environment.

8. The vector population and the fish populations are assumed to be constant. The growth functions are respectively given by $g(N_V)$ and $g(N_F)$. Without loss of generality, we can assume that the growth functions are given by

$$g(N_V) = \mu_V N_V \quad \text{and} \quad g(N_F) = \mu_F N_F.$$

   It is important to note that logistic functions can be chosen as growth functions for richer dynamics. In this work we however assume that the growth functions are linear.

9. There is a proposed hypothesis that environmental mycobacteria in the bottoms of swamps may be mechanically concentrated by small water-filtering organisms such as microphagous fish, snails, mosquito larvae, small crustaceans, and protozoa. We thus assume that fish increase the environmental concentrations of *Mycobacterium ulcerans* at a rate $\sigma_F$.

10. Aquatic bugs release bacteria into the environment at a rate $\sigma_V$.

11. The model does not include a potential route of direct contact with the bacterium in water.

12. The birth rate of the human population is directly proportional to the size of the human population.

The possible interrelations between humans, the water bug and fish are represented by the schematic diagram below as depicted from Figure 4.1.

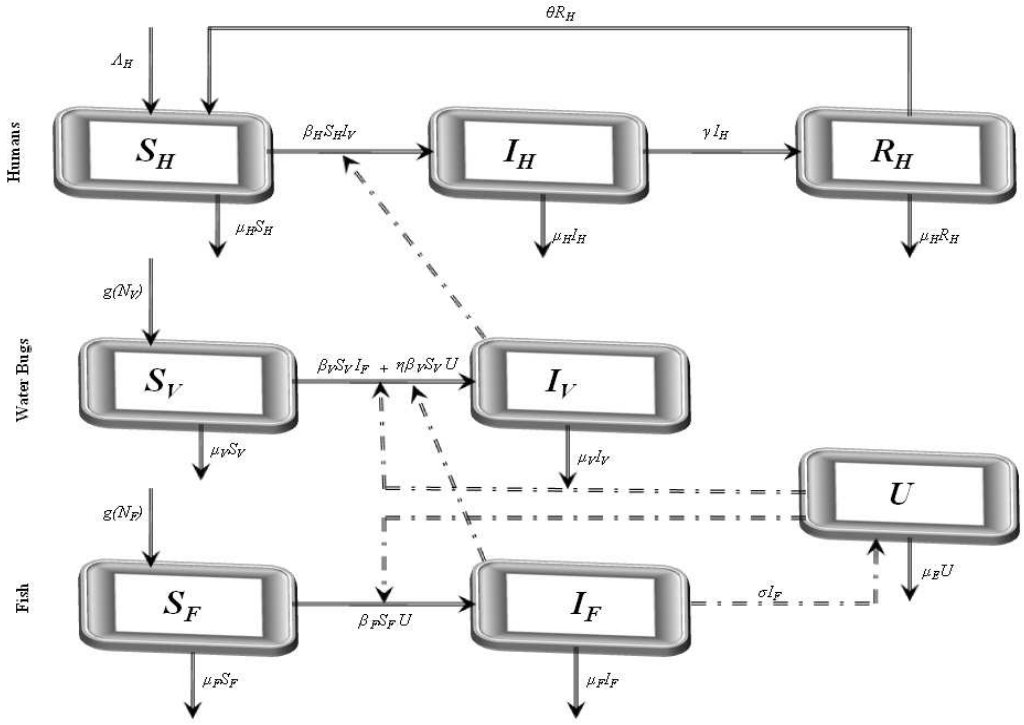



Figure 3.1: Proposed transmission dynamics of the Buruli ulcer among fish, the water bug, humans and density of $MU$ in a environment.

The descriptions of the parameters that describe the flow rates between compartments are given in Table 3.1.

Table 3.1: Description of parameters used in the model.

| Symbol | Description |
|---|---|
| $\beta_H$ | The effective contact rate between the vector and susceptible humans |
| $\beta_V$ | The effective contact rate between fish and susceptible vectors |
| $\beta_F$ | The effective contact rate between the susceptible fish and *Mycobacterium ulcerans* |
| $\gamma$ | The recovery rate of infected humans |
| $\theta$ | Loss of immunity of recovered humans |
| $\mu_H$ | Natural mortality rate/birth rate of the human population |
| $\mu_V$ | Natural mortality rate of the vector population |
| $\mu_F$ | Natural mortality rate of the fish population |
| $r_V$ | The growth rate of the vector population |
| $r_F$ | The growth rate of the fish population |
| $K$ | The environmental carrying capacity of the bacteria population |
| $\sigma$ | Rate of shedding of *Mycobacterium ulcerans* into the environment |
| $\mu_E$ | Rate at which *Mycobacterium ulcerans* naturally die in the environment. |
| $\eta$ | Relative infectivity parameter. |

The dynamics of the Buruli ulcer can be described by the following set of nonlinear differential equations:

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \mu_H N_H + \theta R_H - \beta_H \frac{S_H I_V}{N_H} - \mu_H S_H, \\
\frac{dI_H}{dt} &= \beta_H \frac{S_H I_V}{N_H} - (\mu_H + \gamma) I_H, \\
\frac{dR_H}{dt} &= \gamma I_H - (\mu_H + \theta) R_H, \\
\frac{dS_V}{dt} &= \mu_V N_V - \beta_V \frac{S_V I_F}{N_V} - \eta \beta_V \frac{S_V U}{K} - \mu_V S_V, \\
\frac{dI_V}{dt} &= \beta_V \frac{S_V I_F}{N_V} + \eta \beta_V \frac{S_V U}{K} - \mu_V I_V, \\
\frac{dS_F}{dt} &= \mu_F N_F - \beta_F \frac{S_F U}{K} - \mu_F S_F, \\
\frac{dI_F}{dt} &= \beta_F \frac{S_F U}{K} - \mu_F I_F, \\
\frac{dU}{dt} &= \sigma I_F - \mu_E U.
\end{aligned}\right\} \tag{3.1}$$

We assume that all the model parameters are positive and the initial conditions of the model system (3.1) are given by

$$\begin{aligned} S_H(0) &= S_{H0} > 0, I_H(0) = I_{H0} \geq 0, R_H(0) = R_{H0} = 0,\ S_V(0) = S_{V0} > 0, \\ I_V(0) &= I_{V0} \geq 0,\ S_F(0) = S_{F0} > 0,\ I_F(0) = I_{F0} \geq 0 \quad \text{and} \quad U(0) = U_0 > 0. \end{aligned}$$

We make arbitrarily scale the time $t$, with the quantity $\frac{1}{\mu_V}$ by letting $\tau = \mu_V t$. We therefore introduce the following dimensionless parameters;

$\tau = \mu_V t,\ \beta_h = \dfrac{\beta_H}{\mu_V},\ \mu_h = \dfrac{\mu_H}{\mu_V},\ \theta_h = \dfrac{\theta}{\mu_V},\ \gamma_h = \dfrac{\gamma}{\mu_V},\ m_1(N_H, N_V) = \dfrac{N_H}{N_V}$ , $\beta_v = \dfrac{\beta_V}{\mu_V}$,
$m_2(N_V, N_F) = \dfrac{N_F}{N_V},\ \mu_f = \dfrac{\mu_F}{\mu_V},\ \beta_f = \dfrac{\beta_F}{\mu_V},\ \sigma_e = \dfrac{\sigma}{\mu_V}$.
So, system (3.1) can be non dimensionalised by setting

$$s_h = \frac{S_H}{N_H},\ i_h = \frac{I_H}{N_H}, r_h = \frac{R_H}{N_H},\ i_v = \frac{I_V}{N_V},\ s_f = \frac{S_F}{N_F},\ i_f = \frac{I_F}{N_F} \text{ and } u = \frac{U}{K}.$$

It is more convenient to maintain the capitalised subscripts so that we can still write $s_h,\ i_h,\ i_v,\ i_f$ and $u$ as $S_H,\ I_H,\ I_V,\ I_F$ and $U$.

Given that $S_H + I_H + R_H = 1,\ S_V + I_V = 1,\ S_F + I_F = 1$ and $0 \leq U \leq 1$, system

(3.1) can be reduced to the following system of equations:

$$\left.\begin{aligned}
\frac{dS_H}{d\tau} &= (\mu_h + \theta_h)(1 - S_H) - \theta_h I_H - m_1\beta_h S_H I_V, \\
\frac{dI_H}{d\tau} &= m_1\beta_h S_H I_V - (\mu_h + \gamma_h) I_H, \\
\frac{dI_V}{d\tau} &= m_2\beta_v(1 - I_V) I_F + \eta\beta_v(1 - I_V)U - I_V, \\
\frac{dI_F}{d\tau} &= \beta_f(1 - I_F)U - \mu_f I_F, \\
\frac{dU}{d\tau} &= \tilde{\sigma} I_F - \mu_e U,
\end{aligned}\right\} \tag{3.2}$$

where $\tilde{\sigma} = \dfrac{\sigma_e N_F}{K}$.

### 3.2.2 Basic properties

Note that $\dfrac{dU}{d\tau} = \tilde{\sigma} I_F - \mu_e U \leq \tilde{\sigma} - \mu_e U$. We can thus easily obtain $U \leq \dfrac{\tilde{\sigma}}{\mu_e}$. The feasible region (the region where the model makes biological sense) for the system (3.2) is in $\mathbb{R}^5_+$ and is represented by the set

$$\begin{aligned}
\Omega = \Big\{ &(S_H, I_H, I_V, I_F, U) \in \mathbb{R}^5_+ | S_H, I_H, I_V, I_F, U \geq 0, 0 \leq S_H + I_H \leq 1, 0 \leq I_V \leq 1, \\
&0 \leq I_F \leq 1, 0 \leq U \leq \frac{\tilde{\sigma}}{\mu_e} \Big\},
\end{aligned}$$

where the basic properties of local existence, uniqueness and continuity of solutions are valid for the Lipschitzian system (3.2). The populations described in this model are assumed to be constant over the modelling time. The solutions of system (3.2) starting in $\Omega$ remain in $\Omega$ for all $\tau > 0$. Thus , $\Omega$ is positively invariant and it is sufficient to consider solutions in $\Omega$.

### 3.2.3 Positivity of solutions

We desire to show that for any non-negative initial conditions of system (3.2), say $(S_{H0}, I_{H0}, I_{V0}, I_{F0}, U_0)$, the solutions remain non-negative for all $t \in [0, \infty)$. A prove is made that all the state variables remain non-negative and the solutions of the system (3.2) with positive initial conditions will remain positive for all $\tau > 0$. The following lemma are stated.

**Lemma 3.2.1** *Given that the initial conditions of system (3.2) are positive, the solutions*
$S_H(\tau),\ I_H(t),\ I_V(\tau),\ I_F(\tau)$ *and* $U(\tau)$ *are non-negative for all* $\tau > 0$.

**Proof** Assume that

$$\hat{\tau} = \sup\{\tau > 0 : S_H > 0, I_H > 0, I_V > 0, I_F > 0, U > 0\} \in (0, \tau].$$

Thus $\hat{\tau} > 0$, and it follows directly from the first equation of the system (3.2) that

$$\frac{dS_H}{d\tau} \leq (\mu_h + \theta_h) - [(\mu_h + \theta_h) + \lambda]S_H, \text{ where } \lambda = m_1\beta_h I_H > 0.$$

We thus have

$$\frac{d}{d\tau}\left[S_H(\tau)\exp\left\{(\mu_h + \theta_h)\tau + \int_0^\tau \lambda(s)ds\right\}\right] \leq (\mu_h + \theta_h)\exp\left[(\mu_h + \theta_h)\tau + \int_0^\tau \lambda(s)ds\right].$$

Hence

$$S_H(\hat{\tau})\exp\left[(\mu_h + \theta_h)\hat{\tau} + \int_0^{\hat{\tau}} \lambda(s)ds\right] - S(0) \leq \int_0^{\hat{\tau}} (\mu_h + \theta_h)\exp\left[(\mu_h + \theta_h)\hat{\tau} + \int_0^{\hat{\tau}} \lambda(w)dw\right] d\hat{\tau},$$

so that

$$S_H(\hat{\tau}) \leq S(0)\exp\left[-\left((\mu_h+\theta_h)\hat{\tau}+\int_0^{\hat{\tau}}\lambda(s)ds\right)\right]+\exp\left[-\left((\mu_h+\theta_h)\hat{\tau}+\int_0^{\hat{\tau}}\lambda(s)ds\right)\right]\times \left[\int_0^{\hat{\tau}}(\mu_h+\theta_h)\exp\left((\mu_h+\theta_h)\hat{\tau}+\int_0^{\hat{\tau}}\lambda(w)dw\right)d\hat{\tau}\right]. \quad (3.3)$$

The right hand side of (3.2) is clearly positive. Thus the solution $S_H(\tau)$ will thus be always positive.

From the second equation of (3.2),

$$\frac{dI_H}{d\tau} \geq -(\mu_h+\gamma_h)I_H,$$
$$\Rightarrow I_H \geq I_{H0}\exp -(\mu_h+\gamma_h)\tau > 0.$$

Similarly, it can be shown that $I_V(\tau) > 0,\ I_F(\tau) > 0$ and $U(\tau) > 0$ for all $\tau > 0$, and this completes the proof.

## 3.3 Steady states and the model reproduction number

In this section, the equilibrium points are solved by setting the left hand side of system non - linear equations (3.2) to zero. This direct calculation shows that system (3.2) always has a disease free equilibrium point

$$\mathcal{E}_{\mathbf{0}} = (1,0,0,0,0),$$

and a unique endemic equilibrium $\mathcal{E}_{\mathbf{1}} = (S_H^*, I_H^*, I_V^*, I_F^*, U^*)$ in $\Omega$, which is obtained by considering five equation of the system (3.2), we analyse the model by examining the equilibrium points. Equating the equations of the system (3.2) to zero, we have the system of equations 3.3.

$$
\begin{aligned}
0 &= (\mu_h + \theta_h)(1 - S_H^*) - \theta_h I_H^* - m_1 \beta_h S_H^* I_V^*, \\
0 &= m_1 \beta_h S_H^* I_V^* - (\mu_h + \gamma_h) I_{H,}^* \\
0 &= m_2 \beta_v (1 - I_V^*) I_F^* + \eta \beta_v (1 - I_V^*) U^* - \mu_v I_V^*, \\
0 &= \beta_v (1 - I_F^*) U^* - \mu_f I_F^*, \\
0 &= \tilde{\sigma} I_F^* - \mu_e U^*.
\end{aligned} \tag{3.4}
$$

The state variables of the model of the system (3.2) are computed where

$$
\begin{aligned}
S_H^* &= \frac{(\mu_h + \gamma_h)(\mu_h + \theta_h)[\mu_e \mu_f \Phi_V (\mathcal{R}_b - 1) + \tilde{\sigma} \mu_e \beta_f]}{\mu_e \mu_f \Phi_V \Phi_H (\mathcal{R}_b - 1) + \tilde{\sigma} \mu_e \beta_f (\mu_h + \gamma_h)(\mu_h + \theta_h)}, \\
I_H^* &= \frac{m_1 \beta_h \mu_e \mu_f \Phi_V (\mu_h + \theta_h)(\mathcal{R}_b - 1)}{\mu_e \mu_f \Phi_V \Phi_H (\mathcal{R}_b - 1) + \tilde{\sigma} \mu_e \beta_f (\mu_h + \gamma_h)(\mu_h + \theta_h)}, \\
I_V^* &= \frac{\mu_e \mu_f \Phi_V (\mathcal{R}_b - 1)}{\mu_e \mu_f \Phi_V (\mathcal{R}_b - 1) + \tilde{\sigma} \mu_e \beta_f}, \\
I_F^* &= 1 - \frac{1}{\mathcal{R}_b}, \\
U^* &= \frac{\beta_f}{\mu_f} (\mathcal{R}_b - 1),
\end{aligned}
$$

with $\mathcal{R}_b = \dfrac{\tilde{\sigma} \beta_f}{\mu_e \mu_f}$, $\Phi_V = \beta_v(\eta\tilde{\sigma} + m_2\mu_e)$ and $\Phi_H = (m_1\beta_h + \mu_h)[\theta_h\gamma_h + (\mu_h + \theta_h + \gamma_h)]$. On the existence of the endemic equilibrium the following results are obtained:

**Theorem 3.3.1** *System (3.2) has a unique endemic equilibrium $\mathcal{E}_\mathbf{1}$ when $\mathcal{R}_b > 1$.*

### 3.3.1 The reproduction number

It is important to note that $\mathcal{R}_b$ is the reproduction number. A reproduction number, usually defined as the average of the number of people infected by an index case in a naive population, is a key threshold parameter that determines whether a disease persists or vanishes in a population. Using the next generation operator method (Diekmann et al., 1990; Van den Driessche et al., 2002), we

denote $\mathbf{F}$ and $\mathbf{V}$ respectively as matrices for the new infections generated and the transition terms we obtain

$$\mathbf{F} = \begin{pmatrix} 0 & m_1\beta_h & 0 & 0 \\ 0 & 0 & m_2\beta_v & \eta\beta_v \\ 0 & 0 & 0 & \beta_f \\ 0 & 0 & \tilde{\sigma} & 0 \end{pmatrix} \quad \text{and} \quad \mathbf{V} = \begin{pmatrix} \mu_h + \gamma_h & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & \mu_f & 0 \\ 0 & 0 & 0 & \mu_e \end{pmatrix}.$$

The basic reproduction number $\mathcal{R}_0$ is given as the spectral radius of the matrix $\mathbf{FV}^{-1}$ so that

$$\mathcal{R}_0 = \rho(\mathbf{FV}^{-1}) = \sqrt{\frac{\tilde{\sigma}\beta_f}{\mu_e\mu_f}} = \sqrt{\mathcal{R}_b}.$$

It is noticed that $\mathcal{R}_b$ does not depend on the human and vector populations. So, the infection is driven by the fish population and the density of the bacterium in the environment. The model reproduction number increases linearly with the shedding rate of the *Mycobacterium ulcerans* into the environment and the effective contact rate between fish and *Mycobacterium ulcerans*. It decreases with increasing removal rates of the fish and *Mycobacterium ulcerans*. So the control of the ulcer depends largely on environmental management. (Oluwasanmi et al., 1976; Duker et al., 2006; Asiedu et al., 2000)

### 3.3.2 Stability of the disease free equilibrium

**Theorem 3.3.2** *The disease free equilibrium $\mathcal{E}_\mathbf{0}$ whenever it exists, is locally asymptotically stable if $\mathcal{R}_b < 1$ and unstable otherwise.*

**Proof** The Jacobian matrix of system (3.2) at the equilibrium point $\mathcal{E}_\mathbf{0}$ is given

by

$$J_{\mathcal{E}_0} = \begin{pmatrix} -(\mu_h + \theta_h) & -\theta_h & -m_1\beta_h & 0 & 0 \\ 0 & -(\mu_h + \gamma_h) & m_1\beta_h & 0 & 0 \\ 0 & 0 & -1 & m_2\beta_v & \eta\beta_v \\ 0 & 0 & 0 & -\mu_f & \beta_f \\ 0 & 0 & 0 & \tilde{\sigma} & -\mu_e \end{pmatrix}.$$

It can be seen that the three of the eigenvalues of $J_{\mathcal{E}_0}$ are $\vartheta = -(\mu_h + \theta_h) < 0,\ \vartheta = -(\mu_h + \gamma_h) < 0,\ \vartheta = -1 < 0$ while other two eigenvalues are solutions of the equation

$$\begin{vmatrix} -\mu_f & \beta_f \\ \tilde{\sigma} & -\mu_e \end{vmatrix}$$

$$= A_0\upsilon^2 + B_0\upsilon + C_0 = 0,$$

where the coefficients $A_0, B_0$ and $C_0$ are given by

$$\begin{aligned} A_0 &= 1, \\ B_0 &= (\mu_f + \mu_e), \\ C_0 &= \mu_f\mu_e(1 - R_b), \\ &\quad \mu_f\mu_e(1 - R_b) > 0, \quad \text{if} R_b < 1. \end{aligned}$$

Obviously, $\mathcal{R}_b < 1$ all the eigenvalues of $\mathcal{E}_0$ are negative and we can therefore conclude, based on Routh Hurwitz criterion, that the DFE is locally stable.

### 3.3.3 Global Stability of the Disease Free Steady State

In this section, global stability of the disease free equilibrium is proved $\mathcal{E}_0$ when $\mathcal{R}_b \leq 1$

**Theorem 3.3.3** *The disease free equilibrium point* $\mathcal{E}_\mathbf{0}$ *whenever it exists, is globally asymptotically stable if* $\mathcal{R}_b < 1$ *when all solutions of system* (3.2) *in* $\mathbb{R}^5$ *are bounded.*

**Proof** The proof entails that a suitable Lyapunov function is chosen by taking into account the infective classes of the nonlinear ordinary differential equations of the system (6.12).

$$\mathcal{L}(t) = a_1 I_H + a_2 I_V + a3 I_F + a_4 U, \tag{3.5}$$

where the non-negative constants $a_1, a_2, a_3$ and $a_4$ are to be determined. We note that the Lyapunov function $\mathcal{L}(t) \in C^1$ and is positive definite for all points in $\Omega$ except $\mathcal{E}_\mathbf{0}$ (Perko, 2001). The time derivative of equation (4.10) is

$$\begin{aligned}
\dot{\mathcal{L}} &= a_1 \dot{I}_H + a_2 \dot{I}_V + a3 \dot{I}_F + a_4 \dot{U}, \\
&= a_1[m_1 \beta_h S_H I_V - (\mu_h + \gamma_h) I_H] + a_2[m_2 \beta_v (1 - I_V) I_F + \eta \beta_v (1 - I_V) U - I_V] \\
&\quad a_3[\beta_f (1 - I_F) U - \mu_f I_F] + a_4[\tilde{\sigma} I_F - \mu_e U], \\
&\leq (a_1 m_1 \beta_h S_H - a_2) I_V - a_1(\mu_h + \gamma_h) I_H + (a_2 m_2 \beta_v - a_3 \mu_f + a_4 \tilde{\sigma}) I_F \\
&\quad + (a_2 \eta \beta_v + a_3 \beta_f - a_4 \mu_e) U.
\end{aligned}$$

By taking the coefficients of $I_H, I_V$ and $U$ equal to zero we have $a_1 = a_2 = 0$ and $a_4 = \frac{\beta_f}{\mu_e} a_3$. So

$$\dot{\mathcal{L}} \leq \mu_f a_3 \left( \frac{\beta_f \tilde{\sigma}}{\mu_e \mu_f} - 1 \right) = \mu_f a_3 \left( \mathcal{R}_p - 1 \right).$$

When $\mathcal{R}_p \leq 1$, $\dot{\mathcal{L}}$ is negative semidefinite, with equality at the disease free equilibrium and/or at $\mathcal{R}_p = 1$. So, the largest compact invariant set in $\Omega$ such that $\dot{\mathcal{L}} \leq 0$ when $\mathcal{R}_p \leq 1$ is the singleton $\mathcal{E}_\mathbf{0}$. Therefore by the LaSalle Invariance Principle (LaSalle, 1976) the disease free equilibrium point $\mathcal{E}_\mathbf{0}$ is globally asymptotically stable if $\mathcal{R}_p < 1$ and unstable otherwise.

### 3.3.4 Stability of the endemic equilibrium

The local geometric properties of the endemic equilibrium of system (3.2) is now investigated. We have the following theorem:

**Theorem 3.3.4** *If $\mathcal{R}_b > 1$, the endemic equilibrium point $\mathcal{E}_\mathbf{1}$ of system (3.2), is locally asymptotically stable.*

**Proof** The Jacobian matrix of system (3.2) is considered so that

$$J_{\mathcal{E}_\mathbf{1}} = \begin{pmatrix} -(\mu_h+\theta_h) - m_1\beta_h I_V^* & -\theta_h & -m_1\beta_h S_H^* & 0 & 0 \\ m_1\beta_h I_V^* & -(\mu_h+\gamma_h) & m_1\beta_h S_H^* & 0 & 0 \\ 0 & 0 & -d & m_2\beta_v(1-I_V^*) & \eta\beta_v(1-I_V^*) \\ 0 & 0 & 0 & -\beta_f U^* - \mu_f & \beta_f(1-I_F^*) \\ 0 & 0 & 0 & \tilde{\sigma} & -\mu_e \end{pmatrix}.$$

where $d = \beta_v(m_2 I_F^* + \eta U^*) + 1$.

The eigenvalues of $J_{\mathcal{E}_\mathbf{1}}$ are

$$\begin{aligned} \nu_1 &= -d, \\ \nu_{2,3} &= \frac{-b \pm \sqrt{b^2 - 4[(\mu_h+\gamma_h)((\mu_h+\theta_h) + m_1\beta_h I_V^*) + \theta_h m_1\beta_h I_V^*]}}{2}, \\ \nu_{4,5} &= \frac{-c \pm \sqrt{c^2 - 4(\mathcal{R}_b - 1)\mu_e\beta_F^2 U^*/\mu_f}}{2}, \end{aligned}$$

where $b = (\mu_h+\theta_h) + (\mu_h+\gamma_h) + m_1\beta_h I_V^*$ and $c = \mu_e + \mu_f + \beta_f U^*$.

Clearly, $\nu_2$ and $\nu_3$ both have negative real parts.This is because $b^2 - 4ac$ under the square root sign in $\nu_2$ and $\nu_3$ produce small positive value and when added to or subtracted from negative b and divided by 2 always yield two negative values. Similar situation is also observed in $\nu_4$ and $\nu_5$. If $\mathcal{R}_b > 1$ then $\nu_4$ and $\nu_5$ both also have negative real parts. Therefore $\mathcal{E}_\mathbf{1}$ is locally asymptotically stable if $\mathcal{R}_b > 1$.

**Theorem 3.3.5** *The endemic equilibrium point $\mathcal{E}_\mathbf{1}$ of system (3.2), is globally asymptotically stable.*

**Proof** The global stability of the endemic equilibrium, can be determined by constructing a Lyapunov function $\mathcal{V}(t)$ such that

$$\begin{aligned}\mathcal{V}(t) &= S_H - S_H^* - S_H^* \ln \frac{S_H}{S_H^*} + A\left(I_H - I_H^* - I_H^* \ln \frac{I_H}{I_H^*}\right) + B\left(I_V - I_V^* - I_V^* \ln \frac{I_V}{I_V^*}\right) \\ &\quad + C\left(I_F - I_F^* - I_F^* \ln \frac{I_F}{I_F^*}\right) + D\left(U - U^* - U^* \ln \frac{U}{U^*}\right). \end{aligned} \tag{3.6}$$

The corresponding time derivative of $\mathcal{V}(t)$ is given by

$$\begin{aligned}\dot{\mathcal{V}} &= \left(1 - \frac{S_H^*}{S_H}\right)\dot{S}_H + A\left(1 - \frac{I_H^*}{I_H}\right)\dot{I}_H + B\left(1 - \frac{I_V^*}{I_V}\right)\dot{I}_V \\ &\quad + C\left(1 - \frac{I_F^*}{I_F}\right)\dot{I}_F + D\left(1 - \frac{U^*}{U}\right)\dot{U}. \end{aligned} \tag{3.7}$$

At the endemic equilibrium, we have the following relations

$$\begin{aligned}\mu_h + \theta_h &= (\mu_h + \theta_h)S_H^* + \theta_h {I^*}_H + m_1\beta_h S_H^* I_V^*, \\ \mu_h + \gamma_h &= m_1\beta_h \tfrac{S_H^* I_V^*}{{I^*}_H}, \\ 1 &= m_2\beta_v\left(1 - I_V^*\right)\tfrac{I_F^*}{{I^*}_V} + \eta\beta_v\left(1 - I_V^*\right)\tfrac{U^*}{{I^*}_V}, \\ \mu_f &= \beta_f\left(1 - I_F^*\right)\tfrac{U^*}{I_F^*}, \\ \mu_e &= \tilde{\sigma}\tfrac{I_F^*}{U^*}. \end{aligned} \tag{3.8}$$

The relations (3.8) is employed to evaluate the components of the time derivative of the Lyapunov function which help to determine the gobal stabilty of system (3.2). This leads the following

$$\begin{aligned}\dot{\mathcal{V}} &= \left(1 - \frac{S_H^*}{S_H}\right)\left[(\mu_h + \theta_h)S_H^*\left(1 - \frac{S_H}{S_H^*}\right) + \theta_h I_H^*\left(1 - \frac{I_H}{I_H^*}\right) + m_1\beta_h S_H^* I_V^*\left(1 - \frac{S_H I_V}{S_H^* I_V^*}\right)\right] \\ &\quad + A\left(1 - \frac{I_H^*}{I_H}\right)\left[m_1\beta_h S_H^* I_V^*\left(\frac{S_H I_V}{S_H^* I_V^*} - \frac{I_H}{I_H^*}\right)\right] + B\left(1 - \frac{I_V^*}{I_V}\right)\left[m_2\beta_v I_F^*\left(\frac{I_F}{I_F^*} - \frac{I_V}{I_V^*}\right)\right. \\ &\quad \left. + m_2\beta_v I_F^* I_V\left(1 - \frac{I_F}{I_F^*}\right) + \eta\beta_v U^*\left(\frac{U}{U^*} - \frac{I_V}{I_V^*}\right) + \eta\beta_v U^* I_V\left(1 - \frac{U}{U^*}\right)\right] \\ &\quad + C\left(1 - \frac{I_F^*}{I_F}\right)\left[\beta_f U^*\left(\frac{U}{U^*} - \frac{I_F}{I_F^*}\right) + \beta_f U^* I_F\left(1 - \frac{U}{U^*}\right)\right] \\ &\quad + D\left(1 - \frac{U^*}{U}\right)\left[\tilde{\sigma}{I_F}^*\left(\frac{I_F}{I_F^*} - \frac{U}{U^*}\right)\right]. \end{aligned} \tag{3.9}$$

Let

$$v = \frac{S_H}{S_H^*}, \quad w = \frac{I_H}{I_H^*}, x = \frac{I_V}{I_V^*}, y = \frac{I_F}{I_F^*} \quad \text{and} \quad z = \frac{U}{U^*}. \tag{3.10}$$

Substituting (3.10) into (3.9), we obtain

$$\dot{\mathcal{V}} = -(\mu_h + \theta_h) S_H^* \frac{(1-v)^2}{v} + \mathcal{H}(v, w, x, y, z), \tag{3.11}$$

where

$$\begin{aligned}
\mathcal{H} = {} & \theta_h I_H^* \left(1 - w - \frac{1}{v} + \frac{w}{v}\right) + m_1 \beta_h S_H^* I_V^* \left(1 - \frac{1}{v} - x + \frac{x}{v}\right) \\
& + A m_1 \beta_h S_H^* I_V^* \left(1 + xv - w - \frac{vx}{w}\right) + B m_2 \beta_v I_F^* \left(1 + y - x - \frac{x}{v}\right) \\
& + B m_2 \beta_v I_F^* {I^*}_V x \left(x + y - xy - 1\right) + B \eta \beta_v U^* \left(1 + z - x - \frac{z}{x}\right) \\
& + B \eta \beta_v U^* {I^*}_V x \left(x + z - xz - 1\right) + C \beta_f U^* \left(1 + z - y - \frac{z}{y}\right) \\
& + C \beta_f U^* {I^*}_F y \left(y + z - yz - 1\right) + D \tilde{\sigma} {I_F}^* \left(1 + y - z - \frac{y}{z}\right).
\end{aligned} \tag{3.12}$$

Next, $A, B, C$ and $D$ are chosen so that none of the variable terms of $\mathcal{H}$ are positive. The chosen of the letters depend on the expression obtained after some algebraic manipulations. It is important to group together the terms in $\mathcal{H}$ that involve the same state variable terms, as well as grouping all of the constant terms together. So it can be shown that $\mathcal{H} < 0$ by expanding (3.12), writing out the constant term and the coefficients of the variable terms such as $v, w, x, y, z, \frac{1}{v}, \frac{w}{v}, \frac{x}{v}$ and so on. The only variable terms that appear with positive coefficients are $x, y$ and $z$. The Lyapunov coefficients is chosen so as to make the coefficients of $x, y$ and $z$ equal to zero.The reason is to eventually ensure that $\mathcal{H} < 0$. Therefore, this is obtained

$$A = 1, B = \frac{m_1 \beta_h S_H^* I_V^*}{m_2 \beta_v I_V^* (1 - I_F^*) + \eta \beta_v U^* (1 - I_V^*)}$$

The coefficients $C$ and $D$ can similarly be evaluated from the coefficients of $y$ and

$z$. Note that expressions such as

$$m_1\beta_h S_H^* I_V^* \left(2 - \frac{1}{v} - \frac{xv}{w}\right)$$

emanating from the substitution of the coefficients into $\mathcal{H}$, are less than or equal to zero by the arithmetic mean-geometric mean inequality. This is achieved by grouping like terms of the expression in $\mathcal{H}$ which clearly showed less than or equal to zero . This implies that $\mathcal{H} \leq 0$ with equality only if $\frac{S_H}{S_H{}^*} = \frac{I_H}{I_H{}^*} = \frac{I_V}{I_V{}^*} = \frac{I_F}{I_F{}^*} = \frac{U}{U^*} = 1$.

**Theorem 3.3.6** *If a function V (x) is positive definite on the entire state space, and has the additional property that* $|V(x)| \to \infty$ *as* $\|x\| \to \infty$*, and if its derivative V is negative definite on the entire state space, then the equilibrium point at the origin is globally asymptotically stable.*

Therefore, $\dot{\mathcal{V}} \leq 0$ and by the LaSalle's Extension(LaSalle's, 1976), it implies that the omega limit set of each solution lies in an invariant set contained in $\Omega$. The only invariant set contained in $\Omega$ is the singleton $\mathcal{E}_1$. This shows that each solution which intersects $\mathbb{R}_+^5$ limits to the endemic equilibrium and that trivial equilibrium is globally asymptotically stable in the invariant feasible region. This completes the proof.

### 3.3.5 Persistence of the Model

Persistence with a constant flow $\Phi_t$ defined on some set E $\subset \Omega_1$ such that the boundary of E is invariant under the flow $\Phi_t$, has extensive applications in modelling of dynamical behaviour of ecological and epidemiological entities (Magal, 2009; Thieme, 2000 ). Persistence conveys some idea that for interacting populations none of the constituent populations becomes extinct (Butler and Waltman, 1986; Freedman and Ruan, 1995). According to Freedom et al., (1994), persistence criteria have been analysed using Lyapunov-like functions and

analysing the flow on the boundary of E

**Theorem 3.3.7** *The solution to the model system 3.2 is persistent whenever,* $\mathcal{R}_b > 1$.

Before Theorem 3.3.7 is proved, the definition of persistence of the solution of system 3.2 is considered.

**Definition 3.3.1** *The system of equations (3.2) is said to be uniformly persistent if there is an* $\varpi > 0$ *(independent of the initial data) such that every solution of the model* $(S_H(t), I_H(t), I_V(t), I_F(t), U(t))$ *with some initial conditions* $(S_{H0}, I_{H0}, I_{V0}, I_{F0}, U_0)$ *satisfies*

$$\liminf_{t\to\infty} I_H(t) \geq \varpi, \liminf_{t\to\infty} I_V(t) \geq \varpi,$$
$$\liminf_{t\to\infty} I_F(t) \geq \varpi, \liminf_{t\to\infty} U(t) \geq \varpi.$$

**Proof** ( Theorem 3.3.7) To show persistence of the solution , the notion of dynamics of a Euclidean space is taken into consideration. Let $\Omega_1$ be a locally compact metric space with metric $d$ and let $\mathrm{E}_1$, the endemic state be any subset of 1 with boundary $\partial\mathrm{E}_1$ and the interior of $\mathrm{E}_1$, A $\overset{\circ}{\mathrm{E}}_1$. Suppose we have a continuous flow $\Phi_t$ defined on $\mathrm{E}_1$, such that $\partial\mathrm{E}_1$ is invariant under $\Phi(t)$. The flow $\Phi_t$ is said to be point dissipative in $\mathrm{E}_1$ if for each $x \in \mathrm{E}_1$ , $\omega(x) \neq \Phi$ and the invariant set

$$\Omega(\Phi(t)) = \cup_{x\in\mathrm{E}_1}\omega(x)$$

has a compact closure.

If we define the $\omega$ limit set of $\mathrm{E}_1$ as

$$\omega(\mathrm{E}_1) = \bigcap_{T\geq 0} \text{Closure} \cup_{t\geq T} \Phi(t)\mathrm{E}_1,$$

where

$$\Phi(t)\mathrm{E}_1 = \bigcap_{x\in\mathrm{E}_1} \{\Phi(t)x\}$$

Equivalently, this means that $y \in \omega(x)$ if and only if there is a sequence $t_n \to \infty$ as $n \to \infty$ such that $\Phi(t)x \to y$ as $n \to \infty$. To demonstrate persistence of the model population, it is adequate to show that for all $x \in \overset{\circ}{\mathrm{E}_1}$

$$\liminf_{t\to 0} d(\Phi(t)x, \partial \mathrm{E}_1) > 0. \tag{3.13}$$

To show the boundary of $\mathrm{E}_1$, we suppose that the disease persistent equilibrium is globally stable and use a suitable Lyapunov function;

$$Z = \sum_{i=0}^{4} B_i \left(1 - x_i^* - x_i^* In \frac{x_i}{x_i^*}\right),$$

where $x_i$ for $i = 1...4,$, stand for $I_H, I_V, I_F$ and $U$ respectively. We also observe that

$$\frac{\partial Z}{\partial x_i} = B_i \left(1 - \frac{x_i^*}{x_i}\right), \frac{\partial^2 Z}{\partial x_i^2} > 0.$$

Hence, $\mathrm{E}_1^* = (x_1^*, x_2^*, x_3^*, x_4^*)$ is the minimum. Suppose that

$$\liminf_{t\to\infty} I_H(t) \geq \varpi_h, \liminf_{t\to\infty} I_V(t) \geq \varpi_v,$$
$$\liminf_{t\to\infty} I_F(t) \geq \varpi_f, \liminf_{t\to\infty} U(t) \geq \varpi_u.$$

If we let $\mathrm{E}_1^*$ be the boundary of $\Omega_1$ as $t \to \infty$, then the solutions of $\mathrm{E}_1$ do not escape through the boundaries. Therefore, there exists some $\varpi = \min\{\varpi_h, \varpi_v, \varpi_f, \varpi_u\}$ such that

$\liminf_{t\to\infty} x_i(t) \geq \varpi$ for all $i = 1, 2, 3, 4$.

This completes the proof

## 3.4 Numerical simulations

### 3.4.1 Parameter Estimation

A fourth order Rung-Kutta numerical scheme is used to perform numerical simulations in Matlab. The aim is to validate some of the analytical results on the stability of the system (3.2). Some of the parameters to be used in the numerical simulations are estimated and detailed in (3.4.1). The biggest challenge in epidemic modeling, is the estimation of parameters in the model validation process. In this section, an attempt is made to endeavour to estimate some of the parameter values of system (3.2). For the purpose of these simulations, a hypothetical population for susceptible human, infected human, infected water bugs, infected fish and infected environment are considered. The initial data values for these populations are $0.75, 732/10000, 0.2, 0.2$ and $0.5$ respectively. The demographic parameters can however be easily be estimated from census population data. The mortality rate $\mu_h$ is initially estimated. A notice is made that the life expectancy of the human population is 60 years ( Population and Housing Census, 2012) . This translates into $\mu_h = 0.016$ per year or equivalently $4.5 \times 10^{-5}$ per day ( Population and Housing Census, 2012). The Buruli ulcer is currently regarded as a vector borne disease. Recovery rates of vector borne diseases range from $1.6 \times 10^{-5}$ to 0.5 per day (Rascalou et al., 2012).

