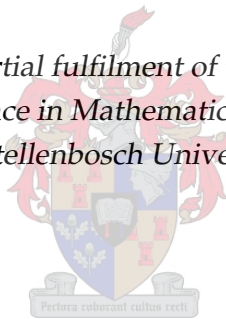


A mathematical model for onchocerciasis and its treatment with ivermectin

by

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*Thesis presented in partial fulfilment of the requirements for the
degree of Master of Science in Mathematics in the Faculty of Science
at Stellenbosch University*



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December 2016

Declaration

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Abstract

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Thesis: MSc. (Mathematics)

December 2016

Onchocerciasis is a human disease that is caused by the filarial worm *Onchocerca volvulus*. It occurs close to oxygen rich flowing streams and rivers in the inter-tropical zones. The disease is a serious public health problem and any control interventions must be effective so as to eliminate it from the population. A rational control intervention method is through mass administration of ivermectin. In this study, a non-linear mathematical model is formulated to model the transmission dynamics and spread of onchocerciasis disease. First, a mathematical model is formulated to evaluate the impact of long term mass treatment of onchocerciasis with ivermectin. The model basic reproduction number is computed and the stability analysis presented. The model is found to exhibit a backward bifurcation so that for R_0 less than unity is not sufficient to eradicate the disease from the population and the need is to lower R_0 to below a certain threshold, R_0^c for effective disease control. Optimal control theory is applied to investigate the control strategies for eliminating onchocerciasis using time dependent controls. The characterization of the optimal control is carried out via the Pontryagin's Maximum Principle. The simulation results demonstrate that the maximum implementation of vector control, personal protection strategies and enhanced mass treatment with ivermectin strategies in the epidemic are of very critical impacts in the optimal control. This gives a theoretical interpretation to the practical experiences that the insecticide and use of insect repellents are important in the control of onchocerciasis. The model is extended

to assess the effectiveness of mass administration using impulsive differential equations since the treatment itself is considered to be impulsive. The basic reproduction number is derived and we establish that the global dynamics are completely determined by the values of R_0 . The disease-free equilibrium is globally asymptotically stable for basic reproduction number $R_0 < 1$, while for $R_0 > 1$, a unique endemic equilibrium exists and is globally asymptotically stable. We then use the model to determine the threshold for the proportion of infected individuals that reduces the infection in the human (host) population. Finally, we present numerical simulations results. Sensitivity analysis reveals that the most sensitive parameters in the onchocerciasis epidemic are the human transmission contact rate β_h , the vector transmission contact rate β_v and vector death rate μ_v . The numerical results show that efficiency of the mass administration of ivermectin contributes a greater impact on the disease dynamics and moves the system towards the disease free state.

Keywords: Onchocerciasis, ivermectin, mathematical model, reproduction number, backward bifurcation, optimal control, impulsive equations, sensitivity, simulations, population.

Opsomming

'N Wiskundige model vir onchocerciasis en die behandeling daarvan met ivermektien

(“ *A mathematical model for onchocerciasis and its treatment with ivermectin* ”)

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Onchocerciasis is 'n menslike siekte wat veroorsaak word deur die filariese wurm *Onchocerca volvulus*. Dit kom voor naby suurstofryke vloeiende strome en riviere in intertropiese sones. Hierdie siekte is 'n ernstige publieke gesondheidsgevaar en enige kontrole ingrypings moet effektief wees om dit uit die bevolking uit te wis. 'n Rationele kontrole ingrypingsmetode is die massa toedien van ivermektien. In hierdie studie word 'n nie-linéêre wiskundige model geformuleer om die oordrags- en verspreidingsdinamika van die onchocerciasis siekte te modelleer. Eerstens word 'n wiskundige model geformuleer om die impak van langtermyn massabehandeling van onchocerciasis met ivermektien te bepaal. Die model se basiese voortplantingsgetal word bereken en die stabiliteitsanalise word aangebied. Die model word bevind om 'n terugwaardse bifurkasie ten toon te stel sodat die voorwaarde R_0 kleiner as eenheid nie genoeg is om die siekte uit die bevolking uit te wis nie en dat dit nodig is om R_0 te verlaag tot onder 'n sekere drumpel R_0^c vir effektiewe siektekontrole. Optimale kontrole teorie word met tydafhanklike kontroles toegepas om die kontrole strategieë om onchocerciasis uit te wis te bestudeer. Die karakterisering van die optimale kontrole word uitevoer met Pontryagin se Maksimumbeginsel. Die uitslae van die simulاسie wys dat die maksimum uitvoering van vektorkontrole, persoonlike beskermingstrategieë en verbeterde massabehandeling

met ivermektien strategieë in die epidemie van kritiese belang is in die optimale kontrole. Dit gee 'n teoretiese verklaring vir die praktiese ondervinding dat insekgif en die gebruik van (insek) afweermiddels belangrik is in die kontrole van onchocerciasis. Die model word uitgebrei om die effektiwiteit van massa toedien vas te stel deur die gebruik van impulsiewe differensiaalvergelykings aangesien die behandeling self as impulsief beskou word. Die basiese voorplantingsgetal word afgelei en ons bevestig dat die globale dinamika volledig bepaal word deur die waardes van R_0 . Die siektevrye ewewig is globaal asimptoties stabiel wanneer die voortplantingsgetal $R_0 < 1$, terwyl daar vir $R_0 > 1$ 'n unieke endemiese ewewig bestaan wat globaal asimptoties stabiel is. Ons gebruik dan die model om die drumpel van persentasie van besmette individue te bepaal wat die besmetting in die menslike (gasheer) bevolking verminder. Laastens bied ons uitslae van numeriese simulaties aan. Sensitiwiteitsanalise toon aan dat die mees sensitiewe parameters in die onchocerciasis epidemie die menslike oordragsverhouding β_h , die vektoroordragskontakverhouding β_v en die vektordoodsverhouding μ_v is. Die numeriese uitslae toon dat die effektiwiteit van massa toedien van ivermektien 'n groter invloed op die siekte se dinamika het en die stelsel na die siektevrye toestand beweeg.

Sleutelwoorde: Onchocerciasis, ivermektien, wiskundige model, voortplantingsgetal, terugwaardse bifurkasie, optimale kontrole, impulsiewe vergelykings, sensitiwiteit, simulaties, bevolking.

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Dedications

This thesis is dedicated to God Almighty for giving me wisdom and good health. To my dad and mum Leonard and Helida Omondi for their love and support. To my siblings George, Celline, Cornel, Maurine, Lillian, Josephine, Jackline and Kennedy Omondi. To my lovely daughter Elliana Daisha Otieno. I love you. May God bless you.

Publications

The following publications are extracts from this thesis. They are appended at the end of the thesis.

1. Application of optimal control to the onchocerciasis transmission model with treatment (*Submitted to the Bulletin of Mathematical Biology*).
2. Modelling the impact of mass administration of ivermectin in the treatment of onchocerciasis (river blindness) (*Submitted to the Journal of Theoretical Population Biology*).

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Chapter 1

Introduction

1.1 Background to onchocerciasis

Onchocerciasis is a vector-borne parasitic disease. This is a human disease caused by the filarial (thread like) worms *Onchocerca volvulus* in human hosts and is transmitted by the blackfly (*Simulium damnosum*) [87]. It occurs close to oxygen rich flowing streams and rivers in the inter-tropical zones [24, 47]. This is because the egg, larvae and pupa stages of *Simulium damnosum* are aquatic giving rise to the common name of river blindness. The prevalence of infection and disease in a community is related to the proximity to riverine breeding sites of the black flies. The highest burden of infection and disease are in communities adjacent to rivers. Prevalence of infection rises with age until around 30 years, after which infection profiles vary between geographical region and sex, with higher rates of microfilaridemia and morbidity reported in men than in women [8].

Studies show that about 90% of onchocerciasis cases occur in Africa and are predominantly found in West Africa. It is also found in six countries in Latin America and in Yemen in the Arabian Peninsula [98]. Onchocerciasis is a serious public health problem. It is a major constraint to social and economic development [21, 37]. This disease is responsible for ugly skin disease with depigmentation, severe unrelenting itching and blindness [23, 97]. Figure 1.1 shows the world distribution of onchocerciasis disease. Figure 1.1 (a) shows the African countries with endemic onchocerciasis. Countries participating in the former Onchocerciasis Control Program region in West Africa are shown in yellow and those participating in the African Program for Onchocerciasis Control are shown in brown. Figure 1.1 (b) shows the endemic foci in Latin America.

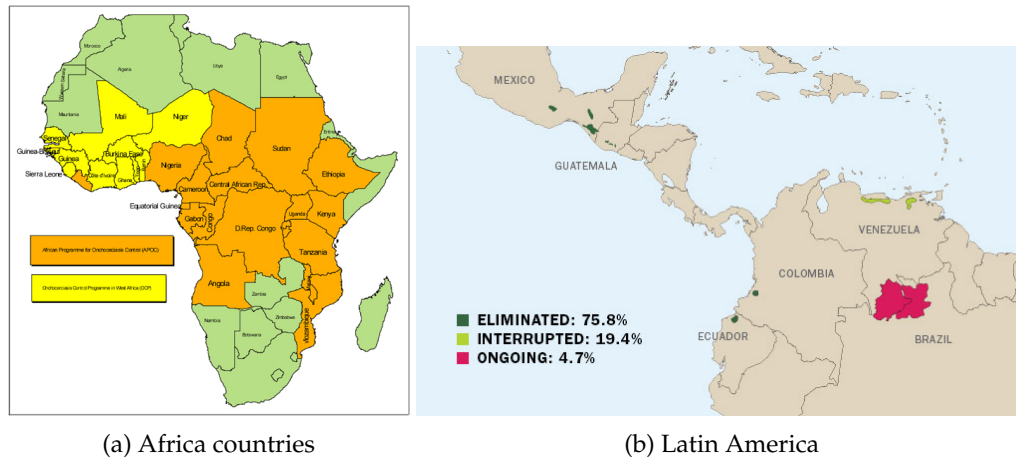


Figure 1.1: World distribution of *Onchocerca volvulus*: Source [96].

1.2 Life cycle of *Onchocerca volvulus*

Onchocerciasis is caused by *Onchocerca volvulus* and is transmitted from person to person by blackflies that belong to genus *Simulium* [2]. The only natural definitive host of *Onchocerca volvulus* is human. The intermediate host is a black-fly in the genus *Simulium* [52]. The infection of onchocerciasis begins at the third larvae stage (L3) [20]. An infected blackfly (genus *Simulium*) introduces the filarial larvae into the skin of the human host during blood meal. The L3 larvae develops into adult filariae in the subcutaneous tissues and reside in nodules in subcutaneous connective tissues. The worms mature slowly and may require as long as a year to reach full size [32]. The adult worms can live in the nodules for approximately 15 years [20, 47, 55]. Fertilised female worms can produce millions of embryos (microfilariae) [47]¹. The microfilariae are found in the skin and in the lymphatics of connective tissues where they can live as long as 30 months [60]. During blood meal, the microfilariae are ingested by blackfly. Most of the microfilariae ingested die or are digested together with the blood meal. Few penetrate the wall of the blackfly's stomach and migrate from the blackfly's midgut through the hemocoel to the thoracic muscles. In 6-13 days, the microfilariae then develop into first-stage larvae (L1), moult into stage two larvae (L2) and subsequently into infective third-stage larvae (L3) [52]. The (L3) larvae migrate to the blackfly's proboscis and infect another human when the blackfly takes a blood meal. Upon gaining entry into a human host, the L3 worms develop into adults in 1-3 months. After initial infection, microfilariae from the adults will appear in 10-20 months [52].

¹Each female can produce 1000 to 3000 microfilariae per day.

The life span of *Simulium damnosum* is short and last only for 2-3 weeks [68]. The life expectation of *Onchocerca volvulus* larvae in the *Simulium damnosum* is estimated to be 14-28 days [60]. The earliest appearance of microfilariae in humans² after a primary infection is about 6-7 months [55]. It was estimated in the Cameroon forest that 80% of the infective larvae escape from the fly and 40% of the infective flies become non-infective [60]. Figure 1.2 gives the summary of the life cycle of *Onchocerca volvulus*.

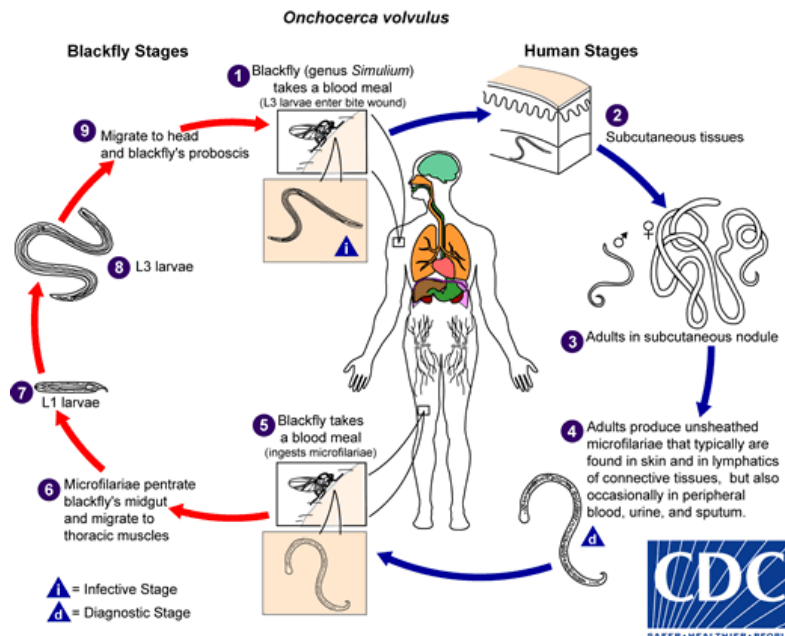


Figure 1.2: Life cycle of *Onchocerca volvulus* relevant for the model considered in this thesis project: Source [20].

1.3 Pathology of onchocerciasis

Onchocerca volvulus has a long-term persistence pathology. This is attributed to the fact that it has developed a highly adaptive mechanisms of immune evasion [16]. The spectrum of onchocerciasis manifestation in the infected individuals varies and the diversity in the clinical responses is associated with the intensity and the type of immune responses to the *Onchocerca volvulus* parasite [16, 48, 84]. The appearance of onchocerciasis pathology is linked to the reactions to moribund microfilariae in the skin or the

²The total microfilarial load in highly infected human hosts is more than 100 million.

eye. Studies indicate that the most severe disease manifestation is elicited by the death of microfilariae passing through the cornea [39, 42, 47, 48]. During the migration of microfilariae, they invade the conjunctiva, cornea and the posterior regions of the eye [16, 17, 47]. Continued exposure of the cornea leads to the inflammation of the iris which results in permanent visual impairment and sometimes blindness [16].

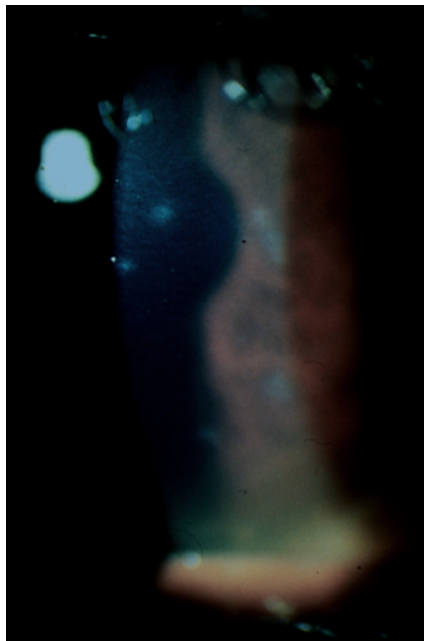
Patients suffering from human onchocerciasis are classified into three groups: 1) asymptomatic individuals, persons with so called generalized onchocerciasis (GEO) who have palpable nodules in their skin; 2) patients with severe pathology (termed hyperreactive form) and 3) putative immune individuals who never develop any signs of parasitemia or clinical onchocerciasis, despite their lifelong exposure to the parasite [83]. It is believed that most of the affected individuals in the areas where this disease is endemic belong to the asymptomatic form of onchocerciasis. Patients with chronic infection can develop depigmentation (leopard skin) and loss of skin elasticity and structure, leading to signs of premature skin ageing (eg, lizard skin or hanging groin) [62]. A rare form of skin disease can happen in immunologically hyperactive individuals with severe chronic papular dermatitis, hyperpigmentation [16]. In addition, these individuals are characterised by low numbers of parasites and increased immune responses, particularly of the Th2 type [16, 27, 86].

Figure 1.3 shows the effect of onchocerciasis disease in an infected human. Figure 1.3 (a) depicts a sclerosing keratitis. It is known as ocular onchocerciasis and begins with microfilariae migration to the cornea. Early infection usually presents with a tearing, irritated conjunctivitis, often with a hypersensitivity to light. Figure 1.3 (b) shows onchocercal punctate keratitis with dead microfilariae in cornea surrounded by white cell infiltrate [75]³. Figure 1.3 (c) shows the pathology of onchocerciasis associated with the skin. This is the typical dermatitis and is known as onchodermatitis. This pathogenesis comes with mild itching or discolouring of the skin.

³White cell infiltrates form around dead microfilariae in the cornea, causing "snowflake opacities". Punctate keratitis is reversible.



(a) Ocular onchocerciasis



(b) Punctate keratitis



(c) Onchodermatitis

Figure 1.3: Pathology of *Onchocerca volvulus*: Source [42].

1.4 Treatment strategies

The struggle to eradicate onchocerciasis is currently led by the African Program of onchocerciasis Control (APOC) [43]. The main control measure for the eradication of onchocerciasis in the countries where the disease is endemic such as Ghana is through community directed treatment with ivermectin. The drugs are distributed by MectizanTM Donation Program (MDP) by Merck and Co., Inc., [22]. Ivermectin is an antimicrofilarial agent that acts as both the primary and secondary form of prevention for individuals with onchocerciasis. It degenerates intrauterine microfilariae thereby suppressing the release of new microfilariae for up to 3-4 months after which it is still possible to continue producing microfilariae until it dies naturally [63]. The standard dose of ivermectin is 150 μ g/kg and children who weigh 15 kg or more are eligible. Ivermectin leads to hyperpolarisation of glutamate-sensitive channels and immobilisation of microfilariae [95]. Ivermectin, when given four times every year for consecutive years, can have a moderate macrofilaricidal effect [29]. However, the macrofilaricidal effect is too minimal and for successful control of onchocerciasis, repeated treatment with ivermectin spanning for 10-15 years has to be administered to correspond to the life span of adult worm [38]. The following control programmes have been used in the fight to eradicate onchocerciasis:-

- The Onchocerciasis Control Programme (OCP, 1974 to 2002) - The OCP was an international partnership that applied aerial larviciding of rivers for vector control covering 11 West African countries [11, 41].
- The Onchocerciasis Elimination Program in the Americas (OEPA, 1991 to 2012) - The OEPA comprised of partnerships between the governments of the endemic countries, the Pan American Health Organization (PAHO), the Carter Center, Lions Clubs International, the Bill and Melinda Gates Foundation, and the Mectizan Donation Program. Used mass ivermectin therapy every six months to fight onchocerciasis [43].
- The African Program for Onchocerciasis Control (APOC, 1995 to 2025) - The program covers 19 African countries using annual ivermectin treatment delivered by community distributors chosen by the communities themselves [43].

The treatment of onchocerciasis is designed to reduce morbidity and mortality by ensuring that rapid and complete eradication of onchocerciasis infection is achieved so that fatal and severe disease situations including cases of chronic infections are prevented.

Another important objective of effective treatment of onchocerciasis with ivermectin is to reduce the human reservoir of infection so that disease transmission can be minimised [87]. APOC aims to tackle onchocerciasis infection through mass administration of ivermectin for 15-17 years. In support of the fight against onchocerciasis, WHO⁴ has set the time frame for the elimination of onchocerciasis and other neglected tropical diseases to be 2020-2025 [57, 87].

In APOC countries, onchocerciasis treatment is done through the community directed treatment with ivermectin programs (CDTI) [46]⁵. For example, studies in hyperendemic foci in Mali, Cameroon and Senegal indicate that 15 to 17 years of annual mass administration of ivermectin had eliminated onchocerciasis transmission and that mass treatment could be safely stopped [25]. This provides an evidence that onchocerciasis elimination will be dependent on administration of ivermectin to the endemic areas⁶.

1.5 Motivation and objectives of the study

1.5.1 Motivation

In Sub-Saharan Africa, onchocerciasis remains a major health challenge. In Ghana for instance, 3,400,000 in 3204 communities in 66 endemic districts are at risk of acquiring onchocerciasis [59]. Many strategies have been used to eradicate this disease from the population. Mass administration of ivermectin has remained the main strategy in the fight against onchocerciasis. Several epidemiological research work on onchocerciasis have focused on the EPIONCHO⁷ model to understand the dynamics of this disease and its treatment in the population [10, 87, 88, 89, 90]. Unlike other vector-borne diseases such as malaria, very minimal research work has been done on the mathematical modelling of onchocerciasis [47]. In this work, onchocerciasis disease model is formulated and the model extended to incorporate compartments with individuals on treatment. The effectiveness of ivermectin treatment is analysed using impulsive differential equations. In addition, we introduce optimal control theory to investigate optimal control strategies for controlling onchocerciasis using insect repellent and both insecticide and larvicide as system control variables.

⁴World Health Organisation.

⁵Annual mass treatment with ivermectin through community-directed treatment is preferred as a good and less expensive method for controlling onchocerciasis in endemic African countries with assistance from APOC.

⁶Elimination of onchocerciasis is considered successful when the microfilaria prevalence in skin snips is less than 5% [25].

⁷Onchocerciasis transmission model.

1.5.2 Objectives

The main objective of this thesis is to model the infection dynamics and optimal control of onchocerciasis and its treatment.

The specific objectives are;

- To develop a mathematical model to describe the dynamics of onchocerciasis in both the human and the vector populations, and to carry out a detailed mathematical analysis of the model in order to gain the understanding of the model behaviour based on the computation of the model basic reproduction number, equilibrium points and their corresponding stability analysis.
- To carry out numerical simulations of the model and establish the conditions for the persistence of onchocerciasis in the populations.
- To investigate the conditions under which onchocerciasis epidemics would persist or die out in the population.
- To carry out sensitivity analysis so as to establish the key vital parameters in the model.
- To investigate the effect of time-dependent control (policies) on the dynamics of onchocerciasis epidemics.
- To explore the effect of ivermectin treatment on onchocerciasis through impulsive treatment.

1.6 Mathematical preliminaries

1.6.1 Basic reproduction number

Basic reproduction number, R_0 , is the threshold for many mathematical models. It is defined as the expected number of secondary cases of infections arising from a single infected case in a completely susceptible population during the entire period of infectiousness [36]. Basic reproduction number is a key concept in epidemiology. It serves as a threshold parameter that predicts whether an infection dies out or persists [36]. When $R_0 < 1$, then, on average, infectious individuals introduced in a population produce less than one new infection during their period of infectiousness. The disease may therefore

be eradicated from the population. When $R_0 > 1$, introduction of an infectious individual in the population produces more than one new cases of infection. In this case the disease persists in the population. In this work, we adopt the method of next generation method in computing the model reproduction number as is described by Van den Driessche and Watmough [92].

1.6.2 Optimal control technique

Optimal control theory is a mathematical tool derived from the calculus of variation. Application of optimal control is vital to decision making in terms of viable control strategies to be employed to eradicate the epidemic [82]. There is usually a general assumption that there exists a way to control the state variable(s) y , through a suitable control u . The ultimate goal is to adjust control u to minimize or maximize a given objective function $J(u(t), y(t), t)$ [58]. Various methods exist for calculating the optimal control for specific models. For instance, Pontryagin's Maximum Principle allows for the calculation of the optimal control for an ordinary differential equation system with given constraints [44]. According to Lenhart and Workman [51], a general optimal control problem is constructed as follows;

$$\max_u \left[\phi(T, x(T)) + \int_0^T g(t, x(t), u(t)) dt \right], \quad (1.6.1)$$

where $x = [x_1(t), x_2(t), \dots, x_n(t)]$ and $u = [u_1(t), u_2(t), \dots, u_m(t)]$ are state and control variables, respectively. The following system of first order ordinary differential equations describe the dynamics of the state and control variables

$$\frac{dx}{dt} = f(t, x(t), u(t)), \quad x_0 = x(0), \quad 0 \leq t \leq T. \quad (1.6.2)$$

1.6.3 Impulsive differential equations

An impulsive differential equation is usually defined as an ordinary differential equation coupled with a difference equation [3]. Impulsive differential equations are very helpful in studying many biological systems and population dynamics that have sudden change in their states [4, 28, 65]. In epidemiology, impulsive differential equations assess the vaccination programme that consists of periodical repetitions of impulsive vaccinations in a population, on all the age cohorts. At each vaccination time a constant fraction of susceptible people is vaccinated. Mathematically these equations take the form

$$\begin{aligned} x'(t) &= f(t, x(t)), & h(t, x(t)) &\neq 0, \\ \Delta x(t) &= I(t, x(t)), & h(t, x(t)) &= 0, \end{aligned} \quad (1.6.3)$$

where $\Delta x(t) = x(t^+) - x(t^-)$. Here, $x(t^+)$ is the value immediately after impulsive effect. Thus, as long as we have $h(t, x(t)) \neq 0$, then the evolution of the state is governed by the ordinary differential equations. At such time that $h(t, x(t)) = 0$, then the state undergoes an impulse and instantly changes by some amount $I(t, x(t))$.

1.7 Thesis outline

In this thesis, our work is organised as follows: In Chapter 2, we provide literature review based on mathematical models of onchocerciasis and EPIONCHO models. In Chapter, 3 we derive the deterministic model and its analytical solutions. We also introduce time-dependent controls (policies) in the model and discuss the effects of the controls on the dynamics of the model. Numerical simulation results are also presented and discussed. In Chapter 4 we provide the analysis of the model with impulsive effect. In Chapter 5 we give relevant discussion and conclude our work with relevant recommendation for further research work.