The rate of loss of immunity $\theta_h$ for vector borne diseases range between 0 and $1.1 \times 10^{-2}$ per day (Rascalou et al., 2012). The mortality rate of the water bugs is assumed to be 0.15 per day (Aidoo et al., 2007). The same rate for water bug species is adopted because of the same species being studied

In this model, it is assumed that there more water bugs than humans so that $m_1 > 1$. Since the water bugs prey on the fish a reasonable food chain structure leads to the assumption that there are more fish than water bugs hence $m_2 > 1$. If the water bug is assumed to interact more with the environment than fish

then $\eta > 1$ otherwise $0 < \eta < 1$. The natural mortality of small fish in rivers is not well documented and data on the mortality of river fish in Ghana is not available. For the purpose of our simulations, an assumption is made that $3 \times 10^{-4} < \mu_f < 7 \times 10^{-4}$ per day. Given that $K \geq N_F$ we have $0 \leq \frac{N_F}{k} \leq 1$. Assuming that $\sigma_e < 1$ we have $0 < \hat{\sigma_e} < 1$. For this simulations, most of the parameters are estimated by initially guessing followed by least square estimates.Those parameters value that provide the best fit with least error are chosen for the simulations. The the remaining parameters are summarised in the 6.1.

Table 3.2: Parameter values used for the simulations and sensitivity analysis.

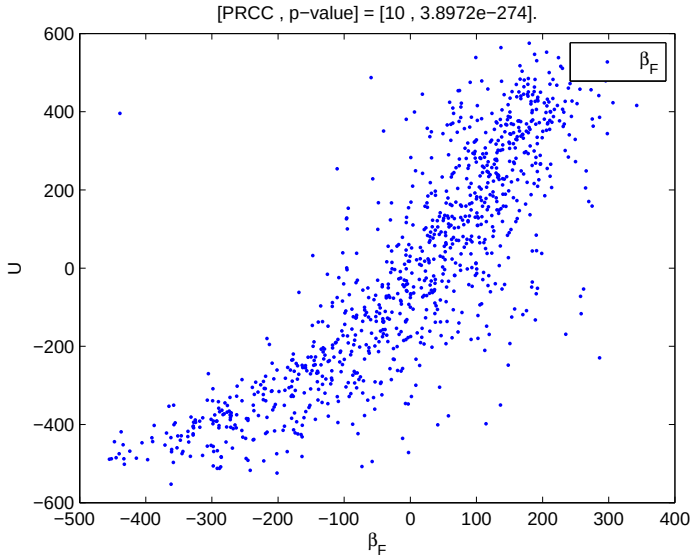
| Parameter | Value/Range | Source |
|---|---|---|
| $\mu_h$ | $4.5 \times 10^{-5}$ | (Population and House Census, 2012) |
| $\gamma_h$ | $1.6 \times 10^{-5} - 0.5$ | (Rascalou et al., 2012) |
| $\theta_h$ | $0 - 1.1 \times 10^{-2}$ | (Rascalou et al., 2012) |
| $m_1$ | $m_1 > 1$ | Estimated |
| $m_2$ | (0,1) | Estimated |
| $\beta_h$ | (0,1) | Estimated |
| $\beta_v$ | (0,1) | Estimated |
| $\eta$ | $\eta > 1$ | Estimated |
| $\beta_f$ | (0,1) | Estimated |
| $\mu_f$ | $3 \times 10^{-4} - 7 \times 10^{-5}$ | Estimated |
| $\tilde{\sigma}$ | (0,1) | Estimated |
| $\mu_e$ | (0,1) | Estimated |

### 3.4.2 Sensitivity Analysis

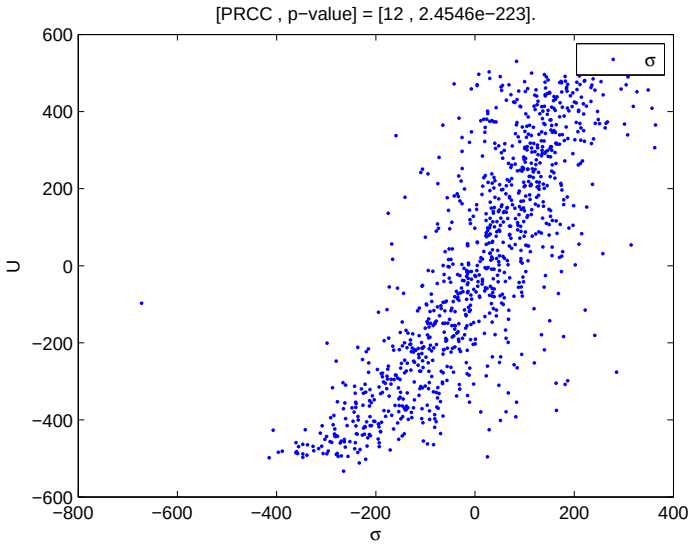
Many of the parameters used in this work are determined base on estimation techniques. Therefore, their accuracy maybe relatively little different from experimental data values. This can be overcome by observing responses of such parameters and their influence on the model. These can be established by through sensitivity and uncertainty analysis. In this subsection, the sensitivity analysis of the model parameters is presented to ascertain the degree to which the parameters affect the outputs of the model. The Partial Correlation Coefficients (PRCCs) of the parameters are determined. The parameters with negative PRCCs reduce the

severity of the BU epidemic while those with positive PRCCs aggravate it. Using Latin Hypercube Sampling (LHS) scheme with 1000 simulations for each run, with $U$ as the outcome variable, we will only have four significant parameters, whose scatter plots are shown in Figure 3.2.

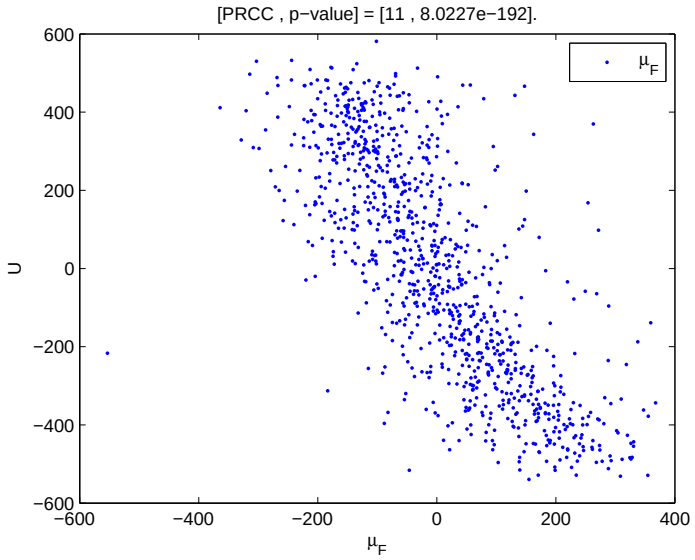
The observation is made that the parameters $\beta_f$ and $\sigma_e$ aggravate the BU epidemic while $\mu_f$ and $\mu_e$ reduce its severity. These results suggest that efforts to remove MU and infected fish from the environment will greatly reduce the epidemic although the later will be impracticable.



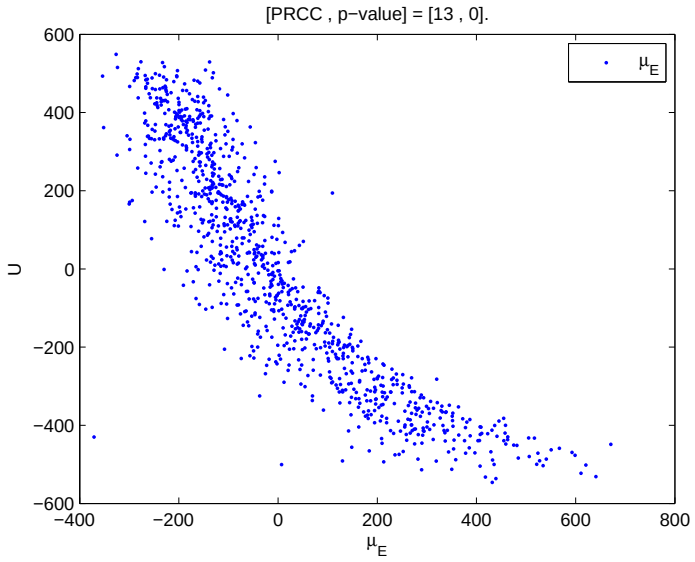

(a)




(b)




(c)

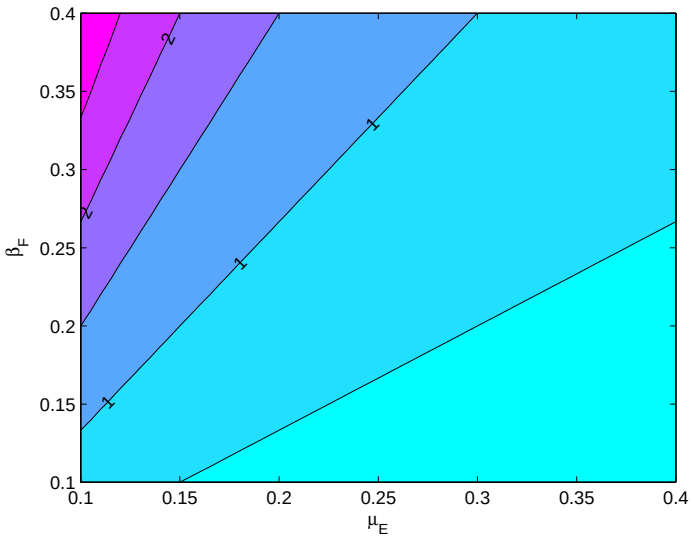



(d)

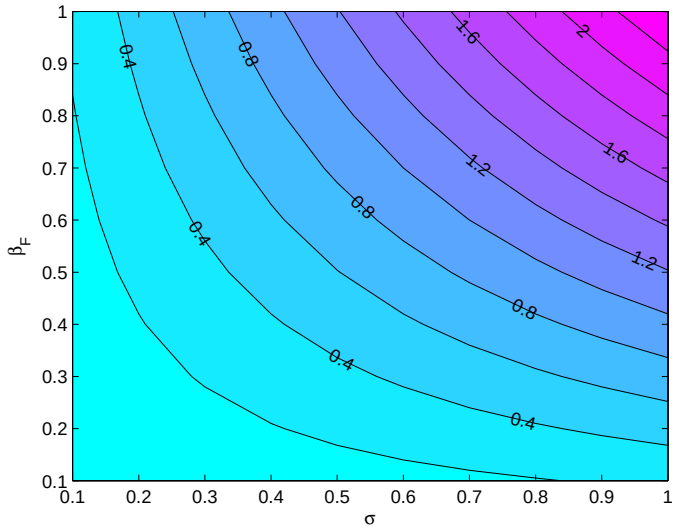
Figure 3.2: The PRCC plots for the parameters $\beta_f$,$\sigma_e$, $\mu_f$ and $\mu_e$.

The relationship between parameters that form the reproduction number can be investigated through contour plots. The relationship between $\beta_f$ and, $\mu_e$ and $\sigma_e$ are shown in Figures (3.3(a)) and Figure (3.3(b)). Figure (3.3(a)) shows that $\beta_f$ significantly increases $\mathcal{R}_p$ when compared to $\mu_f$, therefore any policy designed to curd the disease should focus at reducing the infection rate of the fish population. On the other hand $\beta_f$ and $\sigma_e$ equally influence $\mathcal{R}_p$. The increase leads to an increase in the BU epidemic. The fight against the disease should thus focus on the reduction of these two parameters. Note that $\mathcal{R}_p$ does not necessary influence

the dynamics in the human population. However $\mathcal{R}_p$ impacts the environment and the carriers of the bacteria. In fact $\mathcal{R}_p$ affects the fish population which in turn affect the water bugs that transmit the infection to the human population. Figures 3.4 and 3.5 show the phase diagrams of the prevalence of infected fish




(a)

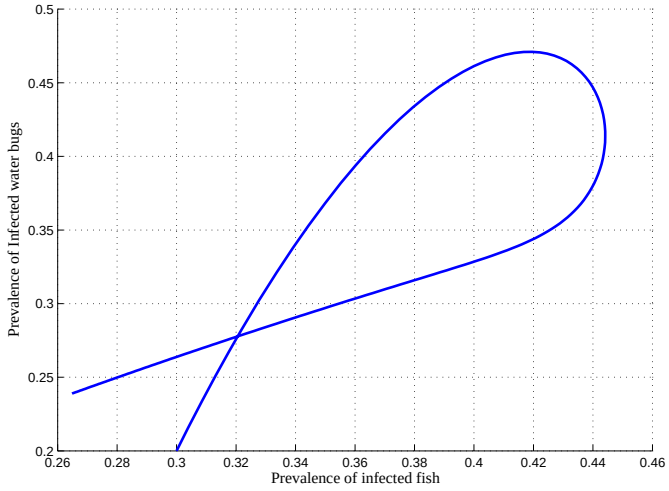



(b)

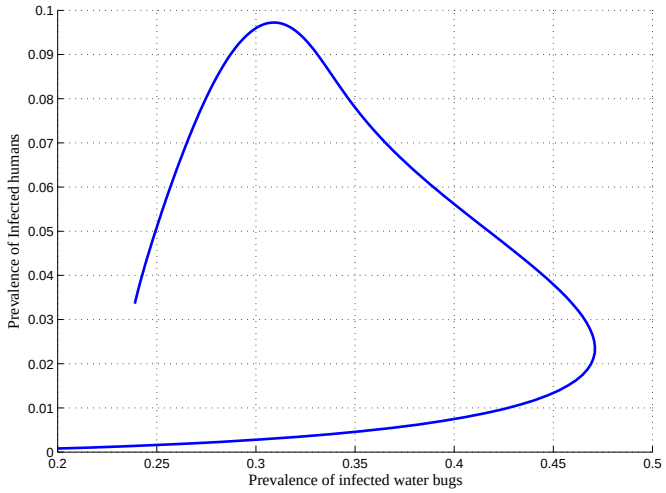
Figure 3.3: The contour plots for the parameters

and water bugs, infected water bugs and infected humans for $\mathcal{R}_p > 1$ and $\mathcal{R}_p < 1$ respectively. Figure 3.4(a) shows that infected fish aid the growth of infected water bugs at the beginning of the epidemic. After the peak of the epidemic the infected water bugs decrease as infected fish decrease.

A similar pattern is observed for water bugs and infected humans in Figure 3.4(b). However in Figure 3.4(b), if the fraction of infected water bugs is above a certain threshold, in this case 0.32 for the chosen set of parameter values, then the number of infected humans increases during the course of the epidemic.



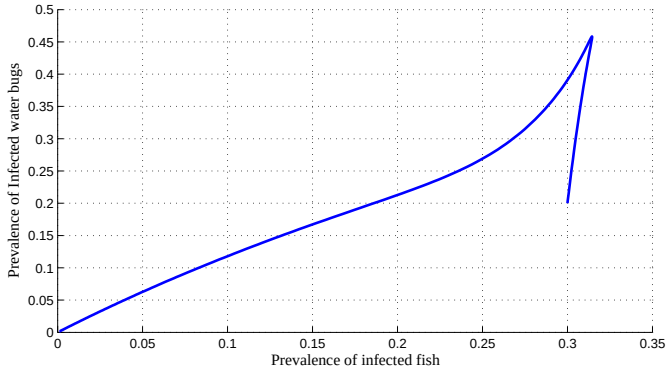

(a)



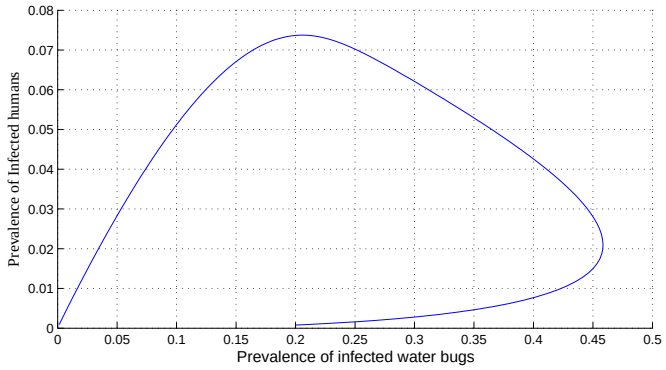

(b)

Figure 3.4: A phase plots of the infected populations for $\mathcal{R}_p = 1.1619$.

Figure 3.5(a) show that as the prevalence of infected fish decreases, that of the infected water bugs decreases as long as $\mathcal{R}_p < 1$. However, Figure 3.5(b) shows that infected humans increase as long as there are enough infected water bugs to sustain the infection. For the given parameter values, the fraction of water bugs must be above 0.2 to sustain the infection in the human population and thereafter decreases to zero.




(a)




(b)

Figure 3.5: A phase plots of the infected populations for $\mathcal{R}_p = 0.6364$.

Figures 3.6, 3.7 and 3.8 show the changes in the prevalence of infected fish, water bugs and humans respectively when $\tilde{\sigma}$, the shading rate of MU in the environment is varied. A simulated was made on prevalence of infected fish by varying $\sigma_e$ for four instances. The parameter has greater influence on the fish population. For instance of when $\mathcal{R}_p = 1.1619$, if $\sigma_e$ is increased by 11% the prevalence of infected fish increases by 28% while the prevalence of infected water bugs increases by 25%. . By increasing $\sigma_e$ values the $\mathcal{R}_p$ also increases for both prevalence in fish and

water bugs. For instance, when $\sigma_e = 0.12$ the $\mathcal{R}_p = 1.3416$. Similarly, when $\sigma_e = 0.1619$ the $\mathcal{R}_p = 1.3416$ for both prevalence of infected fish and water bug. It is however, observed in Figure 3.8 that $\sigma_e$ has no significant impact in the long term dynamics of the BU with regards to the prevalence of the human population but it impacts the size is the peak during an out break of an epidemic. From the first peak to the second peak, $\mathcal{R}_p$ increase by 45% and the corresponding increase in the prevalence of infected humans in 43%.

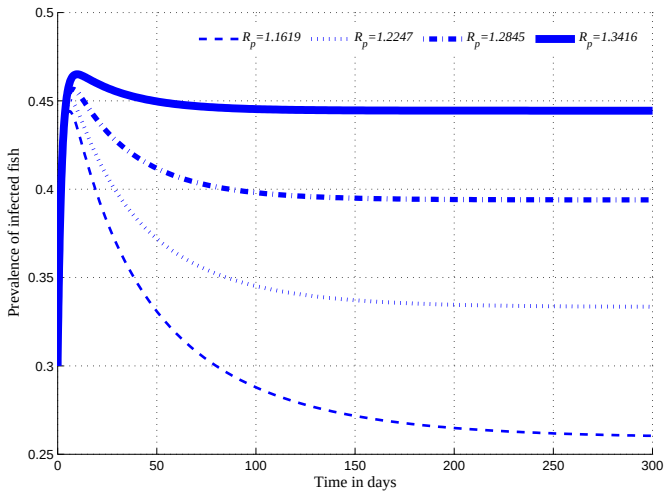



Figure 3.6: The prevalence of infected fish when $\sigma_e$ is varied. The values of the reproduction number are depicted for each curve for $\sigma_e = 0.09, \sigma_e = 0.1$, $\sigma_e = 0.11$ and $\sigma_e = 0.12$.

Figure 3.6 is the plot of prevalence of infected fish against time in days . Figure 3.6 is obtained by varying $\sigma_e$ and keeping all other parameters constant. The respective reproduction numbers for each situation are recorded. This was analysed in matlab software. Similarly, Figure 3.7 depicts the graph of prevalence of water bugs against time in days. The simulation is done by varying $\sigma_e$ and keeping all other parameters constants at the same time recording reproduction numbers for each variation. Finally, Figure 3.8 indicates the prevalence in humans against time in days. Similar simulations is done by varying $\sigma_e$ and keeping all parameters constant.

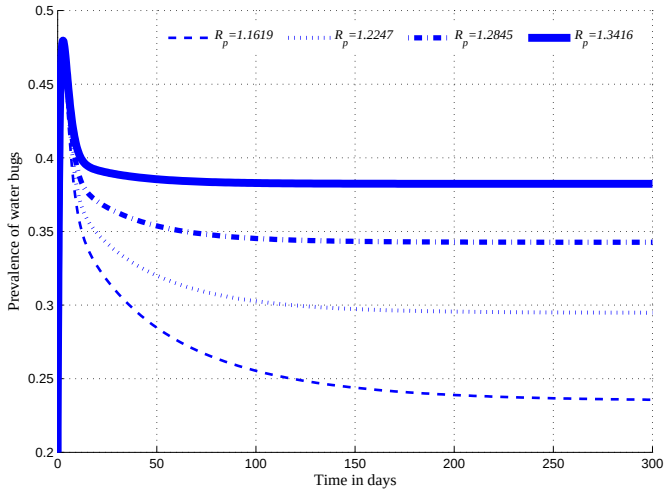



Figure 3.7: The prevalence of the infected water bugs when $\sigma_e$ is varied. The values of the reproduction number are depicted for each curve for $\sigma_e = 0.09, \sigma_e = 0.1,\ \sigma_e = 0.11$ and $\sigma_e = 0.12$.

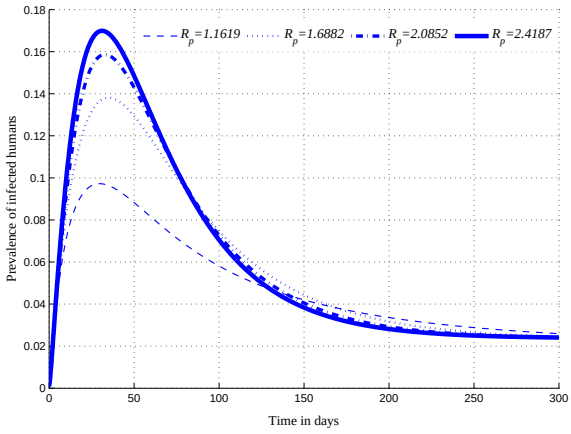



Figure 3.8: The prevalence the infected humans when $\sigma_e$ is varied. The values of the reproduction number are depicted for each curve for $\sigma_e = 0.09, \sigma_e = 0.19,\ \sigma_e = 0.29$ and $\sigma_e = 0.39$.

### 3.4.3 Data and the fitting process

One of the most important steps in the model building chronology is model validation. A focus is now made on the data provided by the Ashanti Regional Disease Control Office for BU cases in Ghana per 100,000 people. The data is given in the table below for the years 2003 to 2012.

Table 3.3: Data on BU cases in Ghana

| Year | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|
| BU Cases | 739 | 1159 | 1201 | 1096 | 1136 | 1300 | 1158 | 1428 | 1324 | 1292 |

We fit the model system (3.2) to the data of BU cases expressed as fractions. This fraction was done by using Matlab code to divide each dataset by $10^4$. The reason is to help obtain a good fit. We use the least squares curve fit routine (lsqcurvefit) in Matlab with optimisation to estimate the parameter values. Many parameters are known to lie within limits. Only a few parameters are known exactly, especially the demographic parameters and it is thus important to estimate the others. The process of estimating the parameters aims at finding the best concordance between computed and observed data. One tedious way to do it is by trial and error or by the use of software programs designed to find parameters that give the best fit. Here, the fitting process involves the use of the least squares-curve fitting method. A Matlab code is used where unknown parameter values are given a lower and upper bound from which the set of parameter values that produce the best fit are obtained.

### 3.4.4 Results

Figure 3.9 shows how system (3.2) fits to the available data on the incidence of the BU. The incidence solution curve shows a very reasonable fit to the data.
In planning for a long term response to the BU epidemic, it is important to have some reasonable projections to the epidemic. The fitting process allows us to envisage the BU epidemic in future. it is important to note that the projections

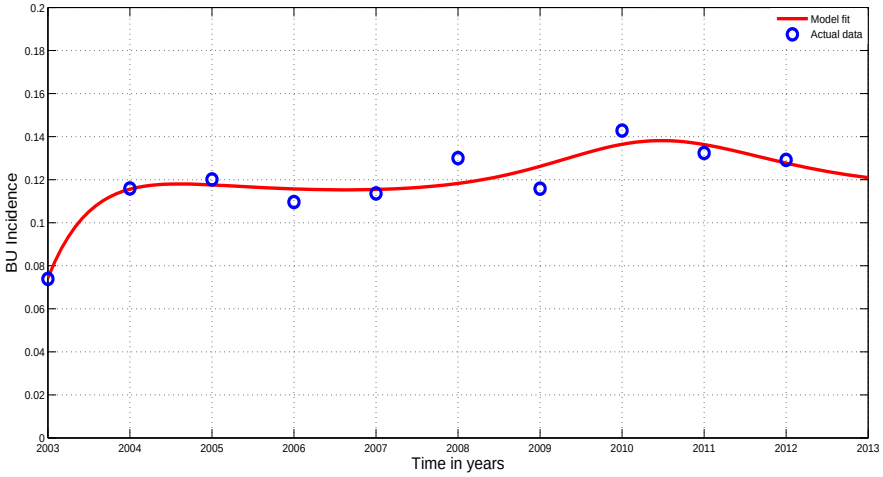



Figure 3.9: Model system (3.2) fitted to data of BU cases in Ghana. The circles indicate the actual data and the solid line indicates the model fit to the data.

are reasonably good over a short period of time since the current is evolving gradually based on the available data. We chose to project the epidemic beyond 5 years to 2017. Figure 3.10 shows the projected BU epidemic.

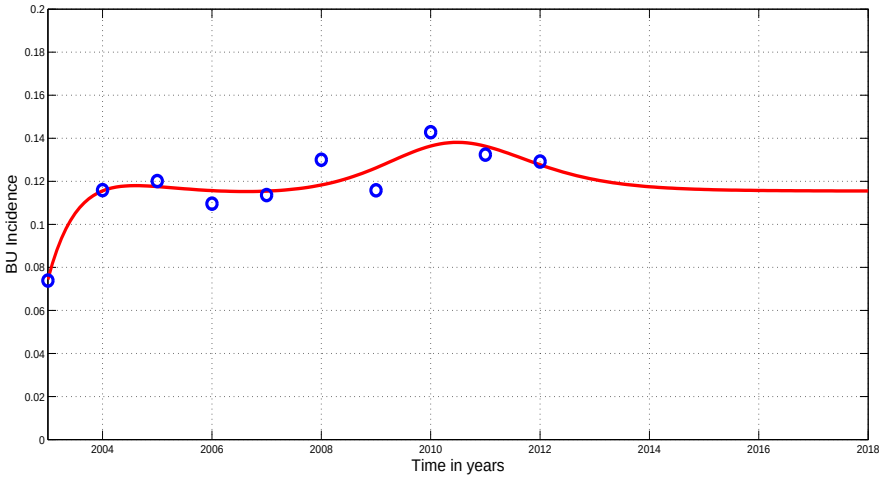



Figure 3.10: Projection to fit in Figure 3.9.

## 3.5 Summary

In this chapter, a deterministic model on the dynamics of the BU is presented. The model steady state are determined and the global stability of each steady state determined. The model has a global stable disease free equilibrium when $\mathcal{R}_p < 1$. The endemic equilibrium is found to be globally stable if $\mathcal{R}_p > 1$. We carried out a parameter estimation because not much of the disease is understood, parameter estimation was difficult. So we had to reasonably estimate some of the parameter using the fact that BU is a vector borne disease. Due to the estimation of essential parameters sensitivity analysis was necessary and very important to determine how these parameters influence the model. Through the simulation the variation of the prevalence of BU in the human population with time was determined for different values of $\mathcal{R}_p$. The study revealed that the values of $\mathcal{R}_p$ only impacts on at the initial phases of the epidemic. The changes of the prevalence of the fish and water bug population that carry the bacterial are also determined. The model is then fitted to data on the BU in Ghana. The model reasonably fits the data. The challenge in the fitting process was that the data appears to indicate that the BU has reached a steady state. This then produce some parameter values that appeared unreasonable. Despite these challenges, the fit produced reasonable projections on the future of the ulcer. The model shows that in the near future the number cases will not change if everything remains the same. The implications of varying some of the important epidemiological parameters such as the shedding rates was investigated. We found out that the management of BU depends mostly on the environmental management.

# CHAPTER 4

# INCLUSION OF TREATMENT IN BASIC MODEL FOR BURULI ULCER DISEASE TRANSMISSION

## 4.1 Introduction

For BU, the number of people admitted for treatment is limited due to the capacity of health care service, the cost of treatment, distance to the hospitals and health care facilities that are often few. The demand for the health services exceeds the capacity of provision (Stienstra et al., 2002: Agbenorku, 2011). The basic properties of the model is formulated and basic properties are established. The steady states of the model are studied. Parameter estimation and sensitivity analysis are given. Numerical results on the behavour of the model are also presented in this section.

## 4.2 Model formulation

### 4.2.1 Description

The transmission dynamics of the BU involves three populations: that of humans, water bugs and the M. ulcerans. Our model is thus a coupled system of two sub-models. The sub-model of the human population is an ($SITR$) type model, with $S_H$ denoting the susceptible humans, $I_H$ those infected with the BU, $T_H$ those in treatment and $R_H$ the recovered. The total human population is given by

$$N_H = S_H + I_H + T_H + R_H.$$

The sub-model of the water bugs and M. ulcerans has three compartments. The population of water bugs comprises of susceptible water bugs $S_W$ and the infected water bugs $I_W$. The total water bugs population is given by

$$N_W = S_W + I_W.$$

The third compartment $D$, is that of M. ulcerans in the environment whose carrying capacity is $K_d$. The possible interrelations between humans, the water bugs and environment are represented by the schematic diagram below. We

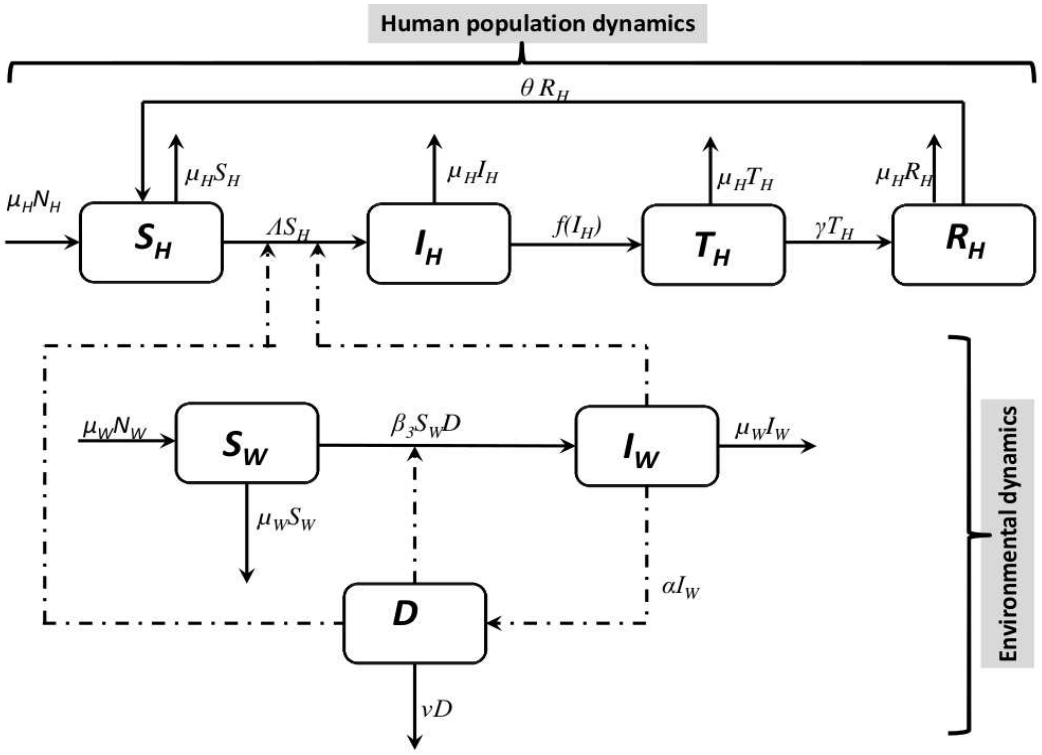



Figure 4.1: A schematic diagram for the model.

present the dynamics of the Buruli ulcer in the following set of nonlinear

differential equations:

$$\begin{aligned}
\frac{dS_H}{dt} &= \mu_H N_H + \theta R_H - \Lambda S_H - \mu_H S_H, && (4.1)\\
\frac{dI_H}{dt} &= \Lambda S_H - f(I_H) - u_H I_H, && (4.2)\\
\frac{dT_H}{dt} &= f(I_H) - (\mu_H + \gamma) T_H, && (4.3)\\
\frac{dR_H}{dt} &= \gamma I_H - (\mu_H + \gamma) R_H, && (4.4)\\
\frac{dS_W}{dt} &= \mu_W N_W - \beta_3 \frac{S_W D}{K_d} - \mu_W S_W, && (4.5)\\
\frac{dI_W}{dt} &= \beta_3 \frac{S_W D}{K_d} - \mu_W I_W, && (4.6)\\
\frac{dD}{dt} &= \alpha I_W - \mu_d \frac{D}{K_d}, && (4.7)
\end{aligned}$$

$$\begin{aligned}
S_H(0) &= S_{H0} > 0, I_H(0) = I_{H0} > 0, T_H(0) = T_{H0} > 0, R_H(0) = R_{H0} = 0, S_W(0) = S_{W0} > 0,\\
I_V(0) &= I_{V0}, D(0) = D_0 > 0.
\end{aligned}$$

where $\Lambda = \frac{\beta_1 I_W S_H}{N_H} + \frac{\beta_2 D S_H}{K_{50} + D}$ and $f(I_H)$ is a function that models saturation in treatment of BU. As in (Gao et al., 2011; Zhang et al., 2008), we also assume a saturation treatment function of the form

$$f(I_H) = \frac{\sigma I_H}{1 + I_H},$$

where $\sigma$ is the maximum treatment rate. A different function can, however, be chosen depending on the modelling assumptions. The saturation treatment describes the amount of service that can be made available to BU patients at all heath care facilities. In other words, the capacity at which health facilities can attend to BU patient in a given geographical environment. The parameters $\beta_1$ and $\beta_2$ are the effective contact rates of susceptible humans with the water bugs and the environment respectively. Here $\beta_1$ is the product of the biting frequency of the water bugs on humans, density of water bugs per human host and the probability that a bite will result in an infection. Also, $\beta_2$ is the product of

density of M. ulcerans per human host and the probability that a contact will result in an infection. For the purpose of this work, it is assumed that parameter $K_{50}$ gives the concentration of M. ulcerans in the environment that yield 50% chance of infection with BU. The 50% is chosen because the chance of infection with BU given other factors is not automatic (Portals, 2000). The function that models the interaction between humans and M. ulcerans has been used to model cholera epidemics (Mukandavire, 2011) and the references cited therein. We note that if BU cases are few then $f(I_H) \approx \sigma I_H$, which is a linear function assumed in many compartmental models incorporating treatment, see for instance (Nyabadza 2008; Marsollier et al., 2012) . On the other hand, if BU case are many, then $f(I_H) \approx \sigma$ a constant. So for very large values of $I_H$ the uptake of BU patients into treatment becomes constant, thus reaching a saturation level.

We now describe briefly, the dynamics of each equation of system (4.1)-(4.7): Equation (4.1) represents the dynamics of the susceptible population, for which a new susceptible enter at a rate of $\mu_H N_H$. BU sufferers do not recover with permanent immunity, they loose immunity at a rate $\theta$ and become susceptible again. The third term models the rate of infection of a susceptible and the last term describes the natural mortality of the susceptible. In this model, the human population is assumed to be constant over the modeling time with the birth and death rates being equal.

Equation (4.2) depicts changes in the infected BU cases. The first term represents individuals who enter from the susceptible pool driven by the force of infection $\Lambda$. The second term represents the treatment of BU cases modelled by the treatment function $f(I_H)$. The last term represents the natural mortality of infected humans.

Equation (4.3) models the human BU cases under treatment. In this regard, the first term represents the movement of BU cases into treatment and the second term with rates $\mu_H$ and $\gamma$ respectively, represents natural mortality and recovery. The fourth equation represents those individuals who would have recovered from

the infection after treatment. The first term denotes those who recover at a per capita rate $\gamma$ and the second term with rates $\mu_H$ and $\theta$ respectively represents the natural mortality and lose of immunity.

Equation (4.5) tracks susceptible water bugs. The first term is the recruitment of water bugs at a rate of $\mu N_W$. The second and third term model the infection rate of water bugs by M. ulcerans at the rate of $\beta_3$ and the natural mortality of the water bugs at a rate $\mu_W$. Equation (4.6) deals with infectious class of water bug population. The first term simply models the infection of water bugs and the second term models the natural mortality rate of infected water bugs at a rate $\mu_W$. The dynamics of M. ulcerans in the environment are modelled by the last equation. The first term models the shedding of M. Ulcerans by infected water bugs into the environment and the second term represents the removal of M. ulcerans from the environment at the rate $\mu_d$.

### 4.2.2 Non-dimensionalisation

Using the following substitutions:

$s_h = \frac{S_H}{N_H},\ i_h = \frac{I_H}{N_H},\ \tau_h = \frac{T_H}{N_H},\ r_h = \frac{R_H}{N_H},\ s_w = \frac{S_W}{N_W},\ i_w = \frac{I_W}{N_W},\ x = \frac{D}{K_d}$ and $m_1 = \frac{N_W}{N_H}$,

and given that $s_h + i_h + \tau_h + r_h = 1$, $s_w + i_w = 1$ and $0 \leq x \leq 1$, system (4.1)-(4.7) when decomposed into its sub-systems becomes;

$$\begin{cases} \frac{ds_h}{dt} = (\mu_H + \theta)(1 - s_h) - \theta(i_h + \tau_h) - \tilde{\Lambda} s_h, \\ \\ \frac{di_h}{dt} = \tilde{\Lambda} s_h - \frac{\sigma i_h}{1 + N_H i_h} - \mu_H i_h, \\ \\ \frac{d\tau_h}{dt} = \frac{\sigma i_h}{1 + N_H i_h} - (\mu_H + \gamma)\tau_h \end{cases} \tag{4.8}$$

$$\begin{cases} \frac{di_w}{dt} = \beta_3(1-i_w)x - \mu_W i_w, \\ \\ \frac{dx}{dt} = \tilde{\alpha} i_w - \mu_d x, \\ \\ \end{cases} \tag{4.9}$$

where $\tilde{\alpha} = \dfrac{\alpha N_W}{K_d}$, $\tilde{\Lambda} = \beta_1 m_1 i_w + \frac{\beta_2 x}{\tilde{K}+x}$ and $\tilde{K} = \frac{K_{50}}{K_d}$. Given that the total number of bites made by the water bugs must equal the number of bites received by the humans, $m_1(NW, NH)$ is a constant, see ( Garba et al., 2008).

## 4.3 Model analysis

The model has two sub-systems that are only coupled through infection. The analysis will thus focus on the dynamics of the environment first and then consideration is made on how these dynamics subsequently affect the human population. The properties of the overall system is considered before the decoupled system is examined.

### 4.3.1 Invariant Region

Since the model monitors changes in the populations of humans and water bugs, and the density of M. ulcerans in the environment, the model parameters and variables are non-negative. The biologically feasible region for the system (4.8)-(4.9) is in $\mathbb{R}^5_+$ and is represented by the set

$$\Gamma = \left\{ (s_h, i_h, \tau_h, i_w, x) \in \mathbb{R}^5_+ | 0 \leq s_h + i_h + \tau_h \leq 1, 0 \leq i_w \leq 1, 0 \leq x \leq \frac{\tilde{\alpha}}{\mu_d} \right\},$$

where the basic properties of local existence, uniqueness and continuity of solutions are valid for the Lipschitzian system (4.8)-(4.9). The populations described in this model are assumed to be constant over the modelling time. The positive invariance of $\Gamma$. can easily be established

**Lemma 4.3.1** *The solutions of the normalized model system (4.8)-(4.9) are contained in the region* $\Gamma \in \mathbb{R}^5_+$ *( Nyabadza, 2008).*

**Proof** We first show that all feasible solutions are uniformly-bounded in a proper subset of $\Gamma \in \mathbb{R}^5_+$. Let $\{s_h(t), i_h(t), \tau_h(t), i_w(t), x(t)\} \in \mathbb{R}^5_+$ non-negative initial conditions. From the normalised model system (4.8)-(4.9) we have

$$\frac{ds_h}{dt} = (\mu_H + \theta)(1 - s_h) - \theta(i_h + \tau_h) - \tilde{\Lambda} s_h,$$

Thus

$$\frac{ds}{dt} \leqslant \mu - \mu_H s_h$$

It then follows that

$$\frac{ds}{dt} + \mu_H s_h \leqslant \mu_H.$$

This is a first order homogeneous differential equation and applying Birkhoff and Rota's theorem on differential inequality as $t \to \infty$ yields

$$0 < s(t) \leqslant 1, \quad \forall t \geqslant 0.$$

$$\frac{ds_h}{dt} + \frac{di_h}{dt} + \frac{d\tau_h}{dt} = 0$$

meaning that

$$\frac{dn}{dt} = 0$$

Integrating on both sides leads

$$n = c$$

where $c$ is the constant of integration Since

$$n = s_h + i_h + \tau_h = 1$$

It follows that $c = 1$, indicating that the population is constant, positive and equal to 1. Given that $\frac{dx}{dt} = \tilde{\alpha} i_w - \mu_d x \leq \tilde{\sigma} - \mu_d x$, we have $x \leq \frac{\tilde{\alpha}}{\mu_d}$. The solutions of system (4.8)-(4.9) starting in $\Gamma$ remain in $\Gamma$ for all $t > 0$. The limit sets of system (4.8)-(4.9) are contained in $\Gamma$. It thus suffices to consider the dynamics of our system in $\Gamma$, where the model is epidemiologically and mathematically well posed.

### 4.3.2 Positivity of solutions

For any non-negative initial conditions of system (4.8)-(4.9), the solutions remain non-negative for all $t \in [0, \infty)$. Here, a prove is made that all the state variables remain non-negative and the solutions of the system (4.8)-(4.9) with positive initial conditions will remain positive for all $t > 0$. The following proposition is obtained.

**Proposition 4.3.2** *For positive initial conditions of system (4.8)-(4.9), the solutions $s_h(t)$, $i_h(t)$, $\tau_h(t)$, $i_w(t)$ and $x(t)$ are non-negative for all $t > 0$.*

**Proof** Assume that

$$\hat{t} = \sup \{t > 0 : s_h > 0, i_h > 0, \tau_h > 0, i_w > 0, x > 0\} \in (0, t].$$

Thus $\hat{t} > 0$, and it follows directly from the first equation of the sub-system (4.8) that

$$\frac{ds_h}{dt} \leq (\mu_H + \theta) - [(\mu_H + \theta) + \Lambda] s_h.$$

This is a first order differential equation that can easily be solved using an integrating factor. For a non-constant force of infection $\Lambda$, have

$$\begin{aligned} s_h(\hat{t}) &\leq s_h(0) \exp\left[ -\left( (\mu_H + \theta)\hat{t} + \int_0^{\hat{t}} \Lambda(s) ds \right) \right] \\ &+ \exp\left[ -\left( (\mu_H + \theta)\hat{t} + \int_0^{\hat{t}} \Lambda(s) ds \right) \right] \left[ \int_0^{\hat{t}} (\mu_H + \theta) e^{\left( (\mu_H + \theta)\hat{t} + \int_0^{\hat{t}} \Lambda(l) dl \right)} d\hat{t} \right]. \end{aligned}$$

Since the right hand side of sub-system (4.8) of of the first equation is always positive, the solution $s_h(t)$ will always be positive. If $\Lambda$ is constant, this result still holds.

From the second equation of sub-system (4.8),

$$\frac{di_h}{dt} \geq -(\mu_H + \sigma)i_h \geq i_h(0)\exp[-(\mu_H + \sigma)t] > 0.$$

The third equation of sub-system (4.8) yields

$$\frac{d\tau_h}{dt} \geq -(\mu_H + \gamma)\tau_h \geq \tau_h(0)\exp[-(\mu_H + \gamma)t] > 0.$$

The first equation of sub-system 4.9 leads

$$\frac{di_w}{dt} \geq -\mu_W i_w \geq i_w(0)\exp[-(\mu_W)t] > 0.$$

Finally, the last equation of the sub-system 4.9 gives

$$\frac{dx}{dt} \geq -\mu_d x \geq x(0)\exp[-(\mu_d)t] > 0.$$

and this completes the proof.

### 4.3.3 Environmental dynamics

The sub-system (4.9) represents the dynamics of water bugs and M. ucerans in the environment. From the second equation we have

$$x^* = \frac{\tilde{\alpha}{i^*}_w}{\mu_d} \quad \text{and} \quad {i^*}_w = 0 \quad \text{or} \quad {i^*}_w = \mu_d\mu_W(\mathcal{R}_T - 1) \quad \text{where,} \quad ,$$

$$\mathcal{R}_T = \frac{\tilde{\alpha}\beta_3}{\mu_d\mu_W}.$$

In this case $x^* = \tilde{\alpha}\mu_W(\mathcal{R}_T - 1)$.

The case ${i^*}_w = 0$ yields the infection free equilibrium point of the environmental

dynamics sub-model given by

$$\mathbb{E}_0 = (0, 0).$$

The sub-model also has an endemic equilibrium given by

$$\mathbb{E}_1 = \Big(\tilde{\alpha}\mu_W(\mathcal{R}_T - 1), \mu_d\mu_W(\mathcal{R}_T - 1)\Big).$$

**Remark**:

It is important to note the $\mathcal{R}_T$ is the model reproduction number for the BU epidemic which is driven by the dynamics of the water bug and M. ulcerans in the environment. A reproduction number, usually defined as the average of the number of secondary cases generated by an index case in a naive population, is a key threshold parameter that determines whether the BU disease persists or vanishes in the population. In this case, it represents the number of secondary cases of infected water bugs generated by the shaded M. ulcerans in the environment. $\mathcal{R}_T$ determines whether the infection in the environment and subsequently in the human population. Alternatively, the next generation operator method (Diekmann et al., 1990; Van den Driessche et al., 2002) can be used to derive the reproduction number. A similar value was obtained under a square root sign in this case.

The reproduction number is independent of the parameters of the human population even when the two sub-models are combined. It depends on the life spans of the water bugs and M. ulcerans in the environment, the shedding and infection rates of the water bugs. So, the infection is driven by the water bug population and the density of the bacterium in the environment. The model reproduction number increases linearly with the shedding rate of the M. ulcerans into the environment and the effective contact rate between the water bugs and M. ulcerans. This implies that the control and management of the ulcer largely depends on environmental management.

**Stability $\mathbb{E}_0$**

The global stability of disease free equilibrium is examined for environmental dynamics. By infections contribution of each equation of the sub-system 4.9 a Lyapunov function of the form $\mathcal{V}(t) = i_w + \frac{\beta_3}{\mu_d}x$ is proposed.

**Theorem 4.3.3** *The infection free equilibrium $\mathbb{E}_0$ is globally stable when $\mathcal{R}_T < 1$ and unstable otherwise.*

**Proof** We propose a Lyapunov function of the form

$$\mathcal{V}(t) = i_w + \frac{\beta_3}{\mu_d}x. \tag{4.10}$$

The time derivative of equation (4.10) is

$$\begin{aligned} \frac{\mathcal{V}}{dt} &= \frac{di_w}{dt} + \frac{\beta_3}{\mu_d}\frac{dx}{dt}, \\ &\leq \mu_W\left(\mathcal{R}_T - 1\right) i_w. \end{aligned}$$

When $\mathcal{R}_T \leq 1$, $\frac{\mathcal{V}}{dt}$ is negative semidefinite, with equality at the infection free equilibrium and/or at $\mathcal{R}_T = 1$. So the largest compact invariant set in $\Gamma$ such that $\frac{\mathcal{V}}{dt} \leq 0$ when $\mathcal{R}_T \leq 1$ is the singleton $\mathbb{E}_\mathbf{0}$. By LaSalle Invariance Principle (LaSalle, 1976) the infection free equilibrium point $\mathcal{E}_\mathbf{0}$ is globally asymptotically stable if $\mathbb{R}_T < 1$ and unstable otherwise.

**Stability $\mathbb{E}_1$**

**Theorem 4.3.4** *The endemic steady state $\mathbb{E}_1$ of the sub-system (4.9) is locally asymptotically stable if $\mathcal{R}_T > 1$.*

**Proof** The Jacobian matrix of system (4.9) at the equilibrium point $\mathbb{E}_\mathbf{1}$ is given

by

$$J_{\mathbb{E}_1} = \begin{pmatrix} -\mu_W & \beta_3 \\ \tilde{\alpha} & -\mu_d \end{pmatrix}.$$

Given that the trace of $J_{\mathbb{E}_1}$ is negative and the determinant is negative if $\mathcal{R}_T > 1$, thus a conclusion can be made that the unique endemic equilibrium is locally asymptotically stable whenever $\mathbb{R}_T > 1$.

**Theorem 4.3.5** *If $\mathcal{R}_T > 1$, then the unique endemic equilibrium $\mathbb{E}_1$ is globally stable in the interior of $\Gamma$.*

**Proof** We now prove the global stability of endemic steady state $\mathbb{E}_1$ whenever it exists, using the Dulac criterion and the Poincaré-Bendixson theorem. This theorem determines if a system wi have no periodic orbit. The principle behind this theorem is that the sub - system 4.8 is planar system. Then the ultimate goal here is to apply Poincaré-Bendixson theorem to ensure that solution obtained from sub-system (4.9) has no periodic orbit. The proof entails that we begin by ruling out the existence of periodic orbits in $\Gamma$ using the Dulac criteria (Hale, 1969) . Defining the right-hand side of the equations of (4.9) by $(F(i_w, x), G(i_w, x))$ and we can construct a Dulac function

$$\mathcal{B}(i_w, x) = \frac{1}{\beta_3 i_w x}, \quad i_w > 0, x > 0.$$

We will thus have

$$\frac{\partial(F\mathcal{B})}{\partial i_w} + \frac{\partial(G\mathcal{B})}{\partial x} = -\left(\frac{1}{{i^2}_w} + \frac{\tilde{\alpha}}{\beta_3 x^2}\right) < 0.$$

Thus, sub-system (4.9) does not have a limit cycle in $\Gamma$. From Theorem 4.3.4 if $\mathcal{R}_T > 1$, then $\mathbb{E}_1$ is locally asymptotically stable. A simple application of the classical Poincaré-Bendixson theorem and the fact that $\Gamma$ is positively invariant, suffices to show that the unique endemic steady state is globally asymptotically

stable in $\Gamma$.

### 4.3.4 Dynamics of BU in the human population

The ultimate interest is to determine how the dynamics of water bugs and M. ulcerans impact the human population. The overall goal is to mitigate the influence of the M. ulcerans on the human population. The force of infection can be evaluated so that

$$\tilde{\Lambda} = (\mathcal{R}_T - 1)\,\mu_W \left( m_1 \beta_1 \mu_d + \frac{\tilde{\alpha}\beta_2}{\tilde{K} + \tilde{\alpha}\,(\mathcal{R}_T - 1)\,\mu_W} \right).$$

This means that the analysis of sub-model (4.8) is subject to $\mathcal{R}_T > 1$. The force of infection is thus now a function of the reproduction number of sub-model (4.9) and is constant for any given value of the reproduction number. Below is a plot of $\tilde{\Lambda}$vs$\mathcal{R}_T$.

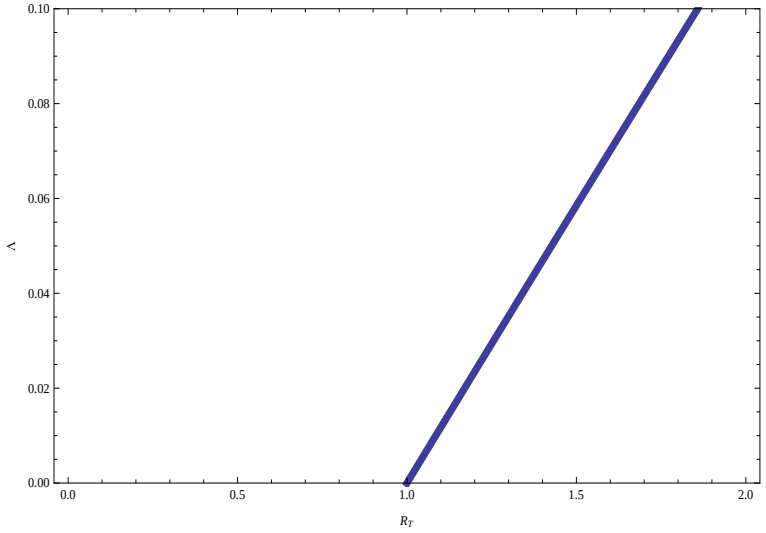



Figure 4.2: The plot of the force of infection as a function of $\mathcal{R}_T$. The force of infection increases linearly with the reproduction number

Using the second equation of system (4.8), the ${s^*}_h$ can be evaluated so that

$${s^*}_h = \frac{[\sigma {i^*}_h + \mu_h i_h(1 + N_H {i^*}_h)][\tilde{K} + \tilde{\alpha}\mu_W(\mathcal{R}_T - 1)]}{(1 + N_H {i^*}_h)[m_1\beta_1\mu_d\mu_W(\mathcal{R}_T - 1)\{\tilde{K} + \tilde{\alpha}\mu_W(\mathcal{R}_T - 1)\} + \tilde{\alpha}\beta_2\mu_W(\mathcal{R}_T - 1)]}.$$

From the third equation of (4.8) this is obtained

$${\tau^*}_h = \frac{\sigma {i^*}_h}{(1 + N_H {i^*}_h)(\gamma + \mu_H)}.$$

Substituting for ${s^*}_h$ and ${\tau^*}_h$ in the first equation of (4.8) at the steady state yields a quadratic equation in ${i^*}_h$ given by

$$a{i^*}_h^2 + b{i^*}_h + c = 0, \tag{4.11}$$

where

$$\begin{aligned}
a &= N_H(\mu_H + \gamma)(\mu_H + \theta)\left(\tilde{\alpha}\beta_2\mu_W(\mathcal{R}_T - 1) + \left(\tilde{K} + \tilde{\alpha}(\mathcal{R}_T - 1)\mu_W\right)[\mu_H + m_1\beta_1\mu_d\mu_W(\mathcal{R}_T - 1\right.\\
b &= \tilde{K}\gamma\theta\sigma + \tilde{K}\mu_H[\theta\sigma + \gamma(\theta + \sigma) + \mu_H(\mu_H + \gamma + \theta + \sigma)]\\
&\quad + (R_p - 1)[\tilde{\alpha}(\mu_H + \gamma)(\mu_H + \theta)(\mu_H + \sigma) + \tilde{\alpha}\beta_2(\gamma\theta + (\gamma + \theta)\sigma\\
&\quad -N_H(\mu_H + \gamma)(\mu_H + \theta) + \mu_H(\mu_H + \gamma + \theta + \sigma))\\
&\quad +\tilde{K}m_1\beta_1\mu_d\{\gamma\theta + (\gamma + \theta)\sigma - N_H(\mu_H + \gamma)(\mu_H + \theta) + \mu_H(\mu_H + \gamma + \theta + \sigma)\}\Big]\mu_W\\
&\quad -\tilde{\alpha}m_1(R_p - 1)^2\beta_1\mu_d\Big(-(\theta\sigma + \gamma(\theta + \sigma)) + N_H(\gamma + \mu_H)(\theta + \mu_H) - \mu_H(\gamma + \theta + \sigma + \mu_H)\Big)\\
c &= -\mu_W(\mu_H + \gamma)(\mu_H + \theta)\left[\tilde{\alpha}\beta_2 + m_1\beta_1\mu_d\left(\tilde{K} + \tilde{\alpha}\mu_W(\mathcal{R}_T - 1)\right)\right](\mathcal{R}_T - 1).
\end{aligned}$$

Clearly the model has two possible steady states given by

$$\mathbb{E}_2^a = (s_h^*, {i^*}_h^+, \tau_h^*) \quad \text{and} \quad \mathbb{E}_2^b = (s_h^*, {i^*}_h^-, \tau_h^*),$$

where ${i^*}_h^{\pm}$ are roots of the quadratic equation (4.11). It is noticed that if $\mathcal{R}_T > 1$, then $a > 0$ and $c < 0$. By the Decartes's rule of signs, irrespective of the sign of $b$, the quadratic equation (4.11) has one positive root, the endemic equilibrium

$\mathbb{E}_2^a = \mathbb{E}_2$. The following result thus archived :

**Theorem 4.3.6** *System (4.8) has a unique endemic equilibrium* $\mathbb{E}_2$ *whenever* $\mathcal{R}_T > 1$.

**Remark:**

It is important to note that when sub system (4.9) is at its infection free steady state then the human population will also be free of the BU. It can easily be established the BU free equilibrium in humans as $\mathbb{E}_0^h = (1, 0, 0)$. The existence of $\mathbb{E}_0^h$ is thus subject to the water bugs and the environment being free of M. ulcerans.

**Local Stability of** $\mathbb{E}_0^h$

**Theorem 4.3.7** *The disease free equilibrium* $\mathbb{E}_0^h$ *whenever it exists, is locally asymptotically stable if* $\mathbb{R}_T < 1$ *and unstable otherwise.*

**Proof** When $\mathbb{R}_T < 1$, then there are no infections in the water bugs. So $\mathbb{E}_0^h$ exists. The Jacobian matrix of system (4.8) at the disease free equilibrium point $\mathbb{E}_0^h$ is given by

$$J_{\mathbb{E}_0^h} = \begin{pmatrix} -(\mu_H + \theta) & -\theta & -\theta \\ 0 & -(\mu_H + \sigma) & 0 \\ 0 & \sigma & -(\mu_H + \gamma) \end{pmatrix}.$$

The eigenvalues of $J_{\mathbb{E}_0^h}$ are $\lambda_1 = -(\mu_H + \theta)$, $\lambda_2 = -(\mu_H + \sigma)$ and $\lambda_3 = -(\mu_H + \gamma)$. We can thus conclude that the disease free equilibrium is locally asymptotically stable whenever $\mathbb{R}_T < 1$.

**Local Stability of** $\mathbb{E}_2$

**Theorem 4.3.8** *The unique endemic equilibrium point* $\mathbb{E}_2$ *is locally asymptotically stable for* $\mathbb{R}_T > 1$.

**Proof** The Jacobian matrix at the endemic steady state $\mathbb{E}_2$ is given by

$$J_{\mathbb{E}_2} = \begin{pmatrix} -(\mu_H+\theta)-\tilde{\Lambda} & -\theta & -\theta \\ \tilde{\Lambda} & -\mu_H - \frac{\sigma}{(1+i_h^*)^2} & 0 \\ 0 & \frac{\sigma}{(1+i_h^*)^2} & -(\mu_H+\gamma) \end{pmatrix}.$$

If we let $\psi = \frac{\sigma}{(1+i_h^*)^2}$, then the eigenvalues of $J_{\mathbb{E}_2}$ are given by the solutions of the characteristic polynomial

$$\vartheta^3 + \eta_1\vartheta^2 + \eta_2\vartheta + \eta_3 = 0,$$

where

$$\begin{aligned} \eta_1 &= (\mu_H+\gamma) + (\mu_H+\theta) + (\mu_H+\psi) + \tilde{\Lambda}, \\ \eta_2 &= (\mu_H+\theta)(\mu_H+\gamma\tilde{\Lambda}) + (\mu_H+\gamma)(\mu_H+\psi+\tilde{\Lambda}) + (\mu_H+\theta)(\mu_H+\psi) + \tilde{\Lambda}\psi, \\ \eta_3 &= \theta\tilde{\Lambda}(\gamma+\psi) + \gamma(\theta+\tilde{\Lambda})\psi + \mu_H\Big(\tilde{\Lambda}\psi + \theta(\tilde{\Lambda}+\psi) \\ &\quad +\gamma(\theta+\tilde{\Lambda}+\psi) + \mu_H\Big(\gamma+\theta+\tilde{\Lambda}+\psi+\mu_H\Big)\Big). \end{aligned}$$

Using the Routh-Hurwitz criterion, we note that $\eta_1 > 0, \eta_2 > 0$ and $\eta_3 > 0$. The evaluation of $\eta_1\eta_2 - \eta_3$ yields

$$\begin{aligned} &(\theta+\tilde{\Lambda})(\theta+\psi)(\tilde{\Lambda}+\psi) + \gamma^2(\theta+\tilde{\Lambda}+\psi) + \gamma(\theta+\tilde{\Lambda}+\psi)^2 + 2\mu_H\Big(\gamma^2+\theta^2+\tilde{\Lambda}^2 \\ &+3\tilde{\Lambda}\psi + \psi^2 + 3\theta(\tilde{\Lambda}+\psi) + 3\gamma(\theta+\tilde{\Lambda}+\psi) + 4\mu_H\Big(\gamma+\theta+\tilde{\Lambda}+\psi+\mu_H\Big)\Big) > 0. \end{aligned}$$

This establishes the necessary and sufficient conditions for all roots of the the characteristic polynomial to lie on the left half of the complex plane. So the endemic equilibrium $\mathbb{E}_2$ is locally asymptotically stable.

In the next section we establish the global stability of the endemic equilibrium using the approach due to Li and Muldowney (Li et al., 1996) based on monotone dynamical systems and outlined in Appendix A of (Buonomo et al.,2008; Yang

et al., 2010).

**Global stability of the endemic equilibrium**

We begin by stating the following theorem

**Theorem 4.3.9** *If* $\mathbb{R}_T > 1$, *system (4.8) is uniformly persistent in* $\hat{\Gamma}$ *the interior of* $\Gamma$.

The existence of $\mathbb{E}_0^h$ only if $\mathbb{R}_T > 1$, guarantees uniform persistence (Freedman et al., 1994). System (4.8) is said to be uniformly persistent if there exist a positive constant $c$ such that any solution $(s_h(t), i_h(t), \tau_h(t))$ with initial conditions $(s_h(0), i_h(0), \tau_h(0)) \in \hat{\Gamma}$ satisfies:

$$\liminf_{t\to\infty} s_h(t) > c, \quad \liminf_{t\to\infty} i_h(t) > c, \quad \liminf_{t\to\infty} \tau_h(t) > c.$$

The proof of uniform persistence can be done using uniform persistence results in (Freedman et al., 1994; Li et al., 1999).

**Theorem 4.3.10** *If* $\tilde{\Lambda} > \gamma$, *the endemic equilibrium point* $\mathbb{E}_2$ *of system* (4.8), *is globally asymptotically stable when* $\mathbb{R}_T > 1$.

**Proof** Using the arguments in (Li et al., 1999), system (4.8) satisfies assumptions $H(1)$ and $H(2)$ in $\hat{\tilde{\Lambda}}$. Let $x = (s_h, i_h, \tau_h)$ and $f(x)$ be the vector field of system (4.8). The Jacobian matrix corresponding to system (4.8) is

$$J_{(s_h,i_h,\tau_h)} = \begin{pmatrix} -(\theta + \tilde{\Lambda} + \mu_H) & -\theta & -\theta \\ \tilde{\Lambda} & -\left(\frac{\sigma}{(1+N_H i_h)^2} + \mu_H\right) & 0 \\ 0 & \frac{\sigma}{(1+N_H i_h)^2} & -(\mu_H + \gamma) \end{pmatrix}.$$

The second additive compound matrix $J^{[2]}_{(s_h,i_h,\tau_h)}$ is given by

$$J^{[2]}_{(s_h,i_h,\tau_h)} = \begin{pmatrix} -\left[\theta + \tilde{\Lambda} + 2\mu_H + \frac{\sigma}{(1+N_H i_h)^2}\right] & 0 & \theta \\ \frac{\sigma}{(1+N_H i_h)^2} & -(\theta + \tilde{\Lambda} + 2\mu_H + \gamma) & 0 \\ 0 & \tilde{\Lambda} & -\left(2\mu_H + \gamma + \frac{\sigma}{(1+N_H i_h)^2}\right) \end{pmatrix}.$$

We let the matrix function $P$ take the form

$$P(s_h, i_h, \tau_h) = \mathrm{diag}\left\{\frac{i_h}{\tau_h}, \frac{i_h}{\tau_h}, \frac{i_h}{\tau_h}\right\}.$$

We thus have

$$P_f P^{-1} = \mathrm{diag}\left\{\frac{i'_h}{i_h} - \frac{\tau'_h}{\tau_h}, \frac{i'_h}{i_h} - \frac{\tau'_h}{\tau_h}, \frac{i'_h}{i_h} - \frac{\tau'_h}{\tau_h}\right\}$$

and

$$PJ^{[2]}P^{-1} = \begin{pmatrix} -\left[\theta + \tilde{\Lambda} + 2\mu_H + \frac{\sigma}{(1+N_H i_h)^2}\right] & 0 & \theta \\ \frac{\sigma}{(1+N_H i_h)^2} & -(\theta + \tilde{\Lambda} + 2\mu_H + \gamma) & -\theta \\ 0 & \tilde{\Lambda} & -\left(2\mu_H + \gamma + \frac{\sigma}{(1+N_H i_h)^2}\right) \end{pmatrix},$$

where $'$ represents the derivative with respect to time.

The matrix $Q = P_f P^{-1} + PJ^{[2]}P^{-1}$ can be written as a block matrix so that

$$Q = \begin{pmatrix} Q_{11} & Q_{12} \\ Q_{21} & Q_{22} \end{pmatrix},$$

where

$$Q_{11} = -\left[\theta + \tilde{\Lambda} + 2\mu_H + \frac{\sigma}{(1+N_H i_h)^2}\right] + \frac{i'_h}{i_h} - \frac{\tau'_h}{\tau_h}, \quad Q_{12} = \begin{pmatrix} 0 & \theta \end{pmatrix}, \quad Q_{21} = \begin{pmatrix} \frac{\sigma}{(1+N_H i_h)^2} \\ 0 \end{pmatrix},$$

$$Q_{22} = \begin{pmatrix} -(\theta + \tilde{\Lambda} + 2\mu_H + \gamma) + \frac{i'_h}{i_h} - \frac{\tau'_h}{\tau_h} & -\theta \\ \tilde{\Lambda} & -\left(2\mu_H + \gamma + \frac{\sigma}{(1+N_H i_h)^2}\right) + \frac{i'_h}{i_h} - \frac{\tau'_h}{\tau_h} \end{pmatrix}.$$

Let $(x, y, z)$ denote the vectors in $\mathbb{R}^3$ and the norm in $\mathbb{R}^3$ be defined by

$$|(x, y, z)| = \max\{|x|, |y + z|\}.$$

Also let $\mathcal{L}$ denote the Lozinskiĭ measure with respect to this norm. Following (Martin,1974) we have:

$$\begin{aligned}\mathcal{L}(Q) &\leq \sup\{g_1, g_2\}, &(4.12)\\ &\equiv \sup\{\mathcal{L}_1(Q_{11}) + |Q_{12}|, \mathcal{L}_1(Q_{22}) + |Q_{21}|\}, &(4.13)\end{aligned}$$

where $|Q_{12}|$ and $|Q_{21}|$ are the matrix norms with respect to the vector norm $L^1$, and $\mathcal{L}_1$ the Lozinskiĭ measure with respect to the $L^1$ norm.

In fact

$$\begin{aligned}\mathcal{L}_1(Q_{11}) &= -\left[\theta + \tilde{\Lambda} + 2\mu_H + \frac{\sigma}{(1+N_H i_h)^2}\right] + \frac{i'_h}{i_h} - \frac{\tau'_h}{\tau_h},\\ |Q_{12}| &= \theta,\\ |Q_{21}| &= \frac{\sigma}{(1+N_H i_h)^2},\\ \mathcal{L}_1(Q_{22}) &= -(\theta + 2\mu_H + \gamma) + \frac{i'_h}{i_h} - \frac{\tau'_h}{\tau_h}.\end{aligned}$$

We now have

$$\begin{aligned}g_1 &= \frac{i'_h}{i_h} - \left[\tilde{\Lambda} + 2\mu_H + \frac{\sigma}{(1+N_H i_h)^2}\right] - \frac{\tau'_h}{\tau_h}, &(4.14)\\ g_2 &= \frac{i'_h}{i_h} - (\theta + 2\mu_H + \gamma) + \frac{\sigma}{(1+N_H i_h)^2} - \frac{\tau'_h}{\tau_h} &(4.15)\end{aligned}$$

The third equation of (4.8) gives

$$\frac{\tau'_h}{\tau_h} = \left(\frac{\sigma}{(1+N_H i_h)}\right)\left(\frac{i_h}{\tau_h}\right) - (\mu_H + \gamma). \qquad (4.16)$$

Substituting (4.16) into equations (4.14) and (4.15) yields

$$\begin{aligned}g_1 &= \frac{i'_h}{i_h} - \left[\tilde{\Lambda} + 2\mu_H + \frac{\sigma}{(1+N_H i_h)^2}\right] - \frac{\tau'_h}{\tau_h},\\ &= \frac{i'_h}{i_h} - \left[\tilde{\Lambda} + 2\mu_H + \frac{\sigma}{(1+N_H i_h)^2}\right] - \left\{\left(\frac{\sigma}{(1+N_H i_h)}\right)\left(\frac{i_h}{\tau_h}\right) - (\mu_H + \gamma)\right\},\\ &\leq \frac{i'_h}{i_h} - \left\{\tilde{\Lambda} - \gamma + \mu_H + \frac{\sigma}{(1+N_H c)^2} + \left(\frac{\sigma}{(1+N_H c)^2}\right)\right\},\end{aligned}$$

and

$$\begin{aligned} g_2 &= \frac{i'_h}{i_h} - (\theta + 2\mu_H + \gamma) + \frac{\sigma}{(1+N_H i_h)^2} - \frac{\tau'_h}{\tau_h}, \\ &= \frac{i'_h}{i_h} - (\theta + \mu_H) + \left(\frac{\sigma}{(1+N_H i_h)}\right)\left(\frac{1}{(1+N_H i_h)} - \frac{i_h}{\tau_h}\right), \\ &\leq \frac{i'_h}{i_h} - \left[(\theta + \mu_H) - \left(\frac{\sigma}{(1+N_H c)}\right)\left(\frac{1}{(1+N_H c)} - 1\right)\right], \end{aligned}$$

where $c$ is the constant of uniform persistence.

If we impose the condition $\tilde{\Lambda} > \gamma$ then

$$\begin{aligned} \mathcal{L}(Q) &\leq \sup\{g_1, g_2\}, \\ &= \frac{i'_h}{i_h} - \omega, \end{aligned}$$

where $\omega = \min\{\omega_1, \omega_2\}$ with

$$\begin{aligned} \omega_1 &= \tilde{\Lambda} - \gamma + \mu_H + \frac{\sigma}{(1+N_H c)^2} + \left(\frac{\sigma}{(1+N_H c)^2}\right), \\ \omega_2 &= (\theta + \mu_H) - \left(\frac{\sigma}{(1+N_H c)}\right)\left(\frac{1}{(1+N_H c)} - 1\right). \end{aligned}$$

Hence

$$\frac{1}{t}\int_0^t \mathcal{L}(Q)ds \leq \frac{1}{t}\log\frac{i_h(t)}{i_h(0)} - \omega.$$

The imposed condition implies that the infection rate is greater than the recovery rate. The result follows based on the Bendixson criterion proved in (Li et al., 1996) .

## 4.4 Numerical simulations

In this section endevour is made to give some simulation results for the combined subsystems,(4.8) and (4.9). The simulations were performed using Matlab, and

time was set in days. The sensitivity analysis carry out to determine the effects of a chosen parameter on the state variables. Specifically, focus are made on the parameters that make up the model reproduction number. This is because parameters that aid the reduction of the BU epidemic is of the interest. The sensitivity analysis results were obtained using Matlab. A brief exposition on parameter estimation are now given.

### 4.4.1 Parameter Estimation

The estimation of parameters in the model validation process is a challenging process. Some hypothetical assumptions are made for the purpose of illustrating the usefulness of the model in tracking the dynamics of the BU. Demographic parameters are the easiest to estimate. For the mortality rate $\mu_H$, an assumption is made that the life expectancy of the human population is 60 years. This value has been the approximation of the life expectancy in Ghana (Population and Housing Census, 2012) and is indeed applicable to Sub-Saharan Africa. This translates into $\mu_H = 0.0166$ per year or equivalently $4.5 \times 10^{-5}$ per day. Buruli ulcer is a vector borne disease and some of the parameters can be estimated from literature on vector borne diseases. Recovery rates of vector borne diseases range from $1.6 \times 10^{-5}$ to 0.5 per day (Rascalou et al., 2012).

The rate of loss of immunity $\theta$ for vector borne diseases ranges between 0 and $1.1 \times 10^{-2}$ per day (Rascalou et al., 2012). The mortality rate of the water bugs, though not known, is assumed to be 0.15 per day (Aidoo et al., 2007). It is assumed that there are more water bugs than humans so that $m_1 > 1$. Some of the parameters were very difficult to obtain for the simulations and therefore, initially guessed their values.The least square method was employed to estimate those parameters to ensure that minimum error occurred whilst getting the best fits. The remaining parameters in given in Table **??**;

Table 4.1: Parameter values used in the simulations and sensitivity analysis with units per day

| Parameter | Value/Range | Source |
|---|---|---|
| $\mu_H$ | $4.5 \times 10^{-5}$ | (Population and Housing Census, 2012) |
| $\gamma$ | $1.6 \times 10^{-5} - 0.5$ | (Rascalou et al., 2012) |
| $\theta$ | $0 - 1.1 \times 10^{-2}$ | (Rascalou et al., 2012) |
| $m_1$ | $m_1 > 1$ | Estimated |
| $\beta_1$ | (0,1) | Estimated |
| $\beta_2$ | (0,1) | Estimated |
| $\beta_2$ | (0,1) | Estimated |
| $\beta_3$ | (0,1) | Estimated |
| $\mu_W$ | 0.15 | Aidoo et al., 20007) |
| $\tilde{\alpha}$ | (0,1) | Estimated |
| $\mu_d$ | (0,1) | Estimated |
| $\sigma$ | (0,1) | Estimated |
| $K$ | 400 | Estimated |

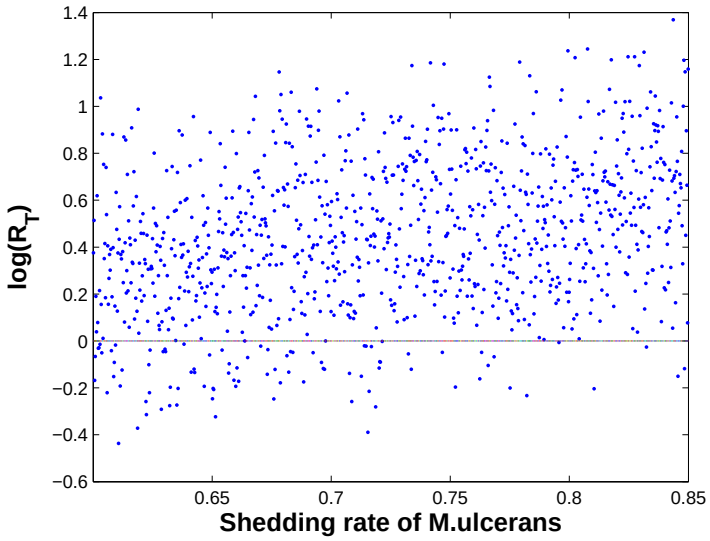
### 4.4.2 Sensitivity Analysis

In this section, a sensitivity analysis was carried out to ascertain the contribution of some very essential parameters to the dynamics of the model and establish unprecedented behaviour of the model if such input parameters are varied. This helps to allot qualitatively and quantitatively, the variation in the output of the mathematical model to different input variables. A variety of methods such as differential sensitivity analysis, one-at-a-time sensitivity measures, factorial design, sensitivity index, significance factors, and subjective sensitivity analysis (Hamby, 1994), have been used to perform sensitivity analysis. Of all these methods, subjective sensitivity analysis is the only qualitative method and it relies on the opinion of experienced investigators (Hamby, 1994).

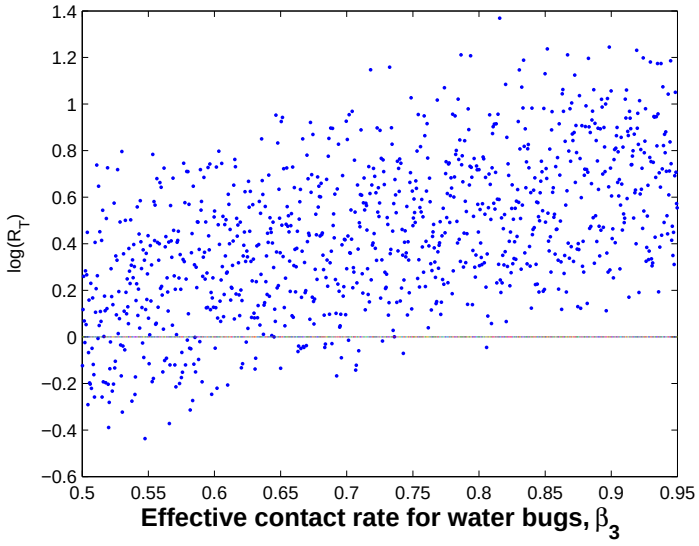
In this thesis, the sensitivity indices was used by determining the relative change in the reproduction number when a model parameter changes. The normalised forward sensitivity index of the reproduction number to the model parameters described in (Chitnis et al., 2008; Hamby, 1994) was employed. This is defined as the relative change in the variable $R_0$ to the relative change in the parameter. These parameters influence only sub-model (4.9). The scatter plots are shown in

Figure 6.3.

Figures 4.3(a) and 4.3(b), depict parameters with a positive correlation with the reproduction number. They show a monotonic increase of $\mathbb{R}_T$ as $\alpha$ and $\beta_3$ increase. This means that to curtail the epidemic the reduction in the shedding rate and infection of water bugs by M. ulcerans is of paramount importance. On the other hand, Figures 4.3(c) and 4.3(d) show a negative correlation with the reproduction number. This means that the clearance of the water bug and the M. ulcerans in the environment will reduce the spread of BU epidemic.




(a)



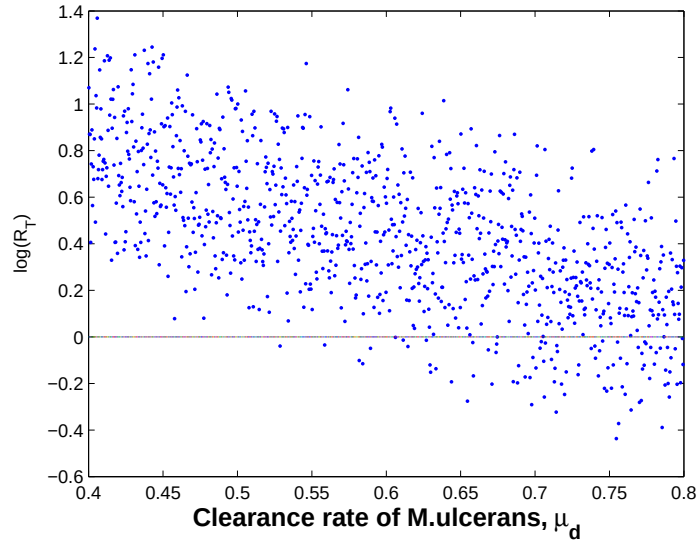

(b)

A more informative comparison of how the parameters influence the model is given in Figure 4.4. The Tornado plot shows that the parameter $\alpha$ affects the reproduction more than any of the other parameters considered. So interventions targeted towards the reduction in the shedding rate of M. ulcerans into the environment will significantly slow the epidemic.