Chapter 2

Literature Review

Understanding the dynamics of onchocerciasis is very vital in the fight towards its eradication. In order to develop a plausible mathematical model that captures the dynamics of this disease in the population, it is important to understand the biological evolution of this disease as well as the appropriate mathematical tools that give logical qualitative and quantitative results. In this section we review related models that have been used to explain the transmission dynamics of onchocerciasis and its treatment.

2.1 Mathematical models

Oguoma and Acho [68] modelled the spread and control of onchocerciasis in Tropical Countries and looked at a case study in Nigeria. They adopted a deterministic approach in their model. The objective of their work was to assess the prevalence and intensity of microfilariae of *Onchocerca volvulus* in Imo River Basin, Imo state, Southeastern Nigeria. The human population was sub-divided into three compartments and the vector population sub-divided into two compartments. They carried out stability analysis and used homotopy decomposition method to solve the mathematical sets of equations derived from the model. The stability analysis from their study indicated that it would be possible to eradicate the parasite *Onchocerca volvulus* within a definite time. The study results from their numerical simulations showed that both the number of susceptible human and vector sub-populations decreased and the infective human and vector sub-populations increased. This reflects a real world biological situation and therefore having a disease free population is feasible given treatment with ivermectin in a hygienic environment that does not allow the breeding and survival of blackflies.

Basáñez and Ricárdez-Esquinca [7, 9] did a study on models for the population biology and control of human Onchocerciasis. Their aim was to evaluate the various interventions combining the removal of adult worms (nodulectomy) and the microfilaricidal and the sterilizing effect of ivermectin. They used a model comprising three ordinary differential equations describing the rate of change with respect to time of the mean number of adult worms, mean number of microfilariae per person and the mean number of L3 larvae per fly.

Basáñez and Ricárdez-Esquinca derived a threshold condition for disease control involving the vector biting rate and the basic reproduction number. They estimated that the annual biting rate for the *Simulium onchraceum s.l* is 7665 bites per person per year. This is the minimum below which human onchocerciasis would be unable to become endemic in Central America since the basic reproduction number R_0 would be less than unity. The study showed that the threshold biting rate for endemic onchocerciasis in West Africa lies between 288 and 720 bites per person per year for the savannah *Simulium damnosum s.l*. The R_0 of *Onchocerca volvulus* varies between 3 and 167. They related this to the ocular morbidity and thus predicted a serious recrudescence even after 20 years of successful vector control.

Poolman and Galvani [74] modelled the targeted ivermectin treatment for controlling river blindness. They obtained the basic reproduction number R_0 which they defined as the lifetime number of adult female worms produced by each female worm. They performed numerical simulations through to infection equilibrium for four different treatment regimens and compared them to the corresponding baseline, that is, 30%, 60% and 90% of the target population. Their results indicated a settlement into a stable equilibria. This showed a linear relationship between R_0 and mean population worm burden arises from density-dependent reproduction. They also discovered that ivermectin treatment of the uniform population results in coverage dependent percentage decreases in the mean worm burden relatively across R_0 and between levels of coverage.

Omade et al. [70] modelled onchocerciasis dynamics using an SIR model with demography. The study was conducted in Mubi Village of Gombe state in Northern Nigeria. They used Euler method in providing the numerical solutions to their model. They assumed that the population is dynamic and those who come into the susceptible class did so mainly through birth. In addition, it was also assumed that there is no inherited immunity amongst the susceptible individuals and the recovered individuals become

permanently immune to the disease. The entire model however, worked on the black box model of the disease in which differential behaviour, steady state calculation and disease free equilibrium in terms of R_0 were obtained. In this model they established that about 52% of the population are susceptible to the disease and about on average 50% infection rate is recorded within 14 days after which it declines. The recovery rate recorded in the model is about 37%. It was observed that the endemic onchocerciasis poses a serious risk to the endemic community in the Northern part of Nigeria as its susceptible level is 55% with a high infection rate of 50% on average.

Jimmy and Horst [60] presented a mathematical model to study the dynamics of onchocerciasis under three ways in which the human and the animal disease can interfere. The three ways include: vector diversion, waste parasites on the wrong host, and cross-immunity. They used cross-immunity reaction to give the model the qualitative behaviour of a standard competition model. Their model comprises a system of six equations, which they then reduced to four using quasi-static state approximation. Their model had up to four equilibria, trivial, coexistence and two boundary equilibria. These equilibria exhibited the following stability properties: there is no coexistence equilibrium and only the volvulus boundary equilibrium is stable, there is no coexistence equilibrium and only ochengi boundary equilibrium is stable, both boundary equilibria are stable and coexistence equilibrium unstable (bi-stability), the coexistence equilibrium is stable and both boundary equilibria are unstable, and there exists a continuum of coexistence equilibria. These possibilities of equilibria all held when the basic reproduction ratios of both *Onchocerca volvulus* and *Onchocerca ochengi* were greater than unity. They did global stability for the disease free equilibrium and concluded that the disease both in the animal and the vector could be eradicated provided R_0 is kept below unity.

2.2 EPIONCHO model

Onchocerciasis transmission model (EPIONCHO) has been used extensively by many researchers in explaining the dynamics and treatment of onchocerciasis [10, 87, 88, 89, 90]. Basáñez et.al. [10] investigated the potential long-term consequences of a vaccination programme on human onchocerciasis. They used EPIONCHO to investigate the impact of vaccination in areas where loiasis and onchocerciasis are co-endemic and ivermectin is contraindicated. This model describes the rate of change with respect to time and host age of the mean number of fertile and non-fertile female adult worms per host, the mean number of microfilariae per milligram of skin, and the mean number of L3 lar-

vae per simuliid fly. The model was refined to include age and sex structure of the host population; the population level effects of a single and multiple treatments with ivermectin and increased programmatic realism related to patterns of treatment coverage and systematic non-compliance. Their modelling results indicated that deployment of onchocerciasis vaccine would have a substantial beneficial effect in *Onchocerca volvulus*-*L loa* co-endemic areas where it may not be possible to deliver ivermectin. However, these benefits take a considerable time to accrue since vaccinated individuals need to age through the population into more heavily exposed population age group. Their results indicated that after 15 years of vaccination, the overall mean microfilarial load in the population is projected to decrease by 30% in highly hyper and hyper-endemic onchocerciasis foci and by 32% in mesoendemic foci.

Turner et al. [87] on the other hand conducted the study on modelling the impact of ivermectin on river-blindness and its burden of morbidity and mortality in African Savannah. Their analysis was underpinned by a deterministic onchocerciasis transmission model (EPIONCHO) as used by Basáñez et al. [10]. They then performed sensitivity analysis by varying the rate of decay (mean duration between 5 and 50 years) according to the range considered previously in the modelling of the Schistosomiasis vaccine as well as choosing a more modest 60% coverage of the vaccine. Their results indicated that in the absence of control interventions, onchocerciasis poses a high disease burden which is linearly related to pre-control endemicity level. In addition, they established that long-term annual ivermectin distribution on onchocerciasis prevalence and intensity decreases with increasing levels of baseline (pre-control) endemicity. They established that higher therapeutic coverage and high compliance has a high impact on the elimination of onchocerciasis from the population. This implies that the proportion of the population that sometimes does not comply with the treatment will become very important in the elimination of the parasite from the population. They concluded that the long-term annual ivermectin treatment is highly effective in reducing the morbidity and excess mortality associated with onchocerciasis. The results from Turner et. al. [89] indicate that the biting rates decrease as age increases. It also indicates that the vaccine against onchocerciasis could markedly decrease the chance of onchocerciasis infection re-spreading to areas where treatment has been stopped.

In addition to the mathematical and EPIONCHO models, related studies have been carried out to measure the effectiveness treatment of onchocerciasis with ivermectin. For example, Moses et.al [46] carried out study to investigate the effect of fifteen years of

annual mass treatment of onchocerciasis with ivermectin in the interruption of transmission of onchocerciasis in the west region of Cameroon. They identified issues that could be improved upon in order to attain and sustain the desired treatment coverage of at least 90% of UTG¹. They obtained the results in Table 2.1.

Table 2.1: Comparing reported and validated (through surveys) UTG treatment coverage in West Region from 2003 to 2010 [46].

Year	2003	2004	2005	2006	2007	2008	2009	2010
Reported coverage	102.6	94.4	91.2	97.6	98.3	95.8	98.5	98.3
Verified through surveys	93.2	93.2	96.7	98.6	90.2	91.4	88.2	83.5

The samples from 2003 to 2010 are; 2370, 2370, 2305, 2436, 2453, 694, 713 and 506 respectively. They established that annual mass treatment with ivermectin for 15 years had considerably reduced microfilaria and nodule prevalence in all the sentinel communities of West Region of Cameroon. In addition to treatment, they suggested that complementary strategic options should be adopted as elimination becomes the goal in Africa.

2.3 Our research

From the literature, it is shown that many epidemiological models have been used to explain the dynamics of onchocerciasis and its elimination from the population. However, a few mathematical models are available from the literature. Based on the problem we have described so far, our objective is to derive a mathematical model that can specifically characterise the dynamics of the disease in endemic regions with special interest in its transmission and control. We will employ relevant techniques to analyse the model with the aim of determining possibilities of elimination of the disease.

¹Ultimate Treatment Goal.

Chapter 3

Mathematical model

3.1 Introduction

One of the purposes of modelling epidemics is to provide a rational basis for policies designed to control the spread of a disease. The inclusion of practical optimal strategies in models allow for the assessment of the intervention of public health authorities. Optimal control is a powerful mathematical tool in decision making that involves employing appropriate strategies to eradicate epidemics from the population [56]. The decisions include determining the proportion of the population that should be treated as time evolves in a given epidemic to minimize both the number of infections in the population and the implementation cost. Optimal control has been used to study the dynamics of some diseases such as malaria and West Nile virus [13, 14, 69]. For instance, in [18, 81], optimal control was used to investigate the best strategy for educational campaigns during the outbreak of an epidemic and at the same time minimizing the number of infected humans. It has also been applied in modelling Leukemia [1, 64]. However, to the author's best knowledge, optimal control has not been applied to onchocerciasis disease transmission.

In this Chapter, we develop a mathematical model for onchocerciasis disease transmission with control strategies. The aim is to gain some insights into the best intervention for minimizing and eventual elimination of onchocerciasis from the population. The intervention strategies we incorporate into the model are, personal protection against black-fly, enhanced treatment and insecticide spraying. Three control functions are used, one for vector reduction, one for human protection and another for the reduction of microfilariae in the body following treatment with ivermectin. We characterize the optimal control problem analytically by applying Pontryagin Maximum Principle. We analyse

the model analytically and numerically to find out the threshold conditions under which it is optimal to eradicate onchocerciasis. The asymptotic dynamics of a onchocerciasis disease model using the autonomous model formulated are also studied.

3.2 Model formulation

We consider a habitat with two interacting populations. The two populations are humans (as hosts) and the black-flies (as vectors). The human population is partitioned into six compartments: the susceptible human compartment; S_H , referring to individuals not infected with onchocerciasis but are at risk of infection, the exposed compartment; E_H , referring to the individuals that have been exposed to onchocerciasis through bites but not infectious, the infectious compartment; I_H , referring to individuals with onchocerciasis infection, the susceptible human on ivermectin treatment compartment; S_T , the exposed human on ivermectin treatment compartment; E_T , and the infectious human on ivermectin treatment compartment; I_T . The black-fly population is partitioned into three compartments: susceptible vector; S_V , referring to black-flies that have never been in contact with infected human and have not picked up microfilariae but are at risk of picking up microfilariae during blood meal from an infected human, the exposed vector compartment; E_V , referring to vector that has picked up microfilariae from an infective human during blood meal but does not transmit the infection and the infective vector compartment; I_V , referring to the vector with the infective L3 larvae stage.

Individuals and the vector move from one compartment to another as their disease status evolve. The total human and vector populations at any given time, t , are respectively given by;

$$N = S_H(t) + E_H(t) + I_H(t) + S_T(t) + E_T(t) + I_T(t) \text{ and } V = S_V(t) + E_V(t) + I_V(t). \quad (3.2.1)$$

We assume that the transmission of onchocerciasis in susceptible hosts is only through contact with infectious vector. We also assume that susceptible vector becomes infectious as a result of contact with infectious hosts during blood meal. The population under study is assumed to be large enough to be modelled deterministically. The constant recruitments of new susceptible human and susceptible vector are given by b_1 and b_2 respectively. Assuming β is the black-fly biting rate, that is, the average number of bites per black-fly per unit, the rate of infection per susceptible black-fly can be represented

by

$$\lambda_v(t) = \frac{q\beta(I_H + \kappa I_T)}{N}, \quad (3.2.2)$$

where q is the transmission probability from infectious human to black-flies and κ is the modification parameter which measures the relative ability of individuals in class I_T to cause new infections relative to those in compartment I_H . We assume here that the individuals under treatment have a slightly lower probability to initiate new infections, thus, $0 \leq \kappa \leq 1$. Assuming that the total number of bites made by black-flies equals to the number of bites received by humans, then the average number of bites per human per unit time is $\frac{\beta V}{N}$. Assuming that the transmission probability per bite from infectious black-flies to human is p , the rate of infection per susceptible human is given by

$$\lambda_h(t) = \frac{p\beta V}{N} \frac{I_V}{V} = \frac{p\beta I_V}{N}. \quad (3.2.3)$$

We then introduce $\beta_h = p\beta$ and $\beta_v = q\beta$ parameters to simplify the infection rates per susceptible human and vector respectively. The individuals in class E_H progress to the infectious class I_H at the rate γ . Individuals on ivermectin treatment in class S_T acquire infection at the rate $\delta\lambda_h$. Here, $\delta \in [0, 1]$, defines the reduced effect of infection of the susceptible individuals on ivermectin as a result of treatment. Individuals in class E_T progress to infectious class on ivermectin I_T at the rate $\rho\gamma$, where $\rho \in [0, 1]$ is the reduced effect of progression to class I_T as a result of treatment. The rate of treatments for individuals is given by α . We assume relapse of individuals under treatment due to waning of the drug at the rate φ . We also assume natural mortality rates given by μ_h and μ_v for the human and vector populations respectively.

We further assume that individuals under treatment have no immunity to the disease upon treatment. In addition, we assume that infected vectors and human do not recover from the infection during the modelling time. The dynamics in the human hosts and vector populations is represented in the schematic diagram in Figure 3.1.

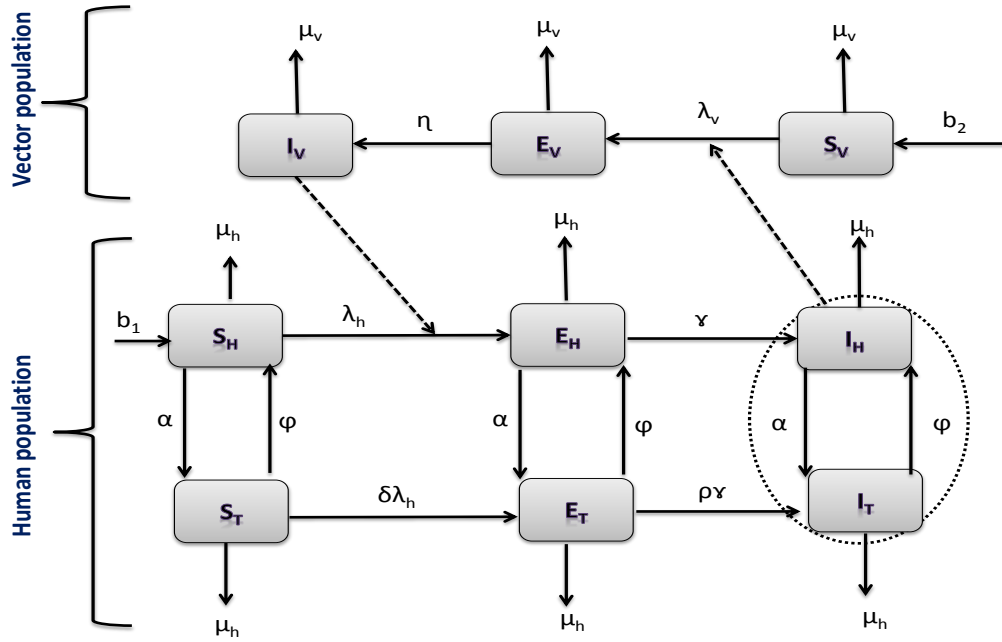


Figure 3.1: A compartmental representation of the model for onchocerciasis and its treatment.

3.2.1 Model equations

Given the dynamics described in Figure 3.1, the following system of non-linear ordinary differential equations, with non-negative initial conditions, describes the dynamics of onchocerciasis epidemics.

$$\left. \begin{aligned}
 \dot{S}_H &= b_1 + \varphi S_T - \lambda_h S_H - (\alpha + \mu_h) S_H, \\
 \dot{E}_H &= \lambda_h S_H + \varphi E_T - (\alpha + \gamma + \mu_h) E_H, \\
 \dot{I}_H &= \gamma E_H + \varphi I_T - (\alpha + \mu_h) I_H, \\
 \dot{S}_T &= \alpha S_H - \delta \lambda_h S_T - (\varphi + \mu_h) S_T, \\
 \dot{E}_T &= \alpha E_H + \delta \lambda_h S_T - (\rho \gamma + \varphi + \mu_h) E_T, \\
 \dot{I}_T &= \alpha I_H + \rho \gamma E_T - (\varphi + \mu_h) I_T, \\
 \dot{S}_V &= b_2 - \lambda_v S_V - \mu_v S_V, \\
 \dot{E}_V &= \lambda_v S_V - (\eta + \mu_v) E_V, \\
 \dot{I}_V &= \eta E_V - \mu_v I_V,
 \end{aligned} \right\} \quad (3.2.4)$$

subject to the following initial conditions

$$\begin{aligned} S_H(0) \geq 0, E_H(0) \geq 0, I_H(0) \geq 0, S_T(0) \geq 0, E_T(0) \geq 0, I_T(0) \geq 0, \\ S_V(0) \geq 0, E_V(0) \geq 0, I_V(0) \geq 0. \end{aligned} \quad (3.2.5)$$

Table 3.1: Description of parameters used in the model.

Parameter	Description
b_1	Human recruitment rate.
μ_h	Natural death rate of the human (host) .
β_h	The rate of transmission of the disease from black-fly to human.
γ	Transfer rate from E_H to I_H class.
α	Rate of mass administration of ivermectin.
φ	Waning rate of ivermectin .
κ, ρ, δ	Modification parameters.
b_2	Vector recruitment rate.
β_v	The rate of transmission of the disease from human to blackfly.
η	Transfer rate from E_V to I_V class.
μ_v	Natural death rate of the black-fly.

3.2.2 Model assumptions

1. There is a constant recruitment to the susceptible human population as well as the susceptible black-fly population.
2. Transmission takes place only from infectious black-flies to susceptible humans and from infectious humans to susceptible black-flies.
3. Infected black-flies do not live long enough to recover from infection.
4. Human hosts do not have immunity to the disease.
5. The waning of the ivermectin after the mass treatment occurs at the same rate in all the treated classes.

3.3 Model analysis

In this section, we analyse the general properties of the system (3.2.4) with positive initial conditions. The system (3.2.4) describes the population dynamics both in human and black-fly populations.

3.3.1 Positivity of solutions of the model

The system (3.2.4) describes the human and black-fly population. It is therefore important to show that all the state variables describing the dynamics of the populations will be non-negative. In particular, we prove that all solutions of the system (3.2.4) with non-negative initial conditions will remain non-negative for all $t > 0$. We have the following theorem.

Theorem 3.3.1. *For non-negative initial conditions of system (3.2.4), the solutions $(S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V, I_V)$ of the system (3.2.4) are all non-negative for all time $t \geq 0$.*

Proof. For the equations in the system (3.2.4), let us take t^* as the maximum time for the epidemics. This implies that;

$$t^* = \sup\{t > 0 : S_H > 0, E_H > 0, I_H > 0, S_T > 0, E_T > 0, I_T > 0, S_V > 0, E_V > 0, I_V > 0\}.$$

Thus, $t^* \geq 0$. Then, from the first equation of the system (3.2.4), we obtain

$$\begin{aligned} \dot{S}_H &= b_1 + \varphi S_T - \lambda_h S_H - (\alpha + \mu_h) S_H \geq -(\lambda_h + (\alpha + \mu_h)) S_H, \\ S_H(t^*) &\geq S_H(0) \exp \left\{ - \left(\int_0^{t^*} \lambda_h(m) dm + (\alpha + \mu_h) t^* \right) \right\}. \end{aligned}$$

This implies that $S_H(t^*) \geq 0$ for all time $t \geq 0$. Similarly, from the seventh equation of the system (3.2.4), we have

$$\dot{S}_V = b_2 - \lambda_v S_V - \mu_v S_V = b_2 - (\lambda_v + \mu_v) S_V. \quad (3.3.1)$$

Equation (3.3.1) can be written as

$$\frac{d}{dt} \left(S_V \exp \left\{ \int_0^t \lambda_v(u) du + \mu_v t \right\} \right) = b_2 \exp \left\{ \int_0^t \lambda_v(u) du + \mu_v(t) \right\},$$

Integrating both sides from $t = 0$ to $t = t^*$, we obtain

$$S_V(t^*) \exp \left\{ \int_0^{t^*} \lambda_v(u) du + \mu_v t^* \right\} - S_V(0) = \int_0^{t^*} b_2 \exp \left\{ \int_0^x \lambda_v(x) dx + \mu_v y \right\} dy,$$

then multiplying both sides by $\exp \left\{ -\int_0^{t^*} \lambda_v(u) du - \mu_v t^* \right\}$, we have

$$S_V(t^*) = S_V(0) \exp \left\{ -\int_0^{t^*} \lambda_v(u) du - \mu_v t^* \right\} + \exp \left\{ -\int_0^{t^*} \lambda_v(u) du - \mu_v t^* \right\} \\ \times \int_0^{t^*} b_2 \exp \left\{ \int_0^x \lambda_v(x) dx + \mu_v y \right\} dy > 0.$$

Hence, $S_V(t^*) \geq 0$ for all $t^* \geq 0$. Therefore, $S_H(t^*)$ and $S_V(t^*)$ being the sum of positive terms are positive. Using the same argument, it can be shown that the quantities $E_H, I_H, S_T, E_T, I_T, E_V$, and I_V are all positive for all $t > 0$. Thus, the solutions of (3.2.4) remain positive for all $t \geq 0$. \square

3.3.2 Invariant region

Lemma 3.3.2. *Let $(S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V, I_V)$ be the solutions of the system (3.2.4) with initial conditions given in (3.2.5) and the biological feasible region given by the set $\Omega = \Omega_H \times \Omega_V$ where*

$$\Omega_H = \left\{ (S_H, E_H, I_H, S_T, E_T, I_T) \in \mathbb{R}_+^6 : N \leq \frac{b_1}{\mu_h} \right\}, \quad \Omega_V = \left\{ (S_V, E_V, I_V) \in \mathbb{R}_+^3 : V \leq \frac{b_2}{\mu_v} \right\}.$$

Proof. Adding the equations in the system (3.2.4) gives

$$\dot{N} = b_1 - \mu_h N, \quad \dot{V} = b_2 - \mu_v V. \quad (3.3.2)$$

It can then be shown that

$$\limsup_{t \rightarrow \infty} N \leq \frac{b_1}{\mu_h} \text{ and } \limsup_{t \rightarrow \infty} V \leq \frac{b_2}{\mu_v}. \quad (3.3.3)$$

Hence, the set Ω is positively invariant, that is, all the solutions in Ω remain in Ω for $t > 0$. We thus conclude that Ω is an attracting set. \square

Therefore every solution of the system (3.2.4), with initial condition in Ω remains there for $t > 0$. In addition, in Ω , the usual existence, uniqueness and continuation results hold for the system. The system (3.2.4) is thus both mathematically and epidemiologically well-posed in the region Ω . Hence, it is sufficient to study the dynamics of the flow generated by the system (3.2.4) in Ω . The the right hand side of the system (3.2.4) is locally Lipschitz continuous implying that the local existence and uniqueness of solutions is ascertained.

3.4 Existence and stability of the equilibrium points

Equilibrium points or steady state solutions are the points at which the differential equations of the system (3.2.4) equal to zero.

3.4.1 Disease-free equilibrium

The disease-free equilibrium (DFE) points are steady state solutions that depict the absence of infection in both the human and black-fly populations. This implies that at onchocerciasis-free equilibrium (E_0), $E_H = I_H = E_T = I_T = E_V = I_V = 0$. Solving the first, fourth and seventh equations of the model system (3.2.4) we obtain

$$E_0 = \left(\frac{b_1}{Q_1(1-\Phi_1)}, 0, 0, \frac{b_1\alpha}{Q_1Q_3(1-\Phi_1)}, 0, 0, \frac{b_2}{\mu_v}, 0, 0 \right), \quad (3.4.1)$$

where

$$\begin{aligned} Q_1 &= \alpha + \mu_h, & Q_2 &= \alpha + \gamma + \mu_h, & Q_3 &= \varphi + \mu_h, & Q_4 &= \rho\gamma + \varphi + \mu_h, \\ Q_5 &= \eta + \mu_v, & \Phi_1 &= \frac{\varphi\alpha}{Q_1Q_3}. \end{aligned}$$

3.4.2 Basic reproduction number

The basic reproduction number is defined as the average number of secondary cases of human/vector onchocerciasis infections generated by a typical infected human/vector in an otherwise disease free population [92]. The basic reproduction number (R_0) of the system (3.2.4) is computed using the next generation matrix method (NGM). Here the matrix \mathcal{F} denotes the rates of appearance of new infections and \mathcal{V} transfer of infection into and out of any compartment respectively. The matrices are given by

$$\mathcal{F} = \begin{bmatrix} \frac{\beta_h I_V S_H}{N} \\ 0 \\ \frac{\delta \beta_h I_V S_T}{N} \\ 0 \\ \frac{\beta_v I_H S_V}{N} + \frac{\kappa \beta_v I_T S_V}{N} \\ 0 \end{bmatrix}, \quad \mathcal{V} = \begin{bmatrix} Q_2 E_H - \varphi E_T \\ -\gamma E_H + Q_1 I_H - \varphi I_T \\ -\alpha E_H + Q_4 E_T \\ -\alpha I_H - \rho\gamma E_T + Q_3 I_T \\ Q_5 E_V \\ -\eta E_V + \mu_v I_V \end{bmatrix}$$

We then evaluate both \mathcal{F} and \mathcal{V} by taking the partial derivatives of the terms in \mathcal{F} and \mathcal{V} at the disease-free equilibrium to obtain a non-negative square matrix \mathbf{F} and a non-

singular matrix \mathbf{V} .

$$\mathbf{F} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\beta_h \mu_h}{Q_1(1-\Phi_1)} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_h \mu_h \alpha \delta}{Q_1 Q_3 (1-\Phi_1)} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{b_2 \beta_v \mu_h}{\mu_v b_1} & 0 & \frac{b_2 \beta_v \kappa \mu_h}{\mu_v b_1} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \quad \mathbf{V} = \begin{bmatrix} Q_2 & 0 & -\varphi & 0 & 0 & 0 \\ -\gamma & Q_1 & 0 & -\varphi & 0 & 0 \\ -\alpha & 0 & Q_4 & 0 & 0 & 0 \\ 0 & -\alpha & -\rho \gamma & Q_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & Q_5 & 0 \\ 0 & 0 & 0 & 0 & -\eta & \mu_v \end{bmatrix}$$

The basic reproduction number (R_0) which is the the spectral radius of the next generation matrix \mathbf{FV}^{-1} is given by;

$$R_0 = \sqrt{\mathcal{R}_0} = \sqrt{R_0^h R_0^v}, \quad (3.4.2)$$

where

$$R_0^h = \frac{\beta_h \gamma \mu_h^2 (\Phi_3 + \alpha \delta (\alpha \kappa \varphi + Q_2 \rho (Q_1 \kappa + \varphi)))}{b_1 Q_1^2 Q_2 Q_3 Q_4 (1 - \Phi_1)^2 (1 - \Phi_2)}, \quad R_0^v = \frac{b_2 \beta_v \eta}{Q_5 \mu_v^2}, \quad \Phi_2 = \frac{\alpha \varphi}{Q_2 Q_4},$$

$$\Phi_3 = Q_3 [\alpha \varphi (\delta + \rho) + Q_1 \alpha \kappa \rho + Q_4 (Q_3 + \alpha \kappa)].$$

The basic reproduction number R_0 , determines whether onchocerciasis dies out or persists in the population. The square root in (3.4.2) agrees with the findings of [53]. This is a biological requirement in the human-vector host model system since the parasite passes through two types of individuals to complete its life cycle. Note that R_0^v is the contribution of the vector population to the overall infection while R_0^h is the contribution of the human population. The following theorem follows directly from [26, 92].

Theorem 3.4.1. *The disease-free equilibrium of the system (3.2.4) exists and is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable otherwise.*

The disease free steady states has a strong influence on the behaviour of the disease transmission dynamics in the population. This implies that if we are looking into eliminating onchocerciasis from the population, we have to establish the conditions necessary for the onchocerciasis free equilibrium to be stable. Epidemiologically, results in 3.4.1 implies that when $\mathcal{R}_0 < 1$, on average each infected individual infects fewer than one individual and the disease dies out. On the other hand, if $\mathcal{R}_0 > 1$, on average each infected individual infects more than one other individual and we would expect the disease to spread.

3.5 Existence of the disease persistent steady states

Let $S_H^*, E_H^*, I_H^*, S_T^*, E_T^*, I_T^*, S_V^*, E_V^*, I_V^*$ be non-trivial the solutions to the endemic equilibrium points. Setting all the equations of the system (3.2.4) to zero and expressing the state variables in terms of the forces of infections λ_h and λ_v , we have

$$\left. \begin{aligned}
 S_H^* &= \frac{b_1(Q_3 + \delta\lambda_h^*)}{Q_1Q_3(1 - \Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*)}, \\
 E_H^* &= \frac{b_1\lambda_h^*(\alpha\delta\varphi + Q_4(Q_3 + \delta\lambda_h^*))}{Q_2Q_4(1 - \Phi_2)(Q_1Q_3(1 - \Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*))}, \\
 I_H^* &= \frac{\gamma b_1\lambda_h^*(\delta\lambda_h^*(\alpha\rho\varphi + Q_3Q_4) + Q_2\alpha\delta\rho\varphi + Q_3(\alpha\varphi(\delta + \rho) + Q_3Q_4))}{Q_1Q_2Q_3Q_4(1 - \Phi_1)(1 - \Phi_2)(Q_1Q_3(1 - \Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*))}, \\
 S_T^* &= \frac{ab_1}{Q_1Q_3(1 - \Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*)}, \\
 E_T^* &= \frac{ab_1\lambda_h^*(Q_3 + \delta(Q_2 + \lambda_h^*))}{Q_2Q_4(1 - \Phi_2)(Q_1Q_3(1 - \Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*))}, \\
 I_T^* &= \frac{ab_1\gamma\lambda_h^*(\alpha\delta\varphi + Q_4(\delta\lambda_h^* + Q_3) + \rho Q_1(\delta(\lambda_h^* + Q_2) + Q_3))}{Q_1Q_2Q_3Q_4(1 - \Phi_1)(1 - \Phi_2)(Q_1Q_3(1 - \Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*))}, \\
 S_V^* &= \frac{b_2}{\lambda_v^* + \mu_v}, \quad E_V^* = \frac{b_2\lambda_v^*}{Q_5(\lambda_v^* + \mu_v)}, \quad I_V^* = \frac{b_2\eta\lambda_v^*}{Q_5\mu_v(\lambda_v^* + \mu_v)}.
 \end{aligned} \right\} \quad (3.5.1)$$

From the results in (3.5.1), we have the following two cases describing the existence of the steady states;

Case 1: $\lambda_h^* = \lambda_v^* = 0$.

This corresponds to the disease-free state treated in (3.4.1), where there is no infection.

Case 2: $\lambda_h^* \neq \lambda_v^* \neq 0$.

This is the scenario in which there is infection in both the population (hosts and vector populations). We describe this state using the following denotation.

$$E_1 = (S_H^*, E_H^*, I_H^*, S_T^*, E_T^*, I_T^*, S_V^*, E_V^*, I_V^*).$$

Substituting the expressions for the state variables I_V^*, I_H^* and I_T^* in (3.5.1) into the expressions for the forces of infection in (3.2.2) and (3.2.3) then simplifying we obtain the following polynomial.

$$\Psi_2\lambda_h^{*2} + \Psi_1\lambda_h^* + \Psi_0 = 0, \quad (3.5.2)$$

where

$$\begin{aligned}\Psi_2 &= Q_5 b_1 \delta \mu_v [Q_1 Q_2 Q_3 Q_4 \mu_v (1 - \Phi_1)(1 - \Phi_2) + \beta_v \mu_h \gamma (\alpha \rho (\kappa Q_1 + \varphi) + Q_4 (\alpha \kappa + Q_3))], \\ \Psi_1 &= -[b_2 \gamma \delta \eta \beta_h \mu_h^2 \beta_v (\alpha \rho (\kappa Q_1 + \varphi) + Q_4 (\alpha \kappa + Q_3)) - b_1 Q_5 \mu_v (\gamma \mu_h \beta_v (\alpha^2 \delta \kappa \varphi \\ &\quad + \alpha \delta \rho Q_2 (\kappa Q_1 + \varphi) + Q_3 (\alpha \varphi (\delta + \rho) + \alpha \kappa \rho Q_1 + Q_4 (\alpha \kappa + Q_3))) \\ &\quad + Q_1 Q_2 Q_3 Q_4 (1 - \Phi_1)(1 - \Phi_2)(\delta Q_1 + Q_3) \mu_v], \\ \Psi_0 &= b_1 Q_1^2 Q_2 Q_3^2 Q_4 Q_5 \mu_v^2 (1 - \Phi_1)^2 (1 - \Phi_2) [1 - \mathcal{R}_0].\end{aligned}$$

The existence and the number of endemic equilibria for the system (3.2.4) is determined by the existence of, and the number of positive roots of the quadratic equation given in (3.5.2). The roots to the quadratic equation (3.5.2) can be obtained by the quadratic formula given by

$$(\lambda_h^*)_{1,2} = \frac{-\Psi_1 \pm \sqrt{\Psi_1^2 - 4\Psi_2\Psi_0}}{2\Psi_2}. \quad (3.5.3)$$

We note that $\Psi_0 > 0$ if $\mathcal{R}_0 < 1$, $\Psi_0 = 0$ if $\mathcal{R}_0 = 1$ and $\Psi_0 < 0$ if $\mathcal{R}_0 > 1$. If $\Psi_0 < 0$, then $\Delta = \Psi_1^2 - 4\Psi_2\Psi_0 > 0$ and equation (3.5.2) has a unique positive solution hence the system (3.2.4) has a unique endemic equilibrium. If $\mathcal{R}_0 < 1$ then $\Psi_0 > 0$ and by adding the conditions $\Psi_1 < 0$ and $\Delta > 0$, we get two positive real equilibria. If $\mathcal{R}_0 = 1$, then $\Psi_0 = 0$ and there is a unique non-zero solution of (3.5.2) which is positive if and only if $\Psi_1 < 0$.

The following theorem summarizes the existence of the endemic equilibria of the system (3.2.4).

Theorem 3.5.1. *The system (3.2.4)*

1. *has no endemic equilibrium if $\mathcal{R}_0 < \mathcal{R}_0^c$ where \mathcal{R}_0^c is referred to as critical \mathcal{R}_0 .*
2. *has a unique endemic equilibrium in Ω if $\mathcal{R}_0 > 1$.*
3. *has two endemic equilibria for some parameter values of $\mathcal{R}_0^c < \mathcal{R}_0 < 1$. In this range, one endemic equilibrium and the disease-free equilibrium are locally stable.*
4. *has one positive equilibrium for $\mathcal{R}_0 = 1$ provided $\Psi_1 < 0$ and $\Delta > 0$, otherwise there is no positive equilibrium.*
5. *has no endemic equilibrium otherwise.*

Proposition 3.5.2. *The system (3.2.4) has a backward bifurcation at $\mathcal{R}_0 = 1$ if and only if $\Psi_1 < 0$ and $\Delta > 0$.*

Epidemiologically, proposition 3.5.2 implies that bringing \mathcal{R}_0 below unity does not suffice for the eradication of onchocerciasis. From the analysis of the existence of the endemic equilibrium, we have established that the system (3.2.4) exhibits backward bifurcation when $\mathcal{R}_0 < 1$. The existence of backward bifurcation indicates that in the neighbourhood of 1, for $\mathcal{R}_0 < 1$, a stable disease-free equilibrium coexists with two endemic equilibria, that is, a smaller equilibrium (smaller number of infectious individuals) which is unstable and a larger equilibrium (with a larger number of infectious individuals) which is stable. These two endemic equilibria disappear by saddle-node bifurcation when the basic reproduction \mathcal{R}_0 is decreased below the critical value \mathcal{R}_0^c . In order to achieve an epidemiological goal of disease eradication, \mathcal{R}_0 must be brought below the critical value \mathcal{R}_0^c . To obtain the critical value \mathcal{R}_0^c , we set the discriminant Δ of the polynomial (3.5.2) to zero and make \mathcal{R}_0 the subject of the relation. Thus, we have

$$\mathcal{R}_0^c = 1 - \frac{\Psi_1^2}{4\Psi_2[b_1Q_1^2Q_2Q_3^2Q_4Q_5\mu_v^2(1-\Phi_1)^2(1-\Phi_2)]}. \quad (3.5.4)$$

3.5.1 Bifurcation analysis

This is a qualitative change in the behaviour of a dynamical system produced by varying a parameter in the equation [67]. Backward bifurcation is an important phenomenon in compartmental epidemiological models. This phenomenon has been observed in numerous disease transmission models [30, 34, 45, 93]. Wang [93] studied backward bifurcation of an epidemic model with treatment. He demonstrated that his model exhibits backward bifurcation behaviour. The existence of such a bifurcation suggests that the basic reproduction number itself is not enough to characterize or decide whether onchocerciasis will prevail or not and if the disease will become endemic also depends on the initial sizes of the involved population. Thus, it is important to identify the backward bifurcation and establish its threshold. We carry out bifurcation analysis to study the behaviour of the system (3.2.4) based on the results in (3.5.2) through numerical simulation over chosen parameter values. It is important to note that the existence of bi-stability is not easy to simulate numerically. This is because a small interval of \mathcal{R}_0 is required for the occurrence of backward bifurcation and very small range of parameters has to be chosen. The qualitative backward bifurcation diagram describing the behaviour of $\mathcal{R}_0 = 1$ is presented in Figure 3.2 where β_h is taken as the bifurcation parameter. The result indicates that in the backward bifurcation, if \mathcal{R}_0 is below unity then

the disease control depends on the initial sizes of the various sub-populations of the system (3.2.4). However, reducing \mathcal{R}_0 below the saddle-node bifurcation value \mathcal{R}_0^c , may result in disease eradication. This is guaranteed provided that the disease-free equilibrium is globally asymptotically stable. Figure 3.3 is obtained after increasing the rate of mass administration of ivermectin to 1. The biological interpretation of this is that increasing treatment can lead to disappearance of backward bifurcation curve and in this case lowering \mathcal{R}_0 below one is sufficient to eliminate the disease from the population. So when the rate of mass treatment is high enough we will have a forward bifurcation and lowering \mathcal{R}_0 below unity would be sufficient to make the disease-free equilibrium globally stable.

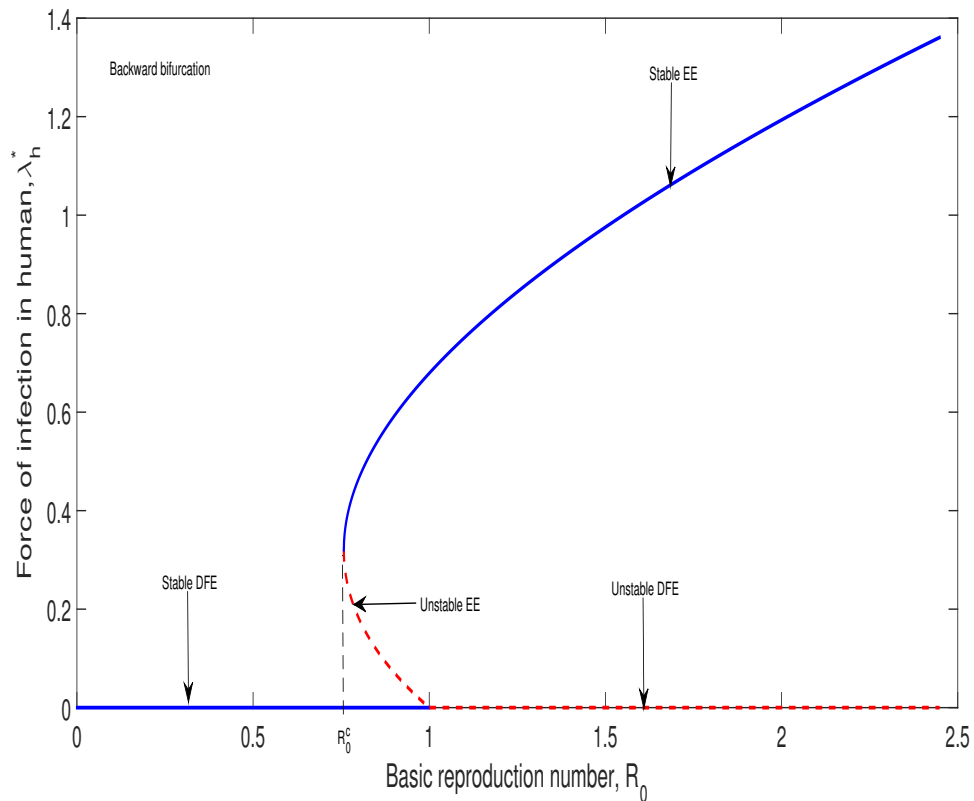


Figure 3.2: Description of the backward bifurcation of the system (3.2.4) with β_h as the bifurcation parameter. We considered $b_1 = 10, b_2 = 50, \mu_h = 0.000150, \gamma = 0.0097, \beta_v = 0.000127, \mu_v = 0.09800, \eta = 0.0884, \varphi = 0.002, \alpha = 0.40, \kappa = 0.005, \delta = 0.0025, \rho = 0.0013$.

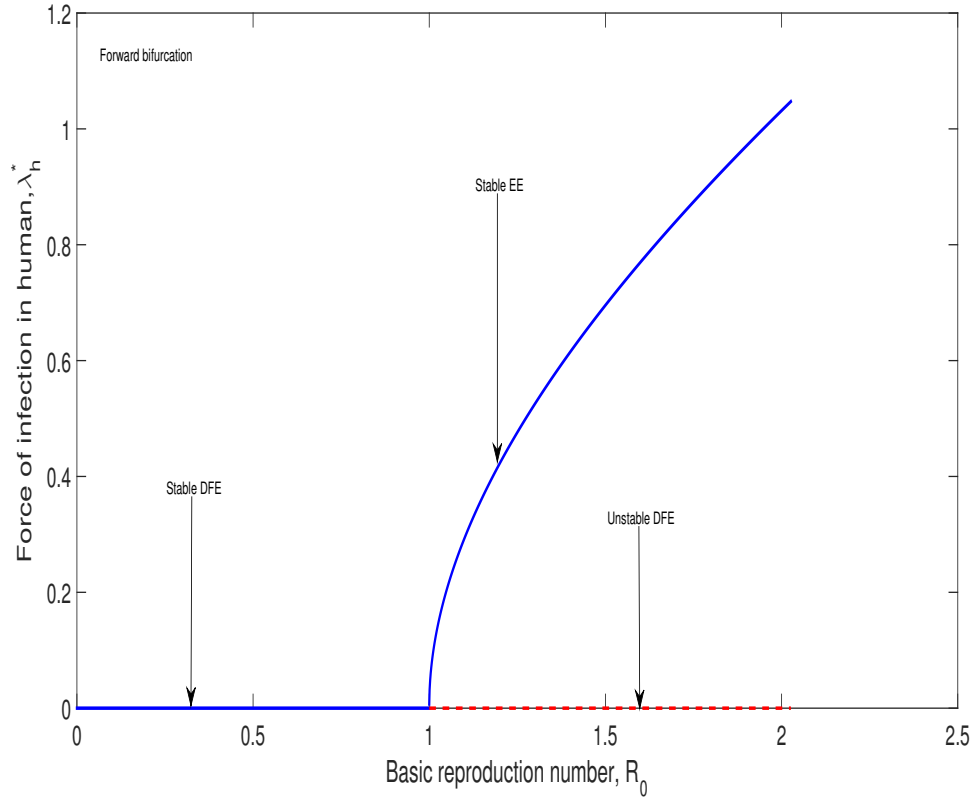


Figure 3.3: Description of forward bifurcation of the system (3.2.4) for parameter values $\kappa = 0.02$, $\alpha = 1$ and all other parameters as used in Figure 3.2.

3.6 Global stability of the disease-free equilibrium

Since the system (3.2.4) has two endemic equilibria when $R_0 < \mathcal{R}_0^c$, it implies that the disease-free equilibrium is globally stable if and only if $\mathcal{R}_0 < \mathcal{R}_0^c$. We therefore establish the global stability of the disease-free equilibrium, E_0 using a Lyapunov function for $\mathcal{R}_0 < \mathcal{R}_0^c$.

Theorem 3.6.1. *The disease-free equilibrium E_0 of system (3.2.4) is globally asymptotically stable if $\mathcal{R}_0 < \mathcal{R}_0^c$ and unstable otherwise.*

Proof. Let $L(E_H, I_H, E_T, I_T, E_V, I_V) = \Phi_4 E_H + \Phi_5 I_H + \Phi_6 E_T + \Phi_7 I_T + \Phi_8 E_V + \Phi_9 I_V$, be a candidate Lyapunov function for some non-negative values of $\Phi_4, \Phi_5, \Phi_6, \Phi_7, \Phi_8$ and Φ_9 .

The time derivative of L is given by;

$$\begin{aligned}
\dot{L} &= \Phi_4 \dot{E}_H + \Phi_5 \dot{I}_H + \Phi_6 \dot{E}_T + \Phi_7 \dot{I}_T + \Phi_8 \dot{E}_V + \Phi_9 \dot{I}_V, \\
&= \Phi_4 \left(\frac{\beta_h I_V S_H}{N} + \varphi E_T - Q_2 E_H \right) + \Phi_5 (\gamma E_H + \varphi I_T - Q_1 I_H) \\
&\quad + \Phi_6 \left(\alpha E_H + \frac{\delta \beta_h I_V S_T}{N} - Q_4 E_T \right) + \Phi_7 (\alpha I_H + \rho \gamma E_T - Q_3 I_T) \\
&\quad + \Phi_8 \left(\frac{\beta_v I_H S_V}{N} + \frac{\kappa \beta_v I_T S_V}{N} - Q_5 E_V \right) + \Phi_9 (\eta E_V - \mu_v I_V), \\
&= (\Phi_5 \gamma + \Phi_6 \alpha - \Phi_4 Q_2) E_H + \left(\Phi_7 \alpha + \Phi_8 \frac{\beta_v b_2 \mu_h}{\mu_v b_1} - \Phi_5 Q_1 \right) I_H + (\Phi_4 \varphi + \Phi_7 \rho \gamma - \Phi_6 Q_4) E_T \\
&\quad + \left(\Phi_5 \varphi + \Phi_8 \frac{\kappa \beta_v b_2 \mu_h}{\mu_v b_1} - \Phi_7 Q_3 \right) I_T + (\Phi_9 \eta - \Phi_8 Q_5) E_V \\
&\quad + \left(\Phi_4 \frac{\beta_h \mu_h}{Q_1 (1 - \Phi_1)} + \Phi_6 \frac{\beta_h \delta \alpha \mu_h}{Q_1 Q_3 (1 - \Phi_1)} - \Phi_9 \mu_v \right) I_V.
\end{aligned}$$

Evaluating the coefficients of the suitable Lyapunov function such that the coefficients of $I_H, E_T, I_T, E_V,$ and I_V are equal to zero we obtain

$$\begin{aligned}
\Phi_4 &= \frac{Q_1^2 Q_3^2 b_1 (1 - \Phi_1)^2 Q_4 Q_5 \mu_v^2 - \beta_h \beta_v \mu_h^2 b_2 \eta \gamma \alpha \delta \rho (Q_1 \kappa + \varphi)}{Q_1 Q_3 \beta_h b_1 \mu_h \mu_v (1 - \Phi_1) (Q_3 Q_4 + \alpha \varphi \delta)}, & \Phi_5 &= \frac{\beta_v \mu_h b_2 \eta (Q_3 + \alpha \kappa)}{Q_1 Q_3 b_1 \mu_v (1 - \Phi_1)}, \\
\Phi_6 &= \frac{Q_1^2 Q_3^2 (1 - \Phi_1)^2 Q_5 b_1 \mu_v^2 \varphi - Q_3 \beta_h \beta_v b_2 \eta \gamma \rho (Q_1 \kappa + \varphi)}{Q_1 Q_3 \beta_h b_1 \mu_h \mu_v (1 - \Phi_1) (Q_3 Q_4 + \alpha \varphi \delta)}, & \Phi_7 &= \frac{\beta_v \mu_h b_2 \eta (\varphi + Q_1 \kappa)}{Q_1 Q_3 b_1 \mu_v (1 - \Phi_1)}, \\
\Phi_8 &= \eta, & \Phi_9 &= Q_5.
\end{aligned}$$

Using these coefficients, the time derivative of the Lyapunov function is given by

$$\dot{L} = \left(\frac{Q_1 Q_2 Q_3 Q_4 Q_5 \mu_v (1 - \Phi_1) (1 - \Phi_2)}{\beta_h \mu_h (Q_3 Q_4 + \alpha \varphi \delta)} \right) [\mathcal{R}_0 - 1] E_H < 0, \quad (3.6.1)$$

It follows that $\dot{L} < 0$ for $\mathcal{R}_0 < \mathcal{R}_0^c$ and $\dot{L} = 0$ if and only if $I_H = E_T = I_T = E_V = I_V = 0$. Therefore, L is a Lyapunov function in $\Omega = (S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V, I_V)$. Since, Ω is invariant and attracting, it follows that the largest possible invariant set in $\{(S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V, I_V) \in \Omega : \dot{L} = 0\}$, is the singleton $\{E_f^0\}$. According to La-Salle's invariance principle [50], E_0 is globally attractive. Therefore, the disease-free equilibrium E_0 is globally asymptotically stable when $\mathcal{R}_0 < \mathcal{R}_0^c$. This completes the proof. \square

In the case of the occurrence of a backward bifurcation in the system (3.2.4), the above result shows that in order to eliminate onchocerciasis, the basic reproduction \mathcal{R}_0 must be lower than the threshold \mathcal{R}_0^c which is strictly less than unity.