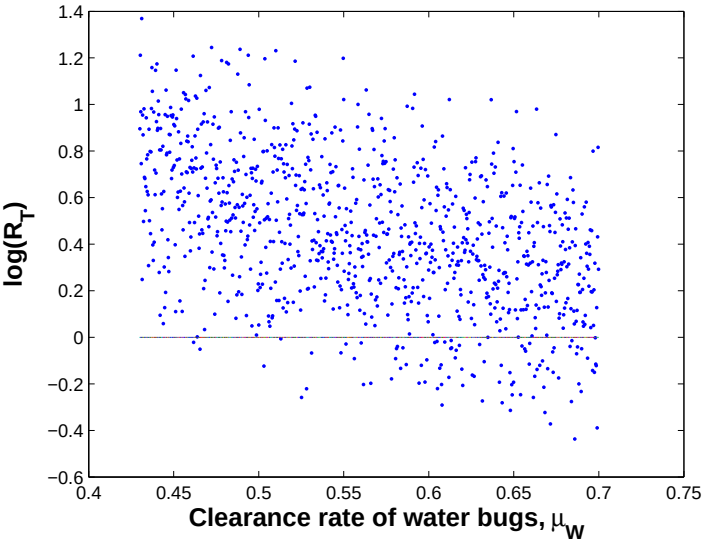
### 4.4.3 Simulation results

To validate our mathematical analysis results, we plot phase diagrams for $\mathbb{R}_T$ less than 1 and greater than 1 for the environmental dynamics. The global properties of the steady states are confirmed in Figures 4.7(a) and 4.7(b). Figure 4.9(a) shows a three dimensional phase diagram for the human population dynamics. The existence of the endemic equilibrium when $\mathbb{R}_T > 1$, is numerically shown here. The plot shows the trajectories of parametric solutions of (4.8) for randomly chosen intial conditions. To validate the mathematical analysis results, a plot is made on the variation of the proportion of each population with time for $\mathbb{R}_T$ less than 1 and greater than 1.

Figure 4.7 shows the variation of the human and water bug populations over time when $\mathbb{R}_T < 1$. It is interesting to note that the water bugs population quickly




(c)




(d)

Figure 4.3: The scatter plots for the parameters $\alpha$, $\beta_3$,$\mu_d$ and $\mu_W$.

reaches the infection free equilibrium when compared to the other variables. For the parameter values chosen, the water bugs reach the steady state after about 22 days while the other parameters take at least about 800 days. This supports our analysis where we used the steady states of the sub-model (4.9) to infer the stability of sub-system (4.8). Overall, Figure 4.7 shows that all the populations turned to zero when the reproduction number is less than one. Figure 4.8 shows the variation of the human and water bug populations when the reproduction number is above one. All the subfigures show that their respective populations

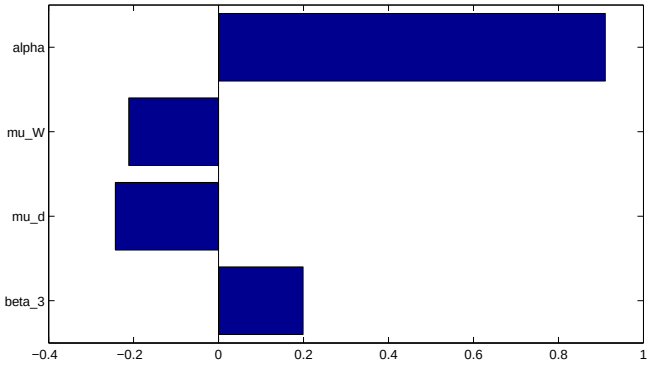
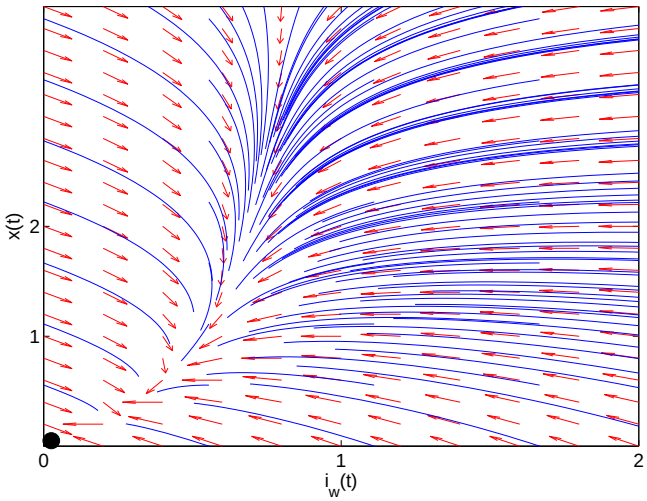
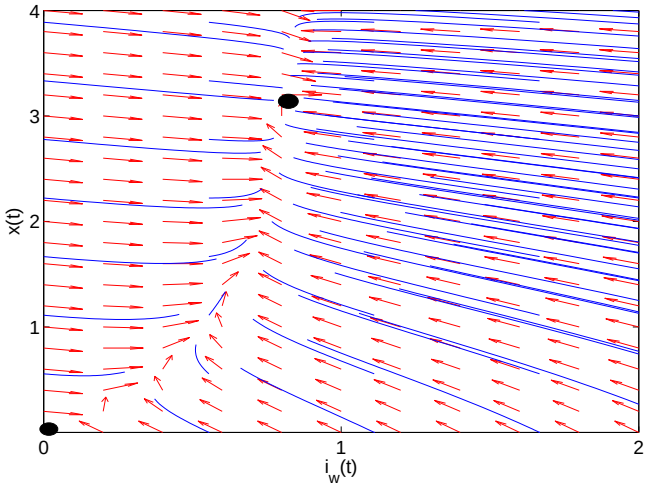



Figure 4.4: The Tornado plots for the four parameters in the model reproduction number




(a)




(b)

Figure 4.5: The phase diagrams for $\mathbb{R}_T = 0.8889$ and $\mathbb{R}_T = 5.3333$.

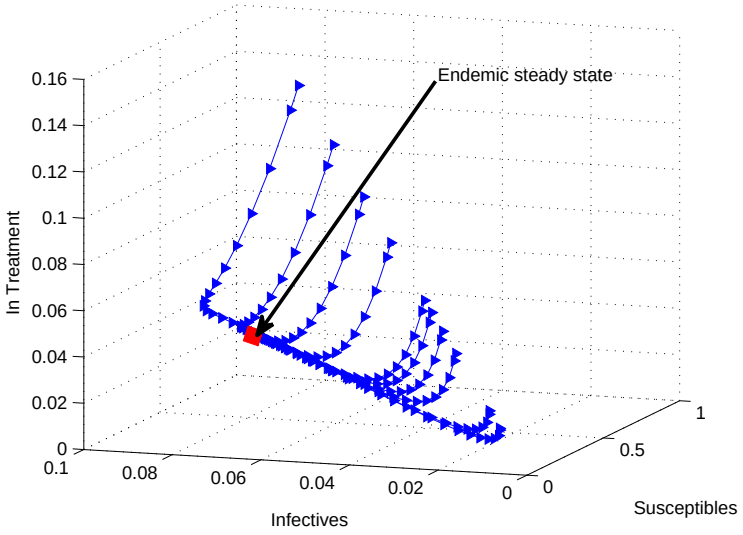
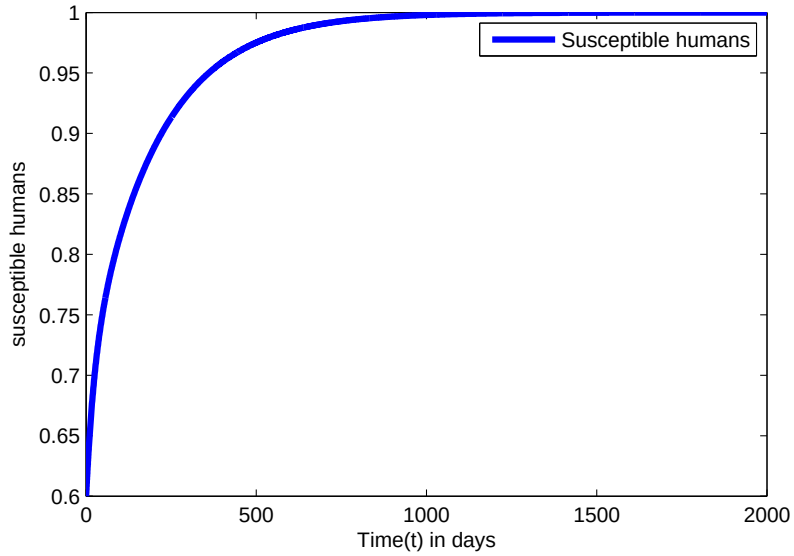
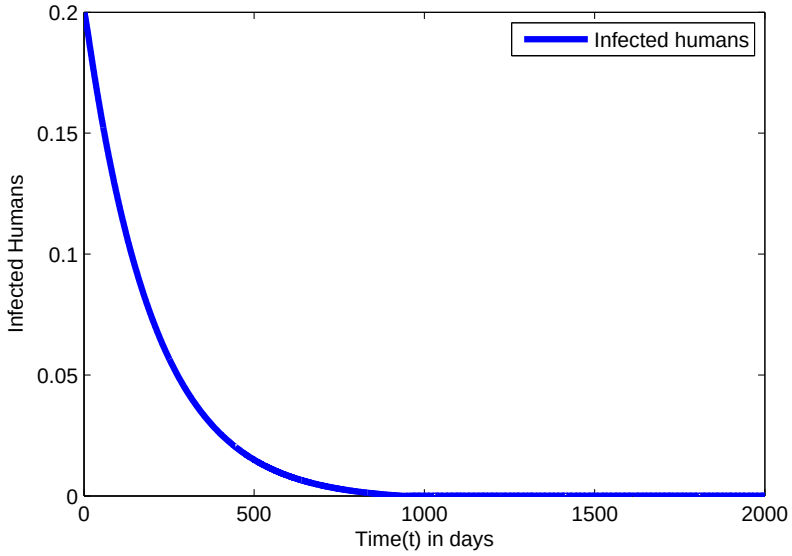



Figure 4.6: The phase diagram for the human population showing the endemic steady state. For a randomly chosen set of initial conditions, all trajectories tend to an endemic equilibrium for the following parameter values, $\mu_H = 0.02,\ \theta = 0.04,\ \Lambda = 0.07,\ \sigma = 0.4,\ \gamma = 0.7$.

approach a non-zero endemic equilibrium when $\mathbb{R}_T > 1$. This confirms the analytic results on the stability of the endemic steady states. It is also interesting to observe that the population of water bugs attains its equilibrium value much faster than the other state variables.

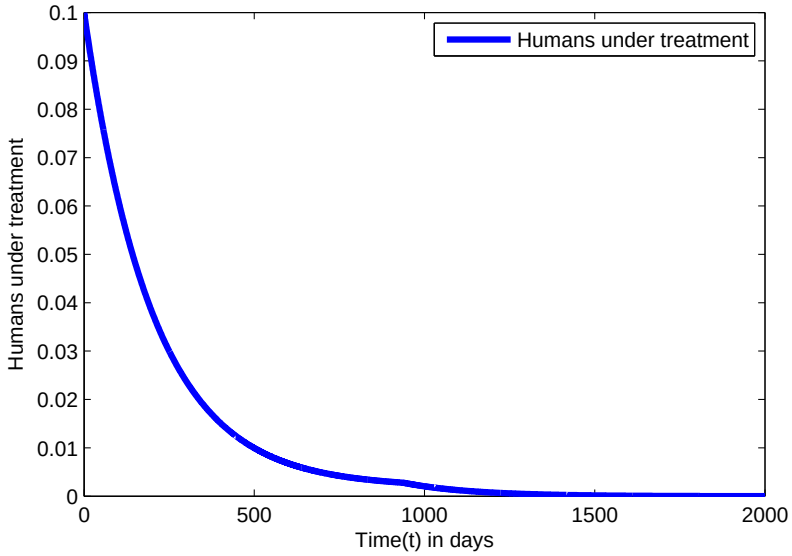



(a)

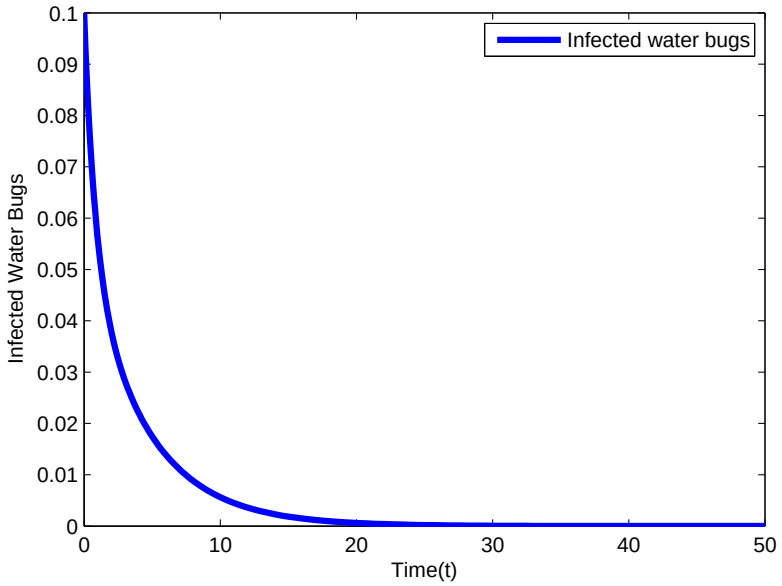



(b)

To determine how the infection of the water bugs translate into the transmission of BU in humans, a plot is made on the prevalence of BU in humans over time while varying $\beta_3$, the infection parameter for the water bugs. Figure 4.10(a) shows how the the prevalence of BU in humans changes with variations in the value of $\beta_3$. The prevalence is evaluated as the sum of the infected humans and those that are under treatment of BU. Figure shows that as the infection the water bugs decrease, this translates into a reduction in the number of infected human cases. Similar results can be obtained if the parameter $\alpha$ is considered. So interventions



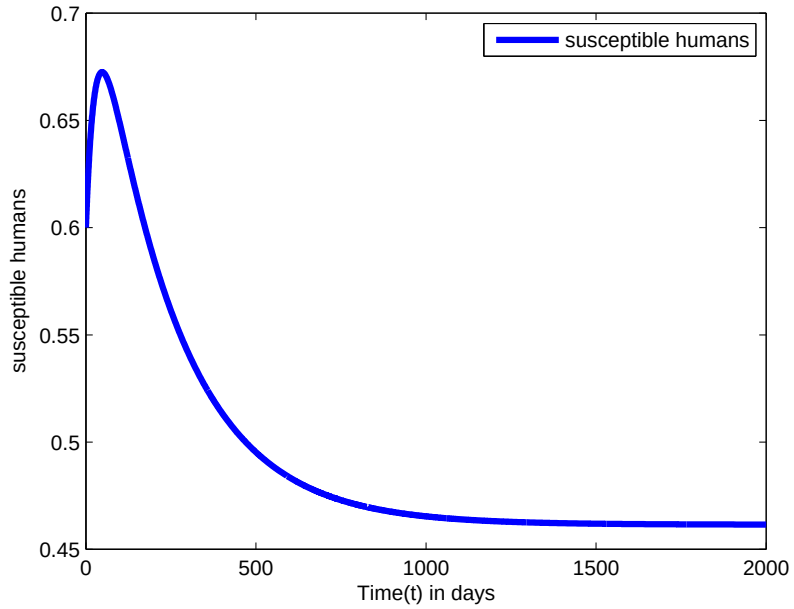

(c)



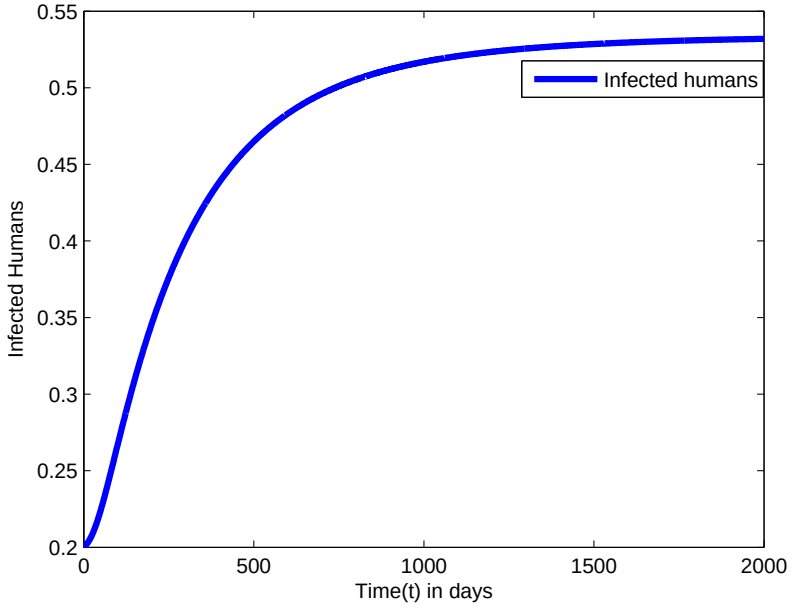

(d)

Figure 4.7: The variation of the populations for $\mathbb{R}_T = 0.4911$

to reduce the impact of the epidemic on humans can also be instituted through a reduction in the infection of water bugs and the shedding of M. ulcerans in the environment. It is important to note that the practicality of such an intervention is a mirage.

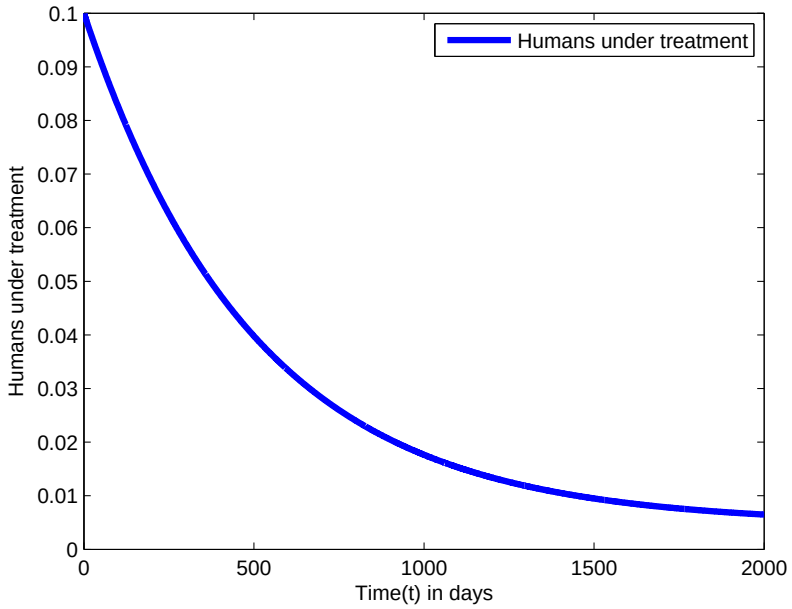



(a)

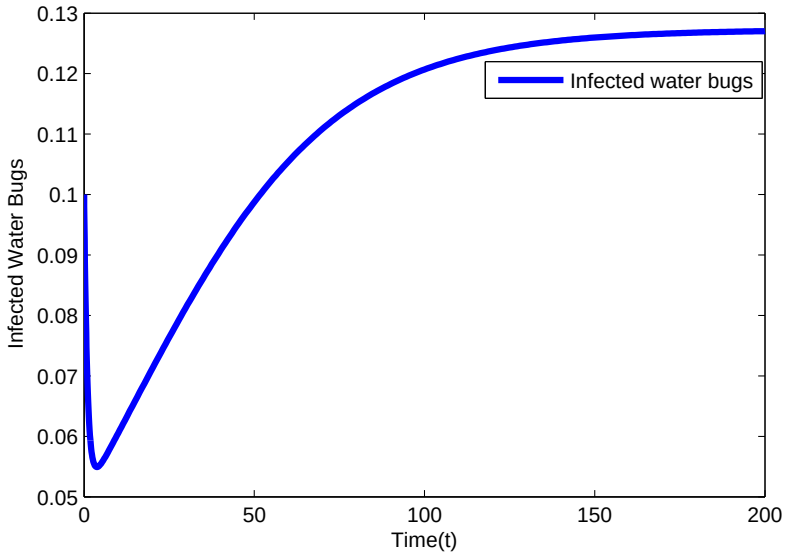



(b)

A determination is made on how the clearance of M. ulcerans affect the prevalence of the human population. As more M. ulcerans are removed from the environment, the prevalence of BU in the population decreases. This is depicted in Figure 4.10(b) The dynamics of infected water bugs and M. ulcerans can be shown through a phase plot. Figure 4.9(a) shows that increasing the density of M. ulcerans in the environment leads to an increase in the number



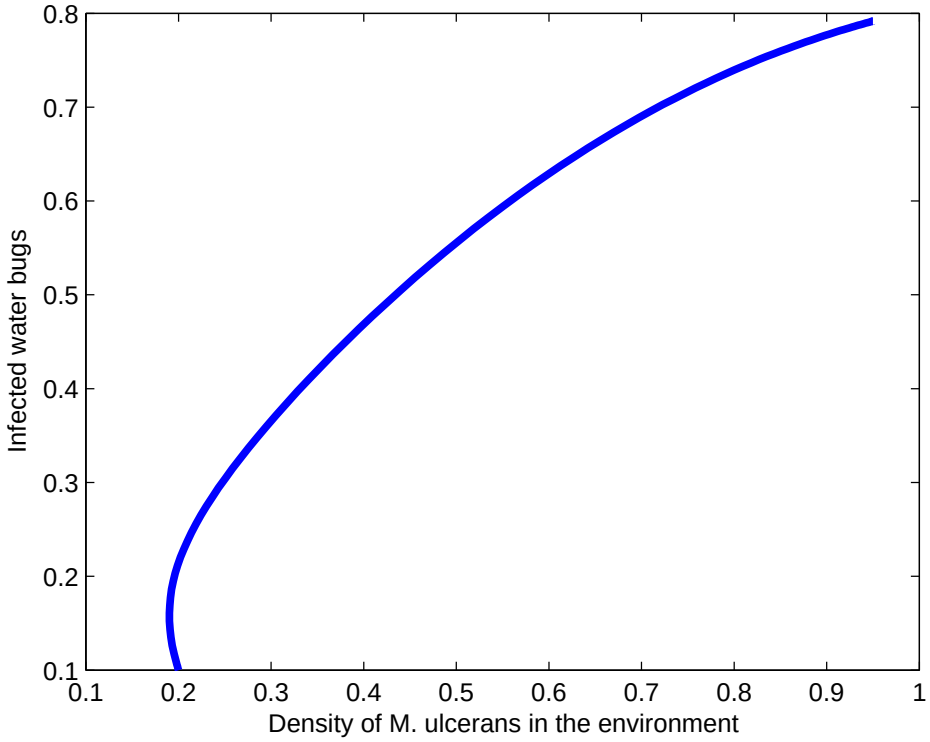

(c)



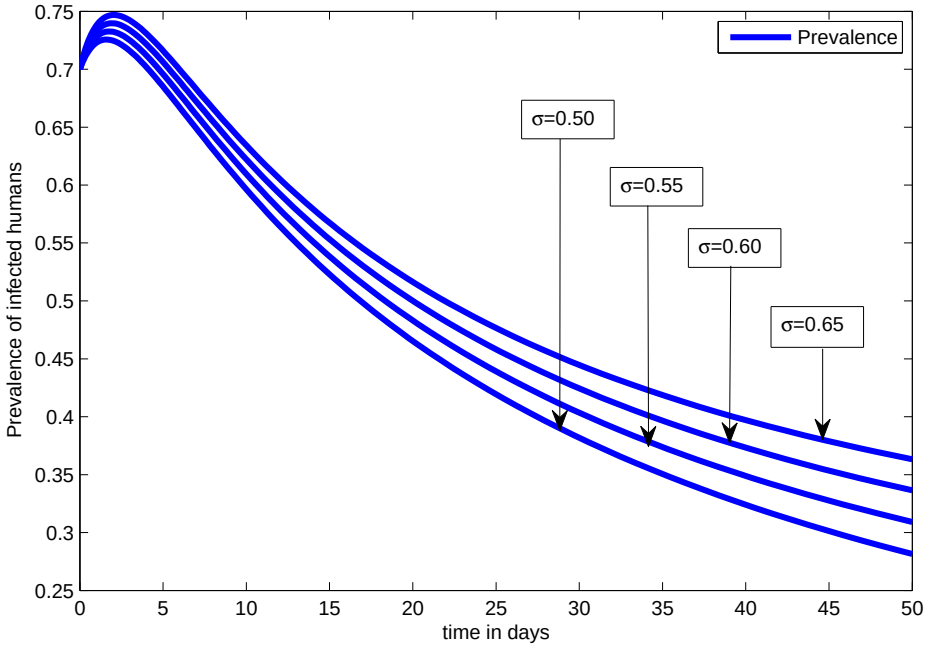

(d)

Figure 4.8: The variation of the populations for $\mathbb{R}_T = 1.1458$

of infected water bugs. For the given parameter values, initially the fraction of infected water bugs is 10% while the density of M. ulcerans in environment is 20%. As the density of M. ulcerans in the environment increases the number of infected water bugs also increases. While this sounds obvious from the model formulation, the quantification of the increase is of critical importance in this case.

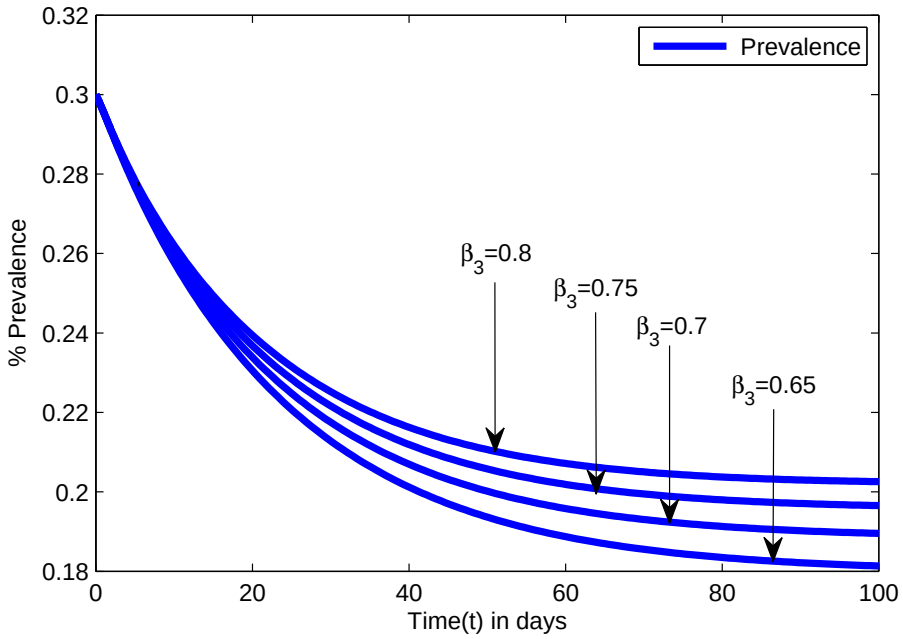



(a)

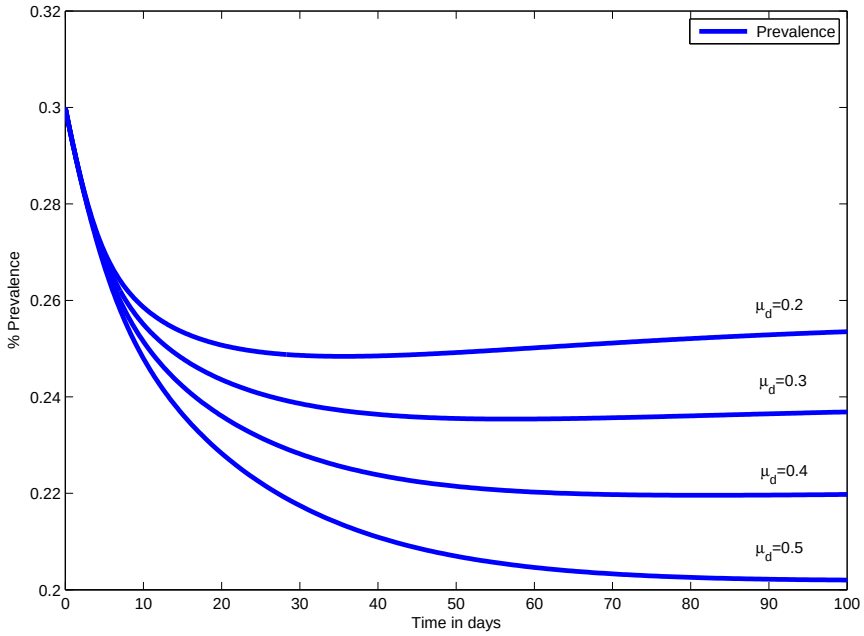



(b)

Figure 4.9: A phase diagram for the infected water bugs and M. ulcerans in the environment and the percentage prevalence in human population when $\sigma$ is varied for $\sigma = 0.65, \sigma = 0.60, \sigma = 0.55, \sigma = 0.50$ given reproduction number $\mathbb{R}_T = 1.6492$




(a)




(b)

Figure 4.10: The percentage prevalence in the human population for $\mathbb{R}_T = 1.6492$ for the parameters $\beta_3$ and $\mu_d$

Figure 4.9 depicts the variation of human prevalence for different values of $\sigma$. The graph shows that as the saturation treatment ($\sigma$) increases with time in the population, human prevalence also increases. For instance, when saturation

treatment $\sigma = 065$ for 50 days the human prevalence is around 40 % and similarly same number of days, when $\sigma = 0.50$ the prevalence is about 28%. This therefore, implies that as human prevalence increases there should be corresponding saturation treatment for Buruli ulcer disease.

## 4.5 Summary

A deterministic model is presented that endevours to capture the two potential routes of transmission and treatment uptake in a resource limited population. This uptake is not linear, and hence a response function is proposed to it. Because of the nature of the infection process, the model is divided into two sub-models that are only coupled through the infection terms. The model is analysed by determining the steady states. The analysis is done through the sub-models. The model in this chapter presented a unique challenge in which the infection in one sub-model takes place at the steady state of the other sub-model. The model analysis is carried out in terms of the model reproduction number $\mathbb{R}_T$. Numerical simulations are carried out. The model parameters were estimated from literature and sensitivity analysis was done because not much of the disease is understood and parameter estimation was difficult. Through the simulation the variation of the prevalence of BU in the human population with time was determined for different values of the infection rate of the water bugs and the clearance of the M. ulcerans. It is observed that the management of BU depends mostly on the environmental management i.e clearance of the bacteria from the environment and reduction in shedding and infection of the water bugs.

# CHAPTER 5

# OPTIMAL CONTROL MODEL FOR THE TRANSMISSION OF BURULI ULCER DISEASE

## 5.1 Introduction

In this chapter, the model is formulated and basic properties are established. A detailed qualitative optimal control analysis of the resulting model is undertaken., and also determined the necessary conditions for optimal control of the disease using Pontryagin Maximum Principle in order to obtain optimal strategies for controlling the spread of the diseases. The steady states are determined and analysed for their stability. Numerical results on the behavour of the model are also presented. Three controls are put on the system 5.1 .

## 5.2 The model and its analysis

### 5.2.1 Model formulation

A reference is made to Chapter 3 (3.2) for the model formulation and for the sake of convenient, the following set of nonlinear ordinary differential equations that describe the possible interactions among humans, water bugs (vector), small fish

population are stated:

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \mu_H N_H + \theta R_H - \beta_H \frac{S_H I_V}{N_H} - \mu_H S_H, \\
\frac{dI_H}{dt} &= \beta_H \frac{S_H I_V}{N_H} - (\mu_H + \gamma) I_H, \\
\frac{dR_H}{dt} &= \gamma I_H - (\mu_H + \theta) R_H, \\
\frac{dS_V}{dt} &= \mu_V N_V - \beta_V \frac{S_V I_F}{N_V} - \eta \beta_V \frac{S_V U}{K} - \mu_V S_V, \\
\frac{dI_V}{dt} &= \beta_V \frac{S_V I_F}{N_V} + \eta \beta_V \frac{S_V U}{K} - \mu_V I_V, \\
\frac{dS_F}{dt} &= \mu_F N_F - \beta_F \frac{S_F U}{K} - \mu_F S_F, \\
\frac{dI_F}{dt} &= \beta_F \frac{S_F U}{K} - \mu_F I_F, \\
\frac{dU}{dt} &= \sigma I_F - \mu_E U.
\end{aligned}\right\} \tag{5.1}$$

An assumption is made that all the model parameters are positive and the initial conditions of the model (5.1) are stated as

$$\begin{aligned}
S_H(0) &= S_{H0} > 0, I_H(0) = I_{H0} \geq 0, R_H(0) = R_{H0} = 0,\ S_V(0) = S_{V0} > 0, \\
I_V(0) &= I_{V0} \geq 0,\ S_F(0) = S_{F0} > 0,\ I_F(0) = I_{F0} \geq 0 \quad \text{and} \quad U(0) = U_0 > 0.
\end{aligned}$$

The SIR buruli ulcer model (5.1) will be analyzed in a biologically feasible region as follows. This region should be feasible for human, water bugs, small fish and *Mycobacterium ulcerans* in the environment populations. More clearly, we have

**Theorem 5.2.1** *If $S_H(0), I_H(0), R_H(0), S_V(0), I_V(0), S_F(0)$ and $U_0$ are non-negative, then so are $S_H(t), I_H(t), R_H(t), S_V(t), I_V(t), S_F(t)$ and $U(t)$ for all $t > 0$.*

*Moreover Furthermore, if in addition* $N_H(0) \leq \frac{N_H}{\mu_H}\left(N_V(0) \leq \frac{N_H}{\mu_H}\right)$ *then* $N_V(t) \leq \frac{N_V}{\mu_V}\left(N_V(0) \leq \frac{N_H}{\mu_H}\right)$, $N_F(0) \leq \frac{N_F}{\mu_F}\left(N_V(0) \leq \frac{N_F}{\mu_F}\right)$,$U(t) \leq \frac{\tilde{\sigma}}{\mu_E}\left(U(0) \leq \frac{\tilde{\sigma}}{\mu_E}\right)$

*In particular, the region*

$$D = D_H \times D_V \times D_F \times D_U$$

$$\begin{aligned} D_H = \left\{(S_H + I_H + R_H) \in \mathbb{R}^3_+ : S_H + I_H + R_H \leqslant \frac{N_H}{\mu_H}\right\} \\ , D_V = \left\{(S_V + I_V) \in \mathbb{R}^2_+ : S_V + I_V \leqslant \frac{N_V}{\mu_V}\right\}, \\ D_F = \left\{(S_F + I_F) \in \mathbb{R}^2_+ : S_F + I_F \leqslant \frac{N_F}{\mu_F}\right\}, \\ D_U = U \leqslant \frac{\tilde{\sigma}}{\mu_E}. \end{aligned}$$

*is positively invariant*

$$\begin{aligned} \frac{dN_H}{dt}(t) &= \mu_H N_H - \mu_H N_H(t), \\ \frac{dN_V}{dt}(t) &= \mu_v N_v - \mu_v N_v(t), \\ \frac{dN_F}{dt}(t) &= \mu_F N_F - \mu_F N_F(t). \end{aligned}$$

By using standard comparison theorem (Lakshmikantham et al., 1989), we have

$$\begin{aligned} N_H(t) &= N_H(0)e^{-\mu_H t} + \frac{N_H}{\mu_H}(1 - e^{-\mu_H t}), \\ N_V(t) &= N_V(0)e^{-\mu_V t} + \frac{N_V}{\mu_V}(1 - e^{-\mu_V t}), \\ N_F(t) &= N_F(0)e^{-\mu_H t} + \frac{N_F}{\mu_F}(1 - e^{-\mu_F t}). \end{aligned}$$

Therefore if

$N_H(t) = N_H(0) \leqslant \frac{N_H}{\mu_H}\left(resp.\ N_V(0) \leqslant \frac{N_V}{\mu_V}, N_F(0) \leqslant \frac{N_F}{,}\mu_F\right)$ then $N_H(t) \leqslant \frac{N_H}{\mu_H}\left(resp.\ N_V(t) \leqslant \frac{N_V}{\mu_V}, N_F(t) \leqslant \frac{N_F}{\mu_F}\right)$

Moreover $\lim_{t\to\infty} N_H(t) = \frac{N_H}{\mu_H}$, $\lim_{t\to\infty} N_V(t) = \frac{N_V}{\mu_V}$ , $\lim_{t\to\infty} N_F(t) = \frac{N_F}{\mu_F}$ and $U \leqslant \frac{\tilde{\sigma}}{\mu_E}$

This establishes the invariance of as stipulated. From this theorem we conclude that it is sufficient to consider the dynamics of (5.1) in $D$. In this region, the model can be considered as being epidemiologically and mathematically well-posed (Hethcote, 2000).

It is noticed that model (5.1) is well positioned in the non-negative region $\mathbb{R}^8_+$ for the fact that the vector and fish as well as the environment do not point to the exterior. By providing an initial condition in the region, then we can define solution for all time $t \geqslant 0$ and remains in the region.

### 5.2.2 Positivity of solutions

We show that for any non-negative initial conditions of the model (5.1) , the solutions still remain non-negative for all $t \in [0, \infty)$ . A desire to prove that all necessary state variables in the model (5.1) remain non-negative and also the solutions of the system with positive initial conditions will stay positive for all . We therefore, propose the following lemma.

**Lemma 5.2.2** *Given that the initial conditions of the model* (5.1) *are positive, the solutions*

*,* $S_H(t)$, $I_H(t)$, $R_H(t)$, $S_V(t)$ $I_V(t)$, $S_F(t)$ $I_F(t)$ *and* $U(t)$ *are non-negative for all* $t > 0$.

**Proof**

Given that

$\hat{t} = \sup\{t > 0 : S_H > 0, I_H > 0, R_H > 0, S_V > 0, I_V > 0, S_F > 0, I_F > 0, U > 0\} \in [0, t]$. More precisely $\hat{t} > 0$, and it implies directly from the first equation of the

model (5.1) that

$$\frac{dS_H}{dt} \leqslant \mu_H N_H - [\mu_H + \lambda] S_H, \text{ where } \lambda = \beta_H \frac{I_V}{N_H} > 0$$

We therefore, have

$$\frac{d}{dt}\left[S_H(t)\exp\left\{(\mu_H)\,t + \int_0^t \lambda(s)ds\right\}\right] \leqslant (\mu_H)\exp\left[(\mu_H)\,t + \int_0^t \lambda(s)ds\right]$$

Thus

$$S_H(\hat{t})\exp\left[(\mu_H)\,\hat{t} + \int_0^{\hat{t}} \lambda(s)ds\right] - S(0) \leqslant \int_0^{\hat{t}} (\mu_H)\exp\left[(\mu_H)\,\hat{t} + \int_0^{\hat{t}} \lambda(z)dz\right] d\hat{t},$$

and that

$$S_H(\hat{t}) \leqslant S(0)\exp\left[-\left((\mu_H)\,\hat{t} + \int_0^{\hat{t}} \lambda(s)ds\right)\right]$$

$$+\exp\left[-\left((\mu_H)\,\hat{t} + \int_0^{\hat{t}} \lambda(s)ds\right)\right]\left[\int_0^{\hat{t}} (\mu_H)\exp\left((\mu_H)\,\hat{t} + \int_0^{\hat{t}} \lambda(z)dz\right) d\hat{t}\right] \quad (5.2)$$

The right hand of 5.2 is obviously positive. Therefore, the solution $S_H(t)$ will at any given instance be positive.