3.7 Application of optimal control

3.7.1 Formulation of optimal control

In this section, we formulate a model framework that minimizes onchocerciasis infection in the human population. In the system (3.2.4), the recruitment rates in each susceptible population is modified to include the density effects. Thus, the density dependent factors for the recruitment rates are $b_1(N)$ for the host population and $b_2(V)$ for the vector population. Personal protection efforts through wearing insect repellents such as N, N-Diethyl-meta-toluamide (DEET) on exposed skin, wearing long sleeves and long pants during the day when black-flies bite, and wearing permethrin-treated clothing minimizes or eliminates black-fly-human contacts [71]. Insecticide spraying with larvicide and adulticide ensures that the breeding sites of the black-flies are minimized. We thus define some linear control functions $u_i(t)$ such that $u_i(t) = 1, i = 1, 2, 3$. It is important to note that controls are fully effective when $u_i(t) = 1$ and not effective control when $u_i(t) = 0$. The forces of infection λ_h and λ_v corresponding to human population and vector population respectively are reduced by factor $(1 - u_1)$, where $u_1(t)$ measures the level of successful exposure prevention efforts. The control $u_1(t)$ represents the use of alternative prevention measures to minimize or eliminate the black-fly-human contacts. Such measures include the use of insect repellents, wearing protective coats and long sleeves and wearing permethrin-treated clothing amongst other. The mass administration of ivermectin as a control is modelled by u_2 . The factor u_2 can be viewed as the coverage of ivermectin. The factor $u_3(t)$, represents the level of larvicide and adulticide use for the elimination of black-flies from the breeding sites. This implies that the reproduction rate of the black-fly population is reduced by a factor of $(1 - u_3(t))$. We assume that, larvicidal spraying increases the mortality rate of the black-flies at a rate proportional to the control factor $u_3(t)$. It is further assumed that the per capita mortality rate of the vector is $r_0 u_3(t)$, where $0 \leq r_0 \leq 1$ is the proportion of effective adulticide spraying. Taking into account the assumptions and extensions made above, we therefore find the most effective strategy that reduces the onchocerciasis infection in the population at a minimum cost. Using bounded lebesgue measurable control, the objective functional to be minimized is given by

$$J(u_1, u_2, u_3) = \int_0^T (A_1 E_H + A_2 I_H + A_3 V + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2)) dt \quad (3.7.1)$$

subject to the state system given in (3.2.4). The dynamics of the control that minimizes the objective functional $J(u_1, u_2, u_3)$ is given by

$$\left. \begin{aligned} \dot{S}_H &= b_1 N + \varphi S_T - \lambda_h S_H(1 - u_1) - (u_2 \alpha + \mu_h) S_H, \\ \dot{E}_H &= \lambda_h S_H(1 - u_1) + \varphi E_T - (u_2 \alpha + \gamma + \mu_h) E_H, \\ \dot{I}_H &= \gamma E_H + \varphi I_T - (u_2 \alpha + \mu_h) I_H, \\ \dot{S}_T &= u_2 \alpha S_H - \delta \lambda_h S_T(1 - u_1) - (\varphi + \mu_h) S_T, \\ \dot{E}_T &= u_2 \alpha E_H + \delta \lambda_h S_T(1 - u_1) - (\rho \gamma + \varphi + \mu_h) E_T, \\ \dot{I}_T &= u_2 \alpha I_H + \delta \gamma E_T - (\varphi + \mu_h) I_T, \\ \dot{S}_V &= b_2 V(1 - u_3) - \lambda_v S_V(1 - u_1) - \mu_v S_V - r_0 u_3 S_V, \\ \dot{E}_V &= \lambda_v S_V(1 - u_1) - (\eta + \mu_v) E_V - r_0 u_3 E_V, \\ \dot{I}_V &= \eta E_V - \mu_v I_V - r_0 u_3 I_V, \end{aligned} \right\} \quad (3.7.2)$$

with the following initial conditions

$$\begin{aligned} S_H(0) &\geq 0, E_H(0) \geq 0, I_H(0) \geq 0, S_T(0) \geq 0, E_T(0) \geq 0, I_T(0) \geq 0, \\ S_V(0) &\geq 0, E_V(0) \geq 0, I_V(0) \geq 0. \end{aligned} \quad (3.7.3)$$

We endeavour to minimize the exposed and infectious human populations (E_H, I_H), the black-fly population and the cost of implementing the control by use of possible minimum variables $u_i, i = 1, 2, 3$. This functional includes the number of exposed, infectious and the black-fly population, respectively, as well as the social costs related to the resources needed for personal protection $\frac{1}{2}B_1 u_1^2$, enhanced mass administration of ivermectin $\frac{1}{2}B_2 u_2^2$ and spraying of larvicide and adulticide operations $\frac{1}{2}B_3 u_3^2$. This implies that we are minimizing the number of exposed, infectious human and susceptible, exposed and infectious black-fly populations as well as the cost based on the implementation of the control functions. The quantities A_1 and A_2 represent the cost associated with minimizing the exposed and infected human population respectively while A_3 represent the cost associated with minimizing total black-fly population. The quantity T is the time period of intervention. The quantities B_1, B_2 and B_3 represent the weight constants for personal protection, enhanced mass administration of ivermectin and spraying of larvicide and adulticide operations. According to [44, 69] the costs associated with $A_1 E_H, A_2 I_H$ and $A_3 V$ are linear while the cost control functions $\frac{1}{2}B_1 u_1^2, \frac{1}{2}B_2 u_2^2$ and $\frac{1}{2}B_3 u_3^2$ should be non-linear and take the quadratic form. We assume that the costs of implementation of the control policies are proportional to the square of the corresponding control function. We seek to minimize the objective functional over the given time interval $[0, T]$. In particular, the aim of the optimal control problem is to seek optimal

control functions $(u_1^*(t), u_2^*(t), u_3^*(t))$ such that

$$J(u_1^*, u_2^*, u_3^*(t)) = \min_{\mathbf{U}} J(u_1, u_2, u_3), \quad (3.7.4)$$

where $\mathbf{U} = \{u_1, u_2, u_3 | 0 \leq u_i(t) \leq 1, i = 1, 2, 3\}$ is the control set and is Lebesgue measurable. Pontryagin's Maximum Principle is used to solve this optimal control problem and the derivation of the necessary conditions. First we prove the existence of an optimal control for the system (3.7.2) and then derive the optimality system.

3.7.2 Existence of control problem

In order to find the optimal solution, we first find the Lagrangian and Hamiltonian for the optimal control problem (3.7.1) and (3.7.2). The Lagrangian of the optimal control problem is given by

$$L = A_1 E_H + A_2 I_H + A_3 V + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2). \quad (3.7.5)$$

We seek for the Lagrangian minimum value. In order to accomplish this, we define the Hamiltonian, H for the control problem. This is given by

$$\left. \begin{aligned} H = & L(E_H, I_H, V, u_1, u_2, u_3) + \lambda_1 \dot{S}_H + \lambda_2 \dot{E}_H + \lambda_3 \dot{I}_H + \lambda_4 \dot{S}_T + \lambda_5 \dot{E}_T + \lambda_6 \dot{I}_T + \lambda_7 \dot{S}_V \\ & + \lambda_8 \dot{E}_V + \lambda_9 \dot{I}_V, \\ = & A_1 E_H + A_2 I_H + A_3 V + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2) \\ & + \lambda_1 [b_1 N + \varphi S_T - \lambda_h S_H (1 - u_1) - (u_2 \alpha + \mu_h) S_H] \\ & + \lambda_2 [\lambda_h S_H (1 - u_1) + \varphi E_T - (u_2 \alpha + \gamma + \mu_h) E_H] + \lambda_3 [\gamma E_H + \varphi I_T - (u_2 \alpha + \mu_h) I_H] \\ & + \lambda_4 [u_2 \alpha S_H - \delta \lambda_h S_T (1 - u_1) - (\varphi + \mu_h) S_T] + \lambda_5 [u_2 \alpha E_H + \delta \lambda_h S_T (1 - u_1) \\ & - (\rho \gamma + \varphi + \mu_h) E_T] + \lambda_6 [u_2 \alpha I_H + \delta \gamma E_T - (\varphi + \mu_h) I_T] \\ & + \lambda_7 [b_2 V (1 - u_3) - \lambda_v S_V (1 - u_1) - \mu_v S_V - r_0 u_3 S_V] \\ & + \lambda_8 [\lambda_v S_V (1 - u_1) - (\eta + \mu_v) E_V - r_0 u_3 E_V] + \lambda_9 [\eta E_V - \mu_v I_V - r_0 u_3 I_V]. \end{aligned} \right\} \quad (3.7.6)$$

Theorem 3.7.1. *There exists an optimal control $u^* = (u_1^*, u_2^*, u_3^*) \in \mathbf{U}$ such that*

$$J(u_1^*, u_2^*, u_3^*) = \min_{(u_1, u_2, u_3) \in \mathbf{U}} J(u_1, u_2, u_3), \quad (3.7.7)$$

subject to the control system (3.7.2) with the initial conditions (3.7.3).

Proof. We prove the existence of the optimal problem following the results in [33, 54]. It is clear that the system of equations given by (3.7.2) is bounded and the state variables are non-negative. In this minimizing problem, the control set \mathbf{U} is convex and

closed by definition. The optimal system is bounded which determines the compactness needed for the existence of the optimal control. The integrand in the objective functional, $A_1 E_H + A_2 I_H + A_3 V + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2)$, is clearly convex on the control set \mathbf{U} . Moreover, we can easily see that, there exists, $\beta > 1$ and positive numbers c_1, c_2 satisfying

$$J(u_1, u_2, u_3) \geq c_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{\beta}{2}} - c_2, \quad (3.7.8)$$

because, the state variables are bounded. This completes the proof. \square

3.7.3 Optimality of the system

In order to find the optimal solution, we employ Pontryagin's Maximum Principle [73] to the Hamiltonian (3.7.6), such that if (x, u) is an optimal solution of an optimal control problem, then there exists a non-trivial vector $\lambda = (\lambda_1, \lambda_2, \dots, \lambda_n)$ satisfying the following inequalities.

$$\frac{dx}{dt} = \frac{\partial H(t, x, u, \lambda)}{\partial \lambda}, \quad 0 = \frac{\partial H(t, x, u, \lambda)}{\partial u}, \quad \lambda' = -\frac{\partial H(t, x, u, \lambda)}{\partial x}. \quad (3.7.9)$$

We, now derive the necessary conditions to the Hamiltonian in (3.7.6) that optimal control functions and corresponding states must satisfy.

Theorem 3.7.2. *Let $S_H^*, E_H^*, I_H^*, S_T^*, E_T^*, I_T^*, S_V^*, E_V^*$ and I_V^* be the solutions of the corresponding optimal control problem (3.7.1)-(3.7.2) associated with the optimal control variables (u_1^*, u_2^*, u_3^*) . Then, there exists adjoint variables $\lambda_i, i = 1, 2, \dots, 9$ satisfying*

$$\left. \begin{aligned} \frac{d\lambda_1(t)}{dt} &= \frac{\beta_h}{N}(\lambda_1 - \lambda_2)(1 - u_1)I_V + (\lambda_1 - \lambda_4)u_2\alpha + \lambda_1\mu_h, \\ \frac{d\lambda_2(t)}{dt} &= (\lambda_2 - \lambda_3)\gamma + (\lambda_2 - \lambda_5)u_2\alpha + \lambda_2\mu_h - A_1, \\ \frac{d\lambda_3(t)}{dt} &= (\lambda_3 - \lambda_6)u_2\alpha + \frac{\beta_v}{N}(\lambda_7 - \lambda_8)(1 - u_1)S_V + \lambda_3\mu_h - A_2, \\ \frac{d\lambda_4(t)}{dt} &= \frac{\delta\beta_h}{N}(\lambda_4 - \lambda_5)I_V(1 - u_1) + (\lambda_4 - \lambda_1)\varphi + \lambda_4\mu_h, \\ \frac{d\lambda_5(t)}{dt} &= (\lambda_5 - \lambda_2)\varphi + (\lambda_5 - \lambda_6)\rho\gamma + \lambda_5\mu_h, \\ \frac{d\lambda_6(t)}{dt} &= (\lambda_6 - \lambda_3)\varphi + \lambda_6\mu_h + \frac{\beta_v\kappa}{N}(\lambda_7 - \lambda_8)S_V(1 - u_1), \\ \frac{d\lambda_7(t)}{dt} &= -b_2\lambda_7(1 - u_3) + \frac{\beta_v}{N}(\lambda_7 - \lambda_8)(1 - u_1)(I_H + \kappa I_T) + \lambda_7\mu_v + \lambda_7r_0u_3 - A_3, \\ \frac{d\lambda_8(t)}{dt} &= -b_2\lambda_7(1 - u_3) + (\lambda_8 - \lambda_9)\eta + \lambda_8\mu_v + \lambda_8r_0u_3 - A_3, \\ \frac{d\lambda_9(t)}{dt} &= -b_2\lambda_7(1 - u_3) + \frac{\beta_h}{N}(\lambda_1 - \lambda_2)(1 - u_1)S_H + \frac{\delta\beta_h}{N}(\lambda_4 - \lambda_5)(1 - u_1)S_T + \lambda_9\mu_v \\ &\quad + \lambda_9r_0u_3 - A_3, \end{aligned} \right\} \quad (3.7.10)$$

with transversality conditions (or boundary conditions)

$$\lambda_i(T) = 0, i = 1, 2, \dots, 9, \quad (3.7.11)$$

expressed as

$$u_i^* = \begin{cases} 0 & \text{if } u_i \leq 0, \\ u_i & \text{if } 0 < u_i < 1, \\ 1 & \text{if } u_i \geq 1. \end{cases} \quad (3.7.12)$$

In addition, the control functions u_1^* , u_2^* and u_3^* are represented by

$$u_1^* = \max \left\{ \min \left\{ \frac{\beta_h(\lambda_2 - \lambda_1)I_V^*S_H^* + \delta\beta_h(\lambda_4 - \lambda_5)I_V^*S_T^* + \beta_v(\lambda_8 - \lambda_7)(I_H^* + \kappa I_T^*)S_V^*}{NB_1}, 1 \right\}, 0 \right\}, \quad (3.7.13)$$

$$u_2^* = \max \left\{ \min \left\{ \frac{\alpha[(\lambda_1 - \lambda_4)S_H^* + (\lambda_2 - \lambda_5)E_H^* + (\lambda_3 - \lambda_6)I_H^*]}{B_2}, 1 \right\}, 0 \right\}, \quad (3.7.14)$$

$$u_3^* = \max \left\{ \min \left\{ \frac{\lambda_7 b_2 V^* + r_0(\lambda_7 S_V^* + \lambda_8 E_V^* + \lambda_9 I_V^*)}{B_3}, 1 \right\}, 0 \right\}. \quad (3.7.15)$$

Proof. To determine the adjoint equations and the transversality conditions, we minimize the Hamiltonian H with respect to the controls (u_1^*, u_2^*, u_3^*) at the optimal control functions. Setting $S_H(t) = S_H^*(t)$, $E_H(t) = E_H^*(t)$, $I_H(t) = I_H^*(t)$, $S_T(t) = S_T^*(t)$, $E_T(t) = E_T^*(t)$, $I_T(t) = I_T^*(t)$, $S_V(t) = S_V^*(t)$, $E_V(t) = E_V^*(t)$ and $I_V(t) = I_V^*(t)$ and differentiating the Hamiltonian (3.7.6) with respect to $S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V$ and I_V , respectively, we obtain (3.7.10). Solving the equations

$$\frac{\partial H}{\partial u_1} = 0, \quad \frac{\partial H}{\partial u_2} = 0, \quad \frac{\partial H}{\partial u_3} = 0, \quad (3.7.16)$$

on the interior of the control set using the optimality conditions and the property of the control set \mathbf{U} , we derive (3.7.13)-(3.7.15). Due to the fact that the state and the adjoint functions are bounded and the Lipschitz structure of the ordinary differential equations, we obtain the uniqueness of the optimal control. This completes the proof. \square

The formulas (3.7.13)-(3.7.15) for u^* are the characteristics of the optimal control. The optimal control are found by solving the optimality system, that consists of the state system (3.7.2), the adjoint system (3.7.10), the initial conditions (3.7.3), boundary conditions (3.7.12) and the characteristic of the optimal control (3.7.13)-(3.7.15). In order to solve the optimality system, we use the initial and transversality conditions alongside the characterization of the optimal control (u_1^*, u_2^*, u_3^*) given in (3.7.13)-(3.7.15). Furthermore, the

second derivative of the Lagrangian with respect to u_1, u_2 and u_3 , respectively, are positive indicating that the optimal control problem is minimum at controls u_1^*, u_2^* and u_3^* . We thus obtain the optimal control through numerical simulation.

3.8 Numerical simulations

In this section, we discuss the numerical solutions of the optimality system (3.7.2) and the corresponding optimal control strategies. In order to solve the optimality system we employ the standard two-boundary point method described in [51]. In our numerical simulations, we first start by solving the state equations (3.7.2) using Runge-Kutta fourth order forward in time with a guess for the controls over simulated time. Based on the transversality conditions (3.7.12), the adjoint equations are solved by backward method. The time varying control values are found by entering the calculated values of the state and adjoint variables in the characterization of optimal controls (3.7.13)-(3.7.15). Convex combination is used to update the control values. In this case, the average of the new and old control values is taken. The convergence is acquired when the values of the variables in the new iteration and the previous iteration are insignificantly close.

3.8.1 Parameter estimation

In this section, we consider average parameter values that encompass features of onchocerciasis disease including rate of infection, incubation period, length of infections period in the vector and host populations. Although estimates of some parameters are given in Table 3.2, here we give additional explanation and description of some of the parameters based on available literature and with reference to Ghana which is one of the onchocerciasis endemic countries.

1. The average birthrate in Ghana was estimated to be 31.09 births/1,000 population in 2015 and 30.60 births/1,000 population in 2014 according to the World Fact Book by Central Intelligence Agency [85] and Ghana Statistical Service report on Demographic and Health Survey [35] respectively. Thus, the recruitment rate is estimated from the range $0.0000819 \leq b_1 \leq 0.000108$ per day.
2. The natural human death rate is estimated based on average life of 50-70 years in accordance to Central Intelligence Agency and 2014 demographic data released by Ghana Statistical Service estimates of life expectancy at birth respectively [35, 85]. The black-fly death rate is estimated based on the average life span lasting for 2-3 weeks, to as long as 85 days [31, 68].

3. It takes $\frac{3}{4}$ to 2 years for the worm to mature and release enough microfilariae to be detectable in the skin of the human host [52, 66, 76]. Therefore, a reasonable estimate of the incubation rate γ is $0.00137 \leq \gamma \leq 0.00365$ per day. On the other hand, the average incubation period in the black-fly is 1-2 weeks [52, 72, 76]. Thus, a reasonable value for η is $0.0714 \leq \eta \leq 0.1667$ per day.
4. The modification parameters (κ , δ and ρ) have been estimated to be between 0 and 1 due to the reduced ability of individuals to cause infections following ivermectin treatment.
5. The rate of protection following mass administration of ivermectin α is estimated to be between 0% and 100%.
6. We balance the host populations and control functions by arbitrarily choosing weight constant values $A_1 = A_2 = A_3 = 1$, $B_1 = 10, B_2 = 10, B_3 = 10$ in the objective functional (3.7.1). These weight parameters determine the importance of variables in the objective functional [51]. The estimate for rate constant r_0 is given as 0.06.

For illustration purpose, we consider the parameter estimates in Table 3.2 with the following initial conditions;

$$S_H(0) = 16200, \quad E_H(0) = 1500, \quad I_H(0) = 100, \quad S_T(0) = 2000, \quad E_T(0) = 300, \\ I_T(0) = 10, \quad S_V(0) = 2500, \quad E_V(0) = 250, \quad I_V(0) = 10.$$

In the simulation, we consider the treatment rate as the protection rate upon the mass administration of ivermectin.

3.8.2 Sensitivity analysis

Sensitivity analysis is introduced to study the strength of the basic reproduction number for the model parameters. Due to the unavailability of data, uniform distribution is used for the set of parameters in Table 3.2 peaked at the median. Tornado plot for the normalised sensitivity index for different parameters is given in Figure 3.4. If the sensitivity index is positive, then R_0 increases along with increasing value of the parameter. On the other hand, if the sensitivity index is negative, then R_0 decreasing with the increasing value of the parameter. The transmission contact rates in human and the vector have the greatest effect on the disease transmission. The results in Figure 3.4 indicate that the basic reproduction number increases with increase in the transmission contact rate in both the human (host) and the vector whereas the basic reproduction number

Table 3.2: Parameters used for numerical simulation. The rates are given per day.

Parameter	Range	Point value	Source
b_1	0.0000819-0.001085	0.001	Estimated.
μ_h	0.0000391-0.0000548	0.000052	[35, 85].
β_h	0.0-0.0180	0.00214	Estimated.
γ	0.00137-0.00365	0.0023	[52, 66, 76].
α	0-1.0	0.0165	[94].
φ	0.01-0.1	0.0013	[89].
κ	0.00-1.0	0.002	Estimated.
ρ	0.0-0.1.0	0.012	Estimated.
δ	0.00-1.0	0.001	Estimated.
b_2	0.0177-0.0871	0.0643	Estimated .
β_v	0.0-0.0245	0.00104	Estimated.
η	0.0714-0.1667	0.074	[52, 72, 76].
μ_v	0.0118-0.0714	0.065	[31, 68].

decreases with increase in the vector death rate. The results therefore suggest that if the transmission of onchocerciasis in both the vector and the human (host) can be reduced and the vector death rate increased, then the disease can be easily controlled. On the other hand, Fig. 3.5 shows that an increase in both κ and δ increases R_0 . Thus, the effectiveness of ivermectin in the treatment of onchocerciasis is critical in eliminating new cases of infections in the treated population.

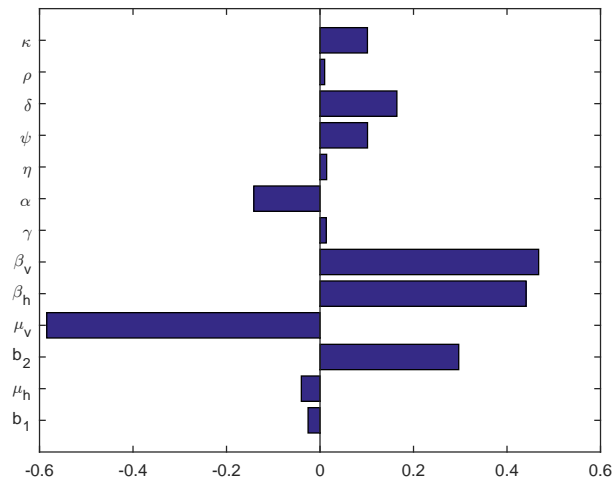


Figure 3.4: Tornado plots of partial rank correlation coefficients (PRCCs) of the parameters that influence R_0 for the input parameters using the values in Table 3.2. Parameters with $\text{PRCC} > 0$ increases R_0 when they are increased whereas parameters with $\text{PRCC} < 0$ decreases R_0 when they are increased.

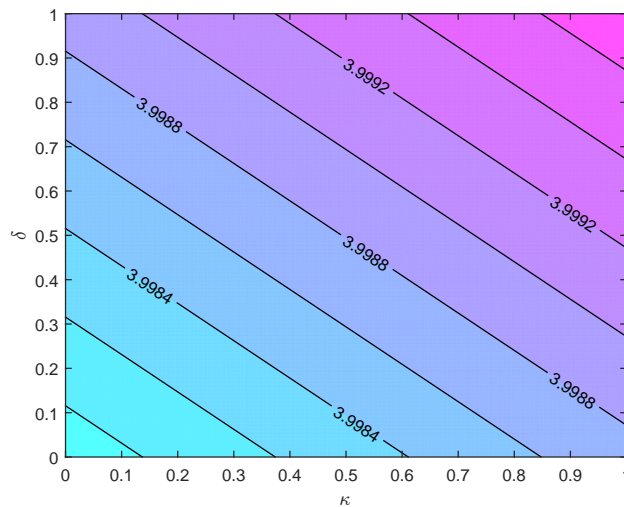


Figure 3.5: Contour plot showing the effect of modification parameters δ and κ on R_0 .

3.8.3 Simulation results

Figure 3.6, represents the population of susceptible, exposed, infected individuals (human) in two systems, (3.2.4) without control and (3.7.2) with control. The red line denotes the population of individuals in the system (3.2.4) without control while the blue dotted line denotes the population of individuals in the system (3.7.2) with control. Onchocerciasis infection is shown to be contained much earlier in time when appropriate and aggressive optimal controls are applied to the onchocerciasis epidemic. Part (a) of Figure 3.6 reveals that without controls, the susceptible human (hosts) population not on ivermectin gets depleted at a higher rate due to unchecked transmission. However, with controls, more individuals stay in the susceptible class (humans). In addition, part (b) of Figure 3.6 shows that more susceptible individuals stay protected with ivermectin when there is control as compared to when there is no control. Part (c) and (e) of Figure 3.6 show that the populations of exposed and infected individuals with control are more decreased than the individuals without control. The results suggest that much less time is taken to clear onchocerciasis disease when optimal control measures are applied than without controls.

Figure 3.7 reveals that the population of the susceptible vector with optimal control is more sharply decreased while the population without control grows and settles at endemic state. The population of susceptible vector with control decreases to zero. We observe in Figure 3.7 (b) and (c) that the exposed and infected vector without control rise during the initial stages of epidemic followed by a decrease then remains at endemic stage. However, in the presence of control we observe a decrease which ends at onchocerciasis free stage. The results illustrate the importance of control in the reduction of onchocerciasis infection in the population.

Figure 3.8 shows the evolution of the control profiles over time. The results show that the controls u_1 , u_2^* and u_3^* all start at the upper bound. However, the first control, u_1 , declines after about 75 days and u_3^* declines after about 50 days. The control profile u_2 maintains its upper bound and declines at near 400 days. This can be explained by the fact that in the treatment of onchocerciasis with ivermectin, the drug is administered for the entire period corresponding with the lifespan of filarial adult worms. The simulation shows that a lot more emphasis should be put in reducing the contact that results into onchocerciasis infection. More emphasis should be put on vector eradication that poses danger on the continuous spread of the disease. We suggest that treatment services should be patient specific, proper, efficient and timely.

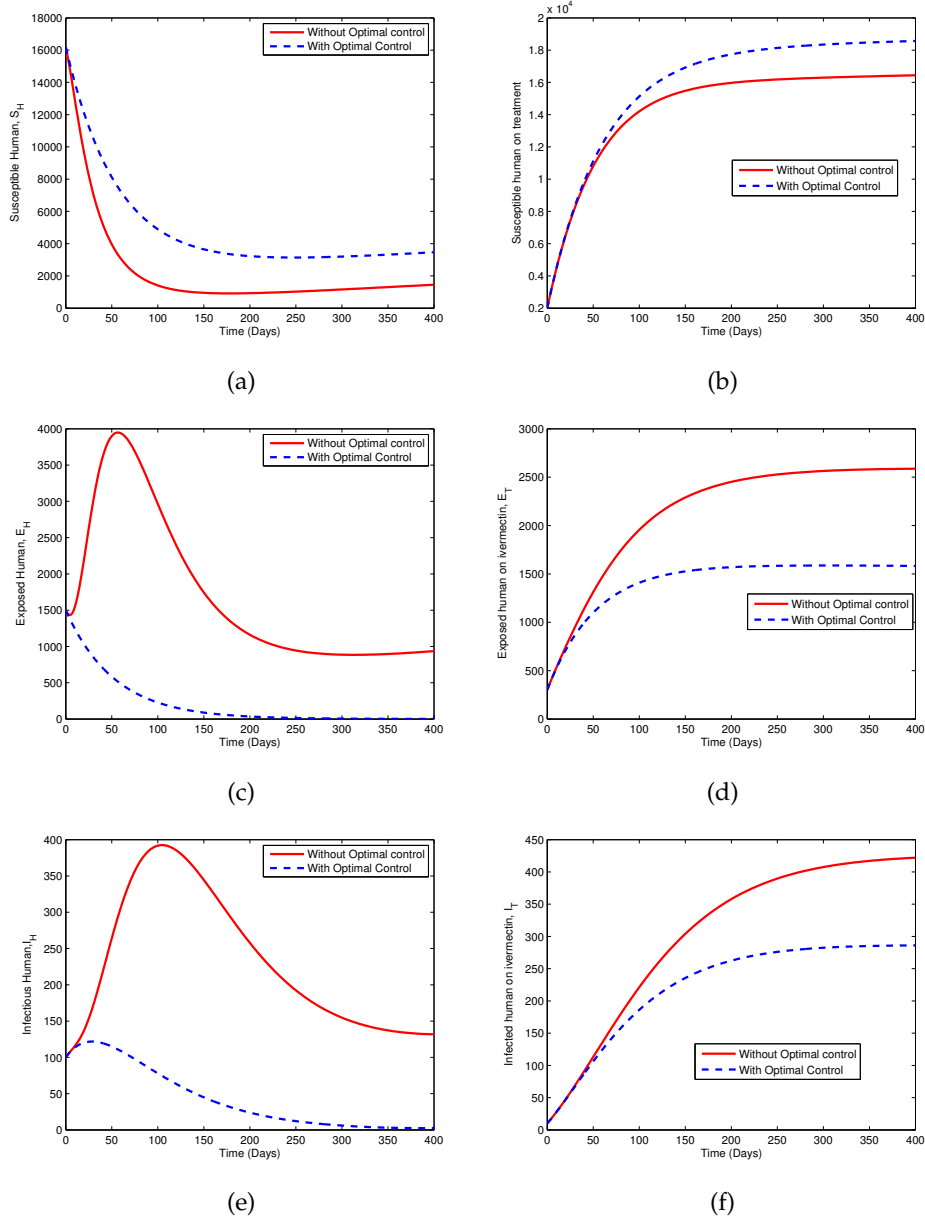


Figure 3.6: The plot represents population of susceptible not on ivermectin, exposed not on ivermectin, infected not on ivermectin, susceptible on ivermectin, exposed on ivermectin and infected on ivermectin human host both with control (blue dotted line) and without control (red line).

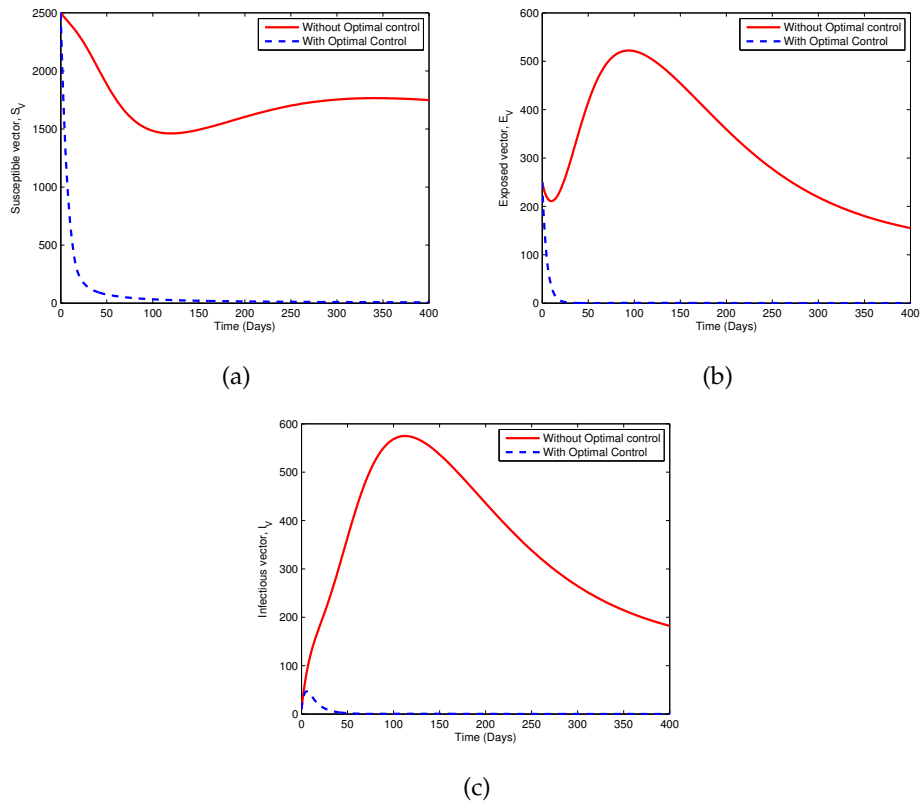


Figure 3.7: The plot represents population of susceptible , exposed and infected vector both with control (blue dotted line) and without control (red line).

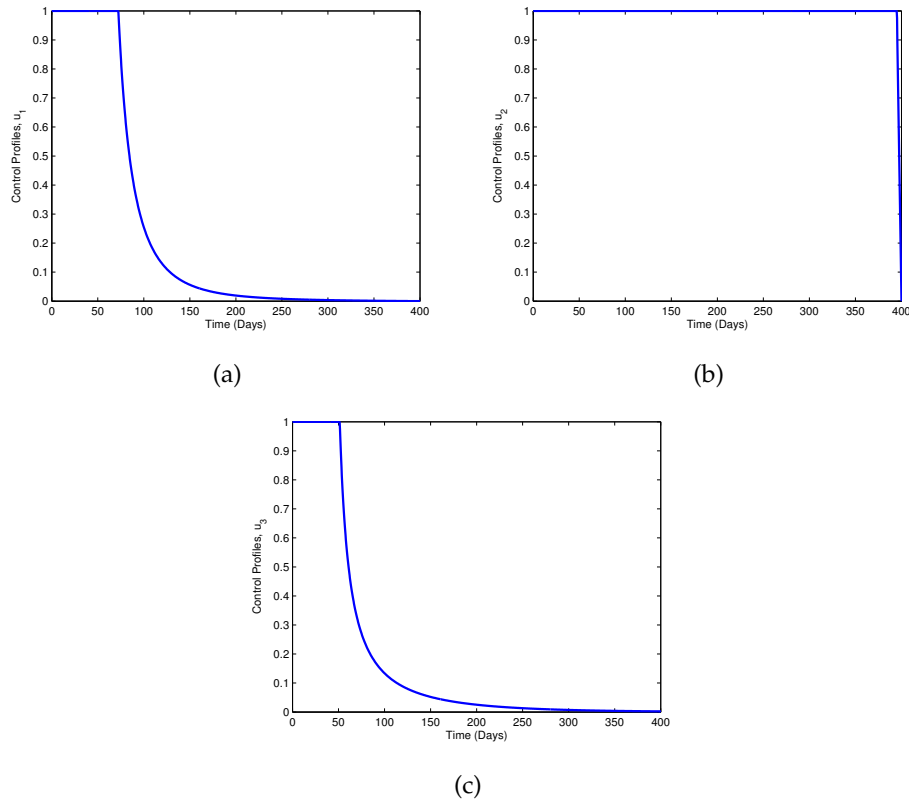


Figure 3.8: Profiles of personal protection control u_1 , the treatment efficiency control u_2 and insecticide u_3 .

3.9 Conclusion

In this chapter, we investigated the application of optimal control strategies in the ochocerciasis disease model. The model system formulated is composed of 6 variables describing the dynamics of the disease in the humans and 3 variables describing the dynamics of the disease in the vectors (black-flies). Both the autonomous and the optimal control systems have been analysed. We have demonstrated that the autonomous model is epidemiologically feasible and mathematically well-posed in the specific domain. The basic reproduction number was determined and the existence of both the disease-free and endemic equilibrium points studied. Our analysis showed that for $R_0 < 1$, the disease-free equilibrium is globally asymptotically stable and unstable otherwise. The model is found to exhibit a backward bifurcation phenomenon which gives rise to exis-

tence of multiple endemic equilibria. This implies that having $R_0 < 1$ is not sufficient to eliminate the disease from the population. Therefore reducing R_0 below a certain threshold, R_0^c is critical for effective disease control.

We performed the optimal analysis of the non-autonomous control model considering three controls, one for black-fly-reduction strategies and the other two for personal (human) protection and enhanced mass administration of ivermectin respectively. A comparison between optimal control system and system without control is presented. The numerical simulation results shows that optimal control system has desirable impact on the reduction of the number of exposed and infected humans (hosts) and the vector population. The results indicate that treatment with ivermectin remains the most effective and recommended methodology to control onchocerciasis disease. Thus, it would be of great epidemiological significance for us to investigate the effect of mass administration of ivermectin in the treatment of onchocerciasis. This is done in the next chapter in which is assumed that mass administration of ivermectin is carried out half-yearly and hence motivating the use of impulsive differential equations.

Chapter 4

Application of impulsive differential equations

4.1 Introduction

The theory of impulsive differential equations is relatively new. This theory has been used in many areas where evolution process undergo rapid changes at certain times of their development [5]. Quite often, ordinary differential equations are used in disease modelling. They give continuous assessment of the disease dynamics in the population. However, the ordinary differential equations ignore the assessment of periodic administration of treatment in the eradication of diseases [99]. On the other hand, impulsive differential equations give piece-wise continuous solutions to differential equations and can be used to assess the impact of periodic treatment of infectious diseases [5]. Mass administration of ivermectin is the most common form of treatment for onchocerciasis. Initially, the strategy was to administer ivermectin annually. A change of strategy to six-monthly was implemented to increase the probability of eliminating the parasite [6, 94].

Impulsive differential equations have been used to study the dynamics of some diseases such as cutaneous leishmaniasis and bieber fever [12, 91]. For instance, authors in [80] used impulsive differential equations to predict the potential impact of a cytotoxic T-lymphocyte HIV vaccine. Their main objective was to determine how often should the vaccination be done and how strong should the vaccine be? Impulsive differential equations have also been applied in modelling an outbreak of zombie infection [61]. However, onchocerciasis models with impulsive effects are not extensive. Pulse introduced into onchocerciasis model greatly enriches the biological background and assessment of

periodic treatments.

In this chapter, we extend the mathematical model for onchocerciasis disease transmission in chapter 3 to include pulse vaccination. The aim is to gain some insights into the impact of periodic mass administration of ivermectin in the eradication of onchocerciasis. We examine the effects of mass administration of ivermectin using a mathematical model of impulsive differential equations. We determine the threshold for the proportion of the individuals with onchocerciasis that will reduce the infection of the onchocerciasis in the population. In addition, we determine the maximum interval for the mass administration of ivermectin to eradicate onchocerciasis.

4.2 Model formulation

The infection by onchocerciasis is believed to be reduced by some proportion α . This therefore results in a system of impulsive differential equations [5, 49]. We assume that the mass administration of ivermectin is carried out at a fixed time t_k . For the purposes of our model, we assume that the effect of ivermectin is instantaneous, whereby the solutions are continuous for $t \neq t_k$. This satisfy the associated system of ordinary differential equations and undergo an instantaneous change in the state when $t = t_k$. Given the dynamics described in Figure 3.1 and the parameter values described in Chapter (3), now allowing criss-cross interaction between humans and blackflies, the following system of non-linear ordinary differential equations, with non-negative initial conditions, describes the dynamics of onchocerciasis epidemics.

$$\left. \begin{aligned} \dot{S}_H &= b_1 + \varphi S_T - \frac{\beta_h I_V S_H}{N} - \mu_h S_H, \\ \dot{E}_H &= \frac{\beta_h I_V S_H}{N} + \varphi E_T - (\gamma + \mu_h) E_H, \\ \dot{I}_H &= \gamma E_H + \varphi I_T - \mu_h I_H, \\ \dot{S}_T &= -\frac{\delta \beta_h I_V S_T}{N} - (\varphi + \mu_h) S_T, \\ \dot{E}_T &= \frac{\delta \beta_h I_V S_T}{N} - (\rho \gamma + \varphi + \mu_h) E_T, \\ \dot{I}_T &= \rho \gamma E_T - (\varphi + \mu_h) I_T, \\ \dot{S}_V &= b_2 - \frac{\beta_v I_H S_V}{N} - \frac{\kappa \beta_v I_T S_V}{N} - \mu_v S_V, \\ \dot{E}_V &= \frac{\beta_v I_H S_V}{N} + \frac{\kappa \beta_v I_T S_V}{N} - (\eta + \mu_v) E_V, \\ \dot{I}_V &= \eta E_V - \mu_v I_V. \end{aligned} \right\}, \quad t \neq t_k, \quad (4.2.1)$$

subject to the following initial conditions.

$$\begin{aligned} S_H(0) &\geq 0, E_H(0) \geq 0, I_H(0) \geq 0, S_T(0) \geq 0, E_T(0) \geq 0, I_T(0) \geq 0, \\ S_V(0) &\geq 0, E_V(0) \geq 0, I_V(0) \geq 0. \end{aligned}$$

The following are the impulsive conditions of the system of ODES described in Figure 3.1.

$$\left. \begin{aligned} \Delta S_H &= -\alpha S_H, & \Delta E_H &= -\alpha E_H, & \Delta I_H &= -\alpha I_H, \\ \Delta S_T &= +\alpha S_H, & \Delta E_T &= +\alpha E_H, & \Delta I_T &= +\alpha I_H, \end{aligned} \right\}, \quad t = t_k, \quad (4.2.2)$$

Here, it is assumed that treatments against onchocerciasis are given at a regular interval time intervals (τ).

4.3 System without impulses

4.3.1 Well-posedness

The system (4.2.1) describes a human-vector population, it is therefore necessary to prove that the solutions of the system (4.2.1) with positive initial conditions remain positive for all time $t \geq 0$ and are bounded in the region

$$\Omega = \left\{ (S_H, E_H, I_H, S_T, E_T, I_T) \in \mathbb{R}_+^6 : N \leq \frac{b_1}{\mu_h}, \quad (S_V, E_V, I_V) \in \mathbb{R}_+^3 : V \leq \frac{b_2}{\mu_v} \right\}. \quad (4.3.1)$$

Theorem 4.3.1. *For non-negative initial conditions of system (4.2.1), the solutions $(S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V, I_V)$ of the system (4.2.1) are positive for all $t \geq 0$. In addition, the region Ω is positively invariant and all solutions starting in Ω approach, enter, or stay in Ω .*

Proof. Let $t^* = \sup\{t > 0 : S_H(t) > 0, E_H(t) > 0, I_H(t) > 0, S_T(t) > 0, E_T(t) > 0, I_T(t) > 0, S_V(t) > 0, E_V(t) > 0, I_V(t) > 0\}$. Thus, $t^* \geq 0$. Then, from the first equation of our system (4.2.1), we obtain

$$\begin{aligned} \dot{S}_H &= b_1 + \varphi S_T - \frac{\beta_h I_V S_H}{N} - \mu_h S_H \geq -(\lambda_h + \mu_h) S_H, \\ S_H(t^*) &\geq S_H(0) \exp \left\{ - \left(\int_0^{t^*} \lambda_h(m) dm + \mu_h t^* \right) \right\}. \end{aligned}$$

Similarly, one can show that $E_H \geq 0, I_H \geq 0, S_T \geq 0, E_T \geq 0, I_T \geq 0, S_V \geq 0, E_V \geq 0, I_V \geq 0$. This completes the proof for positivity.

The total population of the human population N evolves according to the sum of the

first six equations of system (4.2.1) and that of the vector population V evolves according to the sum of the last three equations of system (4.2.1). Therefore the evolution of these two populations is governed by

$$\dot{N} = b_1 - \mu_h N, \quad \dot{V} = b_2 - \mu_v V. \quad (4.3.2)$$

Therefore, it can be shown that,

$$\limsup_{t \rightarrow \infty} N \leq \frac{b_1}{\mu_h} \text{ and } \limsup_{t \rightarrow \infty} V \leq \frac{b_2}{\mu_v}. \quad (4.3.3)$$

Therefore $N(t)$ and $V(t)$ are bounded. Hence the domain of biological significance is positively invariant and attracting. Thus, all solutions starting in Ω remain in Ω . \square

4.3.2 Maximal solution

Next we overestimate the number of infectious individuals in the population. From the system (4.2.1), we have established that the total human (host) population is bounded above by $\frac{b_1}{\mu_h}$. Thus, from the fifth equation of the system (4.2.1) we have

$$\frac{dE_T}{dt} = \frac{\delta\beta_h I_V S_T}{N} - (\rho\gamma + \varphi + \mu_h)E_T.$$

If we bound S_T by the total human population and I_V by the total vector population, we have

$$\frac{dE_T}{dt} \leq \frac{\delta\beta_h b_2}{\mu_v} - (\rho\gamma + \varphi + \mu_h)E_T. \quad (4.3.4)$$

Solving the inequality in (4.3.4), we obtain

$$E_T \leq \frac{\delta\beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} + \left[E_T(0) - \frac{\delta\beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} \right] e^{-(\rho\gamma + \varphi + \mu_h)t}. \quad (4.3.5)$$

As t approaches infinity, then the solution in (4.3.5) is bounded by

$$E_T \leq \frac{\delta\beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)}. \quad (4.3.6)$$

Substituting the expression in (4.3.6) into the sixth equation of the system (4.2.1), we have

$$\frac{dI_T}{dt} \leq \frac{\delta\beta_h \rho\gamma b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} - (\varphi + \mu_h)I_T,$$

whose solution can be expressed as

$$I_T \leq \frac{\delta\beta_h \rho\gamma b_2}{\mu_v(\varphi + \mu_h)(\rho\gamma + \varphi + \mu_h)}. \quad (4.3.7)$$

Using the solutions obtained in (4.3.6) and (4.3.7) in the second and third equations in the system (4.2.1) respectively, we have

$$E_H \leq \left[\frac{\beta_h b_2}{\mu_v} + \frac{\delta \varphi \beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} \right], \quad (4.3.8)$$

$$I_H \leq \gamma \left[\frac{\beta_h b_2}{\mu_v} + \frac{\delta \varphi \beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} \right] + \varphi \left[\frac{\delta \beta_h \rho \gamma b_2}{\mu_v(\varphi + \mu_h)(\rho\gamma + \varphi + \mu_h)} \right]. \quad (4.3.9)$$

The significance of these inequalities is that they overestimate the number of people with onchocerciasis in the population without necessarily solving the original systems of the differential equations. We will make use of these overestimates shortly.

4.4 Stability of the model equilibria

4.4.1 Disease-free equilibria

The disease-free equilibrium (DFE) for the model without impulse is given by

$$E_0 = (\hat{S}_H, \hat{E}_H, \hat{I}_H, \hat{S}_T, \hat{E}_T, \hat{I}_T, \hat{S}_V, \hat{E}_V, \hat{I}_V) = \left(\frac{b_1}{\mu_h}, 0, 0, 0, 0, 0, \frac{b_2}{\mu_v}, 0, 0 \right). \quad (4.4.1)$$

4.4.2 The basic reproduction number

The basic reproduction number for the system (4.2.1) is obtained using the next generation method described [92]. This is given by

$$R_0 = \sqrt{\mathcal{R}_0} = \sqrt{\frac{b_2 \gamma \eta \beta_h \beta_v}{b_1 \mu_v^2 (\gamma + \mu_h) (\eta + \mu_v)}}. \quad (4.4.2)$$

From Theorem 2 of [26, 92], we have the following results.

Proposition 4.4.1. *The disease-free equilibrium of the system (4.2.1) exists and is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable otherwise.*

Theorem 4.4.2. *The disease free equilibrium E_0 is globally stable whenever, $\mathcal{R}_0 < 1$ and unstable otherwise*

Proof. Let $V = \theta_1 E_H + \theta_2 I_H + \theta_3 E_T + \theta_4 I_T + \theta_5 E_V + \theta_6 I_V$ be a candidate Lyapunov function. The constants θ_i for $i = 1, 2, 3, 4, 5, 6$ are non negative. We can find the constants θ_i such that the Lyapunov candidate is positive definite. The derivative of the Lyapunov

function is given by

$$\begin{aligned}
\frac{dV}{dt} &= \theta_1 \frac{dE_H}{dt} + \theta_2 \frac{dI_H}{dt} + \theta_3 \frac{dE_T}{dt} + \theta_4 \frac{dI_T}{dt} + \theta_5 \frac{dE_V}{dt} + \theta_6 \frac{dI_V}{dt}, \\
&= \theta_1 \left[\frac{\beta_h I_V S_H}{N} + \varphi E_T - Q_1 E_H \right] + \theta_2 [\gamma E_H + \varphi I_T - \mu_h I_H] + \theta_3 \left[\frac{\delta \beta_h I_V S_T}{N} - Q_3 E_T \right] \\
&\quad + \theta_4 [\rho \gamma E_T - Q_2 I_T] + \theta_5 \left[\frac{\beta_v I_H S_V}{N} + \frac{\kappa \beta_v I_T S_V}{N} - Q_4 E_V \right] + \theta_6 [\eta E_V - \mu_v I_V], \\
&= [\theta_2 \gamma - \theta_1 Q_1] E_H + \left[\frac{\theta_5 \mu_h b_2 \beta_v}{\mu_v b_1} - \theta_2 \mu_h \right] I_H + [\theta_1 \varphi + \theta_4 \rho \gamma - \theta_3 Q_3] E_T \\
&\quad + \left[\theta_2 \varphi + \frac{\theta_5 \kappa \beta_v \mu_h b_2}{\mu_v b_1} - \theta_4 Q_2 \right] I_T + [\theta_6 \eta - \theta_5 Q_4] E_V + [\theta_1 \beta_h - \theta_6 \mu_v] I_V,
\end{aligned}$$

where

$$Q_1 = \gamma + \mu_h, \quad Q_2 = \varphi + \mu_h, \quad Q_3 = \rho \gamma + \varphi + \mu_h, \quad Q_4 = \eta + \mu_v.$$

Setting the coefficients to I_H, E_T, I_T, E_V and I_V to zero, we obtain

$$\begin{aligned}
\theta_1 &= \frac{Q_4 \mu_v}{\beta_h}, \quad \theta_2 = \frac{b_2 \beta_v \eta}{b_1 \mu_v}, \quad \theta_3 = \frac{b_2 \eta \kappa \rho \gamma \mu_h \beta_v}{b_1 Q_2 Q_3 \mu_v} + \frac{b_2 \eta \rho \gamma \varphi \beta_v}{b_1 Q_2 Q_3 \mu_v} + \frac{Q_4 \varphi \mu_v}{Q_3 \beta_h}, \\
\theta_4 &= \frac{b_2 \beta_v \eta (\kappa \mu_h + \varphi)}{Q_2 b_1 \mu_v}, \quad \theta_5 = \eta, \quad \theta_6 = Q_4.
\end{aligned} \tag{4.4.3}$$

We then use the coefficients obtained in (4.4.3) into the candidate Lyapunov function. The derivative of the resulting Lyapunov function becomes

$$\frac{dV}{dt} = \frac{Q_1 Q_4 \mu_v}{\beta_h} [\mathcal{R}_0 - 1]. \tag{4.4.4}$$

We note that whenever $\mathcal{R}_0 < 1$ then $\frac{dV}{dt} < 0$. Therefore, by the LaSalle Invariance principle [50], the disease free equilibrium is globally stable whenever $\mathcal{R}_0 < 1$. This completes the proof. \square

4.4.3 Endemic equilibrium

The endemic equilibrium points, E_1 , is found by equating the right-hand of the system (4.2.1) to zero. Expressing all the variables in terms of I_H , we get

$$\begin{aligned}
S_H^* &= b_1 \left(\frac{1}{\mu_h} - \frac{b_2 \eta \beta_h I_H^* \beta_v}{b_1 Q_4 \mu_v (b_1 \mu_v + \mu_h I_H^* \beta_v) + b_2 \eta \beta_h \mu_h I_H^* \beta_v} \right), \\
E_H^* &= \frac{b_1 b_2 \eta \beta_h \mu_h I_H^* \beta_v}{Q_1 (b_1 Q_4 \mu_v (b_1 \mu_v + \mu_h I_H^* \beta_v) + b_2 \eta \beta_h \mu_h I_H^* \beta_v)}, \quad S_T^* = E_T^* = I_T^* = 0, \\
S_V^* &= \frac{b_1 b_2}{\beta_v \mu_h I_H^* + b_1 \mu_v}, \quad E_V^* = \frac{b_2 \beta_v \mu_h I_H^*}{Q_4 (\beta_v \mu_h I_H^* + b_1 \mu_v)}, \quad I_V^* = \frac{b_2 \beta_v \mu_h \eta I_H^*}{Q_4 \mu_v (\beta_v \mu_h I_H^* + b_1 \mu_v)}.
\end{aligned}$$

After some algebraic manipulations, we either have $I_H^* = 0$ or

$$I_H^* = \frac{Q_1 Q_4 b_1^2 \mu_v^2}{Q_1 \beta_v \mu_h (b_2 \beta_h \eta + Q_4 b_1 \mu_v)} [\mathcal{R}_0 - 1]. \quad (4.4.5)$$

The case where $I_H^* = 0$, gives the disease-free equilibrium, treated earlier. From expression (4.4.5), one sees that when $\mathcal{R}_0 < 1$, then $I_H^* < 0$, implying that the system (4.2.1) has no positive solution. However, when $\mathcal{R}_0 > 1$, then $I_H^* > 0$ and a unique endemic equilibrium exists.