In examining the second equation of 5.1,

$$\frac{dI_H}{dt} \geq -(\mu_H + \gamma_H)I_H,$$
$$\Rightarrow I_H \geq I_{H0}\exp -(\mu_H + \gamma_H)t > 0.$$

Similarly, it can be determined that $R_H(t) > 0,\ S_V(t) > 0,\ I_V(t) > 0,\ S_F(t) > 0,\ I_F(t) > 0$ and $U(t) > 0$ for all $t > 0$, and this leads to the completion of the

proof

## 5.3 Steady states and the model reproduction number

In this section, the equilibrium points is computed by equating the right side of model (5.1) to zero. This direct computation indicates that model (5.1) always possesses a disease free equilibrium point $E_0 = (S_H^0, 0, 0, S_V^0, 0, S_F^0, 0, 0)$ where $S_H^0 = N_H, S_V^0 = N_V, S_F^0 = N_F$ and a unique endemic equilibrium $E_1 = (S_H^*, I_H^*, R_H^*, S_V^*, I_V^*, S_F^*, I_F^*, U^*)$ in $\Omega$

where

$$S_H^* = I_H \mathrm{N_H} N_V^2 \beta_H \beta_V^2 (\eta\sigma \mathrm{N_F} \mathrm{N_V} \beta_F + K\mu_E (I_F \beta_F - \eta \mathrm{N_V} \mu_F))$$

$$\left(\eta\sigma \mathrm{N_F} \mathrm{N_V} \beta_F + K\mu_E \left(\mathrm{N_F} - \eta \mathrm{N_V} \mu_F - \frac{K\mu_E\mu_F}{\sigma}\right)\right)(\gamma + \mu_H)$$

$$I_H^* = \frac{\beta_H^2 I_H \mathrm{N_H} N_V^2 \beta_V^2 \bar{M} \left(\eta\sigma \mathrm{N_F} \mathrm{N_V} \beta_F + K\mu_E \left(\mathrm{N_F} - \eta \mathrm{N_V} \mu_F - \frac{K\mu_E\mu_F}{\sigma}\right)\right)}{\mathrm{N_H}(\mu_H + \theta)}$$

where $\bar{M} = (\eta\sigma \mathrm{N_F} \mathrm{N_V} \beta_F + K\mu_E (I_F \beta_F - \eta \mathrm{N_V} \mu_F))$

$$\frac{(\gamma + \mu_H)\left(\sigma \mathrm{N_V} \beta_V (\eta\sigma \mathrm{N_F} \mathrm{N_V} \beta_F + K\mu_E (I_F \beta_F - \eta \mathrm{N_V} \mu_F))\right)}{\left(\beta_V (\eta\sigma \mathrm{N_V} + K\mu_E)(\sigma \mathrm{N_F} \beta_F - K\mu_E\mu_F) + K\sigma \mathrm{N_V} \beta_F \mu_E \mu_V\right) \mathrm{N_H}(\mu_H + \theta)}$$

$$R_H^* = \frac{\gamma I_H}{\theta + \mu_H}$$

,

$$S_V^* = \frac{K\sigma \mathrm{N_V^2} \beta_F \mu_E \mu_V}{\beta_V (\eta\sigma \mathrm{N_V} + K\mu_E)(\sigma \mathrm{N_F} \beta_F - K\mu_E\mu_F) + K\sigma \mathrm{N_V} \beta_F \mu_E \mu_V}$$

,

$$I_V^* = \frac{\sigma \mathrm{N_V} \beta_V (\eta\sigma \mathrm{N_F} \mathrm{N_V} \beta_F + K\mu_E (I_F \beta_F - \eta \mathrm{N_V} \mu_F))}{\beta_V (\eta\sigma \mathrm{N_V} + K\mu_E)(\sigma \mathrm{N_F} \beta_F - K\mu_E\mu_F) + K\sigma \mathrm{N_V} \beta_F \mu_E \mu_V}$$

,

$$S_F^* = \frac{K\mathrm{N_F}\mu_F}{U\beta_F + K\mu_F}$$

,

$$I_F^* = \mathrm{N_F} - \frac{K\mu_E\mu_F}{\sigma\beta_F},$$

$$\mathrm{U}^* = \frac{\sigma\mathrm{N_F}\beta_F - K\mu_E\mu_F}{\beta_F\mu_E}$$

$$E_0 = (S_H^0, 0, 0, S_V^0, 0, S_F^0, 0, 0)$$

### 5.3.1 The model reproduction number

Basic reproduction ratio is the expected numbers of secondary cases of infection per primary case of infection in a virgin population during the infectious period of primary case (Diekmann et al., 1990). By applying the next generation operator approach Van den Driessch et al., 2002), F and V are represented as matrices respectively for the new infections generated and the transition terms is then obtained as

$$F = \begin{pmatrix} 0 & \beta_H \frac{S_H(0)}{N_H} & 0 & 0 \\ 0 & 0 & \beta_V \frac{S_V(0)}{N_V} & \beta_V \eta \frac{S_V(0)}{K} \\ 0 & 0 & 0 & \beta_F \frac{S_F(0)}{N_F} \\ 0 & 0 & \sigma & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} (\mu_H + \gamma) & 0 & 0 & 0 \\ 0 & \mu_V & 0 & 0 \\ 0 & 0 & \mu_F & 0 \\ 0 & 0 & 0 & \mu_E \end{pmatrix}$$

$$\Re_0 = \rho\left(FV^{-1}\right) = \sqrt{\frac{\beta_F\sigma}{K\mu_E\mu_F}}$$

The basic reproduction number $\Re_0$ is expressed as the spectral radius of the matrix $\mathbf{FV}^{-1}$ and therefore $\Re_0 = \sqrt{\frac{\beta_F \sigma}{K \mu_E \mu_F}}$ The model reproduction number is determined by fish population and the density of Mycobacterium ulcerans in the environment. The reproduction number of the model (5.1) appears to be in ascendancy linearly with shedding rate of MU into the environment and effective contact rate between fish and MU. The spread of BU from model (5.1) does not depend on humans and the vector.

### 5.3.2 Stability of the disease free equilibrium

**Theorem 5.3.1** *The disease free equilibrium $E_0$ whenever it exists is locally asymptotically stable if $\Re < 1$ and unstable otherwise.*

The Jacobian matrix of model (5.1) at the equilibrium point $E_0$ is expressed by

$$J_{E_0} = \begin{pmatrix} -\mu_H & 0 & \theta & 0 & -\beta_H \frac{S_H}{N_H} & 0 & 0 & 0 \\ 0 & (\mu_H + \gamma) & 0 & 0 & \beta_H \frac{S_H}{N_H} & 0 & 0 & 0 \\ 0 & \gamma & (\mu_H + \theta) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_V & 0 & 0 & -\beta_V \frac{S_V}{N_V} & -\eta \beta_V \frac{S_V}{K} \\ 0 & 0 & 0 & 0 & -\mu_V & 0 & \beta_V \frac{S_V}{N_V} & \eta \beta_V \frac{S_V}{K} \\ 0 & 0 & 0 & 0 & 0 & -\mu_F & 0 & \beta_F \frac{S_F}{K} \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_F & \beta_F \frac{S_F}{K} \\ 0 & 0 & 0 & 0 & 0 & 0 & \sigma & -\mu_E \end{pmatrix}$$

It can be observed that the eigenvalues of $J_{E_0}$ are $(\mu_H + \gamma), (\sigma + \mu_H), -\mu_F, -\mu_H, -\mu_V, -\mu_V$ and the roots of quadratic equation $Q(\lambda) = \lambda^2 + (\mu_H + \mu_F)\lambda + \mu_H \mu_F (1 - \Re_0) = 0$. The computational results of $Q(\lambda) = 0$ shows to have negative parts only if $\Re < 1$. A conclusion can be made that the disease free equilibrium is locally asymptotically stable whenever$\Re > 1$.

### 5.3.3 Stability of the disease endemic equilibrium

The local geometric characteristics of the endemic equilibrium of model (5.1) is examined. The following theorem are stated:

**Theorem 5.3.2** *If* $\Re > 1$ *the endemic equilibrium point* $E_1$ *model* (5.1)*, is locally asymptotically stable.*

However, it is difficult to deal with stability of endemic equilibrium $E_1$ analytically because it contains a quadratic equation. By numerical approach, the endemic equilibrium is locally asymptotically stable. This is depicted in (5.1). Three different initial conditions for the simulation are applied. Those orbits shown to be the same point as time evolves.

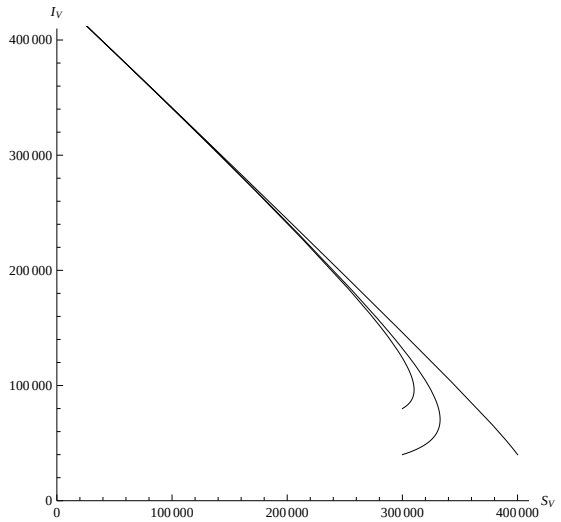



Figure 5.1: A phase potrait of model (5.1) in $S_V$ — $I_V$ plane.

## 5.4 Analysis of Optimal Control

The state system is the following system of eight ordinary differential equations

$$
\left.
\begin{aligned}
\frac{dS_H}{dt} &= \mu_H N_H + \theta R_H - \beta_H(1-u_1(t))\frac{S_H I_V}{N_H} - \mu_H S_H, \\
\frac{dI_H}{dt} &= \beta_H(1-u_1(t))\frac{S_H I_V}{N_H} - (\mu_H + u_1(t)\gamma) I_H, \\
\frac{dR_H}{dt} &= u_1(t)\gamma I_H - (\mu_H + \theta) R_H, \\
\frac{dS_V}{dt} &= \mu_V N_V - \beta_V(1-u_2(t))\frac{S_V I_F}{N_V} - \eta\beta_V \frac{S_V U}{K} - \mu_V S_V, \\
\frac{dI_V}{dt} &= \beta_V(1-u_2(t))\frac{S_V I_F}{N_V} + \eta\beta_V \frac{S_V U}{K} - \mu_V I_V, \\
\frac{dS_F}{dt} &= \mu_F N_F - \beta_F(1-u_3(t))\frac{S_F U}{K} - \mu_F S_F, \\
\frac{dI_F}{dt} &= \beta_F(1-u_3(t))\frac{S_F U}{K} - \mu_F I_F, \\
\frac{dU}{dt} &= \sigma I_F - \mu_E U.
\end{aligned}
\right\} \tag{5.3}
$$

The control $u_1(t)$, deals with reducing the exposure of susceptible humans to those infected water bugs. This can be achieved by using insecticides and preventing the exposure of the human body from biting by water bugs where where $(0 \leqslant u_1 \leqslant 1)$. The control $u_2(t)$, models the efforts needed in bringing down effective contact between the water bugs and small fishes which can result into water bug infection where $(0 \leqslant u_2 \leqslant 1)$. The last control $u_3(t)$ examines the efforts required in reducing the infection between the water bugs and the environment where $(0 \leqslant u_3 \leqslant 1)$. In order to achieve a successful control of BU, the effort is needed in the determination of the infected and also strictly putting measures to reduce it.

The objective is to minimize the number of infected humans in a settlement $(I_H)$ while maintaining the cost associated to control $u_1, u_2$ and $u_3$ as much as

possible. We seek to minimize the number of Buruli ulcer infected host and cost of employing mass treatment, insecticide controls and reducing the number of infected fishes. The proposed optimal control problem with objectives functional is expressed as

$$J(u_1, u_2, u_3) = \int_0^{t_f} \left[ I_H(t) + I_V(t) + I_F(t) + \frac{Q_1}{2}u_1^2(t) + \frac{Q_2}{2}u_2^2(t) + \frac{Q_3}{2}u_3^2(t) \right] dt \tag{5.4}$$

where $Q_1, Q_2$ and $Q_3$, are the weighting constants for the mass treatment human host, insecticide activities and mass education for fish farmers and are nonlinear and are of quadratic forms. We, seek an optimal control $u_1^*, u_2^*$ and $u_3^*$ such that

$$J(u_1^*, u_2^*, u_3^*) = \min_{\Omega} J(u_1, u_2, u_3) \tag{5.5}$$

where

$$\Omega = \{(u_1, u_2, u_3) \in L^1(0, t_f) \big| \, d_i \leqslant u_i \leqslant e_i, i = 1, 2, 3\}$$

We analyze model 5.3 in other words model of the spread of Buruli ulcer in population applying optimal perspective. We take into account the objective function 5.4 to model 5.3. Pontryagins Maximum Principle employed to determine the optimal control $u_1^*, u_2^*$ and $u_3^*$ with necessary conditions. The necessary conditions to establish optimal control $u_1^*, u_2^*$ and $u_3^*$ that meet condition 5.5 and its constraint model 5.3 will be determined by applying Pontryagins Maximum Principle ( Pontryagin) . The principle changes (5.3), (5.4) and (5.5) into a problem of minimizing pointwise a Hamiltonian, $H$, with respect to $(u_1, u_2, u_3)$, simply

$$\begin{aligned} &\mathrm{H}(S_H, I_H, R_H, S_V, I_V, S_F, I_F, U, u_1, u_2, u_3, \lambda_1, \lambda_2, \lambda_3\lambda_4, \lambda_5, \lambda_6, \lambda_7, \lambda_8) \\ &= I_H(t) + I_V(t) + I_F(t) + \frac{Q_1}{2}u_1^2(t) + \frac{Q_2}{2}u_2^2(t) + \frac{Q_3}{2}u_3^2(t) + \sum_{i=1}^{8} \lambda_i g_i \end{aligned}$$

where $g_i$ is the right hand side of the differential equations of the *ith* state variable. By using Pontryagins Maximum Principle and the existence of results obtained for optimal control, we obtain

**Theorem 5.4.1** *There exists an optimal control* $u_1^*, u_2^*, u_3^*$ *and corresponding solution,* $S_H^*, I_H^*, R_H^*, S_V^*,$
$I_V^*, S_F^*, I_F^*$ *and* $U^*$*,that minimizes* $J(u_1, u_2, u_3)$ *over* $\Omega$*. Furthermore, there exist adjoint functions* $\lambda_1(t), ..., \lambda_8(t)$ *such that*

$$\frac{d\lambda_1}{dt} = \lambda_1\left(\beta_H(1-u_1(t))\frac{I_V^*}{N_H} + \mu_H\right) + \lambda_2\left(-\beta_H(1-u_1(t))\frac{I_V^*}{N_H}\right)$$

$$\frac{d\lambda_2}{dt} = -1 + \lambda_2\left(\mu_H + u_1(t)\gamma\right) + \lambda_3\left(-\gamma u_1(t)\right)$$

$$\frac{d\lambda_3}{dt} = \lambda_3\left(\mu_H + \theta\right) - \lambda_1\theta$$

$$\frac{d\lambda_4}{dt} = \lambda_4\left(\beta_V(1-u_2(t))\frac{I_F^*}{N_V} + \eta\beta_V\frac{U^*}{K} + \mu_V\right) + \lambda_5\left(-\beta_V(1-u_2(t)\frac{I_F^*}{N_V} - \eta\beta_V\frac{U^*}{K}\right)$$

$$\frac{d\lambda_5}{dt} = -1 + \lambda_5\mu_V + \lambda_1\left(\beta_H(1-u_1(t))\frac{S_H^*}{N_H}\right) + \lambda_2\left(-\beta_H(1-u_1(t))\frac{S_H^*}{N_H}\right)$$

$$\frac{d\lambda_6}{dt} = \lambda_6\left(\beta_F(1-u_3(t))\frac{U^*}{K} + \mu_F\right) + \lambda_7\left(\beta_F(1-u_3(t))\frac{U^*}{K}\right)$$

$$\frac{d\lambda_7}{dt} = -1 + \lambda_7\mu_F + \lambda_4\left(\beta_V(1-u_2(t))\frac{S_V^*}{N_V}\right) + \lambda_5\left(-\beta_V(1-u_2(t))\frac{S_V^*}{N_V}\right) + \lambda_6\left(-\sigma\right)$$

$$\frac{d\lambda_8}{dt} = \lambda_8\mu_E + \lambda_4\left(\eta\beta_V\frac{S_V^*}{K}\right) + \lambda_5\left(-\eta\beta_V\frac{S_V^*}{K}\right) + \lambda_6\left(\beta_F(1-u_3(t))\frac{S_F^*}{K}\right) + \lambda_7\left(-\beta_F(1-u_3(t))\frac{S_F^*}{K}\right) \tag{5.6}$$

with transversality conditions

$$\lambda_i(t_f) = 0, i = 1..., 8 \tag{5.7}$$

By using Pontryagin's Maximum Principle and the existence result for the optimal control (Makinde et al., 2011), we arrive at the following theorem.

**Theorem 5.4.2** *The optimal control* $(u_1^*, u_2^*, u_3^*$ *) that minimizes* $J(u_1, u_2, u_3)$

*over* $\Omega$ *is expressed as*

$$u_1^* = \max\left\{0, \min\left\{1, \frac{(\lambda_2 - \lambda_1)\,\beta_H u_1(t))\frac{I_V}{N_H} + (\lambda_2 - \lambda_3)\,\gamma + (\lambda_2 - \lambda_1)\,\beta_H \frac{S_H}{N_H}}{Q_1}\right\}\right\}$$

$$u_2^* = \max\left\{0, \min\left\{1, \frac{(\lambda_5 - \lambda_4)\,\frac{I_F}{N_V} + (\lambda_5 - \lambda_4)\,\beta_V \frac{S_V}{N_V}}{Q_2}\right\}\right\}$$

$$u_3^* = \max\left\{0, \min\left\{1, \frac{(\lambda_7 - \lambda_6)\,\beta_F \frac{U}{K} + (\lambda_7 - \lambda_6)\,\beta_F \frac{S_F}{K}}{Q_3}\right\}\right\} \tag{5.8}$$

**Proof** (Fleming et al., 1975) provides the existence of an optimal control due to the convexity of integrand with respect to $(u_1, u_2, u_3)$, a *priori* boundedness of the state solutions, and the *Lipschitz* property of the state system with respect to the state variables. Employing Pontryagins Maximum Principle, we have

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{S_H}, \lambda_1(t_f) = 0,$$

$$\frac{d\lambda_8}{dt} = -\frac{\partial H}{U}, \lambda_8(t_f) = 0, \tag{5.9}$$

Computed at the optimal control pair and respective corresponding states, which leads to the stated adjoint system 5.6 and 5.7, (Kamien et al. 1991). By taking into account the optimality conditions,

$$\frac{\partial H}{u_1} = 0, \frac{\partial H}{u_2} = 0, \frac{\partial H}{u_2} = 0$$

and determine the values for $u_1^*, u_2^*, u_3^*$, subject to the constraints, the characterizations (5.8) can be obtained. We illustrate the characterization of $u_2^*$, we obtain

$$\frac{\partial H}{\partial u_2} = u_2 Q_2 - \lambda_5 \frac{I_F}{N_V} + \lambda_4 \frac{I_F}{N_V} - \lambda_5 \beta_V \frac{S_V}{N_V} + \lambda_4 \beta_V \frac{S_V}{N_V} = 0$$

By considering the bounds on $u_2^*$, the characteristics of $u_2^*$ in 5.8 is obtained. By the fact that there is a *priori* boundedness of the state and adjoint functions and the resulting *Lipschitz* structure of the Ordinary Differential Equations (ODEs), the uniqueness of the optimal control for small value of $t_f$ is obtained. The uniqueness of the optimal control based on the uniqueness of the optimality system, which is made up of (5.3) and (5.6), (5.7) with characterization (5.8). In order to guarantee the uniqueness of the optimal system, a restriction is put on the length of the time interval. The restriction on the length of time is as a result of opposite orientation of (5.3), (5.6) and (5.7). The stated problem contains the initial values and the adjoint problem contains final values.

## 5.5 Numerical Results

In this section , we study numerically an optimal treatment strategy of our Buruli ulcer dynamics model. The optimal strategy is obtained by solving the optimally system, made up of 16 ODEs from the state and adjoint equations. An iterative approach is employed for computing the optimality system. We begin by solving the state equations with a guess for the controls on the simulated time applying a forward fourth order Runge- Kutta scheme. By the fact that we have transversality conditions(5.7), the adjoint equations are overcome by a backward fourth order Runge -Kutta scheme applying the immediate iteration solution of the state equations. There after, the controls are updated by employing a convex combination of the previous controls and value obtained with respect to characterizations (5.8). The process is repeated and stopped if the values of unknowns at the formal iteration are very close to the ones at the current iteration (Lenhart et al., 2007).

In order to present numerical simulations, we use parameter values as in Table (5.1), and our initial condition $y(0) = (400, 40, 100, 100, 20, 100, 10, 10)$ and the weighting control is stated as $Q_1 = 50, Q_2 = 20, Q_3 = 30$ . We assume

the weighting factor $Q_1$ in connection with mass treatment control $u_1^*$ is greater than $Q_2$ and $Q_3$ which is associated with insecticide and mass public education respectively. The cost of mass treatment includes the cost of screening , cost of medications, expenditure on the person taking care of the BU patient. Cost of insecticide also includes the cost of machines for spraying and labour cost and the cost of transportation of the personnel and chemicals.With regard to mass public education, the cost involved includes the cost of labour, cost of transportation, cost of manual materials. With respect to time horizon, we use 100 days.

In order to achieve the objective, the state system 5.3, costate system (5.6) and the optimal characterization (5.7) are solved numerically with the following algorithm:

**Step 1.** Subdivide the time interval $[t_0, t_f]$ into $N$ equal subintervals and assume a piecewise-constant control $u_j^0(t)$, $t \in [t_k, t_{k+1}]$, where $k = 0, 1, ..., N$ and $j = 1, 2$.

**Step 2.** Applying the assumed control $u_j^0(t)$, to integrate the state system with an initial condition $\bar{x}(t_0) = \bar{x}(0)$ $(\bar{x}(0) = S_H(0), I_H(0), R_H(0), S_V(0), I_V(0), S_F(0), I_F(0), U(0))$, forward in time $[t_0, t_f]$ using the fourth - order Runge- Kutta method.

**Step 3.** Applying the assumed control $u_j^0(t)$, to integrate the state system with with transversality condition $\lambda_i(t_f) = 0, i = 1..., 8$ backward in time $[t_0, t_f]$ using the fourth-orderRunge-Kutta method.

**Step 4.** Check if the current state, costate solution and control values are sufficiently close to a successive iteration.

**Step 5.** If Step 4 is satisfied STOP the iteration (the optimal control is achieved) otherwise update the control using a convex combination of the current and previous control together with the characterization 5.7 and go to Step 2.

The least square method was applied to estimate most of the parameters since they cannot be obtained from any literature or experimental set up. This was done by initially guessing parameter values and carefully observing fit of graphs till a time that a good fit with least error was obtained.

Table 5.1: Parameter values used for the simulations

| Parameter | Value/Range | Source |
|---|---|---|
| $\mu_H$ | 0.004566 | (Aidoo et al.,2007) |
| $\gamma_H$ | 0.04 | (Aidoo et al., 2007) |
| $\theta$ | 0.4 | (Aidoo et al.,2007 ) |
| $K$ | 10000 | Estimated |
| $\beta_H$ | 0.80 | (Aidoo et al., 2007) |
| $\beta_V$ | 0.45 | Estimated |
| $\eta$ | 0.004 | Estimated |
| $\beta_F$ | 0.5 | Estimated |
| $\mu_F$ | 0.004 | Estimated |
| $\mu_V$ | 0.06 | Estimated |
| $\sigma$ | 0.8 | Estimated |
| $\mu_E$ | 0.65 | Estimated |

### 5.5.1 Mass treatment control

In this section, we consider only control $u_1^*$ on mass treatment and both control $u_2^*$ and $u_3^*$ are set zero. The profile of the optimal control $u_1^*$ is depicted in Figure (5.2). In order to do away with Buruli ulcer disease in 100 days, the treatment should be held intensively almost 100 days.

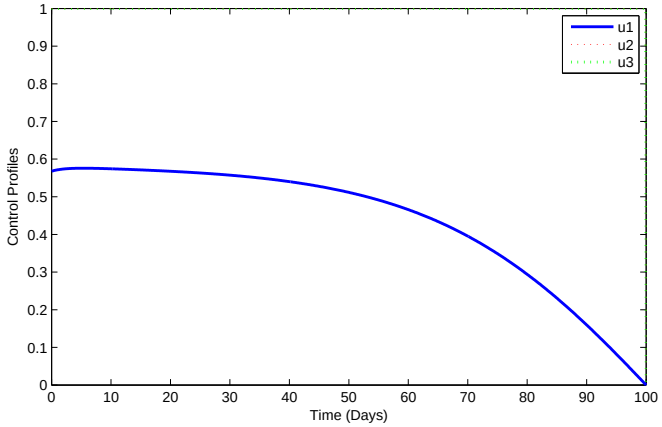
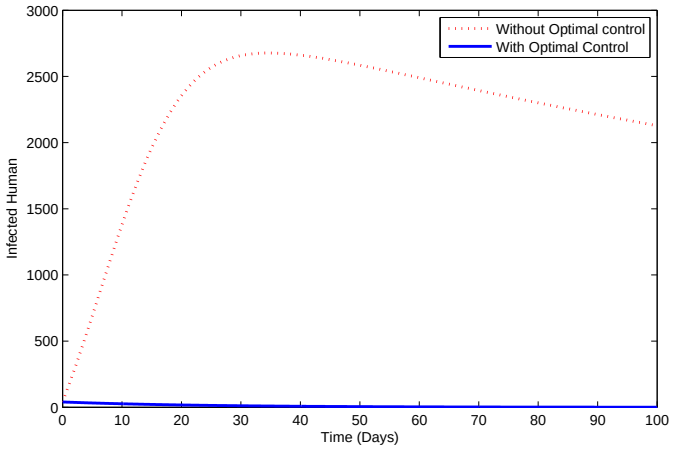
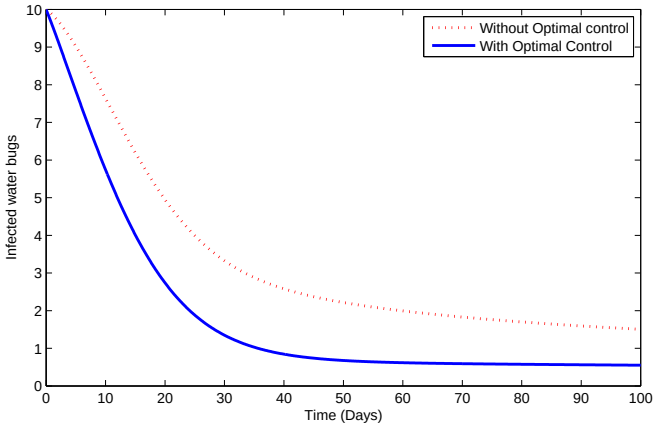



Figure 5.2: The profile of the optimal control $u_1$ via mass treatment only

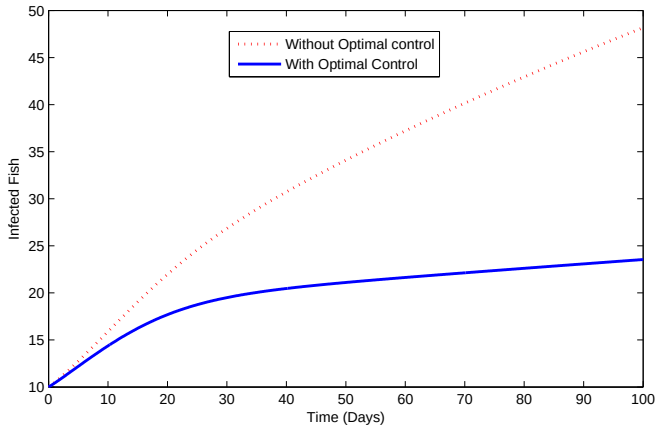



(a)

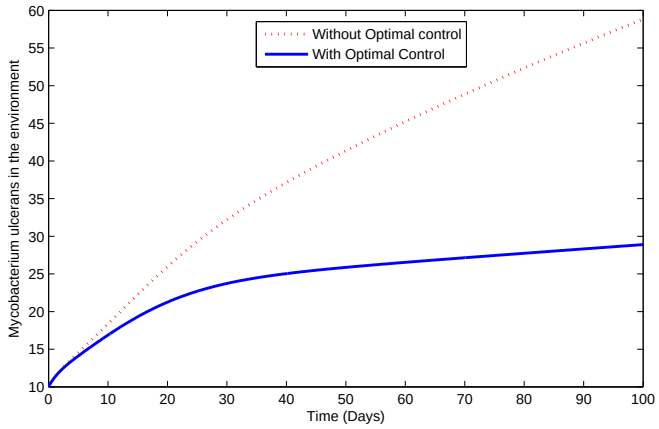



(b)

By applying optimal control $u_1^*$ in Figure (5.2), we show the dynamics of infected humans, water bug, small fishes and Mycobacterium in the environment as observed in Figures 5.3(a),5.3(b), 5.3(c) and 5.3(d) respectively. These numbers




(c)




(d)

Figure 5.3: The optimal solution for infected humans,water bugs, small fish and MU in environment $(I_H, I_V, I_F, U)$ via mass treatment only

increase without optimal control $u_1^*$ and that is to say if there is no mass treatment. It is interesting to observe from Figure 5.3(b) that without the mass treatment the number of infected water bug decreases. However, the addition of the this control $u_1^*$ increases the rate of the reduction of the infection and slows the reduction otherwise.

### 5.5.2 Insecticide control

In this regard, we set both mass treatment control $u_1^*$ and mass education control $u_3^*$ we then activate only $u_2^*$ which is the insecticide as shown in Figure (5.4). The profile of the optimal control $u_2^*$ on insecticide Figure (5.4) is shown. It is observed in Figure 5.5(a) that the number of infected humans drastically decreases with the application of insecticide control. This situation reverses without the control $u_2^*$. In Figure 5.5(b), the infected water bug reduces without the control $u_2^*$ but with the control the reduction is higher. This process reduces without the application of insecticide. Figure 5.5(c) depicts that infected small fish reduces with insecticide control $u_2^*$ and increases without the control $u_2^*$. An observation was also made in Figure 5.5(d) that the shedding of MU in the environment decreases with insecticide control $u_2^*$ and increases in the environment without the control. That is to say, increase in shedding of MU in the environment.

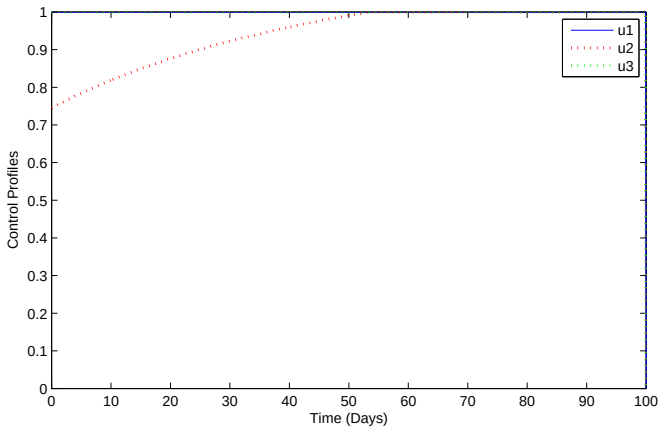
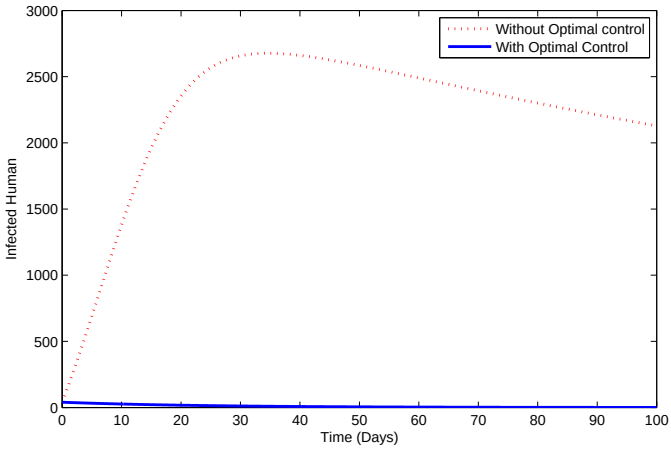
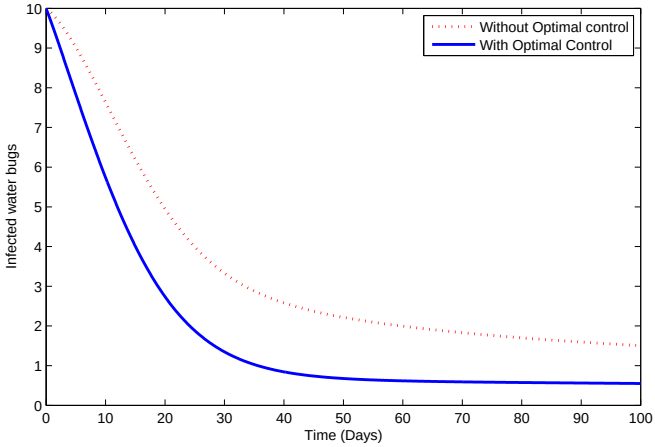


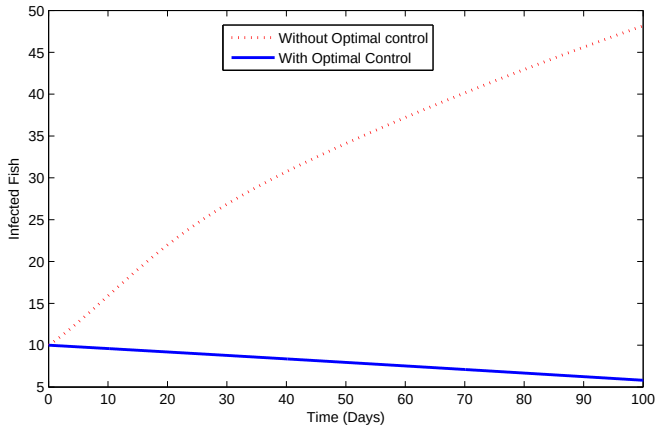

Figure 5.4: The profile of the optimal control $u_2$ via insecticide application only


Without Optimal control
With Optimal Control
Infected Human
Time (Days)
0
500
1000
1500
2000
2500
3000
0
10
20
30
40
50
60
70
80
90
100

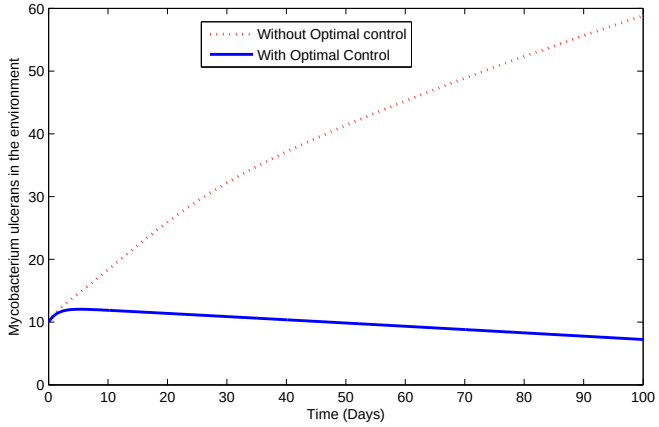
(a)


Without Optimal control
With Optimal Control
Infected water bugs
Time (Days)
0
1
2
3
4
5
6
7
8
9
10
0
10
20
30
40
50
60
70
80
90
100

(b)




(c)




(d)

Figure 5.5: The optimal solution for infected humans,water bugs, small fish and MU in environment $(I_H, I_V, I_F, U)$ via insecticide application only

### 5.5.3 Mass Education

In this scenario, we activate only the control $u_3^*$ on mass education while both controls $u_1^*$ and $u_2^*$ are set to zero. Figure (5.6) depicts optimal control $u_3^*$. In order to eliminate BU in 100 days, the mass education must be carried out intensively for almost 100 days as observed in Figure (5.6). In Figure 5.7(a), the number of infected humans decreases drastically with control $u_3^*$. That is to say, mass education and situation increase without mass education control $u_3^*$. Interestingly, in Figure 5.7(b) infected water bugs decreases sharply with mass education which is control $u_3^*$ and infected water bugs increase otherwise.

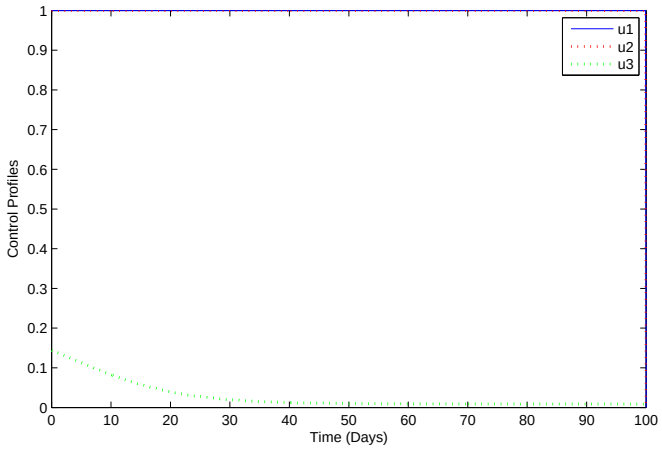
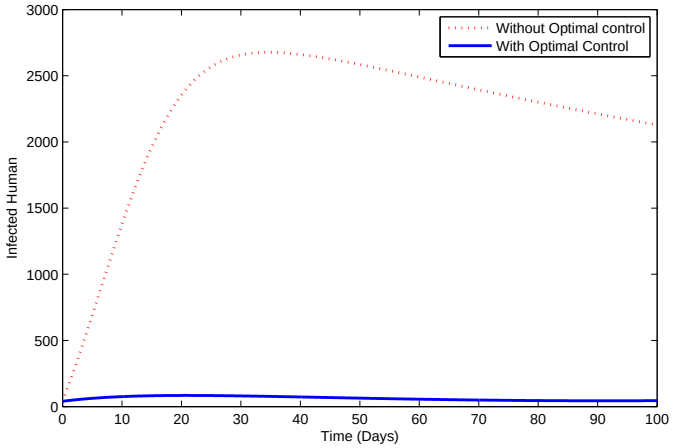
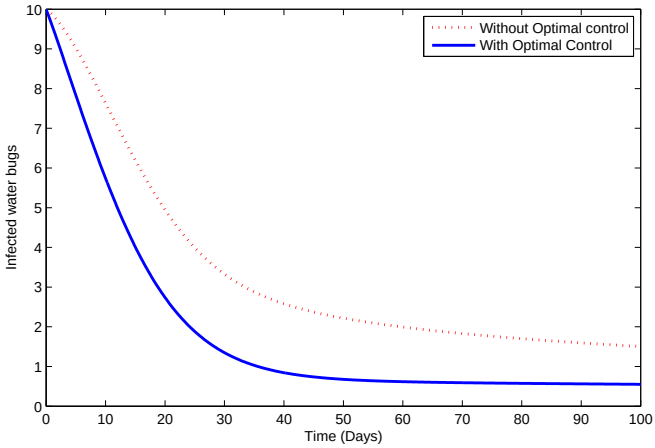



Figure 5.6: The profile of the optimal control $u_3$ via mass education only



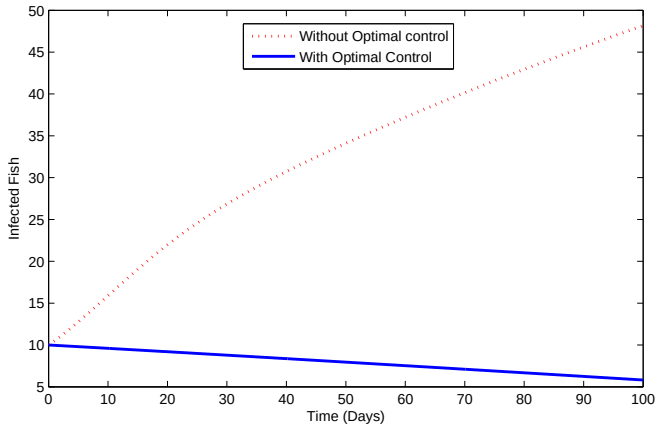

(a)



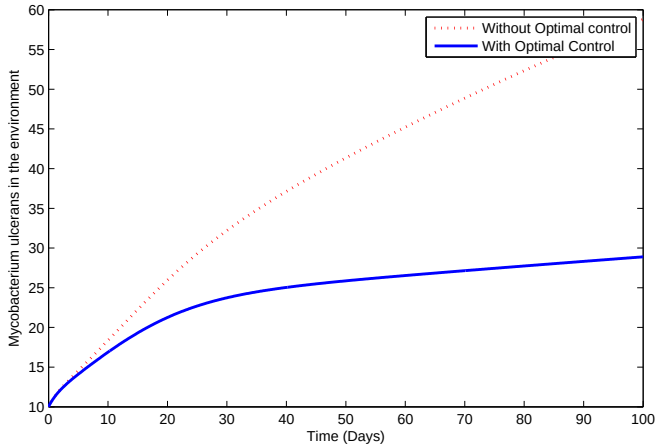

(b)

Figure 5.7(c) depicts that infected small fishes decrease with mass education control $u_3^*$ and increase with the control $u_3^*$. We observed in Figure 5.7(d) that

the shedding of MU in the environment reduces with control $u_3^*$ that is to say mass education and the situation reverses without the mass education.