Theorem 4.4.3. *The endemic E_1 , is locally asymptotically stable whenever $\mathcal{R}_0 > 1$ and unstable otherwise.*

Proof. The stability and the direction of bifurcation $\mathcal{R}_0 = 1$ of the endemic equilibrium is proved by the direct use of the Center Manifold Theory (CMT) as described in [19]. We avoid re-stating the theorem and adopting notations as described in [19], we compute the values of \mathbf{a} and \mathbf{b} whose signs determine local dynamics of the model (4.2.1). The basic reproduction of the system (4.2.1) is established to be

$$\mathcal{R}_0 = \frac{b_2 \gamma \eta \beta_h \beta_v}{b_1 \mu_v^2 (\gamma + \mu_h) (\eta + \mu_v)}. \quad (4.4.6)$$

Suppose, we choose $\theta = \beta_h$ as the bifurcation parameter so that when $\mathcal{R}_0 = 1$, we have

$$\theta = \frac{b_1 \mu_v^2 (\gamma + \mu_h) (\eta + \mu_v)}{b_2 \gamma \eta \beta_v}. \quad (4.4.7)$$

In order to apply the Center Manifold Theory (CMT), it is necessary to make the following changes to the state variables, we let $S_H = x_1, E_H = x_2, I_H = x_3, S_T = x_4, E_T = x_5, I_T = x_6, S_V = x_7, E_V = x_8, I_V = x_9$. The system (4.2.1) can now be written in the form $\frac{df}{dx} = f(x)$, where $x = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9)$. The system (4.2.1) therefore becomes

$$\left. \begin{aligned} \dot{x}_1 &= b_1 + \varphi x_4 - \frac{\beta_h x_9 x_1}{N} - \mu_h x_1, \\ \dot{x}_2 &= \frac{\beta_h x_9 x_1}{N} + \varphi x_5 - Q_1 x_2, \\ \dot{x}_3 &= \gamma x_2 + \varphi x_6 - \mu_h x_3, \\ \dot{x}_4 &= -\frac{\delta \beta_h x_9 x_4}{N} - Q_2 x_4, \\ \dot{x}_5 &= \frac{\delta \beta_h x_9 x_4}{N} - Q_3 x_5, \\ \dot{x}_6 &= \rho \gamma x_5 - Q_2 x_6, \\ \dot{x}_7 &= b_2 - \frac{\beta_v x_3 x_7}{N} - \frac{\kappa \beta_v x_6 x_7}{N} - \mu_v x_7, \\ \dot{x}_8 &= \frac{\beta_v x_3 x_7}{N} + \frac{\kappa \beta_v x_6 x_7}{N} - Q_4 x_8, \\ \dot{x}_9 &= \eta x_8 - \mu_v x_9. \end{aligned} \right\} \quad (4.4.8)$$

The system (4.4.8) with the bifurcation point θ , has a simple zero eigenvalue. Thus, it enables us to use the Center Manifold Theory to analyse the stability of the system (4.4.8) near $\beta_h = \theta$. Therefore a right eigenvector w associated with zero eigenvalue has components

$$\begin{aligned} w_1 &= -\frac{b_1\mu_v^2(\gamma + \mu_h)(\eta + \mu_v)}{b_2\gamma\eta\mu_h\beta_v}, & w_2 &= \frac{b_1\mu_v^2(\eta + \mu_v)}{b_2\gamma\eta\beta_v}, & w_3 &= \frac{b_1\mu_v^2(\eta + \mu_v)}{b_2\eta\mu_h\beta_v}, \\ w_4 &= w_5 = w_6 = 0, & w_7 &= -\frac{(\eta + \mu_v)}{\eta}, & w_8 &= \frac{\mu_v}{\eta}, & w_9 &= 1. \end{aligned} \quad (4.4.9)$$

Similarly, the corresponding left eigenvector v associated with zero eigenvalue has components

$$\begin{aligned} v_1 &= v_4 = v_7 = 0, & v_2 &= 1, & v_3 &= \frac{Q_1}{\gamma}, \\ v_5 &= \frac{Q_1\kappa\beta_v\rho\gamma\mu_h + \beta_v\varphi(\gamma(\rho\gamma + \varphi) + \mu_h(\gamma + \rho\gamma))}{Q_2Q_3\beta_v\gamma}, \\ v_6 &= \frac{Q_1\beta_v(\kappa\mu_h + \varphi)}{Q_2\beta_v\gamma}, & v_8 &= \frac{Q_1b_1\mu_v}{b_2\beta_v\gamma}, & v_9 &= \frac{Q_1Q_4b_1\mu_v}{b_2\beta_v\eta\gamma}. \end{aligned} \quad (4.4.10)$$

We now compute \mathbf{a} and \mathbf{b} as outlined in [19]. From the system (4.4.8), the non-zero partial derivatives of $f(x)$ associated with \mathbf{a} are given by

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_9} = \frac{\theta\mu_h}{b_1}, \quad \frac{\partial^2 f_8}{\partial x_3 \partial x_7} = \frac{\beta_v\mu_h}{b_1}, \quad \frac{\partial^2 f_8}{\partial x_6 \partial x_7} = \frac{\kappa\beta_v\mu_h}{b_1}. \quad (4.4.11)$$

Thus, the expression for \mathbf{a} is given by

$$\begin{aligned} \mathbf{a} &= v_2w_1w_9 \frac{\partial^2 f_2}{\partial x_1 \partial x_9} + v_8w_3w_7 \frac{\partial^2 f_8}{\partial x_3 \partial x_7} + v_8w_6w_7 \frac{\partial^2 f_8}{\partial x_6 \partial x_7}, \\ &= -\left(\frac{b_1\mu_v^3(\gamma + \mu_h)(\eta + \mu_v)^2(\mu_v(\gamma + \mu_h) + \gamma\kappa\beta_v)}{b_2^2\gamma^2\eta^2\beta_v^2} \right) < 0. \end{aligned} \quad (4.4.12)$$

We finally compute the value of \mathbf{b} . The non-zero partial derivatives of $f(x)$ associated with b is given by

$$\frac{\partial^2 f_2}{\partial x_9 \partial \theta} = 1. \quad (4.4.13)$$

Therefore the expression for \mathbf{b} is given by

$$\mathbf{b} = v_2w_9 \frac{\partial^2 f_2}{\partial x_9 \partial \theta} = 1 > 0. \quad (4.4.14)$$

Since, $\mathbf{a} < 0$ and $\mathbf{b} > 0$, we conclude from item (iv) of Center Manifold Theorem [19] that the established endemic equilibrium E_1 is locally asymptotically stable for $\mathcal{R}_0 > 1$ and there exists a positive unstable equilibrium. This completes the proof. \square

4.5 Model with impulse

In this section, we present and analyse the system with pulse treatment of onchocerciasis with ivermectin. Treatment occurs every six months. We therefore first examine the case of fixed times t_k , with individuals treated at rate α . This results in system of impulsive differential equations [5, 49, 79]. The administration of ivermectin is thus approximated by an instantaneous change.

4.5.1 General solution

Here, we overestimate the number of people infected with onchocerciasis in the population. Suppose the maximal number of individuals infected with onchocerciasis is given by inequality (4.3.9). Then the one-dimensional impulsive differential equation given by

$$\begin{aligned} \frac{dI_H}{dt} &= \gamma \left[\frac{\beta_h b_2}{\mu_v} + \frac{\delta \varphi \beta_h b_2}{\mu_v (\rho \gamma + \varphi + \mu_h)} \right] + \varphi \left[\frac{\delta \beta_h \rho \gamma b_2}{\mu_v (\varphi + \mu_h) (\rho \gamma + \varphi + \mu_h)} \right] - \mu_h I_H, \quad t \neq t_k, \\ \Delta I_H &= -\alpha I_H, \quad t = t_k, \end{aligned} \quad (4.5.1)$$

overestimates the number of infected individuals. Letting $I = I_H$ for notational simplicity, from (4.5.1) we have

$$\begin{aligned} I^+ - I^- &= -\alpha I, \\ I^+ &= (1 - \alpha) I^-. \end{aligned}$$

Let $Q_5 = \beta_h b_2 \gamma [\delta \rho \varphi + Q_2 (\delta \varphi + Q_3)]$ and denote $I_k^+ = I(t_k^+)$ and $I_k^- = I(t_k^-)$. Here, $I(t_k^-)$ is the population proportion of infected individuals immediately before the impulse and $I(t_k^+)$ is the value immediately after the impulse. Hence, for a single impulsive cycle $t_k \leq t \leq t_k + 1$, we have

$$\begin{aligned} I'(t) + \mu_h I(t) &= \frac{Q_5}{Q_2 Q_3 \mu_v}, \\ \frac{d}{dt} (e^{\mu_h t} I) &= \frac{Q_5}{Q_2 Q_3 \mu_v} (e^{\mu_h t} I), \\ e^{\mu_h t} I(t) - e^{\mu_h t_k} I(t_k^+) &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} e^{\mu_h t} - \frac{Q_5}{Q_2 Q_3 \mu_h^2 \mu_v} e^{\mu_h t_k}, \\ I(t) &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - e^{\mu_h (t_k - t)} \right) + I(t_k^+) e^{\mu_h (t_k - t)}. \end{aligned}$$

It therefore follows that

$$\begin{aligned} I_{k+1}^- &= \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) \left(1 - e^{\mu_h (t_{k+1} - t_k)} \right) + I_k^+ e^{\mu_h (t_{k+1} - t_k)}, \\ &= \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) \left(1 - e^{-\mu_h (t_{k+1} - t_k)} \right) + (1 - \alpha) I_k^- \left(e^{-\mu_h (t_{k+1} - t_k)} \right). \end{aligned} \quad (4.5.2)$$

The solution obtained in (4.5.2) at the impulse points satisfies

$$\begin{aligned}
I_1^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v}, & I_1^+ &= (1 - \alpha) \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right), \\
I_2^- &= (1 - \alpha) \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) e^{-\mu_h(t_2-t_1)} + \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) (1 - e^{\mu_h(t_2-t_1)}), \\
I_2^+ &= (1 - \alpha) I_2^- = (1 - \alpha)^2 \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) e^{-\mu_h(t_2-t_1)} \\
&\quad + (1 - \alpha) \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) (1 - e^{\mu_h(t_2-t_1)}), \\
I_3^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left((1 - \alpha)^2 e^{-\mu_h(t_3-t_1)} + (1 - \alpha) e^{-\mu_h(t_3-t_2)} \right. \\
&\quad \left. + 1 - (1 - \alpha) e^{-\mu_h(t_3-t_1)} - e^{-\mu_h(t_3-t_2)} \right), \\
I_3^+ &= (1 - \alpha) I_3^- = \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left((1 - \alpha)^3 e^{-\mu_h(t_3-t_1)} + (1 - \alpha)^2 e^{-\mu_h(t_3-t_2)} \right. \\
&\quad \left. + (1 - \alpha) - (1 - \alpha)^2 e^{-\mu_h(t_3-t_1)} - (1 - \alpha) e^{-\mu_h(t_3-t_2)} \right), \\
I_4^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left((1 - \alpha)^3 e^{-\mu_h(t_4-t_1)} + (1 - \alpha)^2 e^{-\mu_h(t_4-t_2)} + (1 - \alpha) e^{-\mu_h(t_4-t_3)} \right. \\
&\quad \left. + 1 - (1 - \alpha)^2 e^{-\mu_h(t_4-t_1)} - (1 - \alpha) e^{-\mu_h(t_4-t_2)} - e^{-\mu_h(t_4-t_3)} \right), \\
I_4^+ &= (1 - \alpha) I_4^-.
\end{aligned}$$

Thus, the general solution becomes

$$\begin{aligned}
I_n^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left((1 - \alpha)^{(n-1)} e^{-\mu_h(t_n-t_1)} + (1 - \alpha)^{(n-2)} e^{-\mu_h(t_n-t_2)} + \dots + (1 - \alpha) e^{-\mu_h(t_n-t_{n-1})} \right. \\
&\quad \left. + 1 - (1 - \alpha)^{(n-2)} e^{-\mu_h(t_n-t_1)} - (1 - \alpha)^{(n-3)} e^{-\mu_h(t_n-t_2)} - \dots - e^{-\mu_h(t_n-t_{n-1})} \right).
\end{aligned} \tag{4.5.3}$$

The general solution obtained in (4.5.3) defines the maximal number of people with onchocerciasis immediately before the mass treatment with ivermectin. This solution depends on the human and vector recruitment rates, the human-vector transmission contact rate, the incubation period in the human, the waning rate of ivermectin, human and vector death rates, treatment times and the treatment effectiveness. A similar approach can be employed to calculate the maximal number of latently infected individuals using the overestimate obtained in (4.3.8). For fixed mass administration of ivermectin, (4.5.3) does not depend on time.

4.5.2 Fixed administration of ivermectin

For a fixed time period $\tau = t_{n+1} - t_n$, we have

$$\begin{aligned} I_n^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 + (1 - \alpha) e^{\mu_h \tau} + (1 - \alpha)^2 e^{-2\mu_h \tau} + \dots + (1 - \alpha)^{(n-1)} e^{-\mu_h (n-1)\tau} \right. \\ &\quad \left. - e^{-\mu_h \tau} \left(1 + (1 - \alpha) e^{-\mu_h \tau} + \dots + (1 - \alpha)^{(n-2)} e^{-\mu_h (n-2)\tau} \right) \right), \\ &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(\frac{1 - (1 - \alpha)^n e^{\mu_h n \tau}}{1 - (1 - \alpha) e^{\mu_h \tau}} - \frac{1 - (1 - \alpha)^{(n-1)} e^{-\mu_h (n-1)\tau}}{1 - (1 - \alpha) e^{\mu_h \tau}} e^{-\mu_h \tau} \right). \end{aligned}$$

Thus

$$\begin{aligned} \lim_{n \rightarrow \infty} I_n^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(\frac{1}{1 - (1 - \alpha) e^{-\mu_h \tau}} - \frac{1}{1 - (1 - \alpha) e^{-\mu_h \tau}} e^{-\mu_h \tau} \right) \\ &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(\frac{1 - e^{-\mu_h \tau}}{1 - (1 - \alpha) e^{-\mu_h \tau}} \right). \end{aligned} \quad (4.5.4)$$

The solution obtained in (4.5.4) is the maximum population of the infected individuals. Note that

$$\lim_{\substack{\tau \rightarrow 0 \\ n \rightarrow \infty}} I_n^- = 0,$$

implying that the total number of infected humans shrinks to zero as the frequency of mass treatment with ivermectin increases (although note that the impulsive assumptions would break down in this limit). In order to keep the infected individuals under a threshold \hat{I} , we have

$$\hat{I} < \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(\frac{1 - e^{-\mu_h \tau}}{1 - (1 - \alpha) e^{-\mu_h \tau}} \right),$$

which implies that

$$\tau < \frac{1}{\mu_h} \ln \left[\frac{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v (1 - \alpha)}{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v} \right] = \tau_{\max}(\alpha). \quad (4.5.5)$$

The expression in (4.5.5) gives the maximum period of mass administration of ivermectin in the population to keep the infection of onchocerciasis below \hat{I} . If we restrict τ to $0 \leq \tau < \tau_{\max}$, then the disease can be controlled below the threshold \hat{I} (but not necessarily eradicated).

4.5.3 Non-fixed administration of ivermectin

In this section, we consider a situation in which the mass administration of ivermectin is carried out at non-fixed times. However, this would require that the entire history

of ivermectin administration is known, which is unlikely to be the case. Thus, we will assume that ivermectin treatment occurring more than two events previously has a negligible effect on the number of currently treated individuals. That is,

$$e^{-\mu_h(t_n-t_k)} \approx 0 \text{ for } k > 2.$$

It then follows from (4.5.2) that

$$\begin{aligned} I_n^- &< \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - e^{-\mu_h(t_n-t_{n-1})} \right), \\ I_{n+1}^- &< \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - e^{-\mu_h(t_n-t_{n-1})} \right) + (1-\alpha) I_n^- e^{-\mu_h(t_n-t_{n-1})}, \\ &< \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - e^{-\mu_h(t_{n+1}-t_n)} \right) + (1-\alpha) \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - \alpha e^{-\mu_h(t_n-t_{n-1})} \right) e^{-\mu_h(t_{n+1}-t_n)}. \end{aligned}$$

The above inequality can be approximated as

$$\hat{I} \equiv \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - e^{-\mu_h(t_{n+1}-t_n)} \right) + (1-\alpha) \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - \alpha e^{-\mu_h(t_n-t_{n-1})} \right) e^{-\mu_h(t_{n+1}-t_n)}. \quad (4.5.6)$$

The expression in (4.5.6) gives the number of infected humans that will be below \hat{I} based on knowing the two previous mass administration times. Then the "next best" mass treatment with ivermectin satisfies the following:

$$\begin{aligned} \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 + (1-\alpha) \right) - \hat{I} &= e^{-\mu_h(t_{n+1}-t_n)} \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) \left(1 + \alpha(1-\alpha) e^{-\mu_h(t_{n+1}-t_n)} \right), \\ e^{-\mu_h(t_{n+1}-t_n)} &= \frac{2-\alpha-Q_5/Q_2 Q_3 \mu_h \mu_v}{1+\alpha(1-\alpha) e^{-\mu_h(t_{n+1}-t_n)}}, \\ t_{n+1} &= t_n - \frac{1}{\mu_h} \ln \left(\frac{2-\alpha-Q_5/Q_2 Q_3 \mu_h \mu_v}{1+\alpha(1-\alpha) e^{-\mu_h(t_{n+1}-t_n)}} \right). \end{aligned}$$

Next we compare fixed and non-fixed mass treatment with ivermectin. Assuming that the mass treatment times in the non-fixed case are constant, \hat{t} , then from (4.5.5), we have

$$\hat{t} = \frac{1}{\mu_h} \ln \left(\frac{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v (1-\alpha)}{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v} \right), \quad (4.5.7)$$

$$\hat{t}|_{\alpha=0} = \frac{1}{\mu_h} \ln \left(\frac{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v}{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v} \right) = 0, \quad (4.5.8)$$

$$\hat{t}|_{\alpha=1} = \frac{1}{\mu_h} \ln \left(\frac{Q_5}{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v} \right). \quad (4.5.9)$$

If there is no impulse, then from (4.5.1), we have $\lim_{t \rightarrow \infty} I = \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v}$. Thus, we can assume that $\hat{I} = \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v}$. Hence,

$$0 < 1 - \frac{Q_2 Q_3 \mu_h \mu_v \hat{I}}{Q_5} < 1, \quad (4.5.10)$$

therefore, $\hat{\tau}_{\alpha=1} > 0$. Assuming that non-fixed mass treatment with ivermectin occurs indefinitely and further letting $\tau_{\max} \equiv t_{n+1} - t_n = t_n - t_{n-1}$, then the minimum treatment effectiveness satisfies

$$\tau_{\max} = \frac{1}{\mu_h} \ln \left(\frac{2 - \alpha - \hat{I} Q_2 Q_3 \mu_h \mu_v / Q_5}{1 + \alpha(1 - \alpha) e^{-\mu_h \tau_{\max}}} \right). \quad (4.5.11)$$

If $\tau_{\max} = 0$, then it follows that (4.5.11) becomes

$$\begin{aligned} \frac{1}{\mu_h} \ln \left(\frac{2 - \alpha - \hat{I} Q_2 Q_3 \mu_h \mu_v / Q_5}{1 + \alpha(1 - \alpha)} \right) &= 0, \\ 2 - \alpha - \hat{I} \frac{Q_2 Q_3 \mu_h \mu_v}{Q_5} &= 1 + \alpha(1 - \alpha), \\ \alpha &= 1 \pm \sqrt{\frac{Q_2 Q_3 \mu_h \mu_v}{Q_5}}. \end{aligned}$$

The larger root exceeds 1 and hence can be discounted. It follows that the smaller root $\alpha_0 = 1 - \sqrt{\frac{Q_2 Q_3 \mu_h \mu_v}{Q_5}}$, satisfies $0 < \alpha_0 < 1$ as stated in (4.5.10). This implies that the mass treatment is only effective in the range $\alpha_0 < \alpha \leq 1$.

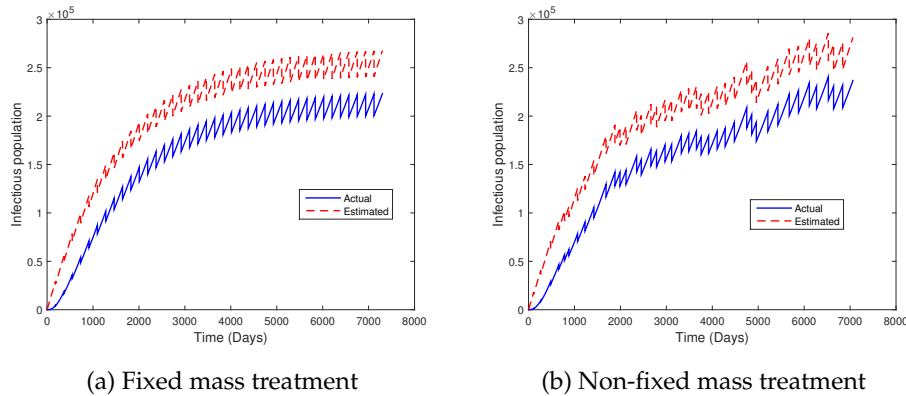


Figure 4.1: Comparison of the actual infected individuals and the estimated infected individuals.

4.6 Numerical simulations

In this section, we carry out parameter estimation, sensitivity analysis of the model parameters, and numerical simulations for the system (4.2.1) to demonstrate the theoretical results. The simulations are performed using the fourth order Runge-Kutta scheme in Matlab 2014a with the given set of parameter values given in Table 4.1. We shall assume some of the parameters in some realistic range with guidance from past literature on onchocerciasis epidemics with reference to Ghana which is one of the onchocerciasis foci.

4.6.1 Parameter estimation

In this section, we consider average parameter values that encompass features of onchocerciasis disease including rate of infection, incubation period, length of infections period in the vector and host populations. Although estimates of some parameters are given in Table 4.1, here we give additional explanation and description of some of the parameters based on available literature and with reference to Ghana which is one of the onchocerciasis endemic countries.

1. The average birthrate in Ghana was estimated to be 31.09 births/1,000 population in 2015 and 30.60 births/1,000 population in 2014 according to the World Fact Book by Central Intelligence Agency [85] and Ghana Statistical Service report on Demographic and Health Survey [35] respectively. Thus, the recruitment rate is estimated from the range $(0.0000819 \leq b_1 \leq 0.00108)N$ per day.
2. The natural human death rate is estimated based on average life of 50-70 years in accordance to Central Intelligence Agency and 2014 demographic data released by Ghana Statistical Service estimates of life expectancy at birth respectively [35, 85]. The black-fly death rate is estimated based on the average life span lasting for 2-3 weeks [31, 40].
3. It takes $\frac{3}{4}$ to 2 years for the worm to mature and release enough microfilariae to be detectable in the skin of the human host [40, 52, 66, 76]. Therefore, a reasonable estimate of the incubation rate γ is $0.00137 \leq \gamma \leq 0.00365$ per day. On the other hand, the average incubation period in the black-fly is 1-2 weeks [40, 52, 72, 76]. Thus, a reasonable value for η is $0.0714 \leq \eta \leq 0.1667$ per day.

4. The modification parameters (κ , δ and ρ) have been estimated to be between 0 and 1 due to the reduced ability of individuals to cause infections following ivermectin treatment.
5. The mass administration of ivermectin reduces the infection by α which is estimated to be between 0% and 100%.

For illustration purpose, we consider the parameter values estimates given in Table 4.1 with $N = 200,000$, $V = 10,000$.

Table 4.1: Estimated parameter values in the model for onchocerciasis case. The rates are given per day.

Parameter	Range	Point value	Source
b_1	0.0000819-0.0001085	0.00009/N	Estimated.
μ_h	0.0000391-0.0000548	0.000052	[35, 85].
β_h	0.0-0.001	0.00198	Assumed.
γ	0.00137-0.00365	0.00139	[40, 52, 66, 76].
α	0-1.0	[0.1, 0.65]	[89, 94].
φ	0.01-0.1	0.0015	[89].
κ	0.00-1.0	0.0083	Assumed.
ρ	0.0-0.1.0	0.001	Assumed.
δ	0.00-1.0	0.002	Assumed.
b_2	0.0214-0.4	0.144/V	Assumed.
β_v	0.0-0.001	0.00079	Assumed.
η	0.0714-0.1667	0.078	[40, 52, 72, 76].
μ_v	0.0118-0.0714	0.068	[31, 40].

4.6.2 Sensitivity analysis

Sensitivity analysis is the study of how uncertainty in the output of a system can be apportioned to different sources of uncertainty in the model input [77, 78]. It is a technique for systematically varying model inputs and determining their effect on the model output. We perform sensitivity analysis in order to investigate the contribution of vital parameters on the model dynamics, specifically to establish the parameters that have significant influence on the onchocerciasis dynamics. We use Latin Hypercube Sampling (LHS), a stratified Monte Carlo sampling scheme applicable to many parameters

from a multidimensional distribution [77, 78]. It allows for simultaneous determination of an unbiased estimate of the model output for a given set of model input. We perform the sensitivity analysis by computing the Partial Rank Correlation Coefficients (PRCCs) for each parameter value, sampled by the LHS scheme [15]. Parameters with positive PRCCs will increase R_0 when they are increased, whereas parameters with negative PRCCs will decrease R_0 when they are increased. The outcome is the reproduction number R_0 derived from the theoretical model. We determine PRCCs with 1000 simulations per run to determine parameters that have a significant influence on R_0 .

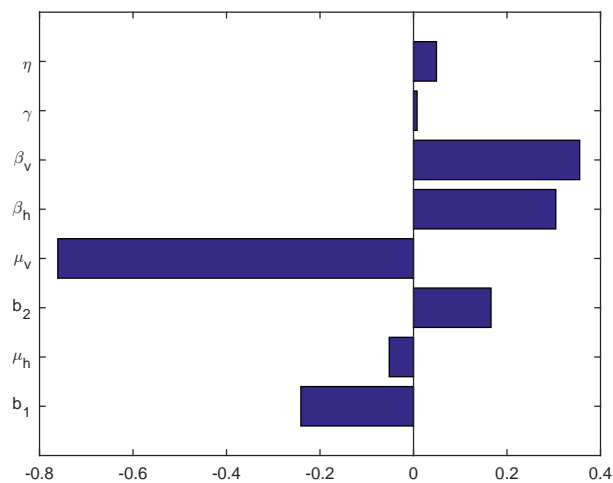


Figure 4.2: Tornado plots of partial rank correlation coefficients (PRCCs) of the parameters that influence R_0 for the input parameters using the values in Table 4.1. Parameters with $\text{PRCC} > 0$ increase R_0 when they are increased whereas parameters with $\text{PRCC} < 0$ decrease R_0 when they are increased.

The PRCCs results in Figure 4.2 illustrate the degree of the effect that each parameter has on the outcome. The three parameters with the most influence on R_0 are the transmission contact rate in humans, β_h , the vector transmission contact rate, β_v , and the vector death rate μ_v .

Figure 4.3 displays 1000 Monte Carlo simulations for the input parameters with the most effect on the basic reproduction number. Scatter plots show that R_0 is monotone increasing with increasing values of β_h and β_v and monotone decreasing with increasing vector mortality rate, μ_v . However, R_0 is only guaranteed to be less than unity when

the human–vector and vector–human contact rates are sufficiently small. These results also suggest that, even if vector death rate is extremely high, eradication is not possible. Transmission rates in both the human and the vector is another strategy of the disease eradication.

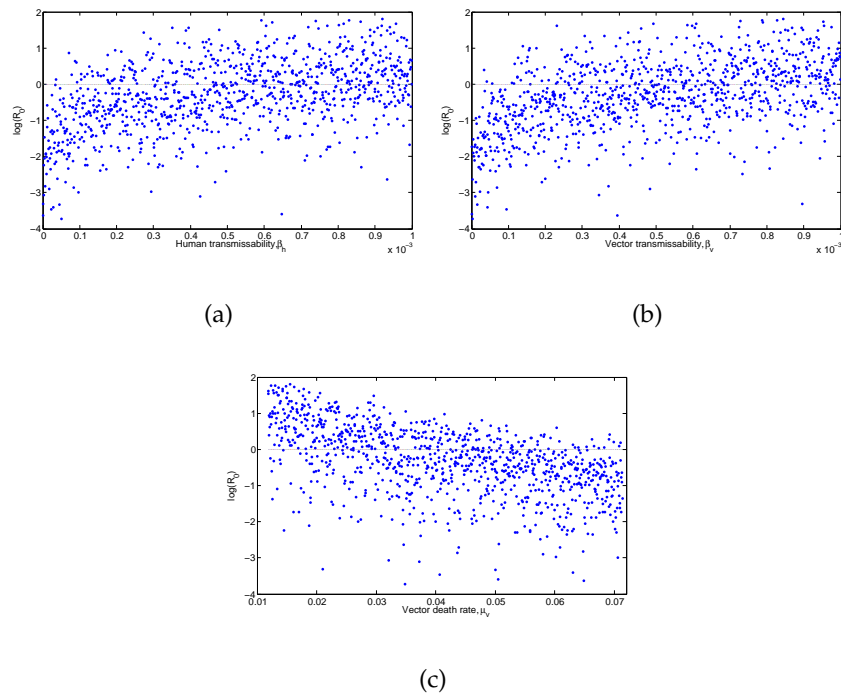


Figure 4.3: The Monte Carlo simulations for the three parameters with the greatest influence on the R_0 : the transmission contact rate in humans, the transmission contact rate in the vector and the vector death rate for the input parameters using the values in Table 4.1 and 1000 simulations per run. Eradication is only possible if the transmissibilities are extremely small or if the vector death rate is extremely high.

In order to gain more insight into the three parameters with the greatest influence on the basic reproduction number, R_0 , all other parameters were fixed at their sample values. A surface plot for $R_0 = 1$ is shown in Figure 4.4. It is observed that for the disease eradication, β_h must be brought to extremely low levels.

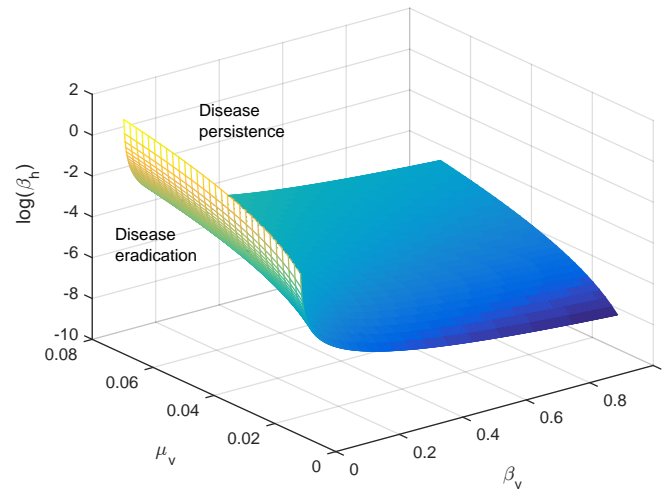


Figure 4.4: Eradication threshold for the three parameters with the greatest influence on R_0 .

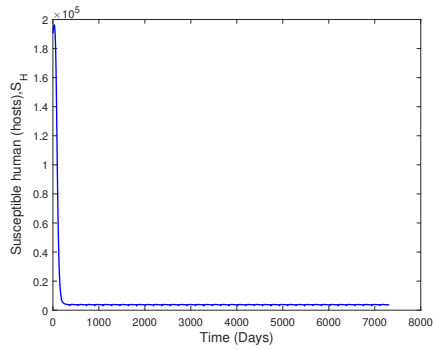
4.6.3 Simulation results

The results presented in this section demonstrate the dynamics of onchocerciasis for the system (4.2.1) obtained using Matlab ODE45 solver, which employs simultaneously the fourth and fifth order Runge–Kutta schemes. Unless otherwise stated, parameters are as stated in Table 4.1. We give results of system (4.2.1) with impulses for both the cases when $R_0 < 1$ and when $R_0 > 1$ as shown in Figures 4.7–4.10 and Figures 4.5–4.6, respectively. In addition, we numerically make a comparison between fixed and non-fixed mass administration of ivermectin in the treatment of onchocerciasis. In order to illustrate the effectiveness of ivermectin, we vary the reduction rate (α) for both the cases of R_0 .

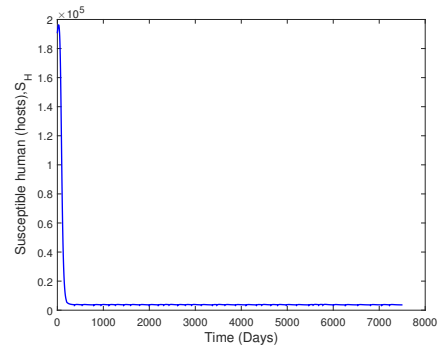
First, we examine the behaviour of the system (4.2.1) when the basic reproduction number, R_0 , is greater than unity for the fixed and non-fixed mass administration of ivermectin. It is seen in Figure 4.5 that when the effectiveness of ivermectin is low, that is, $\alpha = 0.10$, the disease spreads in the population. However, the results in Figure 4.6 show that the endemicity of the disease is reduced when the effectiveness rate of mass administration of ivermectin is increased. We also observe that fixed mass administration yields a better outcome compared to non-fixed mass administration.

We then examine the case when the basic reproduction number is below unity for both

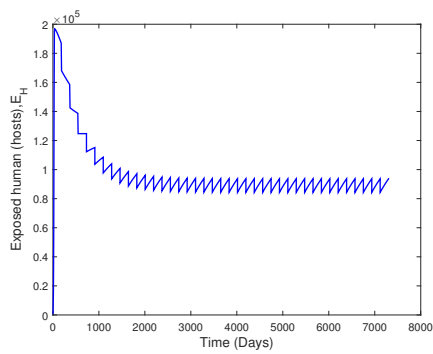
the fixed and non-fixed mass administration of ivermectin. We examine two cases of $R_0 < 1$: when R_0 is close to unity and where R_0 is significantly less than unity. We observe in Figure 4.7 that when R_0 is less than but close to one, the disease may persist in the population when the value of α is small. However an increment in the value of α moves the system towards a disease-free state, but there is no eradication. This is shown in Figure 4.8 with $\alpha = 0.65$. The results in Figure 4.9 show the dynamics of the population under both fixed and non-fixed mass administration of ivermectin at $\alpha = 0.1$ keeping the interval $\tau = 182.5$ days (6 monthly interval) for fixed mass administration. We observe that the system with impulses attains its disease-free state, suggesting that onchocerciasis dies out. These results are consistent with theorem (4.4.2). However, when the ivermectin effectiveness is increased, the system attains the disease free equilibrium much faster as shown in Figure 4.10.



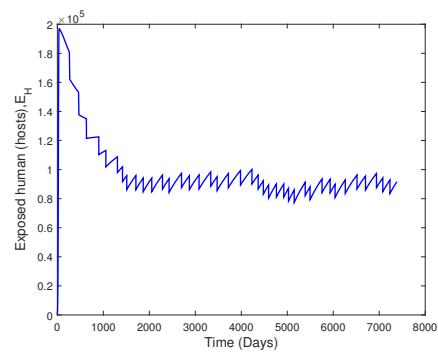
(a) Fixed



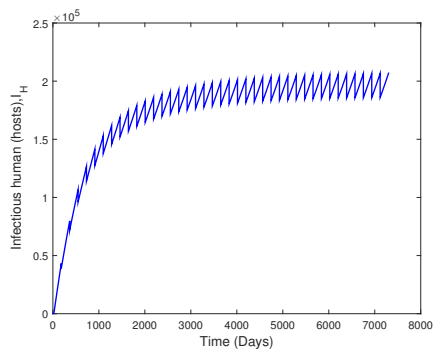
(b) Non-fixed



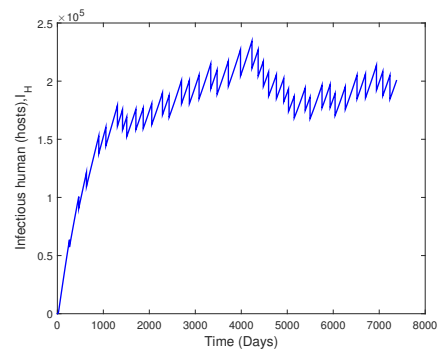
(c) Fixed



(d) Non-fixed

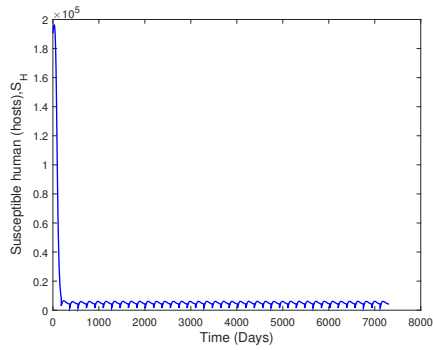


(e) Fixed

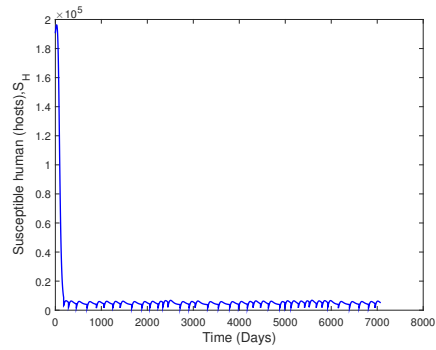


(f) Non-fixed

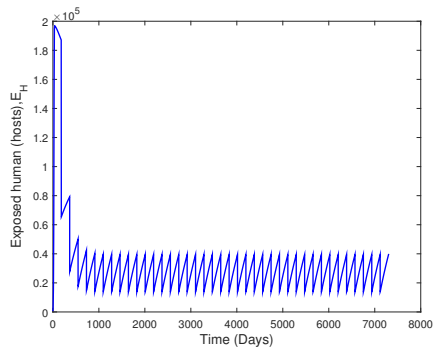
Figure 4.5: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.10$, $R_0 = 1.2412$, $b_1 = 0.0009$, $b_2 = 0.35$, $\beta_h = 0.00562$, $\beta_v = 0.00243$, $\varphi = 0.025$, $\mu_v = 0.012$.



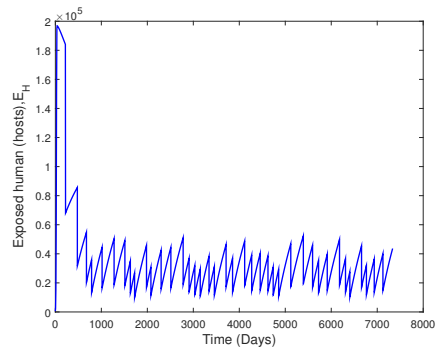
(a) Fixed



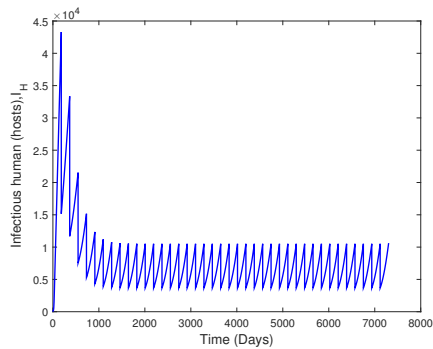
(b) Non-fixed



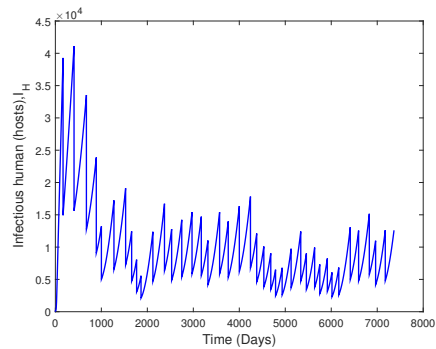
(c) Fixed



(d) Non-fixed

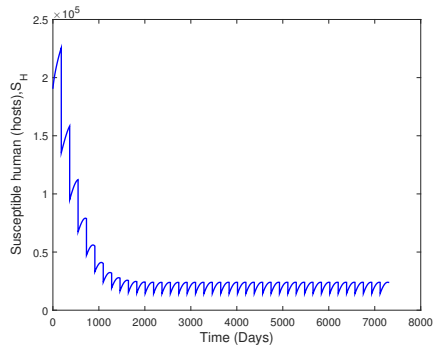


(e) Fixed

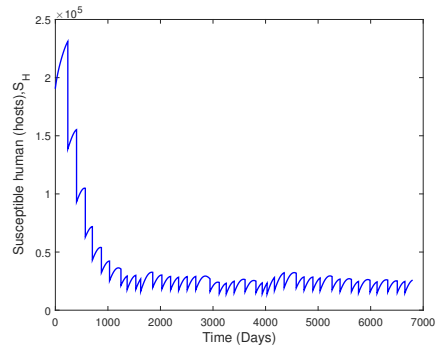


(f) Non-fixed

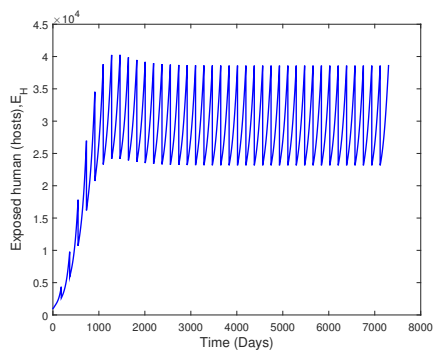
Figure 4.6: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.65$, $R_0 = 1.2412$, $b_1 = 0.0009$, $b_2 = 0.35$, $\beta_h = 0.00562$, $\beta_v = 0.00243$, $\varphi = 0.025$, $\mu_v = 0.012$. Note that increasing α improves the outcome but does not lead to eradication.



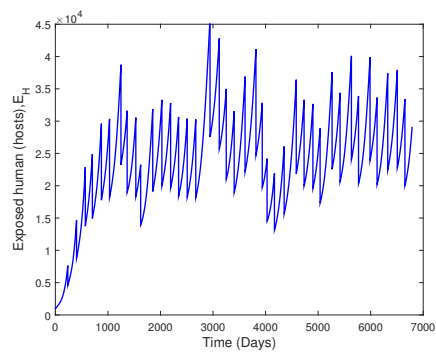
(a) Fixed



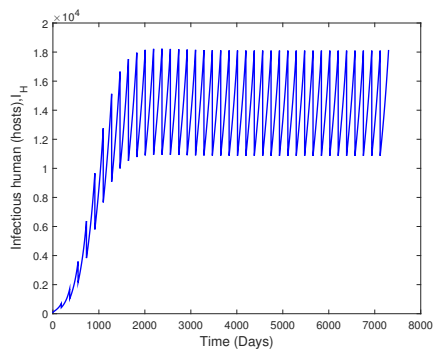
(b) Non-fixed



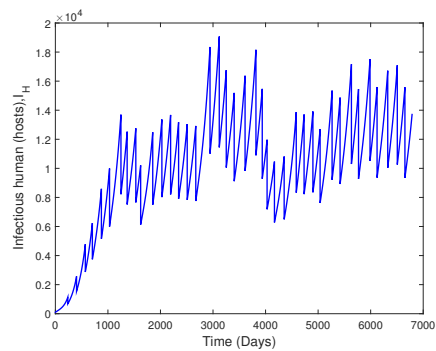
(c) Fixed



(d) Non-fixed



(e) Fixed



(f) Non-fixed

Figure 4.7: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.10$, $R_0 = 0.9352$, $b_1 = 0.0009$, $b_2 = 0.35$, $\beta_h = 0.00443$, $\varphi = 0.025$, $\beta_v = 0.00175$, $\mu_v = 0.012$. Non-fixed administration may produce lower overall numbers of infected individuals, but the outcome is not predictable.

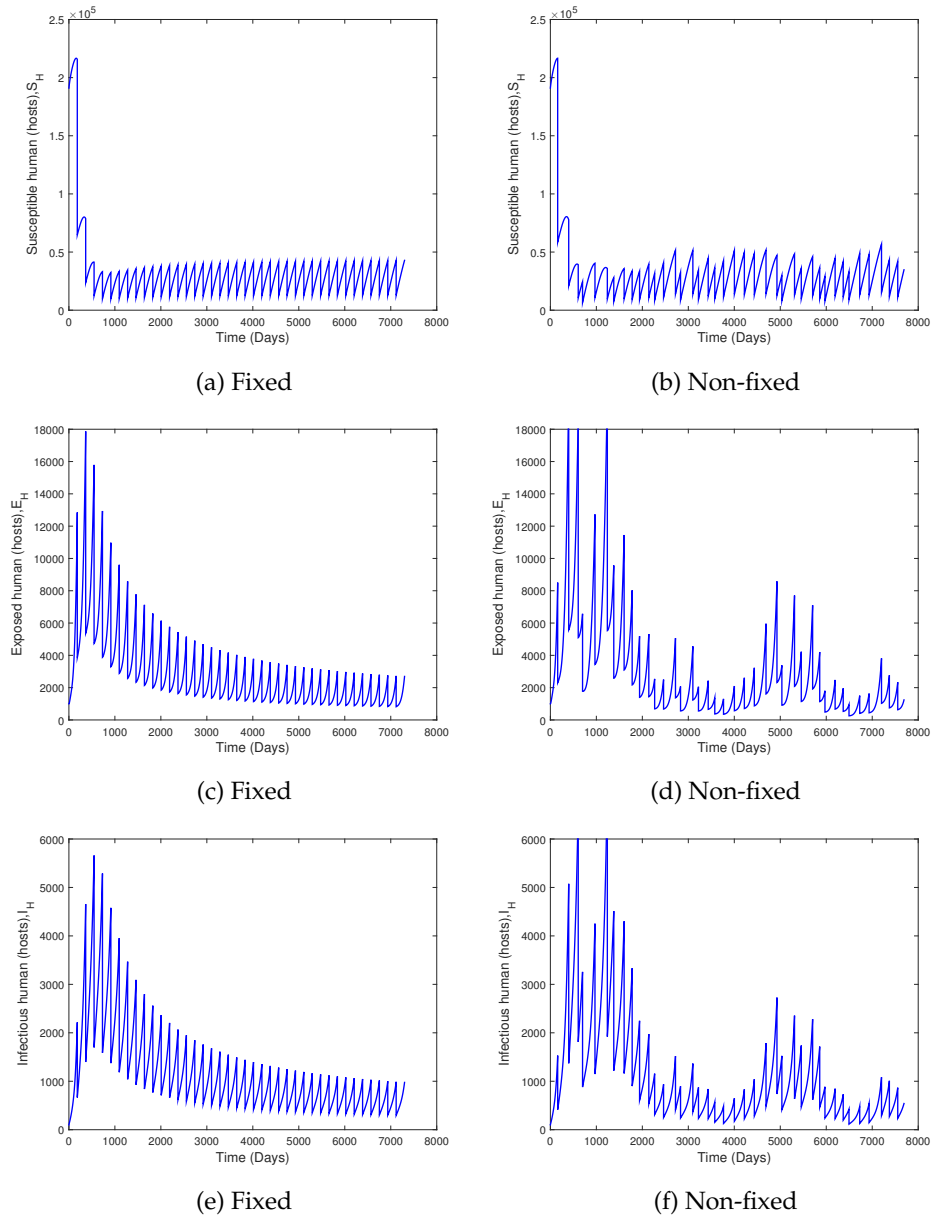
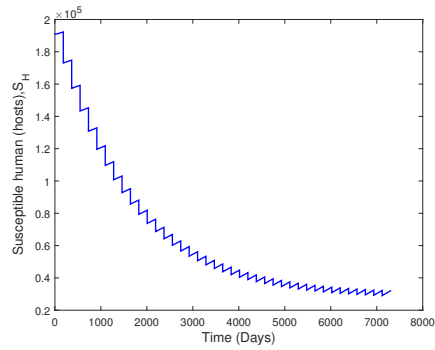
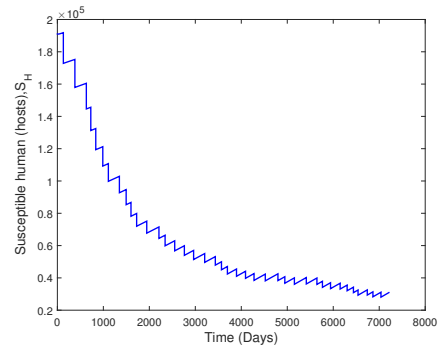


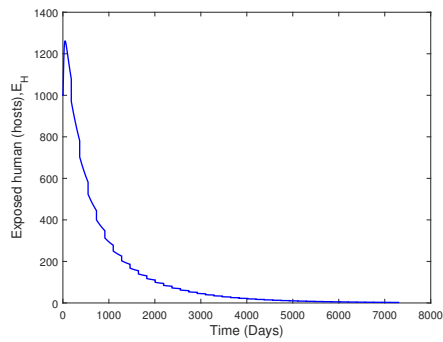
Figure 4.8: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.65$, $R_0 = 0.9352$, $b_1 = 0.0009$, $b_2 = 0.35$, $\beta_h = 0.00443$, $\varphi = 0.025$, $\beta_v = 0.00175$, $\mu_v = 0.012$. Non-fixed administration may produce bursts of infection, even if the disease would be otherwise kept at low levels.



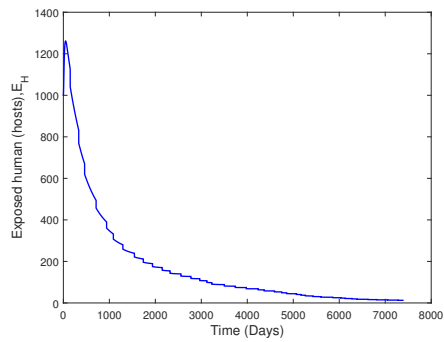
(a) Fixed



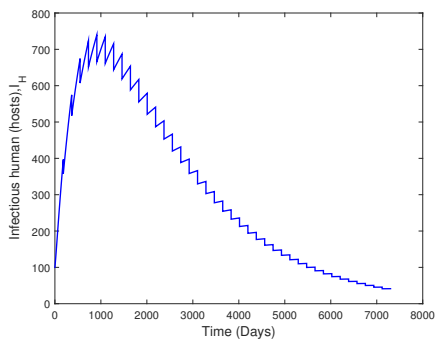
(b) Non-fixed



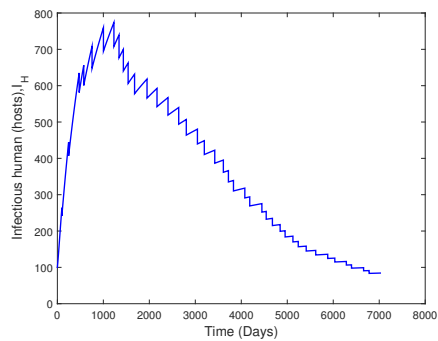
(c) Fixed



(d) Non-fixed

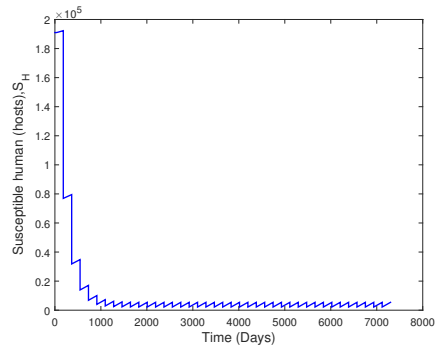


(e) Fixed

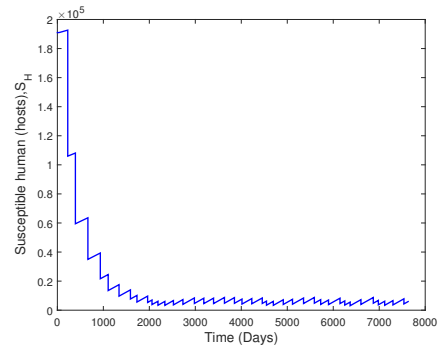


(f) Non-fixed

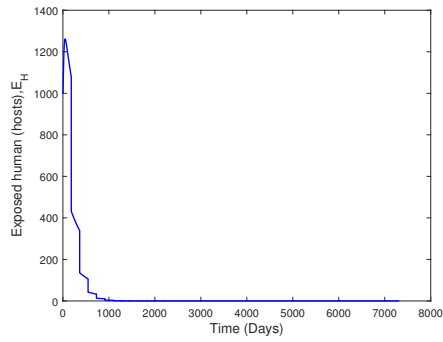
Figure 4.9: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.1, R_0 = 0.1181$ using parameter values in Table 4.1. Note that non-fixed administration may have a delaying or preventative effect on eradication.