(c)




(d)

Figure 5.7: The optimal solution for infected humans,water bugs, small fish and MU in environment $(I_H, I_V, I_F, U)$ via mass education only

### 5.5.4 Mass treatment, Insecticide Control and Mass Education

In this perspective, the mass control $u_1^*$, the insecticide control $u_2^*$ and mass education $u_3^*$ are all activated to optimize the objective function J. The profile of optimal control $u_1^*$, $u_1^*$ and $u_3^*$ in Figure (5.8) are shown. By using the optimal control $u_1^*$, $u_1^*$ and $u_3^*$ as observed in Figure 5.8, the dynamics infected human,water bugs, small fish and MU in the environment are depicted in the Figures 5.9(a), 5.9(b), 5.9(c) and 5.9(d) respectively. In general, it is observed that infected humans as seen in Figure 5.9(a) decrease with the activation of all the controls.

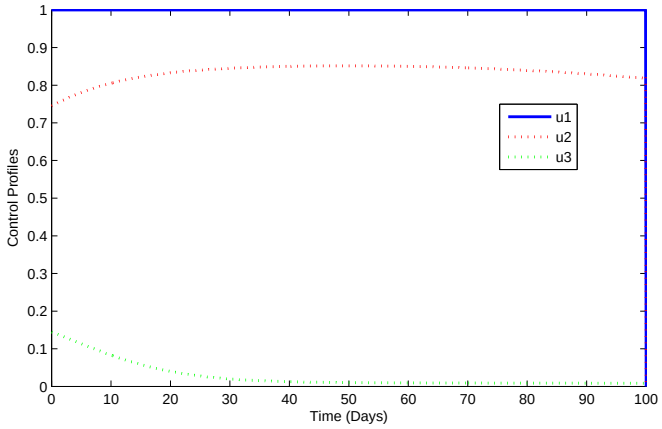
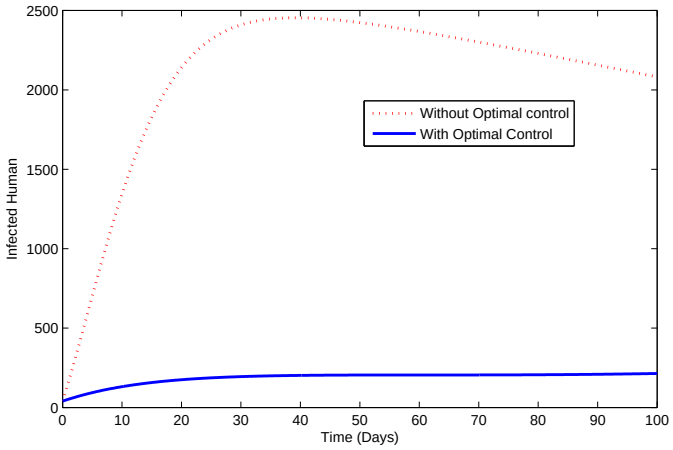
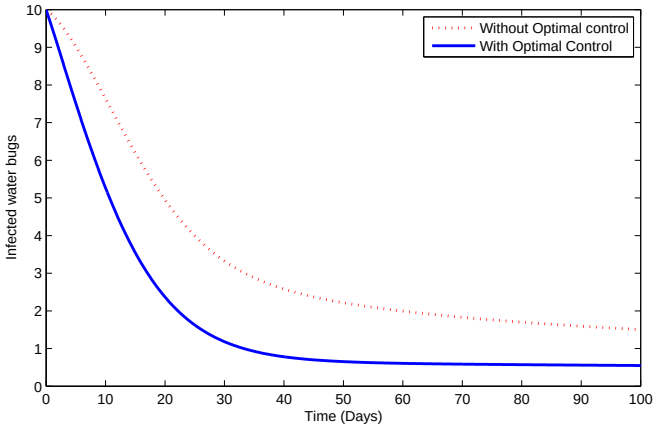



Figure 5.8: The profile of the optimal control $u_1, u_2, u_3$ via mass treatment, insecticide application and mass education

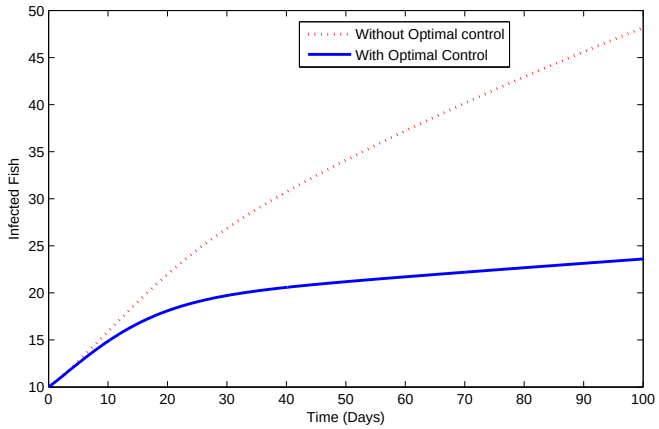



(a)

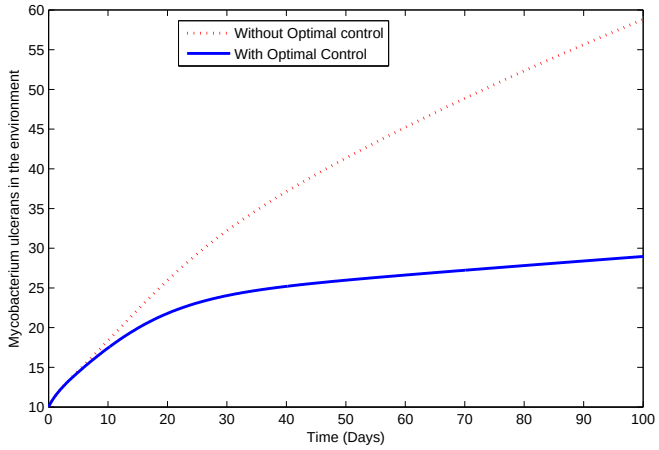



(b)

That is, to say $u_1^*$, $u_1^*$ and $u_3^*$. Similarly in Figures 5.9(b), 5.9(c) and 5.9(d) we can see that the activation of controls $u_1^*$, $u_1^*$ and $u_3^*$ had more reductions with the controls imposed. In other words the mass treatment, insecticide and mass education reduce the spread of Buruli ulcer disease. In the absence of these combinations of controls, the number of infections within respective classes increase.




(c)




(d)

Figure 5.9: The optimal solution for infected humans,water bugs, small fish and MU in environment $(I_H, I_V, I_F, U)$ via mass treatment, insecticide application and mass education

## 5.6 Summary

In this chapter, a deterministic model is derived and analysed for the spread of Buruli ulcer that includes mass treatment, insecticide and mass education. The basic reproduction ratio $Re_0$ is determined. This ratio depicts the existence and the stability of the equilibra of the model. Applying optimal control strategy, a solution to the eradication of BU disease in a finite time can be found. By observing the numerical results, a conclusion can be made that the combination of all the control $u_1^*$, $u_2^*$ and $u_3^*$ are capable of helping reduce the number of infected humans, water bugs, small fishes and MU in the environment.

# CHAPTER 6

# AN AGE STRUCTURE MODEL FOR BURULI ULCER DISEASE TRANSMISSION

## 6.1 Introduction

In this chapter we shall formulate an age-structured BU model. A theoretical and numerical analysis of the model are provided. Subsequently, the system of differential equations along with initial and boundary conditions that form the disease model is examined. A proof is further made on the existence and uniqueness of solution in $L^1$ and $L^\infty$ to the PDE system using a fixed point argument on a representation derived from the method of characteristics. The mathematical well-posedness of the time evolution problem using the semigroup theory approach is established.Then the basic reproduction ratio $R_0$. is determined The numerical method and its implementation as well as conclusion are presented.

## 6.2 The model and its analysis

### 6.2.1 Model formulation

The human population is considered and divided into three subgroups: the susceptible individuals who do not have Buruli ulcer but are at risk of getting it, infected individuals with the ulcer and the recovered, who would have been treated of the disease. Within each category, the age and population changes over time are taken into account. The number of people in each subgroup are expressed as $S = S(a,t)$ , $I = I(a,t)$ and $R = R(a,t)$, each variable is a function of age

$a$ and time $t$. In order to use a dimensional approach in this model, we formally apply units of weeks for the age of humans $a$ and days for the simulation time $t$ . However, conventional units of years are also used in some instances to elucidate the age of human population. The number of susceptible people between, say age $a_1$, and $a_2$ at a time $t$ is expressed as $\int_{a_1}^{a_2} S(a,t)da$ using conventional understanding that all humans from $a = a_0$ year to $a = a_0+1$ years are considered $a_0$ years old. A similar approach is also used for the infected and recovered humans $I(a,t)$ and $R(a,t)$ respectively. There is one water bug compartment of infective M. ulcerans denoted by $B_H = B_H(t)$. The four quantities $S, I, R, B_H$ are dependent variables of the model. Buruli ulcer is considered a water-borne disease and in most cases, transmission of the disease is through contact with contaminated water bodies (Marston et al., 1995; Amofah et al., 1993). In order to account for various factors that influence the dynamics of a BU epidemic, an extra coefficient function which maybe constant or may vary with age or time (or both) have been put in the model. A disturbed environment is taken into account in the model formulation. A human demographic recruitment term $\Lambda(a,t)$ is included alongside natural death rate $\mu_H(a)$.

The possible interrelations between humans, the M. ulcerans are represented by the schematic diagram in Figure (6.1).

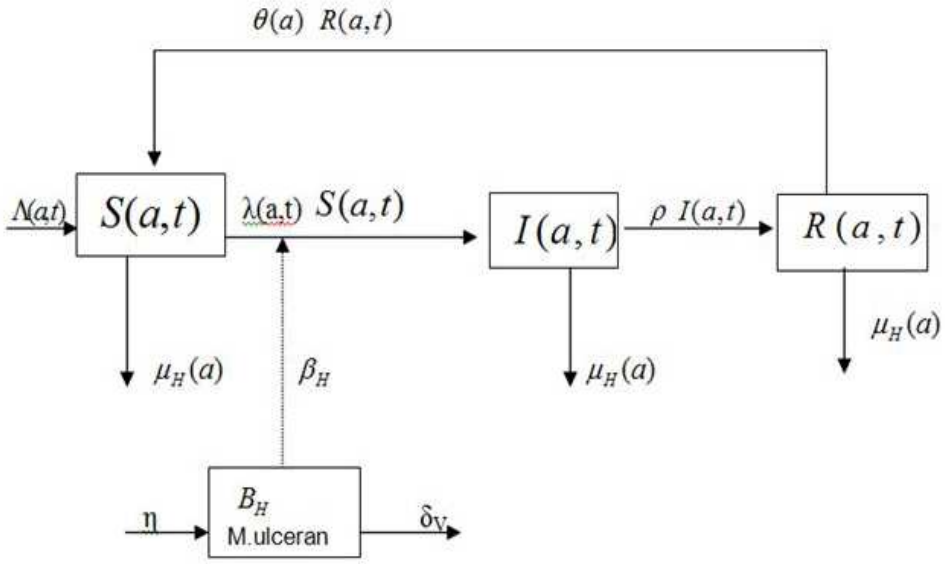



Figure 6.1: Proposed transmission dynamics of the Buruli ulcer between humans and MU in the environment

The susceptible individuals become infected through interacting with the environment with *M. ulcerans* at rate $\beta_H(a)\beta_H(t)/(k_H(a) + \beta_H(t))$ with *M. ulcerans* concentration measured with respect to infectious dose denoted by $g$. The human population suffers a natural per capita mortality rate $\mu_H(a)$. Individuals recover from BU at a rate of $\rho$ which may depend on age (Portaels et al., 1998). The clearance rate of *Mycobacterium ulcerans* in the environment may due to natural removal or predation is denoted by $\sigma_V$. The age – specific contribution of infected humans to the environment is denoted by $\eta$. In this study, a strategy $g(a,t)$ is included that can help reduce the spread of BU that represents antibiotic treatment. This reduces the duration and quantity of infected humans to the concentration of *M.ulcerans* bacteria in the environment. We are interested in investigating the existence of a solution to this nonlinear system in both analytic and numerical perspectives. The age-time domain $P = (0, A) \times (0, \mathrm{T})$ with intervention $(g)$ studied in

$$\Omega = \left\{(h) \in ((L^{\alpha}))^2 \,|0 \leq g(a,t) \leq B\right\} \tag{6.1}$$

where $B_1 \leq 1$ represent maximum fraction of intervention. The variables $S, I, R, B_H$ can be said to satisfy the system.

$$\frac{\partial S}{\partial t} + \alpha \frac{\partial S}{\partial a} = \Lambda(a,t) - \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)} S(a,t) - \mu_H(a) S(a,t) + \theta(a) R(a,t), \tag{6.2a}$$

$$\frac{\partial I}{\partial t} + \alpha \frac{\partial I}{\partial a} = \beta_H(a) \frac{B_H(t)}{k_H(a) + B_H(t)(t)} S(a,t) - \mu_H(a) I(a,t) - \rho_1 (1 - g(a,t)) I(a,t) - \rho_2 g(a,t) I(a,t) \tag{6.2b}$$

$$\frac{\partial R}{\partial t} + \alpha \frac{\partial R}{\partial a} = \rho_1 (1 - g(a,t)) I(a,t) + \rho_2 g(a,t) I(a,t) - \mu_H(a) R(a,t) - \theta(a) R(a,t), \tag{6.2c}$$

$$\frac{dB_H}{dt} = \int_0^\infty \eta I(a,t) da - \delta_V B_H(t) \tag{6.2d}$$

The equations for the quantities S, I and R form a hyperbolic system of PDEs and one additional ODE for $B_H$. For the above equations $\alpha = \frac{1}{7}$ per day is the coefficient introduced to balance the units of age $a$ in weeks and time $t$ in days which is the wave speed. With respect to infected class, the multiplicative factors $\rho_1 (1 - g)$ and $\rho_2 g$ represent the rates of recovery for the individuals who have had no antibiotic treatment and those who have undergone such treatment respectively.

### 6.2.2 The Boundary and Individual Conditions

The boundary conditions for S, I, and R are determined by the following assumptions:

- Newborns are not susceptible.

- Newborns are not infected with Buruli ulcer disease.
- Initially all births are protected.

This is significantly different from most model. We translate this consideration to state the boundary conditions

$$S(0,t) = 0, \tag{6.3a}$$

$$I(0,t) = 0, \tag{6.3b}$$

$$R(0,t) = \int_0^A (S(a,t) + I(a,t) + R(a,t))f(a)da, \tag{6.3c}$$

where the fecundity function $f(a)$ is the age- specific reproduction rate and stated as

$$f(a) \begin{cases} \frac{1}{5}\sin^2\left(\pi\frac{(a-15)}{30}\right) & 15 \leq a \leq 40 \\ 0 \; otherwise \end{cases}$$

The fecundity function $f(a)$ is stated here in units of per year for easier readability and assumes that from age 15 to 40 years a woman give generally give birth to three children, since $\int_0^{a+} f(a)da = 3$ where $a^+ = 60$ is the largest age allowed for the simulation.

The initial conditions are states as

$$S(a,0) = S_0(a), I(a,0) = I_0(a), R(a,0) = R_0(a), B_H(0) = B_H 0 \tag{6.4}$$

| Quantity | Description | Units |
|---|---|---|
| $S(a,t)$ | susceptible humans of age $a$ at $t$ divided uniformly over all ages | $\frac{human}{week}$ |
| $I(a,t)$ | infected humans of age $a$ at $t$ | $\frac{human}{week}$ |
| $R(a,t)$ | removed and immune humans of age $a$ at time $t$ | $\frac{human}{week}$ |
| $B_H(t)$ | Mycrobacterium ulcerans population | $cells/ml$ |
| $\alpha$ | wave speed | $week/days$ |
| $\Lambda(a,t)$ | recruitment rate of human population of age $a$ at time $t$ | $\frac{human}{week}$ |
| $g(a,t)$ | antibiotic treatment rate for humans of age $a$ at time $t$ | |
| $\beta_H(a)$ | contact rate of MU at age $a$ | $1/day$ |
| $\theta(a)$ | rate of waning immunity of humans at age $a$ | |
| $k_H(a)$ | saturation constant of MU at age $a$ | $cells/ml$ |
| $\mu_H(a)$ | natural mortality rate of humans at age $a$ | $1/day$ |
| $\rho_1$ | recovery rate of untreated Buruli ulcer | $1/day$ |
| $\rho_2$ | recovery rate of treated Buruli ulcer | $1/day$ |
| $f(a)$ | maternity rate | per woman |
| $\eta$ | age specific contribution of infected humans to the environment | $1/day$ |
| $\delta_V$ | clearance rate of MU in the environment | $1/day$ |

Table 6.1: Model parameters and the state variables

### 6.2.3 Abstract Cauchy problem formulation

We assume that all the parameters are nonnegative, i.e $\Lambda_H > 0, \mu_H > 0, \delta_V > 0, \beta_H > 0$

The parameters fulfill the following assumptions.

1. The functions $\rho_1(a), \rho_2(a), \eta(a) \in L^\infty(0,\infty)$, where $i = 1,2,3$

2. The functions $\varphi(a)$ is nonnegative and integrable.

### 6.2.4 Abstract Cauchy problem formulation

In this section we seek to deal with quantitative properties of 6.2a- 6.2d as in (Demasse et al., 2014; Kouakep et al., 2013). In order to undertake this, the Banach spaces is considered because We want to apply semigroup theory to obtain the invariant region of the system of equations of the model. Characterize the space of functions

$$Y = \mathbb{R} \times L^1(0,\infty) \times \mathbb{R} \times L^1(0,\infty) \times \mathbb{R} \times L^1(0,\infty),$$

Endowed by the norm

$$\|\phi\|_Y = \sum_{i=1}^{3} \|\phi_i\|_{L^1};$$

where $\phi = (\phi_1, \phi_2, \phi_3)^\Gamma \in Y$. Let us denote $Y_+$ the positive cone of $Y$. It is well known that $(Y, ||\,.\,||_Y)$ is a Banach space. Let $A : D(A) \subset Y \to Y$ be a operator defined by $A\phi = -\phi' - \mu_H \phi$, with the domain

$$D(A) = \left\{ \phi = (\phi_1, \phi_2, \phi_3) \in W^{1,1}(0, a^+, \mathbb{R}^3) \text{ and } \begin{pmatrix} \phi_1(0) \\ \phi_2(0) \\ \phi_3(0) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \int_0^{a+} |f(a)\,[\phi_1(a) + \phi_2(a) + \phi_3(a)]\,da \end{pmatrix} \right.$$

the function $F : \overline{DA} \to Y$ defined by

$$F_1 \begin{pmatrix} \phi_1 \\ \phi_2 \\ \phi_3 \end{pmatrix} = \begin{pmatrix} \Lambda - \beta_H \dfrac{B_H}{k_H + B_H}\phi_1 - \mu_H \phi_1 + \theta \phi_3 \\ \beta_H \dfrac{B_H}{k_H + B_H}\phi_1 - \mu_H \phi_2 - \rho_1(1-g)\phi_2 - \rho_2 g \phi_2 \\ \rho_1(1-g)\phi_2 + \rho_2 g \phi_2 - (\mu_H + \theta)\phi_3 \end{pmatrix}$$

$$F_2 = \int_0^{+\infty} \eta \phi_1 da$$

Let us consider that

$$\overline{DA} = X_0$$

Now by carefully observing $(S(t,.), I(t,.), R(t,.), B_H(t))$ in 6.2a -6.2d together with $u(t) = (0, 0, 0, S(t,.), I(t,.), R(t,.), B_H(t))^\Gamma$,One obtains that $u$ satisfies the following abstract Cauchy problem

$$\frac{du}{dt} = Au(t) + F(ut)), t > 1, \tag{6.5}$$

together with the initial data $u(0) = y = (0, 0, 0, S_0, I_0, R_0, )^\Gamma \in Y_0$. The positive cones also is taken into account

$$\mathrm{Y}_{+} = \left[\mathbb{R}^{+}\right]^{3} \times \left[L^{1}_{+}(0,\infty)\right]^{3},\ \mathrm{Y}_{0+} = \mathrm{Y}_{0} \cap \mathrm{Y}_{+}.$$

**Theorem 6.2.1** *There exists a continuous semiflow* $\{(U(t))\}_{t\geqslant 0}$ *on* $Y_{0+}$ *into itself such that for each* $y \in Y_{0+}$ *, the map* $t \to U(t)y$ *is the unique integrated solution of 6.5 with initial data* $y$*, namely* $t \to U(t)y$ *satisfies*

$$\int_{0}^{t} U(s)yds \in D(A), \forall t \geqslant 0,$$

$$\int_{0}^{t} U(t)y = x + A\int_{0}^{t} U(s)y)ds + F\int_{0}^{t} U(s)y)ds$$

*Moreover we have for each* $y \in Y_{0+}$*.*

$$lim\ sup_{t\to\infty} \| U(t)y\|\, y \leqslant \frac{\Lambda}{\mu_H}$$

**Proof** Let take into consideration that for each $N$ centered at 0 . One gets the existence of maximal positive semiflow for 6.5 on $Y_{0+}$ into itself. It remains to prove that this semiflow is globally defined. In order to achieve this, let $y \in Y_{0+}$ be given and recall that

$$U(t)y = (0,0,0,S(t,.),I(,.),R(,.))^{\Gamma}$$

Also let us consider the quantity

$$Q(t) = \|U(t)y\|\, y = \int_{0}^{\infty} S(t,a)da + \int_{0}^{\infty} I(t,a)da + \int_{0}^{\infty} R(t,a)da$$

the total population at time $t$ . Then it satisfies the differential inequality

$$\limsup_{t\to\infty} \|U(t)y\|\, y \leqslant \frac{\Lambda}{\mu_H},\ \forall y \in Y_{0+} - \mu_H Q(t)$$

Thus the map $t \to Q(t)$ cannot blow up in finite time and the global existence

result follows. Let us in addition, notice that, from this inequality one gets

$$\limsup_{t\to\infty} \|U(t)y\|\, y \leqslant \frac{\Lambda}{\mu_H},\ \forall y \in Y_{0+}$$

One the other hand one has

$$\frac{dQ(t)}{dt} = \Lambda - \mu_H Q(t)$$

$$\geqslant \Lambda - \mu_H$$

so that

$$\liminf_{t\to\infty} \|U(t)y\|\, y \leqslant \frac{\Lambda}{\mu_H},\ \forall y \in Y_{0+},\ \mathrm{B_H}(t) \leqslant \frac{\overline{\eta}\Lambda}{\mu_H \delta_V}$$

This completes the proof of the result.

$$\pi(a) = e^{-u(a)} e^{-\int_0^a (\rho_1(v)+g(v))dv}$$

Let $(S^*(a), I^*(a), R^*(a), B_H^*)$ represent any arbitrary endemic equilibrium of the model (6.2a-6.2d) established. This equilibrium satisfies the following equations

$$\frac{dS^*(a)}{da} = \Lambda(a,t) - \beta_H(a)\frac{B_H^*}{k_H(a)+B_H^*}S^*(a) - \mu_H(a)S^*(a) + \theta(a)R^*(a), \tag{6.6}$$

$$\frac{dI^*(a)}{da} = \beta_H(a)\frac{B_H^*}{k_H(a)+B_H^*}S^*(a) - \mu_H(a)I^*(a) - \rho_1(1-g(a))I^*(a) - \rho_2 g(a)I^*(a), \tag{6.7}$$

$$\frac{dR^*(a)}{da} = \rho_1(1-g(a))I^*(a) + \rho_2 g(a,t)I^*(a) - \mu_H(a)R^*(a) - \theta(a)R^*(a), \tag{6.8}$$

$$\frac{dB_H}{dt} = \int_0^\infty \eta I^*(a)da - \delta_V B_H^* = 0. \tag{6.9}$$

$$\tag{6.10}$$

Solving the second and fourth equations of 6.8- 6.10 respectively, leads

$$I^*(a) = I^*(0)\pi(a),$$

$$B_H^* = \frac{1}{\delta_V} \int_0^{+\infty} \eta I^*(a) da.$$

Let

$$R_0 = \frac{\beta_H \Lambda}{\mu_H \delta_V} \int_0^{\infty} [\eta_1(a)\pi(a)] d \tag{6.11}$$

According to (Diekmann et al.,1990) $R_0$ in 6.11 can be regarded as the basic reproduction number of the disease and explained as follows. Since the total infectivity at time $t$ is the sum of the infectivity in the compartment and the Mycobacterium ulcerans compartment, we define $R_0 = R_I + R_E$ where

$$R_I = \int_0^{\infty} S_0 \beta_H(a)\pi(a) da$$

is the number of secondary cases generated by individual in the infective compartment, and is the number of susceptible individuals in the absence of the disease. The term $S_0 = \Lambda/\mu_H$ is the number of susceptible individuals in the absence of the disease. The term $\pi(a) = e^{-\int_0^a (\mu_H(v)+\rho_1(1-\mathrm{g}(v))+\rho_2 g(v))dv}$ is the survival probability as a function of age in the infected class.

The reproduction number of the infectious caused by the free Mycobacterium ulcerans is

$$RB_H = \frac{\beta_H}{\delta_V} S_0 \int_0^{\infty} \eta(a)\pi(a) da$$

Now we consider the existence of the endemic equilibria. From 6.8 and 6.10, we obtain that the equilibrium level of susceptible individual satisfies the following equations

$$S^* = \frac{k_H + \frac{1}{\delta_V} \int_0^{+\infty} (\eta\pi(a))}{\frac{\beta_H}{\delta_V} \int_0^{+\infty} (\eta\pi(a))} (\mu_H(a) + \rho_1(1 - g(a) + \rho_2 g(a))\, \pi(a)$$

and

$$R^* = \frac{(\rho_1(1-g(a)+\rho_2 g(a))\, I^*(0)\pi(a)}{(\mu_H+\theta)}$$

## 6.3 Existence of the solution to the state system by method of characteristics

The solution of the system is determined using the method of characteristics (Webb, 1985). By using Bananch contraction mapping principle, a prove can be done on the existence and uniqueness of the solutions of the system. To compute the solution representation for the system 6.2a-6.2c, new notations are added to the right hand side of the partial differential equation (PDEs):

$$f_1\left(B_H(t), S(a,t), R(a,t)\right) = \Lambda(a,t) - \beta_H(a)\frac{B_H(t)}{k_H + B_H(t)}S(a,t) + \theta(a)R(a,t) \tag{6.12a}$$

$$f_2\left(B_H(t), S(a,t), I(a,t), g(a,t)\right) = \beta_H(a)\frac{B_H(t)}{k_H + B_H(t)}S(a,t) - \rho_1(1-g(a,t))I(a,t) - \rho_2 g(a,t)I(a, \tag{6.12b}$$

$$f_3\left(S(a,t), I(a,t), R(a,t), g(a,t)\right) = \rho_1(1-g(a,t))I(a,t) + \rho_2 g(a,t)I(a,t) - \theta(a)R(a,t). \tag{6.12c}$$

We note that the $\mu_H(a)S(a,t), \mu_H(a)I(a,t)$ and $\mu_H(a)R(a,t)$ terms are exclusive in the $f$ for $i = 1, 2, 3$ terms. They are integral part in the left hand side of the three partial differential equations 6.2a- 6.2c to make use in the representation of the solution based on method characteristics.

Let B be selected in such a way that

$$0 \leq S_0(a), I_0(a), R_0(a),$$

$$\int_0^A S_0(a)da \leq B, \int_0^A I_0(a)da \leq B, \int_0^A R_0(a)da$$

and $0 \leq B_H(0) \leq B$

The state solution space is defined as

$$Y = \big\{(S, I, R, B_H) \in (L^\infty(0, T; L'(0, A)))^3 \times (L^\infty(0, T))| \\ \sup_t \int_0^A |S(a,t)|da \leq 2B, \sup_t \int_0^A |I(a,t)|da \leq 2B, \\ \sup_t \int_0^A |R(a,t)|da \leq 2B, |B_H(t)| \leq 2B\}$$

Applying the Method of Characteristics as in (Fister et al., 2004) and parametrising in relation to a variable $s$ characteristics can be determined. We foremost organize 6.2a into the structure

$$\frac{\partial W_i}{\partial t} + \frac{\partial W_i}{\partial a} + \omega_i W = P_z(W_i)$$

where $i = S, R$ and $z = i, .., 3$ in order to work out the characteristics and $W_i$ stands for the different classes.

We put

$$\frac{dW_i(s + a - t, s)}{ds} = \frac{\partial W_i(s + a - t, s)}{\partial t} + \frac{\partial W_i(s + a - t, s)}{\partial a},$$

leading

$$\frac{dW_i(s + a - t, s)}{ds} + \omega_i(s + a - t, s)W_i(s + a - t, s) = P_z(W_i)$$

By means of an integrating factor, we can then compute the equation for $a < t$ and $a \geq t$.

We can determine the representation of the solution (if exist) and then use that representation to construct the map to be employed in the fixed point argument for existence and uniqueness. Now we define a map

$L : Y \to Y$ such that

$L(S, I, R, B_H) = (L_1(S, I, R, B_H), L_2(S, I, R, B_H), L_3(S, I, R, B_H), L_4(S, I, R, B_H))$.

where $L_1$ is based on equation $(6.2a)$ and $L_2$ also has to do with equation $(6.2b)$ and that order where

$$[L_1(S,I,R,B_H)(a,t) = \begin{cases} e^{-\int_0^t \mu_H(\alpha\tau-\alpha t+a)d\tau} S_0(a-\alpha t) \\ +\int_0^t \mu_H(\alpha\tau-\alpha t+a)d\tau\times \\ (f_1(B_H(s), S(\alpha s+a-\alpha t,s), \\ R(\alpha s+a-\alpha t,s)))ds \\ if \quad a>\alpha t, \\ \\ \frac{1}{\alpha}\int_s^a e^{-\int_s^a \frac{\mu_H(\tau)}{a}d\tau}\times \\ (f_1(B_H(\frac{s+\alpha t-a}{\alpha}), S(s,\frac{s+\alpha t-a}{\alpha}), \\ R(s,\frac{s+\alpha t-a}{\alpha}))ds \\ if \quad a<\alpha t \end{cases} \tag{6.13}$$

$$L_2(S,I,R,B_H)(a,t) = \begin{cases} e^{-\int_0^t \mu_H(\alpha\tau-\alpha t+a)d\tau} I_0(a-\alpha t) \\ +\int_0^t \mu_H(\alpha\tau-\alpha t+a)d\tau\times \\ (f_2(B_H(s), S(\alpha s+a-\alpha t,s), I(\alpha s+a-\alpha t,s) \\ g(\alpha s+a-\alpha t,s)))ds \\ if \quad a>\alpha t, \\ \\ \frac{1}{\alpha}\int_s^a e^{-\int_s^a \frac{\mu_H(\tau)}{a}d\tau}\times \\ f_2(B_H(\frac{s+\alpha t-a}{\alpha}) \\ S(s,\frac{s+\alpha t-a}{\alpha}), I(s,\frac{s+\alpha t-a}{\alpha}), \\ g(s,\frac{s+\alpha t-a}{\alpha})ds \\ if \quad a<\alpha t \end{cases} \tag{6.14}$$

$$L_3(S,I,R,B_H)(a,t) = \begin{cases} e^{-\int_0^t mu_H(\alpha\tau-\alpha t+a)d\tau} R_0(a-\alpha t) \\ +\int_0^t \mu - H(\alpha\tau-\alpha t+a)d\tau \times \\ (f_3, S(\alpha s+a-\alpha t,s), I(\alpha s+a-\alpha t,s) \\ R(\alpha s+a-\alpha t,s) \\ g(\alpha s+a-\alpha t,s)))ds \\ if \quad a > \alpha t, \\ \\ \frac{1}{\alpha}\int_s^a e^{-\int_s^a \frac{\mu_H(\tau)}{a}d\tau} \times \\ (f_3, S(s, \frac{s+\alpha t-a}{\alpha}) \\ I(s, \frac{s+\alpha t-a}{\alpha}), R(s, \frac{s+\alpha t-a}{\alpha}), \\ g(s, \frac{s+\alpha t-a}{\alpha})ds \\ if \quad a < \alpha t \end{cases} \tag{6.15}$$

$$L_4(S,I,R,B_H)(t) = B_H 0 e^{-\delta_v t} + \int_0^t \eta e^{-\delta_v(t-s)B_H(s)}ds. \tag{6.16}$$

We derive the fixed point of the map $L$, meeting the condition

$$(S,I,R,B_H) = (L_1,L_2,L_3,L_4)(S,I,R,B_H),$$

with each of $S(a,t), I(a,t), R(a,t)$, and $B_H(t)$ being non-negative, will be a solution $(S,I,R,B_H) = (S,I,R,B_H)(g)$ to the state system.

**Theorem 6.3.1** *(Existence and uniqueness of solution) For $g \in \Omega$ as defined in* (6.1) *and $T$ sufficiently small, there exists a unique solution $(S,I,R,B_H)$ to the system 6.2a – 6.2d with boundary and initial conditions 6.3a –6.3c and 6.4*

**Proof** We prove that the map $L : Y \to Y$,
stated above is a strict contraction. Note that the function $f_1, f_2$ and $f_3$ used in the $SIR$ equations are Lipschitz in their arguments with the Lipschitz constants

based on coefficients and parameters from the model and also on B, through the bounds on $S, I, R$ from the set $Y$ (Fister et al., 2004).

In order to show that $L$ maps $Y$ into $Y$, from the definition of the map $L$, we give the definition of the $L_i$ functions for $i = 1, 2, 3$ leads

$$\int_0^A |L_i(S, I, R, B_H)|(a, t)da \leq D_1 BT + B \leq 2B$$

where the single B is the first inequality obtains from the bound of $\int_0^A S_0(a)da$, $\int_0^A I_0(a)da$ or $\int_0^A R_0(a)da$ respectively from $i = 1, 2, 3$. By the fact that $T$ is sufficiently small, then we state that the above estimate is less than or equal to $2B$.

In addition for $j = 4$, we obtain

$$|L_j(S, I, R, B_H)| \leqslant \sup\{B_{H0}\} + D_2 BT \leqslant 2B.$$

The constants $D_1$ and $D_2$ hinge on the coefficients and the parameters in the model. Also for $T$ to be sufficiently small, we obtain the estimate above and hence, we state that $L$ maps $Y$ into $Y$.

Note that for the contraction property, for $i = 1, 2, 3$, we take into account

$$\int_0^A |L_i(S_1, I_1, R_1, B_{H_1}) - L_i(S_2, I_2, R_2, B_{H_2})|(a, t)da.$$

In order to obtain the right results there is a need to examine terms such as $\beta_H(a)\frac{B_H(t)}{K_H(a)+B_H(t)}S(a, t)$ and in specific their differences. The reason being that it is the rate of infection in the model. For instance, we have

$$\frac{B_{H1}(t)}{k_H + B_{H1}(t)} |S_1 - S_2| (a, t) + \frac{S_2 (a, t) k_H |B_{H1} - B_{H2}| (t)}{k_H + B_{H1}(t))(k_H + B_{H2}(t))} \tag{6.17}$$

to consider from equations 6.13 and 6.14. In order to make things simple, we

show an estimate of such a term for $a > \alpha t$ in $L_1(S, I, R, B_H)(a, t)$.

$$\int_0^A \int_0^A \left| e^{-\int_s^t \mu_H(\alpha\tau - \alpha t + a)d\tau} \times B_H(\alpha s + a - \alpha t, s)\left(\frac{B_{H2}(s)}{k_H + B_{H2}(s)} \left|S_2 - S_1\right| (\alpha s + a - \alpha t, s)\right.\right.$$

$$+ \frac{S_1(\alpha s + a - \alpha t, s) k_H \left|B_{H2} - B_{H1}\right| (s)}{(k_H + B_{H1}(s))(k_H + B_{H2}(s))}$$

$$\left.\left. + \theta(\alpha s + a - \alpha t, s)(R_2 - R_1)(\alpha s + a - \alpha t, s)\right| ds da$$

Note that if $s_1 = \alpha(s - t) + a$ and $s_2 = S$, then $0 < -\alpha t + a < \alpha(s - t) + a < a$ or $0 < (s - t) + a < A$ and $0 \leq s_2 < T$.

In addition, the Jacobian for this transformation is finite. We can sufficiently bound the estimate above by (taking the majorant)

$$\int_0^T \int_0^A D_3 \left|S_2 - S_1\right| (s_1, s_2) + D_4 \left|R_2 - R_1\right| (s_1, s_2) ds_1 ds_2$$

$$+ D_5 \int_0^T \int_0^A |S_1(s_1, s_2)| ds_1 \{\left|B_{H2}(s_2) - B_{H1}(s_2)\right| ds_2\}$$

$$\leqslant D_6 T \sup_t \int_0^A (|S_2 - S_1| + |R_2 - R_1|)(a, t) da$$

$$+ D_7 N T \sup_t \left[\left|B_{H2} - B_{H1}\right| (t)\right]$$

We have substituted $s_1$ and $s_2$ by $a$ and $t$ respectively. Again, the constants $D_k$ for $k = 3, ...7$ depend on the bounds of the coefficients. For terms consisting of the fractional parts, we have employed the $2B$ bound for the terms involving the $S_i$ for $i = 1, 2$ in the second term of 6.17 for integrals over $(0, A) \times (0, t)$ when $a > \alpha t$ or for integrals over $(0, A) \times (0, a)$ when $a < \alpha t < \alpha T$. We can determine these estimates which lead

$$\int_0^A |L_1(S_1, I_1, R_1, B_{H1}) - L_1(S_2, I_2, R_2, B_{H2})|(a,t)da$$

$$\leq D_8 T \sup_t \int_0^A (|S_2 - S_1| + |R_2 - R_1|)(a,t)da + D_9 \Omega \sup_t [|B_{H2} - B_{H1}|(t)]$$

Similarly we estimate for $j = 2, 3$.

For $j = 4$, we obtain that

$$|L_j(S_1, I_1, R_1, B_{H1}) - L_j(S_2, I_2, R_2, B_{H2})|(t)$$

$$\leq T \sup_t \int_0^A |I_1 - I_2|(a,t)da + D_{10} T \sup_t |B_{H1} - B_{H2}|(t) < \varepsilon$$

where $K_{10}$ depends on $\eta$ and $\delta$ .

By putting together the work above and carefully selecting $T$ sufficiently smaller than $\varepsilon$ , we obtain the contraction result and therefore , desire fixed point to the system 6.2a –6.2d. By basing on an argument as Chapter 2 in (Webb, 1985) and observing that the right hand side of the differential equations has a common factor S, I, R, respectively, one can obtain the non-negativity of the solutions.

## 6.4 Numerical Simulations

### 6.4.1 Numerical Simulation

Finite differences are used in the simulations, since the software we use does not make provision for first order PDEs. With these simulations we use three-point stencil scheme since a stencil with too few points is not accurate while those with too many stencil points causes computational difficulties. If PDEs get approximated with finite differences they need to get solved on a rectangular domain with $a \in [0, A]$ and $t \in [0, \mathrm{T}]$ where $a$ and $t$ are the respective maximum

age and maximum time consideration. In this study, in order to improve accuracy we use backward finite difference scheme as compare to forward finite difference scheme for the numerical simulations (Strikwerda, 2004). We divide this rectangular domain into a grid, as follows,

$$\frac{u_{i,j+1}-u_{i,j}}{k}+\alpha\frac{u_{i,j}-u_{i-1,j}}{h}=f(a_i,t_j)$$

$$\frac{\partial X(a,t)}{\partial a}+\frac{\partial X(a,t)}{\partial t}\approx\frac{[X(a_i,t_j)+[X(a_{i-1},t_j)]-X(a_{i-1},t_{j-1})]}{h}$$

$$\frac{X(a_i,t_j)-X(a_{i-1},t_{j-1})}{h}$$

$$\frac{X_i^j-X_{i-1}^{j-1}}{h}$$

$$X\in\{S,I,R\}$$

The discretized system equations appears as following:

$$\begin{aligned}
\frac{S_i^j-S_{i-1}^{j-1}}{h}&=\Lambda+\theta_iR_i^j-(\lambda_{Hi}+\mu_{Hi})S_i^j\\
\frac{I_i^j-I_{i-1}^{j-1}}{h}&=\lambda_{Hi}S_i^j-(\mu_{Hi}+(\gamma_{1i}(1-g_i)+\gamma_{2i}g_i))I_i^j\\
\frac{R_i^j-R_{i-1}^{j-1}}{h}&=(\gamma_{1i}(1-g_i)+\gamma_{2i}g_i)I_i^j-\mu_{Hi}R_i^j\\
\frac{B_{Hj+1}-B_{Hj}}{h}&=\left[\frac{h}{2}\delta_V\sum_{i=0}^{n-1}(I_{i+1,j}+I_{ij})\right]-\eta B_{Hj}
\end{aligned}\tag{6.18}$$

$$
\begin{aligned}
S_i^j &= \frac{\Lambda h + \theta_i R_i^j h + S_{i-1}^{j-1}}{1 + h(\lambda_{Hi} + \mu_{Hi})} \\
I_i^j &= \frac{\lambda_{Hi} S_i^j + I_{i-1}^{j-1}}{1 + (\mu_{Hi} + \gamma_{1i}(1 - g_i) + \gamma_{2i} g_i))h} \\
R_i^j &= \frac{h(\mu_{Hi} + \gamma_{1i}(1 - g_i) + \gamma_{2i} g_i))I_i^j + R_{i-1}^{j-1}}{1 + \mu_{Hi} h}
\end{aligned} \tag{6.19}
$$

The boundary conditions are presented as

$$S_0^j = \Omega_j and\ I_0^j = 0 = R_0^j = 0$$

In order to obtain a good plot of our numerical solution on the $[0, A] \times [0, T]$ grid,we modify the finite difference scheme and approximate the derivative by

$$\frac{\partial X(a,t)}{\partial a} + \frac{\partial X(a,t)}{\partial t} \approx \frac{[X(a_i, t_j) - X(a_{i-1}, t_j)] + [X(a_i, t_j) - X(a_i, t_{j-1})]}{h}$$

$$\frac{2X(a_i, t_j) - [X(a_{i-1}, t_j) - X(a_i, t_{j-1})]}{h}$$

$$\frac{2X_i^j - (X_{i-1}^j, + X_i^{j-1})}{h}$$

where $X \in \{S, I, R\}$

$$
\begin{aligned}
\frac{S_i^j - S_{i-1}^j}{h} + \frac{S_i^j - S_i^{j-1}}{h} &= \Lambda + \theta_i R_i^j - (\lambda_{Hi} + \mu_{Hi}) S_i^j \\
\frac{I_i^j - I_{i-1}^j}{h} + \frac{I_i^j - I_i^{j-1}}{h} &= \lambda_{Hi} S_i^j - (\mu_{Hi} + (\gamma_{1i}(1 - g_i) + \gamma_{2i} g_i)) I_i^j \\
\frac{R_j^i - R_{i-1}^j}{h} + \frac{R_j^i - R_i^{j-1}}{h} &= (\gamma_{1i}(1 - g_i) + \gamma_{2i} g_i) I_i^j - \mu_{Hi} R_i^j
\end{aligned} \tag{6.20}
$$

Solving system of equations 6.20 we obtain:

$$S_i^j = \frac{\Lambda h + \theta_i R_i^j h + S_{i-1}^j + S_i^{j-1}}{2 + h(\lambda_{Hi} + \mu_{Hi})}$$

$$I_i^j = \frac{\lambda_{Hi} S_i^j h + I_{i-1}^j + I_i^{j-1}}{2 + (\mu_{Hi} + \gamma_{1i}(1 - g_i) + \gamma_{2i} g_i))h}$$

$$R = \frac{h(\mu_{Hi} + \gamma_{1i}(1 - g_i) + \gamma_{2i} g_i))I_i^j + R_i^{j-1} + R_{i-1}^j}{2 + \mu_{Hi} h}$$

In order to examine the validity of the difference scheme, we need to improve the convergence of the numerical scheme. We note that the error terms for each is stated as

$$\vartheta_i^j = S(a_i, t_j) - S_i^j, \tag{6.21}$$

$$\varsigma_i^j = I(a_i, t_j) - I_i^j, \tag{6.22}$$

$$\xi_i^j = R(a_i, t_j) - R_i^j, \tag{6.23}$$

$$\frac{2S_i^j - S_{i-1}^j + S_i^{j-1})}{h} = \frac{2S_i^j - 2S(a_i, t_j) - S_{i-1}^j + S(a_{i-1}, t_j) - S_i^{j-1} + S(a_i, t_{j-1})}{h}$$

$$+ \frac{2S(a_i, t_j) - S(a_{i-1}, t_j) - S(a_i, t_{j-1})}{h}$$

We arrange our expression in terms of the error terms 6.21. We substitute the 6.21 into above expression to obtain

$$\frac{2S_i^j - S_{i-1}^j + S_i^{j-1}}{h} = -\frac{2\vartheta_i^j - \vartheta_{i-1}^j - \vartheta_i^{j-1}}{h} + \frac{2S(a_i, t_i) - S(a_{i-1}, t_j) - S(a_i, t_{j-1})}{h}$$

$$\frac{2\vartheta_i^j - \vartheta_{i-1}^j - \vartheta_i^{j-1}}{h} = -\frac{2S_i^j - S_{i-1}^j - S_i^{j-1}}{h} + \frac{2S(a_i,t_i) - S(a_{i-1},t_j) - S(a_i,t_{j-1})}{h}$$

$$\frac{2\vartheta_i^j - \vartheta_{i-1}^j - \vartheta_i^{j-1}}{h} = \Lambda + \theta\xi_i^j - (\lambda_{Hi} + \mu_{Hi})\vartheta_i^j + O(h) \tag{6.24}$$

$$\frac{2\varsigma_i^j - \varsigma_{i-1}^j - \varsigma_i^{j-1}}{h} = \lambda_{Hi}\vartheta_i^j - (\mu_{Hi} + (\gamma_{1i}(1-g_i) + \gamma_{2i}g_i))\varsigma_i^j + O(h) \tag{6.25}$$

$$\frac{2\xi_i^j - \xi_{i-1}^j - \xi_i^{j-1}}{h} = (\gamma_{1i}(1-g_i) + \gamma_{2i}g_i)\varsigma_i^j - \mu_{Hi}\xi_i^j + O(h) \tag{6.26}$$

By considering the initial and boundary condition of the system to be

$\vartheta_0^j = \varsigma_0^j = \xi_0^j = 0$ for $j = 1, 2, ..., N$

$\vartheta_i^0 = \varsigma_i^0 = \xi_i^0 = 0$ for $j = 1, 2, ..., M$ in that order

we can determine the solution of equations 6.24 – 6.26 to obtain solutions for $\vartheta_i^j, \zeta_i^j$ and $\xi_0^j$.

$$\vartheta_i^j = \frac{\Lambda h + \theta_i \xi_i^j h + \vartheta_{i-1}^j + \vartheta_i^{j-1}}{2 + h(\lambda_{Hi} + \mu_{Hi})} + 0(h^2) \tag{6.27}$$

$$\varsigma_i^j = \frac{\lambda_{Hi}\vartheta_i^j h + \varsigma_{i-1}^j + \varsigma_i^{j-1}}{2 + (\mu_{Hi} + \gamma_{1i}(1-g_i) + \gamma_{2i}g_i))h} + O(h^2) \tag{6.28}$$

$$\xi_i^j = \frac{h(\mu_{Hi} + \gamma_{1i}(1-g_i) + \gamma_{2i}g_i))\varsigma_i^j + \xi_i^{j-1} + \xi_{i-1}^j}{2 + \mu_{Hi}h} + O(h^2) \tag{6.29}$$

It is essential to prove that expression 6.27 –6.29 of the error terms converges to 0, as $h$ approaches to 0. The validity and stability of the difference scheme are checked by computing truncation error.

### 6.4.2 Computational Experiments and Results

Buruli ulcer disease requires more antibiotic in children than adults.We model the rate of losing immunity of humans at age $a$ by

$$\theta(a) = \begin{cases} 1/365 & \text{for } a \leq 15 \text{ years old,} \\ 1/2.363 & \text{for } a > 15 \text{ years old} \end{cases}$$

The rate of waning is important because it influences our choice of initial condition

### 6.4.3 The reference Simulation with no Infected Population

We assumed a pool of $20,000$ humans distributed uniformly over the age range $0 \leq a \leq A$, for all ages a at $t = 0$. All $20,000$ humans are distributed to the susceptible and removed classes. Based on the rate of losing immunity conditions for children and adult, it is assumed that it takes for a year for a newborn baby to lose his or her immunity and become susceptible to Buruli ulcer. In this regard, we initialize everyone with age less than or equal to one year old in the removed section and everyone older than one year old in the susceptible section. This leads to the initial conditions

$$S(a,0) = \begin{cases} 0 & \text{if } 0 \leq a \leq 40 \text{ weeks,} \\ d & \text{if } a > 40 \text{ weeks,} \end{cases}$$

for the susceptible and

$$R(a,0) = \begin{cases} d & \text{if } 0 \leq a \leq 40 \text{ weeks,} \\ 0 & \text{if } a > 40 \text{ weeks,} \end{cases}$$

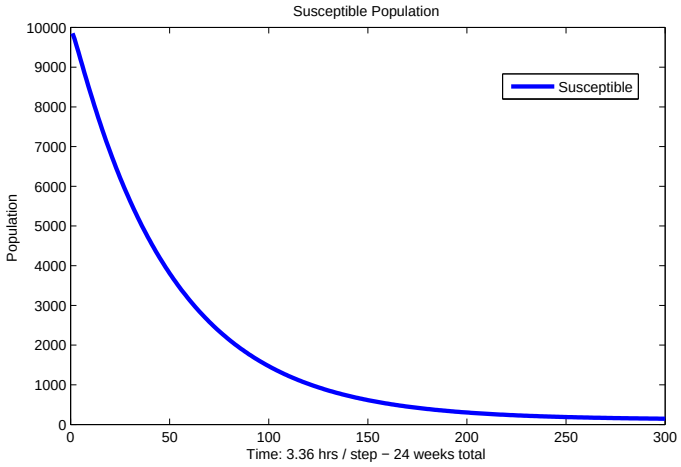
for the removed population, respectively. The numerical value of the age density in the initial conditions depends on the number of humans and the numerical resolution of the age variable. By applying numerical and having age resolution

in weeks, we will then have to have a fixed density $d$ for each age s for $0 \leq a \leq 40$, given by

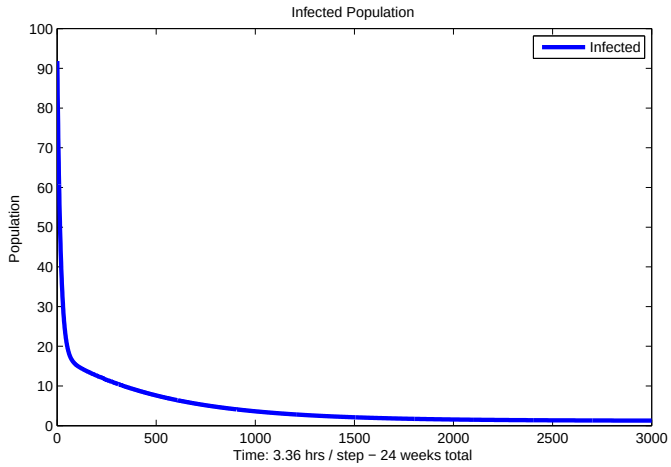
$$d = \frac{20,000(humans)}{50(weeks/year) \times 60(year)} \approx 8.33human/weeks$$

| Parameter | Value/Range | Source |
|---|---|---|
| $\Lambda(a,t)$ | 0 | Estimated |
| $h(a,t)$ | 0.8 | Estimated |
| $B_H$ | 1.5/7 | (Aidoo et al., 2007) |
| $k_H$ | $10^5$ | Estimated |
| $\beta_H$ | 0.00065 | (Aidoo et al., 2007) |
| $g_H$ | 105/600 | Estimated |
| $u_H$ | 0.45 | (Aidoo et al., 2007) |
| $\rho_1$ | 1/5 | Estimated |
| $\rho_2$ | 1/3 | Estimated |
| $\delta_L$ | 1/5 | Estimated |

This provides the values of d in the initial conditions for $S(a,0)$ and $R(a,0)$. Given the age resolution of 1 week, that at the initial time with constant density d, this leads $40 \approx 333$ humans of each age $a$. In other words, we are saying that $20,000$ total humans are distributed to the ages 0 to 60 uniformly as $20,000/60 \approx 333$ humans.

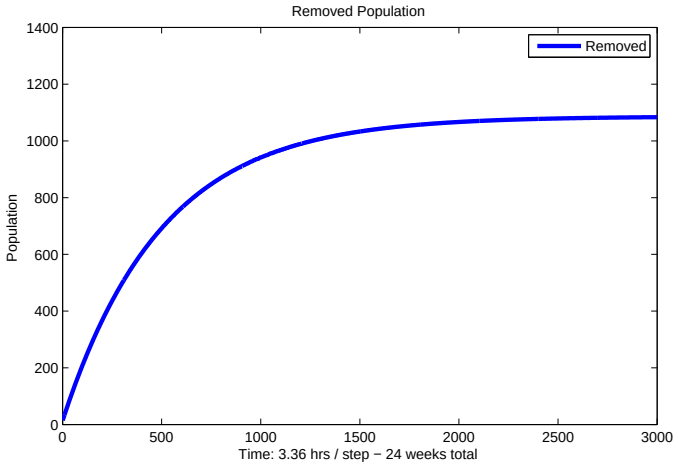



(a)

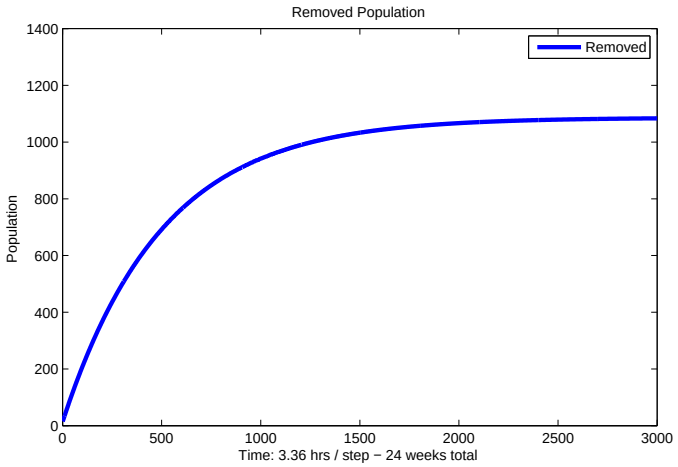



(b)

In Figure 6.2, we show the dynamics in the total population, susceptible population, infected population, and recovered population over time. We note here that the decrease in the susceptible population is attributed to humans who died of natural causes during the period-line of the simulation. Furthermore, we notice an increase in recovered population, which is partly due to antibiotic and partly due to natural recovery of MU by humans. This however, takes sometime for humans to lose immunity to get back to susceptible class and is governed by the rate of waning of immunity. In Figure 6.2(b), we see that the infection reduced with respect to time and this could be inferred from people getting awareness of MU and antibiotic medications which are now available to BU patients. Even though there is no epidemic in this simulation, our model




(c)

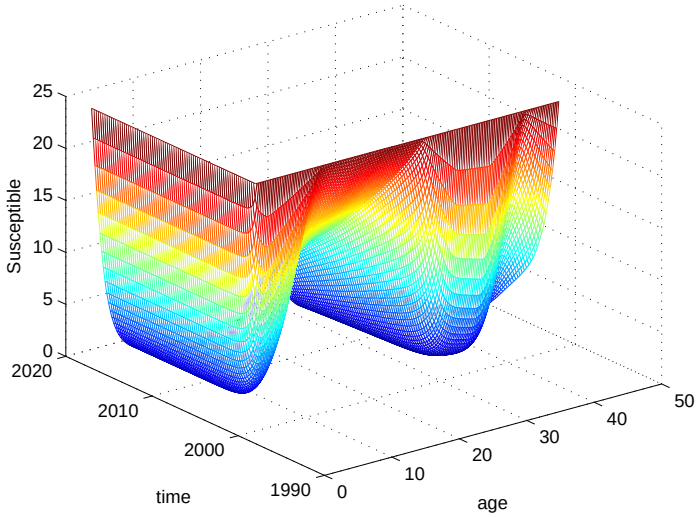



(d)

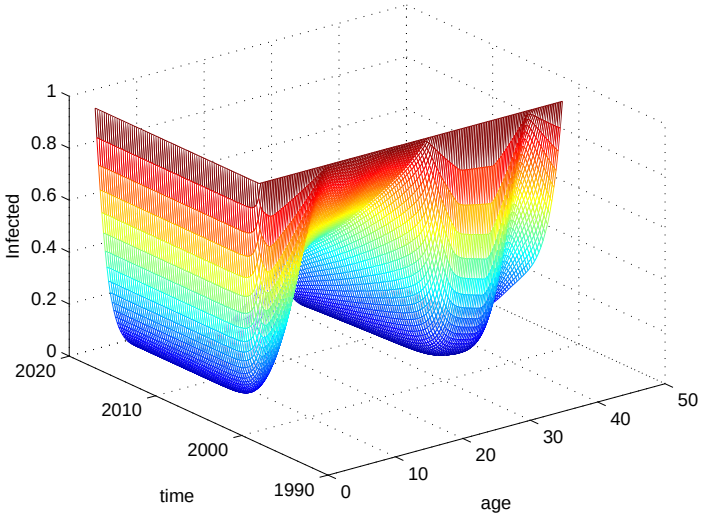
Figure 6.2: The simulations of BU with susceptible, infected population and recovered population dynamics over time.

indicates more than just the population dynamics. Our three-dimensional surface plots in Figure 6.3 depict the advantages of this age-structured model even in this basic simulation. Each plot in Figure 6.3 indicates the number of humans at age $a$ in years at time $t$ in weeks; the color provides the same information as the height of surface.The number of humans at a particular age is calculated by integrating each density. For instance $S(a,t)$ from a years to $a+1$ years by $\int_a^{a+1} S(\overline{a},t)d\overline{a}$ constituting the basic understanding that humans from age $a$ to $a+1$ are considered to be $a$ years old. Notice that we use a resolution of 1 week in age, thus at the initial time with constant density $d$. This leads $52 \approx 120$ humans of each age $a$. We also examined the dynamics of $B_H$ over time which

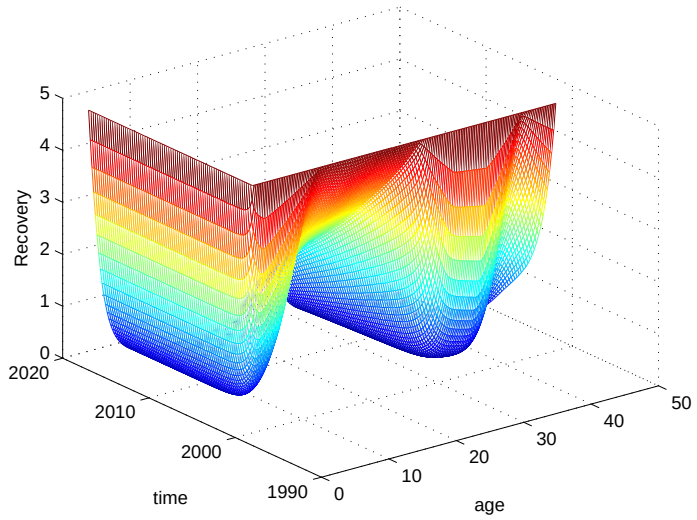
are shown in Figures 6.2(d). It depicts a peak within few days of the spread of BU and this is due to the fact that initially people do not pay attention to the environment. Hence a greater accumulation in the entire area in the curve was observed.




(a)




(b)




(c)

Figure 6.3: The simulation of BU with susceptible, infected population and recovered population dynamics as function of age and time.

To make excessive use of our PDE model, we observe at the model quantities in Figure 6.3 which indicate how the quantities vary over time across different age groups. It is noticed that in Figure 6.3(c) due to infants, the recovered increased at a greater rate. This is assumed to occur as a result of a higher proportion of them having immunity from their mother's milk. For instance, in Figure 6.3, is the surface plot of the susceptible, infected and recovered population, the height (the vertical coordinate) at point $(a, t)$ is the number of susceptible, infected and recovered people of age a at time $t$ as the height of surface respectively. In Figure (6.3(a),6.3(b),6.3(c)) the susceptible and infected populations decline, as anticipated, the recovered rise over time and age. Note that owing to natural recovery and antibiotic treatment, the recovered increase (Etuaful et al., 2005; Sizaire et al., 2006). The decrease in Figure 6.3(a) maybe related to environmental activities that enhance the spread of *Mycobacterium ulcerans* and Figure 6.3(b) is assumed to crop up as a result long duration for humans who have recovered to wan their immunity (Duker et al., 2006; Agbornorku, 2011).

## 6.5 Summary

In this chapter, an age-structured model is developed to explain the infection pathway of Buruli ulcer more enhanced since the risk for contracting the disease has something to do with the age of a human being. We observed that introducing age as another independent variable encompasses solving a system of partial differential equations instead of system of ordinary different equation, and this brings in new challenges for the existence of a solution of the system and for the numerical method. The existence result of the solution for the PDE system applying a fixed point argument is presented. The time dependent simulation is performed. The numerical simulation on both age and time of the dynamics of BU disease is presented. The observation is made that Mycobacterium ulcrans spread is facilitated by the behaviour of humans.

# CHAPTER 7

# CONCLUSION AND RECOMMENDATIONS

## 7.1 Introduction

Mathematical models of interactions of *Mycobacterium ulcerans* and the host have been presented in this study. An age structured model was included to examine age dynamics of the spread of Buruli ulcer. The mathematical and numerical analysis of these models were discussed. Optimal control was introduced to determine the best strategy to explore in order to reduce the spread of the disease. The results obtained from the models presented in Chapter 3, Chapter 4, Chapter 5 and Chapter 6 respectively are summarised in this Chapter.

## 7.2 Conclusion

In Chapter 3, an SIR model for Buruli ulcer disease was derived and analyzed with *Mycobacterium ulcerans* in the environment inclusive. In Chapter 4, an SITR model for BU disease was derived and analyzed with saturation treatment function which is to help determined how much resources needed to fight against the BU disease. In Chapter 5, control parameters were incorporated into the model in Chapter 3, mainly, mass treatment, spraying of insecticide and mass education to humans. In Chapter 6, an SIR model was derived and analysed which is a hyperbolic system od PDEs and one ODE that described the dynamics of *Mycobacterium ulcerans* in the environment. An extension was made to incorporate antibiotic treatment (infected individuals). We present some of the theoretical and epidemiological findings as follows:

In Chapter 3, a deterministic SIR model was derived and analysed for the transmission of Buruli ulcer disease. The basic reproduction number was determined and analysed. The steady state was investigated to examine the existence and stability of equilibria for both state. The model has a global stable disease free equilibrium when $\mathcal{R}_b < 1$ and globally stable if $\mathcal{R}_b > 1$ for endemic equilibrium. The reproduction number revealed that the spread of BU disease depends on effective contact rate between susceptible small fish and *Mycobacterium ulcerans*. The rate of shedding of *Mycobacterium ulcerans* in the environment and through effective contact between infected and water bugs contribute to the spread of BU disease. It was seen in Chapter 3 that humans are just a victim of circumstance of the spread of the BU disease based on the reproduction number determined. From the Partial Correlation Coefficients (PRCCs) plot in Chapter 3, it was revealed that beta and sigma contribute significantly the spread of BU. The infected humans increased as far as there are enough infected water bugs to sustain the epidemic. The model showed that in the near future the number cases would not vary if everything remains the same as it now. It is therefore, concluded from the simulation in the Chapter 3 that water bugs contribute to the spread Buruli ulcer disease.

In Chapter 4, a deterministic SITR model for Buruli ulcer disease was derived and analyzed to determine saturation treatment for BU disease in Ghana.The basic reproduction number for each sub - model was computed and analysed. It was observed that force of infection is the reproduction number of sub model for the water bugs. The PRCC analysis indicated that the clearance of water bugs and *M. ulcerans* in the environment reduces the spread of BU epidemic. It was also observed that increasing the density of *M. ulcerans* in the environment led to an increase in the number of infected water bugs. It is worth noticing that as the saturation treatment increases with time, human prevalence also increases.

In Chapter 5, a time dependent optimal control was incorporated into a

transmission dynamics model of SIR type in Chapter 3 and with mass treatment, use of insecticides and provision of mass education being the controls. The necessary conditions for the optimal control of BU disease was derived and analysed. It was shown from the simulation that the most effective way of managing the BU disease is combining all the three factors mentioned to reduce the spread of the disease.

In Chapter 6, a hyperbolic (first order) partial differential equations in combination with an ordinary differential equation was derived and analyzed . The reproduction number and steady state of system of the equations determined and analysed which showed that the disease is stable. The method of characteristics and fixed point argument was used to show the existence and uniqueness of a solution to the nonlinear system of equations. The simulation revealed that an increased in recovered human population was attributable to antibiotic treatment and few people getting recovered naturally. It was also revealed that there was a peak for MU spread and subsequently reduced as more susceptible get awareness of the disease. A similar observation was seen in the three dimensions plot of the PDEs.

## 7.3 Limitations and Recommendations

In the light of the detailed nature of the model derived in this study, some of the parameters applied have not been clinically or experimentally determined. This has been a major set back in our assessment. In this thesis the model studied lacked data set that would be fitted on them in order to validate the predictions of the observed outputs. We recommend that the clinicians or experimentalist estimate the unknown and vital parameters including the following: $\beta_F, \beta_H, \beta_V, \mu_H, \mu_V, \mu_F, \mu_E, \theta, K, \rho_1, \rho_2, \delta_H, \alpha, \Lambda(a,t), k_H(a)$
$g(a,t), B_H, \mu_H(a)$ that have effect on the model output.

Since deterministic model in Chapter 3 revealed that small infected fishes play

a major role in the spread of BU disease, we recommend that there should be proper management of all water bodies in the areas where BU has been identified.

In Chapter 4, it has been established that saturation treatment function increase with human prevalence and therefore, government and non governmental organizations should mobilize enough resources to equip more health facilities to enable them to handle BU patients. More health personnel must be encouraged to specialize in BU disease treatment.

In endemic areas, District Health Directorates should form committees to sensitise the public about the necessary measures needed for the control of Buruli ulcer in their area.

It is noticed in Chapter 5 that mass treatment, spraying of insecticide and mass education will help reduce the spread of BU. Government and District Assemblies should make resources available to supply free insecticide, treatment and provision of enough education to inhabitants in the small communities.

It is observed in the age model in Chapter 6, that MU peaks in a short time and therefore health authority should provide early treatment for BU disease. This will prevent the rural folk who are poor to seek early treatment in order to avoid complications. In particular, children below the age of 15 years should be monitored so that they do not get in contact with contaminated environment since their immune system is not fully developed. Finally this model can be used to suggest the type of data that should be collected as research on the BU intensifies

## 7.4 Areas of Possible improvement to the Research

This study does not consider some other factors listed below but may influence the spread of Buruli ulcer. These factor(s) when carefully incorporated may lead to a better understanding of the disease and its control.

**Climate change:** The impact of climate change on the transmission of BU will lead an investigate into the relationship between the spread of BU and climate change during the dry seasons where the spread of BU increases.

**Social interventions:** These models can be improved by considering social interventions such National Health Insurance Scheme on the models. The numerical results of such intervention will help advice the state institutions for the management of the disease.

**Treatment control:** The inclusion of treatment control strategies in an age structured Buruli ulcer model will help in further explanation of the dynamics of Buruli ulcer.

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# Appendix I

## Matlab Code for SIR Model

```
function [t,Sh,Ih,Iv,If,U]=buruli(muH,theta,m1,betaH,gamma,m2,betaV,eta,muV,betaF,muF,s
%RISK_STRUCTURE(mu,betam,kappa,alpha,eta,rho,gammaE,gamma,betav,sm0,im0,sv0,iv0,MaxTime


      muH=0.00045;
      theta=0.001;
      m1=5;
      betaH=0.006;
      gamma=0.056;
      m2=0.3;
      betaV=0.65;
      eta=1.5;
      muV=0.35;
      betaF=0.09;
      muF=0.05;
      sigma=0.09;
      muE=0.4;
      %MaxTime=50;
      Ro=sqrt((sigma*betaF)/((muE*muF)))
  % if Sh0<=0
  %     error('Initial level of susceptible humans (%g)is less than or equal to zero',sm0);
  % end
  % if Ih0<=0
  %     error('Initial level of infectious humans (%g)is less than or equal to zero',im0);
  % end
  % % if sv0<=0
  % %     error('Initial level of susceptible vectorbug (%g)is less than or equal to zero',sv0);
  % % end
  % if Iv0<=0
  %     error('Initial level of infectious vectorbug (%g)is less than or equal to zero',iv0);
  % end
  % if betaM<=0
  %     error('transmission rate of mammal betaM (%g) is less than or equal to zero',betaM);
  % end
  % if betaV<=0
  %      error('transmission rate of water bug, betaV (%g) is less than or equal to zero',betaV);
  % end
  %  if gamma<=0
```

```
%      error('rate of recoverpop of mammal, gamma (%g) is less than or equal to zero',gamma);
%  end
%   if gammaE<=0
%      error('rate of recoverpop of waterbug, gammaE (%g) is less than or equal to zero',gammaE);
%  end
% if mu<=0
%     error ('Birth / Death rate of mammal, mu (%g) is less than or equal to zero',mu);
% end
% if eta<=0
%     error ('Birth / Death rate of waterbug, eta  (%g) is less than or equal to zero',eta);
% end
%
% if alpha<=0
%     error ('rate of acquiring the disease from the environment alpha (%g) is less than
% end
% if kappa<=0
%     error ('ratio of waterbug and mammal population kappa (%g) is less than or equal
% end
% if MaxTime<=0
%     error('Maximum run time (%g) is less than or equal to zero',MaxTime);
% end

       Sh0=0.8;
       Ih0=800/1000000;
       Iv0=0.2;
       If0=0.3;
       U0=0.5;

Init=[Sh0,Ih0,Iv0,If0,U0];
%The main iteration
options=odeset('RelTol',1e-5);
[t,pop]=ode45(@bur,[0 500],[Init],options,[muH,theta,m1,betaH,gamma,m2,betaV,eta,muV,be
Sh=pop(:,1); Ih=pop(:,2);Iv=pop(:,3);If=pop(:,4);U=pop(:,5);

%plots the graphs with scaled colours
figure(1)
g=plot(t,Sh,'-g');
legend(g,'susceptible humans')
xlabel 'Time(t) in days'
ylabel 'susceptible humans'
```

```
  figure(2)
  Q=plot(t,Ih,'-b');
  legend(Q,'Infected humans')
  xlabel 'Time(t) in days'
  ylabel 'Infected Humans'

  figure(3)
  r=plot(t,Iv,'-b');
  legend(r,'Infected vector')
  xlabel 'Time(t) in days'
  ylabel 'Infected Water Bugs'

  figure(4)
  w=plot(t,If,'-b');
  legend(w,'Infected fish')
  xlabel 'Time(t)'
  ylabel 'Infected Fish'



     Sh00=0.8;
     Ih00=800/1000000;
     Iv00=0.2;
     If00=0.3;
     U00=0.5;

  Init1=[Sh00,Ih00,Iv00,If00,U00];

%The main iteration
options=odeset('RelTol',1e-5);
for i=1
[t,pop]=ode45(@bur,[0 200],i*[Init1],options,[muH,theta,m1,betaH,gamma,m2,betaV,eta,muV
Sh=pop(:,1); Ih=pop(:,2);Iv=pop(:,3);If=pop(:,4);U=pop(:,5);

figure(6)
hold on
x=plot(If,Iv,'-b');
%legend(x,'Infected humans')
xlabel 'Prevalence of infected fish'
ylabel 'Prevalence of Infected water bugs'
hold
```

```
figure(7)
hold on
x=plot(Iv,Ih,'-b');
%legend(x,'Infected humans')
xlabel 'Prevalence of infected water bugs'
ylabel 'Prevalence of Infected humans'
hold off
end
 figure(3)
 f=plot(t,Iv,'-g',t,iv,'-k');
legend(f,'susceptible mammal','infectious waterbug')
 xlabel 'Time(t)'
poplabel 'susceptible mammal, infectious waterbug'

figure(4)
 N=plot(t,sm,'-g',t,sv,'-b',t,iv,'-k',t,im,'-m');
 legend(N,'susceptible human','susceptible waterbug','infectious waterbug','infectious
 xlabel 'Time(t)'
 poplabel 'susceptible human,susceptible waterbug,infectious waterbug,infectious mammal'

 figure(5)
 P=plot(t,betaV,'-r',t,Ro,'-k');
 legend(P,'transmission rate of mammal','reproduction number')
 xlabel 'Time(t)'
 poplabel 'transmission rate of mammal, reproduction number'
calculates the differential rates used in the integration.
function dpop=bur(t,pop, parameter);
%parameters

muH=parameter(1);theta=parameter(2);m1=parameter(3);betaH=parameter(4);gamma=parameter(
muV=parameter(9);betaF=parameter(10);muF=parameter(11);sigma=parameter(12);muE=paramete


Sh=pop(1);Ih=pop(2);Iv=pop(3);If=pop(4);U=pop(5);
dpop=zeros(5,1);

    dpop(1) = (muH + theta)*(1 - pop(1)) - theta*pop(2) - m1*betaH*pop(1)*pop(3);
    dpop(2) = m1*betaH*pop(1)*pop(3) - (muH + gamma)*pop(2);
    dpop(3) = m2*betaV*(1 - pop(3))*pop(4) + eta*betaV*(1 - pop(3))*pop(5) - muV*pop(3);
    dpop(4) = betaF*(1 - pop(4))*pop(5) - muF*pop(4);
   dpop(5) = sigma*pop(4) - muE*pop(5);
```

## Appendix II

## Matlab code for fitting data on SIR Model

```
function burulifit(do_estimation)
warning off;

%observed prevalence data from UNAIDS/WHO 2008
% % % data from 1990 to 2007
P_Data(:,1)=[2003,2004,2005,2006,2007,2008,2009,2010,2011,2012];
%I_Data(:,1)=[1996:0.5:2009];
%P_Data(:,2)=[0, 0, 2, 0, 1, 2, 6, 10, 12, 14, 17, 21, 32, 81, 121, 429, 668, 884, 952,
%A fraction of a population of 1 million individuals
P_Data(:,2)=[739,1159,1201,1096,1136,1300,1158,1428,1324,1292]./10000;
% I_Data(:,1)=[1990:2009];

   betaH=0.1;
   muH=0.000045;
   theta=0.1;
   m1=5;
   gamma=0.056;
   betaV=0.000065;
   m2=10;
   eta=1.5;
   muV=0.15;
   betaF=0.00005;
   muF=0.05;
   sigma=0.05;
   muE=0.4;

% Initial values

SH0=0.7592; IH0=0.09; IV0=0.2; IF0=0.5; U0=0.5;

INITIAL=[SH0,IH0,IV0,IF0,U0];
Istart=2003;    %year to start the model simulation
Iend=Istart+10;
```

```
OPTIONS=odeset('AbsTol',0.001,'RelTol',0.001,'MaxStep',1/12);
% tdur=50;

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%Estimate parameters
%by minimizing the sum of squares
%when fitting modeled to real prevalece data


if(do_estimation)
xdata=P_Data(:,1)';
ydata=P_Data(:,2)';
x0(1,1)=0.1;       %betaH
x0(1,2)=0.000045;          %muH
x0(1,3)=0.1;       %theta
x0(1,4)=5;        %m1
x0(1,5)=0.000016;         %gamma
x0(1,6)=0.2;         %betaV
x0(1,7)=10;         %m2
x0(1,8)=1.5;          %eta
x0(1,9)=0.15;         %muV
x0(1,10)=0.00005;      %betaF
x0(1,11)=0.0004;      %muF
x0(1,12)=0.05;     %sigma
x0(1,13)=0.4;       %muE


LB=[0 0   0   1  0   0 1  1 0   0   0   0   0];
UB=[1.0 0.7 0.4 10 0.5 1.1 15 5 0.3 0.4 0.1 0.6 1];
x=lsqcurvefit(@Model_Prev,x0,xdata,ydata,LB,UB,optimset);
%x = fit(@Model_Prev,xdata,ydata,x0,LB,UB,'Robust','on');

'estimated parameters';
betaH=x(1)
muH=x(2)
theta=x(3)
m1=x(4)
gamma=x(5)
betaV=x(6)
m2=x(7)
```

```
eta=x(8)
muV=x(9)
betaF=x(10)
muF=x(11)
sigma=x(12)
muE=x(13)
end

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

[t y] = ode45(@burulifit, [0:1/12:(Iend-Istart)], INITIAL);
SH=y(:,1);
IH=y(:,2);
IV=y(:,3);
IF=y(:,4);
U=y(:,5);


prevalence=IH;
%plwhiv=In+Is+IT+An+As;
close all;
figure (1);
hold on
h_l=plot(Istart+t,prevalence,'r-');
set(h_l,'linewidth',2);
h_2=plot(P_Data(:,1),P_Data(:,2),'bo','Markersize',8);
set(h_2,'linewidth',2);
axis([Istart Iend 0 0.2]);
ylim([0 0.2]) %                                The line added to change the y limit
%title('TB Prevalence(%)');
xlabel('Time in years','fontsize',15)
ylabel('Prevalence','fontsize', 15)
hold off

%  figure(2)
%  hold on
%  h_l1=plot(Istart+t,incidence,'b-');
%  set(h_l1,'linewidth',2);
%  %h_l1=plot(I_Data(:,1),I_Data(:,2),'bo');
%   %set(h_l1,'linewidth',2);
%  %axis([Istart Iend 0 0.25]);
```

```
%  xlabel('Time in years')
%  ylabel('Incidence (%)')
%  %xlim([Istart Iend]);
%  hold off

function [ydot]=burulifit(t,y)

SH=y(1);
IH=y(2);
IV=y(3);
IF=y(4);
U=y(5);

    ydot(1) = (muH + theta)*(1 - y(1)) - theta*y(2) - m1*betaH*y(1)*y(3);
    ydot(2) = m1*betaH*y(1)*y(3) - (muH + gamma)*y(2);
    ydot(3) = m2*betaV*(1 - y(3))*y(4) + eta*betaV*(1 - y(3))*y(5) - muV*y(3);
    ydot(4) = betaF*(1 - y(4))*y(5) - muF*y(4);
    ydot(5) = sigma*y(4) - muE*y(5);

    ydot=ydot';

end% function W1


function prev=Model_Prev(x0,xdata)

prev=0;      %intialization of this not to have an empty array
betaH=x0(1)
muH=x0(2)
theta=x0(3)
m1=x0(4)
gamma=x0(5)
betaV=x0(6)
m2=x0(7)
eta=x0(8)
muV=x0(9)
betaF=x0(10)
muF=x0(11)
sigma=x0(12)
muE=x0(13)
```

```
%%% Initial values
%SH0=0.7592; IH0=1200/10000; IV0=0.2; IF0=0.2; U0=0.5;
SH0=0.7592; IH0=1000/10000; IV0=0.2; IF0=0.5; U0=0.5;
%SH0=0.8592; IH0=800/1000000; IV0=0.02; IF0=0.02; U0=0.5;


INITIAL=[SH0,IH0,IV0,IF0,U0];

OPTIONS=odeset('AbsTol',0.001,'RelTol',0.001,'MaxStep',1/12);
tdur=50;
[t y] = ode45(@burulifit, [0:1/12:Iend-Istart], INITIAL);

SH=y(:,1);
IH=y(:,2);
IV=y(:,3);
IF=y(:,4);
U=y(:,5);

prevalence= IH;

for i=1:length(xdata)

    ind=find(xdata(i)-Istart==t);

    SH=y(ind,1);
    IH=y(ind,2);
    IV=y(ind,3);
    IF=y(ind,4);
    U=y(ind,5);

    prev(i)=IH;  %prevelence

end
end     % end of Model_prev
end     %end of aidssanew1_fit
```

## Appendix III

## Matlab code for SITR Model

```
function [t,y]=buruli2(beta_1,mu_H,m1,theta,gamma,beta_2,beta_3,sigma,K,mu_d, mu_W,N_H,alpha,


%RISK_STRUCTURE(mu,betam,kappa,alpha,eta,rho,gammaE,gamma,betav,sm0,im0,sv0,iv0,MaxTime

   %beta_1=0.0;
   mu_H=0.03;
   m1=15;
   theta=0.006;
   gamma=0.000000056;
   %beta_2=0.0;
   beta_3=0.8;
   mu_d=0.5;
   sigma=0.08;
   K=400;
   mu_W=0.5;
   N_H=100000;
   alpha=0.85;
beta_1=[0 1]
beta_2=[0 1]

%    beta11=beta_1;
%    if (t>=20),
%   beta11=0.008+beta_1;
%    end
%
%    beta12=beta_2;
%    if (t>=20),
%   beta12=1*beta_2;
%    end
   %MaxTime=50;
   R0=sqrt((alpha*beta_3)/((mu_d*mu_W)))
   S_h0=1;
   I_h0=0;
   I_t0=0;
   I_W0=0.7;
   D0=0.5;

Init=[S_h0,I_h0,I_t0,I_W0,D0];
%The main iteration
options=odeset('RelTol',1e-5);
[t,y]=ode45(@bur1,[0 250],[Init],options,[beta_1, mu_H,m1,theta,gamma,beta_2,beta_3 mu_d,sigma,K,mu_W,N_H,alph
```

```
%S_h=y(:,1); I_h=y(:,2);I_t=y(:,3);I_W=y(:,4);D=y(:,5);


% figure(5)
%  hold on
%  x=plot(t,Ih,'-b');
% legend(x,'Prevalence')
%  xlabel 'time in days'
%  ylabel 'Prevalence of infected humans'
%  hold off
%plots the graphs with scaled colours
 figure(1)
 g=plot(t,y(:,1),'-g');
 legend(g,'susceptible humans')
 xlabel 'Time(t) in days'
 ylabel 'susceptible humans'

 figure(2)
 Q=plot(t,y(:,2),'-b');
 legend(Q,'Infected humans')
 xlabel 'Time(t) in days'
 ylabel 'Infected Humans'

figure(3)
r=plot(t,y(:,3),'-b');
legend(r,'Teated')
xlabel 'Time(t) in days'
ylabel 'Humans under treatment'

 figure(4)
 w=plot(t,y(:,4),'-b');
 legend(w,'Infected Water Bugs')
xlabel 'Time(t)'
 ylabel 'Infected Water Bugs'
%figure (5)
 %plot(beta_1,y(:,1),'-r',t,y(:,2),'-b',t,y(:,3),'g');
% legend(w,'Infected Water Bugs')
%xlabel 'Time(t)'
%ylabel 'Proportions of humans'
%    S_h00=0.8;
%    I_h00=800/1000000;
```

```
%    I_t00=0.2;
%    I_W00=0.3;
%    D00=0.5;
%
% Init1=[S_h00,I_h00,I_t00,I_W00,D00];
%
% %The main iteration
% options=odeset('RelTol',1e-5);
% for i=1
% [t,y]=ode45(@bur1,[0 200],i*[Init1],options,[beta_1, mu_H,m1,theta,gamma,beta_2,beta_
% S_h=y(:,1); I_h=y(:,2);I_t=y(:,3);I_W=y(:,4);D=y(:,5);
%
% figure(6)
% hold on
% x=plot(I_W,I_t,'-b');
% %legend(x,'Infected humans')
% xlabel 'Prevalence of infected fish'
% ylabel 'Prevalence of Infected water bugs'
% hold
%
% figure(7)
% hold on
% x=plot(I_t,I_h,'-b');
% %legend(x,'Infected humans')
% xlabel 'Prevalence of infected water bugs'
% ylabel 'Prevalence of Infected humans'
% hold off
% end
% figure(3)
% f=plot(t,I_t,'-g',t,i_t,'-k');
% legend(f,'susceptible mammal','infectious waterbug')
% xlabel 'Time(t)'
% poplabel 'susceptible mammal, infectious waterbug'
%
% figure(4)
% N=plot(t,sm,'-g',t,sv,'-b',t,iv,'-k',t,im,'-m');
% legend(N,'susceptible human','susceptible waterbug','infectious waterbug','infectious
% xlabel 'Time(t)'
% poplabel 'susceptible human,susceptible waterbug,infectious waterbug,infectious mammal'
%
% figure(5)
```

```
      % P=plot(t,betaV,'-r',t,Ro,'-k');
      % legend(P,'transmission rate of mammal','reproduction number')
      % xlabel 'Time(t)'
      % poplabel 'transmission rate of mammal, reproduction number'
      %calculates the differential rates used in the integration.
      function dydt=bur1(t,y,parameter);
      %parameters

beta_1=parameter(1);mu_H=parameter(2);m1=parameter(3);theta=parameter(4);gamma=paramete
mu_d=parameter(8);sigma=parameter(9);K=parameter(10);mu_W=parameter(11);N_H=parameter(1


lambda=beta_1*m1*y(4)+beta_2*y(5)./(K+y(5));


%S_h=y(1);I_h=y(2);I_t=y(3);I_W=y(4);D=y(5);
dy=zeros(5,1);

    dydt = [(mu_H + theta)*(1 - y(1)) - theta*(y(2) + y(3)) - y(1)*(beta_1*m1*y(4) + beta_2*y(5)./(K
            y(1)*(beta_1*m1*y(4) + beta_2*y(5)./(K + y(5))) - sigma*y(2)./(1 + N_H*y(2))
             sigma*y(2)./( 1+ N_H*y(2)) - (mu_H + gamma)*y(3);
             beta_3*(1 - y(4))*y(5) - mu_W*y(4);
             alpha*y(4) - mu_d*y(5)];

      % ydot=ydot';
```

## Appendix IV

## Matlab code for optimal time control on BU disease

```
      function y = buruli_u1u2u3(u_H,u_V,u_F,u_E,theta,gamma,n,K,Q,B_H,B_V,B_F,B1,B2,B3,Nh,
         Sh0,Ih0,Rh0,Sv0,Iv0,Sf0,I_f0,U0, tfinal)

      test = -1;

      delta = 0.001;
      M = 1000;
      t=linspace(0,tfinal,M+1);
      h=tfinal/M;
      h2 = h/2;
```

```
Sh=zeros(1,M+1);
Ih=zeros(1,M+1);
Rh=zeros(1,M+1);
Sv=zeros(1,M+1);
Iv=zeros(1,M+1);
Sf=zeros(1,M+1);
I_f=zeros(1,M+1);
U=zeros(1,M+1);

Sh(1)=Sh0;
Ih(1)=Ih0;
Rh(1)=Rh0;
Sv(1)=Sv0;
Iv(1)=Iv0;
Sf(1)=Sf0;
I_f(1)=I_f0;
U(1)=U0;
lambda1=zeros(1,M+1);
lambda2=zeros(1,M+1);
lambda3=zeros(1,M+1);
lambda4=zeros(1,M+1);
lambda5=zeros(1,M+1);
lambda6=zeros(1,M+1);
lambda7=zeros(1,M+1);
lambda8=zeros(1,M+1);


u1=zeros(1,M+1);
u2=zeros(1,M+1);
u3=zeros(1,M+1);

while(test < 0)

    oldu1 = u1;
    oldu2 = u2;
    oldu3 = u3;
    oldSh = Sh;
    oldIh = Ih;
    oldRh = Rh;
    oldSv = Sv;
```

```
        oldIv = Iv;
        oldSf = Sf;
        oldI_f = I_f;
        oldU=U;
        oldlambda1 = lambda1;
        oldlambda2 = lambda2;
        oldlambda3 = lambda3;
        oldlambda4 = lambda4;
        oldlambda5 = lambda5;
        oldlambda6 = lambda6;
        oldlambda7 = lambda7;
        oldlambda8 = lambda8;

for i = 1:M
    m11 = u_H*Nh - (1-u1(i))*(B_H*Iv(i)*Sh(i))/Nh - u_H*Sh(i)+theta*Rh(i);
    m12 = (1-u1(i))*(B_H*Iv(i)*Sh(i))/Nh - (u_H+gamma*u1(i))*Ih(i);
    m13 =  gamma*u1(i)*Ih(i) - (u_H+theta)*Rh(i);
    m14 = u_V*Nv -(1-u2(i))*(B_V*I_f(i)*Sv(i))/Nv-n*B_V*Sv(i)*U(i)/K-u_H*Sv(i);
    m15  = (1-u2(i))*(B_V*I_f(i)*Sv(i))/Nv+n*B_V*Sv(i)*U(i)/K-u_V*Iv(i);
    m16 = u_F*Nf- (1-u3(i))*(B_F*U(i)*Sf(i))/K-u_F*Sf(i);
    m17 = (1-u3(i))*(B_F*U(i)*Sf(i))/K- u_F*I_f(i);
    m18 = Q*I_f(i)-u_E*U(i);

    m21 = u_H*Nh - (1-0.5*(u1(i)+u1(i+1)))*B_H*(Iv(i)+h2*m15)*(Sh(i)+h2*m11)/Nh -u_H*(Sh(i)+h2*m11)+
    m22 = (1-0.5*(u1(i)+u1(i+1)))*B_H*(Iv(i)+h2*m15)*(Sh(i)+h2*m11)/Nh -(u_H+ gamma*0.5*(u1(i)+u1(i+1)
    m23 = ( gamma*0.5*(u1(i)+u1(i+1))*(Ih(i)+h2*m12)) - (u_H+theta)*(Rh(i)+h2*m13);
    m24 = u_V*Nv -(1-0.5*(u2(i)+u2(i+1)))*B_V*(Sv(i)+h2*m14)*(I_f(i)+h2*m17)/Nv-n*B
    m25 = (1-0.5*(u2(i)+u2(i+1)))*B_H*(Sv(i)+h2*m14)*(I_f(i)+h2*m17)/Nv+n*B_V*(Sv(i
    m26 =u_F*Nf-(1-0.5*(u3(i)+u3(i+1)))*B_F*(Sf(i)+h2*m16)*(U(i)+h2*m18)/K-u_F*(Sf(
    m27 = (1-0.5*(u3(i)+u3(i+1)))*B_F*(Sf(i)+h2*m16)*(U(i)+h2*m18)/K- u_F*(Sf(i)+h2*m16);
    m28 =Q*(I_f(i)+h2*m17)-u_E*(U(i)+h2*m18);

    m31 = u_H*Nh - (1-0.5*(u1(i)+u1(i+1)))*B_H*(Iv(i)+h2*m25)*(Sh(i)+h2*m21)/Nh -u_H*(Sh(i)+h2*m21)+
    m32 = (1-0.5*(u1(i)+u1(i+1)))*B_H*(Iv(i)+h2*m25)*(Sh(i)+h2*m21)/Nh -(u_H+ gamma*0.5*(u1(i)+u1(i+1)
    m33 = ( gamma*0.5*(u1(i)+u1(i+1))*(Ih(i)+h2*m22)) - (u_H+theta)*(Rh(i)+h2*m23);
    m34 = u_V*Nv -(1-0.5*(u2(i)+u2(i+1)))*B_V*(Sv(i)+h2*m24)*(I_f(i)+h2*m27)/Nv-n*B
    m35 =(1-0.5*(u2(i)+u2(i+1)))*B_H*(Sv(i)+h2*m24)*(I_f(i)+h2*m27)/Nv+n*B_V*(Sv(i)
    m36 = u_F*Nf-(1-0.5*(u3(i)+u3(i+1)))*B_F*(Sf(i)+h2*m26)*(U(i)+h2*m28)/K-u_F*(Sf
    m37 = (1-0.5*(u3(i)+u3(i+1)))*B_F*(Sf(i)+h2*m26)*(U(i)+h2*m28)/K- u_F*(Sf(i)+h2*m26);
    m38 =Q*(I_f(i)+h2*m27)-u_E*(U(i)+h2*m28);
```

```
    m41 = u_H*Nh - (1-u1(i+1))*(B_H*(Iv(i)+h*m35)*(Sh(i)+h*m31))/Nh - u_H*(Sh(i)+h*m31)
    m42 = (1-u1(i+1))*(B_H*(Iv(i)+h*m35)*(Sh(i)+h*m31))/Nh-(u_H+ gamma*u1(i+1))*(Ih(i)+h*m3
    m43 = (gamma*u1(i+1))*(Ih(i)+h*m32) - (u_H+theta)*(Rh(i)+h*m33);
    m44 = u_V*Nv -(1-u2(i+1))*(B_V*(I_f(i)+h*m37)*(Sv(i)+h*m34))/Nv-(n*B_V*(Sv(i)+h
    m45 = (1-u2(i+1))*(B_V*(I_f(i)+h*m37)*(Sv(i)+h*m34))/Nv+(n*B_V*(Sv(i)+h*m34)*(U
    m46 = u_F*Nf-(1-u3(i+1))*(B_F*(Sf(i)+h*m36)*(U(i)+h*m38))/K-u_F*(Sf(i)+h*m36);
    m47 =(1-u3(i+1))*(B_F*(Sf(i)+h*m36)*(U(i)+h*m38))/K-u_F*(I_f(i)+h*m37);
    m48 = Q*(I_f(i)+h*m37)-u_E*(U(i)+h*m38);

            Sh(i+1) = Sh(i) + (h/6)*(m11 + 2*m21 + 2*m31 + m41);
            Ih(i+1) = Ih(i) + (h/6)*(m12 + 2*m22 + 2*m32 + m42);
            Rh(i+1) = Rh(i) + (h/6)*(m13 + 2*m23 + 2*m33 + m43);
            Sv(i+1) = Sv(i) + (h/6)*(m14 + 2*m24 + 2*m34 + m44);
            Iv(i+1) = Iv(i) + (h/6)*(m15 + 2*m25 + 2*m35 + m45);
            Sf(i+1) = Sf(i) + (h/6)*(m16 + 2*m26 + 2*m36 + m46);
            I_f(i+1) = I_f(i) + (h/6)*(m17 + 2*m27 + 2*m37 + m47);
            U(i+1) = U(i) + (h/6)*(m18 + 2*m28 + 2*m38 + m48);


end

for i = 1:M
    j = M + 2 - i;
    m11 = lambda1(j)*((1-u1(j))*(B_H*Iv(j)/Nh)+lambda1(j)*u_H + lambda2(j)*(1-u1(j))*-B_H*I
    m12 = -1+lambda2(j)*(u_H+gamma*u1(j)) - lambda3(j)*( gamma*u1(j));
    m13 = lambda3(j)*(u_H+theta) - lambda1(j)*(theta);
    m14 =lambda4(j)*((1-u2(j))*(B_V*I_f(j)/Nv)+lambda4(j)*n*B_V*U(i)/K+ lambda4(j)*u_V+lambda5(j)*
    m15 = -1+lambda5(j)*u_V+lambda1(j)*((1-u1(j))*(B_H*Sh(j)/Nh)) + lambda2(j)*((1-u1(j))*(-B_H
    m16 = lambda6(j)*((1-u3(j))*(B_F*U(j)/K)+lambda6(j)*u_F+lambda7(j)*((1-u3(j))*(
    m17 =-1+ lambda7(j)*u_F+lambda4(j)*((1-u2(j))*B_V*Sv(j)/Nv)+lambda5(j)*((1-u2(j
    m18 = lambda8(j)*u_E+lambda4(j)*n*B_H*Sv(j)/K -lambda5(j)*n*B_H*Sv(j)/K +lambda6(j)*(1-u3(j))*B_F*


    m21 = (lambda1(j)-h2*m11)*(1-0.5*(u1(j) + u1(j-1)))*B_H*0.5*(Iv(j) + Iv(j-1))/Nh
        (lambda2(j)-h2*m12)*(1-0.5*(u1(j) + u1(j-1)))*B_H*0.5*(Iv(j) + Iv(j-1))/Nh;
    m22 = -1+(lambda2(j)-h2*m12)*(u_H+gamma*0.5*(u1(j)+u1(j-1))) -(lambda3(j)-h2*m13)*(
    m23 = (lambda3(j)-h2*m13)*(u_H+theta) -(lambda1(j)-h2*m11)*theta;
    m24 = (lambda4(j)-h2*m14)*(1-0.5*(u2(j) + u2(j-1)))*(B_H*0.5*(Iv(j) + Iv(j-1))/Nv)-
          -(lambda5(j)-h2*m15)*(1-0.5*(u2(j) + u2(j-1)))*(B_H*0.5*(I_f(j) + I_f(j-1))/Nv)-(lambda5(j)-
    m25 = -1+(lambda5(j)-h2*m15)*u_V+(lambda1(j)-h2*m11)*((1-0.5*(u1(j)+u1(j-1)))*B
    m26 =(lambda6(j)-h2*m11)*((1-0.5*(u3(j)+u3(j-1)))*B_F*0.5*(U(j)+U(j-1))/K+(lamb
    m27 =-1+(lambda7(j)-h2*m17)*u_F+(lambda4(j)-h2*m14)*(1-0.5*(u2(j) + u2(j-1)))*B_V*0.5*(Sv(j)+S
```

```
    (lambda5(j)-h2*m15)*(1-0.5*(u2(j) + u2(j-1)))*-B_V*0.5*(Sv(j)+Sv(j-1))/Nv+(
m28 =(lambda8(j)-h2*m18)*u_E+(lambda4(j)-h2*m14)*n*B_H*(Sv(j)+Sv(j-1))/K-(lambd
     (lambda6(j)-h2*m16)*(1-0.5*(u3(j) + u3(j-1)))*-B_F*0.5*(Sf(j)+Sf(j-1))/K-(

m31 = (lambda1(j)-h2*m21)*(1-0.5*(u1(j) + u1(j-1)))*B_H*0.5*(Iv(j) + Iv(j-1))/Nh
    (lambda2(j)-h2*m22)*(1-0.5*(u1(j) + u1(j-1)))*B_H*0.5*(Iv(j) + Iv(j-1))/Nh;
m32 =-1+(lambda2(j)-h2*m22)*(u_H+gamma*0.5*(u1(j)+u1(j-1))) -(lambda3(j)-h2*m23)*(
m33 = (lambda3(j)-h2*m23)*(u_H+theta) -(lambda1(j)-h2*m21)*theta;
m34 =(lambda4(j)-h2*m24)*(1-0.5*(u2(j) + u2(j-1)))*(B_H*0.5*(Iv(j) + Iv(j-1))/Nv)-
      -(lambda5(j)-h2*m25)*(1-0.5*(u2(j) + u2(j-1)))*(B_H*0.5*(I_f(j) + I_f(j-1))/Nv)-(lambda5(j)-
m35 = -1+(lambda5(j)-h2*m25)*u_V+(lambda1(j)-h2*m21)*((1-0.5*(u1(j)+u1(j-1)))*B
m36 =(lambda6(j)-h2*m21)*((1-0.5*(u3(j)+u3(j-1)))*B_F*0.5*(U(j)+U(j-1))/K+(lamb
m37 =-1+(lambda7(j)-h2*m27)*u_F+(lambda4(j)-h2*m24)*(1-0.5*(u2(j) + u2(j-1)))*B_V*0.5*(Sv(j)+S
    (lambda5(j)-h2*m25)*(1-0.5*(u2(j) + u2(j-1)))*-B_V*0.5*(Sv(j)+Sv(j-1))/Nv+(
m38 =(lambda8(j)-h2*m28)*u_E+(lambda4(j)-h2*m24)*n*B_H*(Sv(j)+Sv(j-1))/K-(lambd
     (lambda6(j)-h2*m26)*(1-0.5*(u3(j) + u3(j-1)))*-B_F*0.5*(Sf(j)+Sf(j-1))/K-(



m41 = (lambda1(j)-h*m31)*((1-u1(j-1))*(B_H*Iv(j-1)/Nh)+(lambda1(j)-h*m31)*u_H +
m42 = -1+(lambda2(j)-h*m32)*(u_H+ gamma*u1(j-1))-(lambda3(j)-h*m33)*(gamma*u1(j
m43  = (lambda3(j)-h*m33)*(u_H+theta) - (lambda1(j)-h*m31)*(theta);
m44 = (lambda4(j)-h*m34)*((1-u2(j-1))*(B_V*I_f(j-1)/Nv))+(lambda4(j)-h*m44)*n*B
m45 = -1+(lambda5(j)-h*m35)*u_V+(lambda1(j)-h*m31)*((1-u1(j-1))*(B_H*Sh(j-1)/Nh
m46 =(lambda6(j)-h*m36)*((1-u3(j-1))*(B_F*U(j-1)/K)+(lambda6(j)-h*m36)*u_F+(lam
m47 =-1+ (lambda7(j)-h*m37)*u_F+(lambda4(j)-h*m34)*((1-u2(j-1))*B_V*Sv(j-1)/Nv)
m48 = (lambda8(j)-h*m38)*u_E+(lambda4(j)-h*m34)*n*B_H*Sv(j-1)/K -(lambda5(j)-h*m35)*n*B_H*S

          lambda1(j-1) = lambda1(j) - (h/6)*(m11 + 2*m21 + 2*m31 + m41);
          lambda2(j-1) = lambda2(j) - (h/6)*(m12 + 2*m22 + 2*m32 + m42);
          lambda3(j-1) = lambda3(j) - (h/6)*(m13 + 2*m23 + 2*m33 + m43);
          lambda4(j-1) = lambda4(j) - (h/6)*(m14 + 2*m24 + 2*m34 + m44);
          lambda5(j-1) = lambda4(j) - (h/6)*(m15 + 2*m25 + 2*m35 + m45);
          lambda6(j-1) = lambda4(j) - (h/6)*(m16 + 2*m26 + 2*m36 + m46);
          lambda7(j-1) = lambda4(j) - (h/6)*(m17 + 2*m27 + 2*m37 + m47);
          lambda8(j-1) = lambda4(j) - (h/6)*(m18 + 2*m28 + 2*m38 + m48);
      end

      temp=(B_H.*Iv.*(lambda2-lambda1)./(Nh.*B1))+ ( gamma.*(lambda2-lambda3)./B1)...
          +(B_H.*Sh.*(lambda2-lambda1))./(Nh.*B1);
      u11 = min(1,max(0,temp));
```

```
    u1 = 0.5*(u11 + oldu1);
    tempu2=(I_f.*(lambda5-lambda4)./(Nv.*B2))+ (B_V.*Sv.*(lambda5-lambda4)./Nv.*B2);
     u12 = min(1,max(0,tempu2));
     u2 = 0.5*(u12 + oldu2);
    tempu3=(B_F.*U.*(lambda7-lambda6)./(K.*B3))+ (B_F.*Sf.*(lambda7-lambda6)./K.*B3);
    u13 = min(1,max(0,tempu3));
    u3 = 0.5*(u13 + oldu3);

  temp1 = delta*sum(abs(u1)) - sum(abs(oldu1 - u1));
  temp1a = delta*sum(abs(u2)) - sum(abs(oldu2 - u2));
  temp1b = delta*sum(abs(u3)) - sum(abs(oldu3 - u3));
  temp2 = delta*sum(abs(Sh)) - sum(abs(oldSh - Sh));
  temp3 = delta*sum(abs(Ih)) - sum(abs(oldIh - Ih));
  temp4 = delta*sum(abs(Rh)) - sum(abs(oldRh - Rh));
  temp5 = delta*sum(abs(Sv)) - sum(abs(oldSv - Sv));
  temp6 = delta*sum(abs(Iv)) - sum(abs(oldIv - Iv));
  temp7 = delta*sum(abs(Sf)) - sum(abs(oldSf - Sf));
  temp8 = delta*sum(abs(I_f)) - sum(abs(oldI_f - I_f));
  temp9 = delta*sum(abs(U)) - sum(abs(oldU - U));
  temp10 = delta*sum(abs(lambda1)) - sum(abs(oldlambda1 - lambda1));
  temp11 = delta*sum(abs(lambda2)) - sum(abs(oldlambda2 - lambda2));
  temp12 = delta*sum(abs(lambda3)) - sum(abs(oldlambda3 - lambda3));
  temp13 = delta*sum(abs(lambda4)) - sum(abs(oldlambda4 - lambda4));
  temp14 = delta*sum(abs(lambda5)) - sum(abs(oldlambda5 - lambda5));
  temp15 = delta*sum(abs(lambda6)) - sum(abs(oldlambda6 - lambda6));
  temp16 = delta*sum(abs(lambda7)) - sum(abs(oldlambda7 - lambda7));
  temp17 = delta*sum(abs(lambda8)) - sum(abs(oldlambda8 - lambda8));
  test = min(temp1, min(temp1a,min(temp1b, min(temp2, min(temp3, min(temp4, min(temp5,
       min(temp11, min(temp12,min(temp13,min(temp14,min(temp15,min(temp16,min(temp17))
end

 y(1,:) = t;
 y(2,:) = Sh;
 y(3,:) = Ih;
 y(4,:) = Rh;
 y(5,:) = Sv;
 y(6,:) = Iv;
 y(7,:) = Sf;
 y(8,:) = I_f;
 y(9,:) = U;
 y(10,:)= u1;
 y(11,:)= u2;
 y(12,:)= u3;
```

## Appendix V

## Matlab code for optimal time control

```
clear all;
close all;
clc;
u_H=0.004566;
B_H=0.80;
B_F=0.5;
B_V=0.45;
gamma =0.04;
theta=0.4;
 Q=0.8;
 u_V=0.06;
 u_F=0.004;
 u_E=0.65;
 K= 1000;
 n=0.004;
 U0=100;            % initial MU in the environment
Sh0=400000;         % initial susceptible human
Ih0=40000;          %initial infected humans
Rh0=10000;          %initial recovery human
Nh=Sh0+Ih0+Rh0;      % total human population
Sv0=100;             % initial susceptible vector
Iv0=20;              % initial infeceted vector
Nv=Sv0+Iv0;          % total vector population
Sf0=100;
I_f0=10;
Nf=Sf0+I_f0;
tfinal=100;
B1=60;
B2=20;
B3=20;

y1=buruli_u1u2u3(u_H,u_V,u_F,u_E,theta,gamma,n,K,Q,B_H,B_V,B_F,B1,B2,B3,Nh, Nv,Nf,...
                  Sh0,Ih0,Rh0,Sv0,Iv0,Sf0,I_f0,U0, tfinal);
% disp('               ')
```

```
options = odeset('RelTol',1e-4,'AbsTol',[1e-4 1e-4 1e-5 1e-5 1e-5 1e-5 1e-5 1e-5]);
to = 0;
yo = [Sh0,Ih0,Rh0,Sv0,Iv0,Sf0,I_f0,U0];
[t y] = ode45(@bonyya,[to tfinal],yo,options);
disp('               ')

figure(1)
plot(t,y(:,2),':r',y1(1,:),y1(3,:),'-b')
xlabel('Time (Days)')
ylabel('Infected Human')
legend('Without Optimal control', 'With Optimal Control ')

figure(2)
plot(t,y(:,6),':r',y1(1,:),y1(7,:),'-b')
xlabel('Time (Days)')
ylabel('Infected water bugs')
legend('Without Optimal control', 'With Optimal Control ')

figure(3)
plot(t,y(:,1),':r',y1(1,:),y1(2,:),'-b')
xlabel('Time (Days)')
ylabel('Susceptible Human')
legend('Without Optimal control', 'With Optimal Control ')

figure(4)
plot(y1(1,:),y1(8,:),'-b',y1(1,:),y1(9,:),':r')
xlabel('Time (Days)')
ylabel('Control Profiles')
legend('u1','u2')
axis([0 tfinal 0 1])

% figure(1)
% plot(t,y(:,2),':r')
% xlabel('Time (Days)')
% ylabel('Infected Human')
% legend('Without Treatment and Insecticide')
```

## Appendix VI

## Matlab code for optimal time control

```
function ym =bonyya(t,y)
u_H=0.004566;
B_H=0.80;
B_F=0.5;
B_V=0.45;
 gamma =0.04;
theta=0.4;
 Q=0.8;
 u_V=0.06;
 u_F=0.004;
 u_E=0.65;
 K= 1000;
 n=0.004;
 U0=100;            % initial MU in the environment
Sh0=400000;         % initial susceptible human
Ih0=40000;          %initial infected humans
Rh0=10000;          %initial recovery human
Nh=Sh0+Ih0+Rh0;      % total human population
Sv0=100;             % initial susceptible vector
Iv0=20;              % initial infeceted vector
Nv=Sv0+Iv0;          % total vector population
Sf0=100;
I_f0=10;
Nf=Sf0+I_f0;
ym = zeros(8,1);
ym(1)=u_H*Nh -B_H*y(5)*y(1)/Nh - u_H*y(1)+theta*y(3);
ym(2)=B_H*y(5)*y(1)/Nh - (u_H+gamma)*y(2);
ym(3)=gamma*y(2) - (u_H+theta)*y(3);
ym(4)= u_V*Nv-B_V*y(7)*y(4)/Nv-n*B_V*y(4)*y(8)/K-u_H*y(4);
ym(5)= B_V*y(7)*y(4)/Nv+n*B_V*y(4)*y(8)/K-u_V*y(5);
ym(6)= u_F*Nf-B_F*y(8)*y(6)/K-u_F*y(6);
ym(7)= B_F*y(8)*y(6)/K- u_F*y(7);
ym(8) = Q*y(7)-u_E*y(8);
```

## Appendix VII

## Matlab code for structured age BU Model

```
function [] = SIR_AgeStructured ()
 %% Project - Age Structured Buruli ulcer Model
 % Author : Bonyah
 % Date: 1/15/2014
 %
 % delta -t = 1 week
 %%

 clear all ; % Close /Delete all figures
 close all ; % Free system memory
 clc ; % Clear command window
hmax = 4; % Upper bound of space
kmax = 4; % Upper bound of time
n=10;
m=100;
h = linspace(0,hmax,n+1); % space discretization
k = linspace(0,kmax,m+1); % time discretization
 % Simulation Control Variables
 reference_sim = false ; % i f true , run ref sim (ie. no infected pop )
 %xi = 100; % Lo Rate of shedding of mycobacterium ulcerans from
 % infected human of age a.
 k = 0.01; % detla_t = 1/50 of a week
 h = 0.1; % delta_a = 1 week
%  [X,Y]=meshgrid(h,k);
 alpha = 0.1; % Proportionality factor (wave speed )
 b = 0.2; % normal mortality rate in deaths per week
%  A = 72; % Upper bound on human age
 BL = 0; %  MU Population
 kappa_L = 100000; % cells /ml
 beta_L = 0.65; % per week
 lambda = 0*2; % Human recruitment rate (non - newborns entering pop )
 gamma_1 = 0.04; % recovery rate of untreated Buruli ulcer
 gamma_2 = 0.01; % recovery rate of treated Buruli ulcer
 u = 0*2; % antiboitic treatmnt rate for humans of age a at time t
%  delta_L = 1/30*7; % Death rate of MU in the environment .
% Declare the S, I, R Arrays and zero out all values .
m = 3744; % cols -> total age = 72 * 52 = 3744 weeks
```

```
 n = 24/ k; % rows -> total simulation time = 24 weeks
 S = zeros (m,n); % Susceptible population
 I = zeros (m,n); % Infected population
 R = zeros (m,n); % Recovered population
 omega=0.8; %per day
 %% Boundary Conditions
 % Note: Boundary conditions for R array are created
 % within the main simulation loop.
for t = 0:(n -1)
 % Susceptible and Infected Population
 S(0+1 , t+1) = 0.0;
 I(0+1 , t+1) = 0.0;
 end
 %% Initial Conditions
 % Initial Conditions for R and S
 one_year_old = 52; % Age in weeks
 for a=(m -1): -1:0
 % Susceptible and Recovered Population
 if (a <= one_year_old) % if age < 1 yr old then immune (ie. in R group )
 R(a+1 ,0+1) = 2.67;
 S(a+1 ,0+1) = 0;
 else
 R(a+1 ,0+1) = 0;
 S(a+1 ,0+1) = 2.67; % 2.67 *52 wks *60 yrs = 10000 people
 end
 end
% Initial Conditions for I
 fifteen_years_old = 936; % Age in weeks
 sixteen_years_old = 988; % Age in weeks
 if ( reference_sim == false ) % reference sim contains no infected people
 % Include one 15 year old infected human
 for a=(m -1): -1:0
 if (a >= fifteen_years_old ) && (a<= sixteen_years_old )
 I(a +1 ,0+1) = 1/52;
 else
    I(a +1 ,0+1) = 0;
 end
 end
 end
 total_BL = zeros (n ,1);
 %% Run the Simulation
```

```
  % Generate All Other Interior Grid Points
 for t = 0:(n -1)
 % Susceptible Population - Generate one row
 for a=1:(m -1)
 S(a+1,t +1+1) = (1-k* alpha /h)* S(a+1,t+1)+ k* alpha /h* S(a -1+1 , t+1)+ k* lambda ..
- k* beta_L *BL /( kappa_L +BL )*S(a+1,t +1)...
 - k*b * S(a+1, t+1) ...
 + k* omega*7 * R(a+1, t+1);
 end
 % Infected Population - Generate one row
for a=1:(m -1)
 I(a+1,t+1+1) = ...
 (1-k* alpha /h)* I(a+1,t+1) ...
 + k* alpha /h* I(a -1+1 , t+1) ...
 + k* beta_L *BL /( kappa_L +BL )*S(a+1,t +1)... % BL infected humans
 - k*b * I(a+1, t+1) ... % natural mortalities
- k* gamma_1 *(1-u)*I(a+1,t+1) ... % pop recovering w/o antibiotics
- k* gamma_2 *u*I(a+1, t+1); % pop recovering w antibiotics
end
 % Include new born babies into the recovered population this week
 fecundity = 0;
 for age =779:1:2339
 fecundity = fecundity ...
 + (S(age +1,t +1) + I(age +1, t+1) + R(age +1, t +1))...
 * (1/5) * (sin ((age -780)/1560*3.14159))^2;
 end
 R(0+1 , t+1)= fecundity /52; % Divided by 52 weeks /year
% Recovered Population - Generate one row
 for a =1:(m -1)
 R(a+1,t +1+1) = ...
 (1- k* alpha /h)* R(a+1, t+1) ...
 + k*alpha /h * R(a -1+1 , t+1) ...
 + k* gamma_1 *(1-u)*I(a+1, t+1) ... % pop recovering w/o antibiotics
 + k* gamma_2 *u*I(a+1,t +1) ... % pop recovering with antibiotics
- k*b * R(a+1,t +1) ... % natural mortalities
- k*omega*7 * R(a+1,t +1); % recovered - loosing immunity
 end
 % MU populations (BL)
%  dBH = get_dBH (I,t,BH ,xi ,chi ,eta ,A,k);
%  dBL = get_dBL (chi ,BH ,delta_L ,BL ,k);
%  BH = BH + dBH ;
```

```
%  BL = BL + dBL ;
%  total_BH (t+1) = BH;
%  total_BL (t+1) = BL;
%  fprintf ('%f %f\n',BH ,BL );
 end
 % Print Population Totals
 total_sus_population = zeros (n ,1); % column vector of length n
 total_inf_population = zeros (n ,1); % column vector of length n
 total_rec_population = zeros (n ,1); % column vector of length n
 total_population = zeros (n ,1); % column vector of length n
 fprintf ('\nSUSEPTABLE INFECTED RECOVERED TOTAL - POPULATION \n\n');
 for t = 0:1:(n -1)
 for a =0:(m -1)
 total_sus_population (t +1) = total_sus_population (t+1) ...
 + S(a+1, t+1);
 total_inf_population (t +1) = total_inf_population (t+1) ...
 + I(a+1, t+1);
 total_rec_population (t +1) = total_rec_population (t+1) ...
 + R(a+1, t+1);
 total_population (t+1) = total_sus_population (t+1) ...
+ total_inf_population (t +1)...
 + total_rec_population (t+1);
 end
 fprintf ('%f %f %f %f\n' ,...
 total_sus_population (t +1) ,...
 total_inf_population (t +1) ,...
 total_rec_population (t+1), ...
 total_sus_population (t +1) + total_rec_population (t +1));
 end
 % Produce 2D Plots
 x=1:1: n;
 figure ;
 plot(x, total_sus_population (x));
 title ('Suseptable Population ');
 xlabel ('Time: 3.36 hrs / step - 24 weeks total ');
 ylabel ('Population ');
 grid;
 figure ;
 plot(x, total_inf_population (x));
%  axis ([0 1200 0 10000]);
 title ('Infected Population ');
```

```
 xlabel ('Time: 3.36 hrs / step - 24 weeks total ');
 ylabel ('Population ');
 grid;
 figure ;
 plot(x, total_rec_population (x));
%  axis ([0 1200 0 10000]);
 title ('Recovered Population ');
 xlabel ('Time: 3.36 hrs / step - 24 weeks total ');
 ylabel ('Population ');
 grid;
 figure ;
 plot(x, total_population(x));
 title ('Total Population ');
 xlabel ('Time: 3.36 hrs / step - 24 weeks total ');
 ylabel ('Population ');
 grid;
%  figure ;
 plot(x, total_BL (x));
 title ('BL MU Population ');
 xlabel ('Time: 3.36 hrs / step - 24 weeks total ');
 ylabel ('Population '); grid;
 % 3-D plotting section
%[X,Y] = meshgrid(h,k);
figure
%mesh(X',Y',S');
surf(S);
xlabel('age'); ylabel('time'), zlabel('Solution S')
title('Suseptable Population ')
% figure(2)
% mesh(X',T',I);
% xlabel('age'); ylabel('time'), zlabel('Solution I')
% title(' Infertious')
```