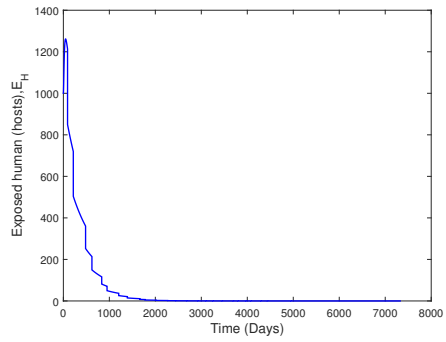
(a) Fixed



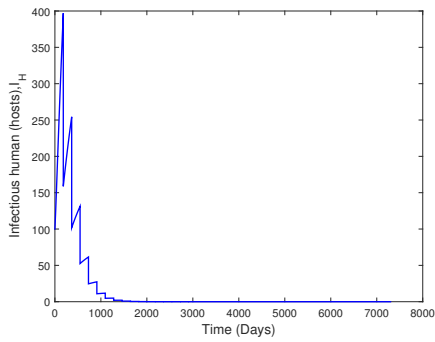
(b) Non-fixed



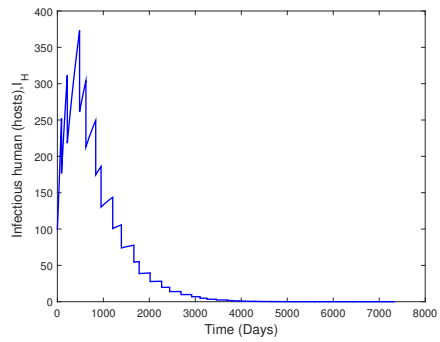
(c) Fixed



(d) Non-fixed



(e) Fixed



(f) Non-fixed

Figure 4.10: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.65$, $R_0 = 0.1181$ using parameter values in Table 4.1. Increasing α hastens eradication, in both the fixed and non-fixed case.

4.7 Conclusion

In this chapter, we extend the mathematical model for onchocerciasis disease transmission in chapter 3 to include pulse vaccination. The aim was to gain some insights into the impact of periodic mass administration of ivermectin in the eradication of onchocerciasis. From the system without impulse, we were able to determine the basic reproduction number. Furthermore, we studied the existence of the disease free and the unique endemic equilibrium points. Our analysis showed that for $R_0 < 1$, the disease free equilibrium is globally asymptotically stable and unstable otherwise. In addition, the unique endemic equilibrium point only exists for $R_0 > 1$ thus transcritical bifurcation.

We have provided the estimates for the necessary frequency and strength of mass administration of ivermectin. We may conclude that the disease can be controlled through mass administration with needed frequency and high strength of ivermectin. We have observed from our numerical results that the eradication of onchocerciasis is possible with tolerable regularity of mass administration of ivermectin provided the basic reproduction number is kept (far) below unity. We can conclude that, in the presence of mass administration of ivermectin with six month intervals, the disease can be controlled. Furthermore, if the frequency of mass administration is increased, the system moves towards a better outcome. Our modelling results show that mass administration of ivermectin at regular interval is an effective method of onchocerciasis eradication if other parameters can be sufficiently controlled.

Chapter 5

Conclusion

5.1 Conclusion

The objective of this thesis was to determine the effect of mass administration of ivermectin on the dynamics of onchocerciasis. A deterministic model showing the dynamics of onchocerciasis in human (host) and vector (black-fly) is presented. In the first part, we analyse the onchocerciasis model without controls while in the second part, we introduce time-dependent control variables (policies) to the onchocerciasis model. For the model without controls, we establish the existence of equilibria points in terms of the basic reproduction number R_0 . By constructing a suitable Lyapunov function, the analysis shows that the disease-free equilibrium of the onchocerciasis model is globally asymptotically stable whenever R_0 is less than unity. The epidemiological implications of this observation is that keeping the reproduction numbers below one is necessary to curb the spread of onchocerciasis disease. The inclusion of occurrence of infections in the individuals protected with ivermectin resulted in the model exhibiting a backward bifurcation. The existence of a backward bifurcation has important implications in the design of policies and strategies to eradicate an epidemic. In the presence of a backward bifurcation, classical policies on disease eradication need to be changed as onchocerciasis can persist even when the threshold parameter R_0 , is less than unity.

We sought to determine control strategies that would minimize the exposed and infected humans (hosts) as well as the vector population and their respective costs. In order to achieve this objective, our model is extended to include three control strategies associated with personal protection, enhanced mass treatment with ivermectin and vector reduction strategies. The optimal control model has been analysed using the objective functional J . The optimal controls u_1, u_2 and u_3 where J was minimised was obtained.

Pontryagin's Maximum Principle was used to analyse the optimal control system for existence of an optimal control. The optimal control system was solved numerically using the state and adjoint system together with characterisation of the optimal control. A comparison between optimal control system and system without control is presented. It is easy to see that the optimal control system has desirable impact on the reduction of the number of exposed and infected humans (hosts) and the vector population. The results show that preventive practices are very effective in reducing the incidence of infectious hosts and vectors.

To investigate the potential impact of mass administration of ivermectin on the dynamics of onchocerciasis, impulsive differential equations are introduced. The analysis of the model without pulse mass administration of ivermectin shows that, the disease-free state exists if $R_0 < 1$. On the other hand, if $R_0 > 1$, the disease-free state loses its stability and the system tends towards the endemic state. We have provided the estimates for the necessary frequency and strength of mass administration of ivermectin. We have observed that the threshold values of time interval with minimum degree of effectiveness is obligatory for the mass administration of ivermectin for fixed time interval. We conclude that the disease can be controlled through mass administration with fixed frequency and high strength of ivermectin of more than 65%. Furthermore, our results suggest that reducing the human-vector contact can be one way of eradicating onchocerciasis from the population. This can be done by implementing personal protection practices such as wearing insect repellent, wearing long sleeves and long pants during the day when black-flies bite. In addition, application of insecticides can be effective in reducing the presence of vector in the environment. If the human-vector contact is reduced to extremely low values then eradication is assured.

We have observed from our numerical results that the eradication of onchocerciasis is possible with tolerable regularity of mass administration of ivermectin provided the basic reproduction number is kept below unity. We can conclude that in the presence of mass administration of ivermectin keeping six months interval, the disease can be easily controlled. Furthermore, if the power of mass administration is increased, the system moves towards better outcome. This implies that the effectiveness of mass administration of ivermectin enhances the system towards the disease-free state. We can conclude that the final steps towards the eradication of onchocerciasis is possible within the next few years in the Sub-Saharan Africa where the disease is endemic. Our modelling results show that mass administration of ivermectin at regular interval is an effective method of onchocerciasis eradication.

5.2 Recommendations

Based on our study findings, we recommend the following

- The use of both ivermectin in the treatment of onchocerciasis and use of insecticides will greatly lead to onchocerciasis eradication.
- The use of personal protection strategies will greatly reduce the cases of infection in the population thus facilitating the disease eradication.

5.3 Limitations and future work

In this thesis, we did not take into account the possibility of drug resistance. We assumed that ivermectin is highly efficacious in the treatment of onchocerciasis. In addition we did take into account all the possible dynamics of onchocerciasis in order to reduce on the complexity of the model. For instance, we did not include the individuals with onchocerciasis in the acute phase. We assumed that the number of individuals that progress to this class are few and can be ignored which is not entirely true. In addition, stochasticity that may be attributed to the climatic conditions which can influence the infection dynamics of this disease was not considered. Consideration of such key phenomenon may give a more realistic picture of the non-constant disease transmission rates.

Mass administration of ivermectin is assumed to occur instantaneously. However, in reality, there is usually a small delay as mass treatment reaches its maximum coverage. It is important to note that the delays do not affect our results provided the time interval of mass administration of ivermectin is significantly larger than the instantaneous approximation.

The major challenge we faced during this study was the fact that we were unable to obtain data for onchocerciasis treatment. Availability of complete trusted dataset on onchocerciasis epidemic would have aided in estimating the disease parameters and testing possible control measures for future reference. Due to the unavailability of data, obtaining of parameter values was a limitation to the study. We could not obtain data in order to validate our models. In addition, our model did not consider the effect of climatic changes in the transmission and dynamics of onchocerciasis. Therefore, for future work, we suggest the following.

- Use of data to validate the model.

- A model explaining the full dynamics of onchocerciasis in human (hosts).
- The impact of climate change on the transmission dynamics of onchocerciasis disease. This will allow the investigation of the relationship between the spread of onchocerciasis and climate changes.
- A model that includes the classes of individuals who are resistant to the ivermectin.

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Application of optimal control to the onchocerciasis transmission model with treatment

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Abstract In this paper, we present a model for onchocerciasis that considers mass administration of ivermectin, contact prevention controls and vector elimination. The model equilibria are computed and stability analysis carried out in terms of the basic reproduction number R_0 . The model is found to exhibit a backward bifurcation so that for R_0 less than unity is not sufficient to eradicate the disease from the population and the need is to lower R_0 to below a certain threshold, R_0^c for effective disease control. Optimal control theory is applied to investigate optimal control strategies for controlling onchocerciasis using insect repellent and both insecticide and larvicide as system control variables. We use Pontryagin's Maximum Principle to show the necessary conditions for the optimal control of onchocerciasis. Numerical simulations of the model show that restricted and proper use of control measures might considerably decrease the number of infections in the human population.

Keywords Onchocerciasis · ivermectin · backward bifurcation · optimal control · simulations

1 Introduction

Onchocerciasis is a vector-borne parasitic disease. This is a human disease caused by the filarial (thread like) worms *Onchocerca volvulus* in human hosts and is transmitted by the *Simulium damnosum* [38]. It occurs close to oxygen rich flowing streams and rivers in the inter-tropical zones [8]. This is because the egg, larvae and pupa stages of *Simulium damnosum* are aquatic. Studies show that about 90% of onchocerciasis cases occur in Africa and is predominantly found in West Africa. It is also found in six countries in Latin America and in Yemen in the Arabian Peninsula [43]. Onchocerciasis is a serious public health problem. It is a major constraint to social and economic development [5, 16]. It is responsible for ugly skin disease with depigmentation, severe unrelenting itching and blindness [7, 42].

In Sub-Sahara Africa, onchocerciasis remains a major health challenge. In Ghana for instance, 3, 400, 000 in 3204 communities in 66 endemic districts are at risk of acquiring onchocerciasis [25]. Many strategies have been used to eradicate this disease from the population. Mass administration of ivermectin has remained the main strategy in the fight against onchocerciasis. In Sub-Sahara Africa, the struggle to combat onchocerciasis is being led by the African Program of Onchocerciasis Control (APOC). The main control measure for the eradication of onchocerciasis in the countries where the disease is endemic such as Ghana is through community directed treatment with ivermectin. The drugs are distributed by MectizanTM Donation Program (MDP) by Merck and Co., Inc., [6]. Ivermectin is an antimicrofilarial agent that acts as both the primary and secondary form of prevention for individuals with onchocerciasis. It degenerates intrauterine microfilariae thereby suppressing the release of new microfilariae for up to 3-4 months. However, when the drug wanes the adult worm is still possible to continue producing microfilariae until it dies naturally [26]. Ivermectin shows no or, if any, little macrofilaricidal effects and therefore does not kill the adult worms [15]. For successful control of onchocerciasis, repeated treatment with ivermectin spanning for 10-15 years has to be administered so as to correspond to the life span of adult worm.

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One of the purposes of modelling epidemics is to provide a rational basis for policies designed to control the spread of a disease. The inclusion of practical optimal strategies in models allow for the assessment of the intervention of public health authorities. Optimal control is a powerful mathematical tool in decision making that involves employing appropriate strategies to eradicate epidemics from the population [24]. The decisions include determining the proportion of the population that should be treated as time evolves in a given epidemic to minimize both the number of infections in the population and the cost of the treatment strategy implementation. Optimal control has been used to study the dynamics of some diseases such as malaria and West Nile virus [2, 3, 31]. For instance, in [4, 36] optimal control was used to investigate the best strategy for educational campaigns during the outbreak of an epidemic and at the same time minimizing the number of infected humans. It has also been applied in modelling Leukemia [1, 27]. However, to the author's best knowledge, optimal control has not been applied to onchocerciasis disease transmission.

In this paper, we develop a mathematical model for onchocerciasis disease transmission with control strategies. The aim is to gain some insights into the best intervention for minimizing and eventual elimination of onchocerciasis from the population. The intervention strategies we incorporate into the model are, personal protection against black-fly, enhanced treatment and insecticide spraying. Three control functions are used, one for vector reduction, one for human protection and another for the reduction of microfilariae in the body following treatment with ivermectin. We characterize the optimal control problem analytically by applying Pontryagin Maximum Principle. We analyse the model analytically and numerically to find out the threshold conditions under which it is optimal to eradicate the disease from the population

This paper, is organised as follows; in Section 2 we give the formulation of the model and provide the mathematical analysis of the model. The optimal control strategies are introduced in Section 3 and numerical simulation results presented in Section 4. Finally, we present the discussion and concluding remarks in Section 5.

2 Mathematical model

2.1 Model formulation

We consider a habitat with two interacting populations. The two populations are humans (as hosts) and the black-flies (as vectors). The total human population is partitioned into six compartments: the susceptible human compartment; S_H , referring to individuals not infected with onchocerciasis but are at risk of infection, the exposed compartment; E_H , referring to the individuals that have been exposed to onchocerciasis through bites but not infectious, the infectious compartment; I_H , referring to individuals with onchocerciasis infection, the susceptible human on ivermectin treatment compartment; S_T , the exposed human on ivermectin treatment compartment; E_T , and the infectious human on ivermectin treatment compartment; I_T . The black-fly population is partitioned into three compartments: susceptible vector; S_V , referring to black-flies that have never been in contact with infected human and have not picked up microfilariae but are at risk of picking up microfilariae during blood meal from an infected human, the exposed vector compartment; E_V , referring to vector that has picked up microfilariae from an infective human during blood meal but does not transmit the infection and the infective vector compartment; I_V , referring to the vector with the infective L3 larvae stage.

Individuals and the vector move from one compartment to another as their disease status evolve. The total human and vector populations at any given time, t , are respectively given by;

$$N = S_H(t) + E_H(t) + I_H(t) + S_T(t) + E_T(t) + I_T(t) \text{ and } V = S_V(t) + E_V(t) + I_V(t). \quad (1)$$

We assume that the transmission of onchocerciasis in susceptible hosts is only through contact with infectious vector. We also assume that susceptible vector becomes infectious as a result of contact with infectious hosts during blood meal. The population under study is assumed to be large enough to be modelled deterministically. The constant recruitments of new susceptible human and susceptible vector are given by b_1 and b_2 respectively. Assuming β is the black-fly biting rate, that is, the average number of bites per black-fly per unit, the rate of infection per susceptible black-fly can be represented by

$$\lambda_v(t) = \frac{q\beta(I_H + \kappa I_T)}{N}, \quad (2)$$

where q is the transmission probability from infectious human to black-flies and κ is the modification parameter which measures the relative ability of individuals in class I_T to cause new infections relative to those in compartment I_H . We assume here that the individuals under treatment have a slightly lower probability to initiate new infections, thus, $0 \leq \kappa \leq 1$. Assuming that the total number of bites made by black-flies equals to the number of bites received by humans, then the average number of bites per human per unit time is $\frac{\beta V}{N}$. Assuming that the transmission probability per bite from infectious black-flies to human is p , the rate of infection per susceptible human is given by

$$\lambda_h(t) = \frac{p\beta V}{N} \frac{I_V}{V} = \frac{p\beta I_V}{N}. \quad (3)$$

We then introduce $\beta_h = p\beta$ and $\beta_v = q\beta$ parameters to simplify the infection rates per susceptible human and vector respectively. The individuals in class E_H progress to the infectious class I_H at the rate γ . Individuals on ivermectin treatment in class S_T acquire infection at the rate $\delta\lambda_h$. Here, $\delta \in [0, 1]$, defines the reduced effect of infection of the susceptible individuals on ivermectin as a result of treatment. Individuals in class E_T progress to infectious class on ivermectin I_T at the rate $\rho\gamma$, where $\rho \in [0, 1]$ is the reduced effect of progression to class I_T as a result of treatment. The rate of treatments for individuals is given by α . We assume relapse of individuals under treatment due to waning of the drug at the rate φ . We also assume natural mortality rates given by μ_h and μ_v for the human and vector populations respectively.

We further assume that individuals under treatment have no immunity to the disease upon treatment. In addition, we assume that infected vectors and human do not recover from the infection during the modelling time. The dynamics in the human hosts and vector populations is represented in the schematic diagram in Fig. 1.

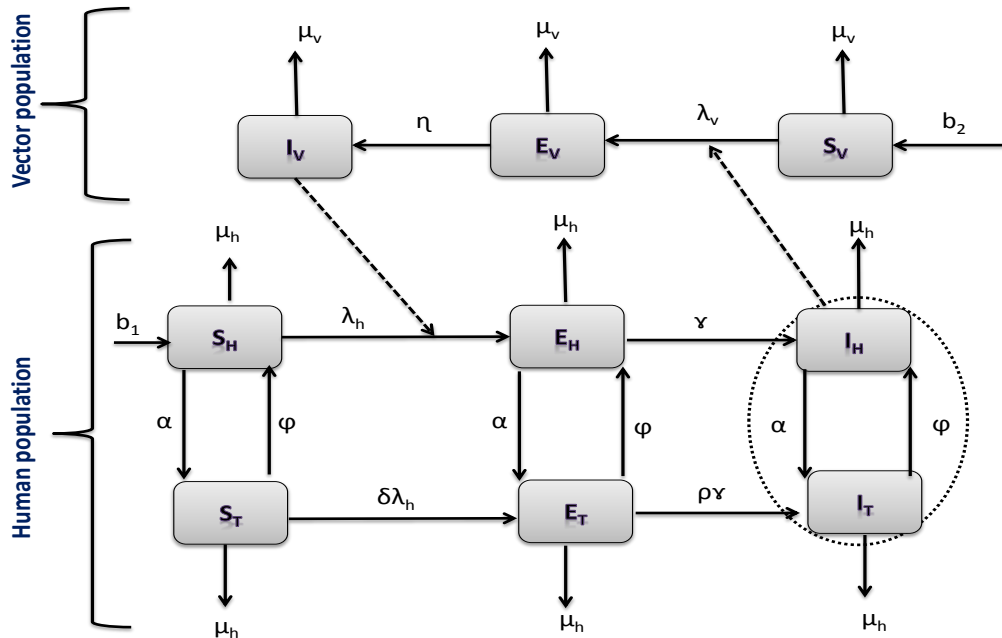


Fig. 1: A compartmental representation of the model for onchocerciasis and its treatment.

2.2 Model equations

Given the dynamics described in Fig. 1, the following system of non-linear ordinary differential equations, with non-negative initial conditions, describes the dynamics of onchocerciasis epidemics.

$$\left. \begin{aligned} \dot{S}_H &= b_1 + \varphi S_T - \lambda_h S_H - (\alpha + \mu_h) S_H, \\ \dot{E}_H &= \lambda_h S_H + \varphi E_T - (\alpha + \gamma + \mu_h) E_H, \\ \dot{I}_H &= \gamma E_H + \varphi I_T - (\alpha + \mu_h) I_H, \\ \dot{S}_T &= \alpha S_H - \delta \lambda_h S_T - (\varphi + \mu_h) S_T, \\ \dot{E}_T &= \alpha E_H + \delta \lambda_h S_T - (\rho \gamma + \varphi + \mu_h) E_T, \\ \dot{I}_T &= \alpha I_H + \rho \gamma E_T - (\varphi + \mu_h) I_T, \\ \dot{S}_V &= b_2 - \lambda_v S_V - \mu_v S_V, \\ \dot{E}_V &= \lambda_v S_V - (\eta + \mu_v) E_V, \\ \dot{I}_V &= \eta E_V - \mu_v I_V, \end{aligned} \right\} \quad (4)$$

subject to the following initial conditions

$$S_H(0) \geq 0, E_H(0) \geq 0, I_H(0) \geq 0, S_T(0) \geq 0, E_T(0) \geq 0, I_T(0) \geq 0, S_V(0) \geq 0, E_V(0) \geq 0, I_V(0) \geq 0. \quad (5)$$

2.3 Model assumptions

1. There is a constant recruitment to the susceptible human population as well as the susceptible black-fly population.
2. Transmission takes place only from infectious black-flies to susceptible humans and from infectious humans to susceptible black-flies.
3. Infected black-flies do not live long enough to recover from infection.
4. human hosts do not have immunity to the disease.
5. The waning of the ivermectin after the mass treatment occurs at the same rate in all the treated classes.

2.4 Model analysis

In this section, we analyse the general properties of the system (4) with positive initial conditions. The system (4) describes the population dynamics both in human and black-fly populations. The system is biologically relevant in the set given by

$$\Omega = \left\{ (S_H, E_H, I_H, S_T, E_T, I_T) \in \mathbb{R}_+^6 : N \leq \frac{b_1}{\mu_h}, \quad (S_V, E_V, I_V) \in \mathbb{R}_+^3 : V \leq \frac{b_2}{\mu_v} \right\}. \quad (6)$$

2.4.1 Positivity of solutions of the model

The system (4) describes the human host and blackflies vector population. It is therefore important to show that all the state variables describing the dynamics of the populations will be non-negative. In particular, we prove that all solutions of the system (4) with non-negative initial conditions will remain non-negative for all $t > 0$. We thus have the following theorem.

Theorem 1 *For non-negative initial conditions of system (4), the solutions $(S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V, I_V)$ of the system (4) are all non-negative for all time $t \geq 0$.*

Proof For the equations in our system, let us take t^* as the maximum time for the epidemics. This implies that;

$$t^* = \sup\{t > 0 : S_H > 0, E_H > 0, I_H > 0, S_T > 0, E_T > 0, I_T > 0, S_V > 0, E_V > 0, I_V > 0\}.$$

Thus, $t^* \geq 0$. Then, from the first equation of the system (4), we obtain

$$\begin{aligned} \dot{S}_H &= b_1 + \varphi S_T - \lambda_h S_H - (\alpha + \mu_h) S_H \geq -(\lambda_h + (\alpha + \mu_h)) S_H, \\ S_H(t^*) &\geq S_H(0) \exp \left\{ - \left(\int_0^{t^*} \lambda_h(m) dm + (\alpha + \mu_h) t^* \right) \right\}. \end{aligned}$$

This implies that $S_H(t^*) \geq 0$ for all time $t \geq 0$. Similarly, from the seventh equation of the system (4), we have

$$\dot{S}_V = b_2 - \lambda_v S_V - \mu_v S_V = b_2 - (\lambda_v + \mu_v) S_V. \quad (7)$$

Equation (7) can be written as

$$\frac{d}{dt} \left(S_V \exp \left\{ \int_0^t \lambda_v(u) du + \mu_v t \right\} \right) = b_2 \exp \left\{ \int_0^t \lambda_v(u) du + \mu_v t \right\},$$

Integrating both sides from $t = 0$ to $t = t^*$, we obtain

$$S_V(t^*) \exp \left\{ \int_0^{t^*} \lambda_v(u) du + \mu_v t^* \right\} - S_V(0) = \int_0^{t^*} b_2 \exp \left\{ \int_0^x \lambda_v(x) dx + \mu_v y \right\} dy,$$

then multiplying both sides by $\exp \left\{ - \int_0^{t^*} \lambda_v(u) du - \mu_v t^* \right\}$, we have

$$\begin{aligned} S_V(t^*) &= S_V(0) \exp \left\{ - \int_0^{t^*} \lambda_v(u) du - \mu_v t^* \right\} + \exp \left\{ - \int_0^{t^*} \lambda_v(u) du - \mu_v t^* \right\} \\ &\quad \times \int_0^{t^*} b_2 \exp \left\{ \int_0^x \lambda_v(x) dx + \mu_v y \right\} dy > 0. \end{aligned}$$

Hence, $S_V(t^*) \geq 0$ for all $t^* \geq 0$. Therefore, $S_H(t^*)$ and $S_V(t^*)$ being the sum of positive terms are all positive. Using the same argument, it can be shown that the quantities $E_H, I_H, S_T, E_T, I_T, E_V$, and I_V are positive for all $t > 0$. Thus the solutions of (4) remain positive for all $t \geq 0$.

2.4.2 Invariant region

Lemma 1 Let $(S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V, I_V)$ be the solutions of the system (4) with initial conditions given in (5) and the biological feasible region given by the set $\Omega = \Omega_H \times \Omega_V$ where

$$\Omega_H = \left\{ (S_H, E_H, I_H, S_T, E_T, I_T) \in \mathbb{R}_+^6 : N \leq \frac{b_1}{\mu_h} \right\}, \quad \Omega_V = \left\{ (S_V, E_V, I_V) \in \mathbb{R}_+^3 : V \leq \frac{b_2}{\mu_v} \right\}.$$

Proof Adding the equations in the system (4) gives

$$\dot{N} = b_1 - \mu_h N, \quad \dot{V} = b_2 - \mu_v V. \quad (8)$$

It can then be shown that

$$\limsup_{t \rightarrow \infty} N \leq \frac{b_1}{\mu_h} \quad \text{and} \quad \limsup_{t \rightarrow \infty} V \leq \frac{b_2}{\mu_v}. \quad (9)$$

Hence, the set Ω is positively invariant, that is, all the solutions in Ω remain in Ω for $t > 0$. We thus conclude that Ω is an attracting set.

Therefore every solution of the system (4), with initial condition in Ω remains there for $t > 0$. In addition, in Ω , the usual existence, uniqueness and continuation results hold for the system. The system (4) is thus both mathematically and epidemiologically well-posed in the region Ω . Hence, it is sufficient to study the dynamics of the flow generated by the system (4) in Ω . The right hand side of the system (4) is locally Lipschitz continuous implying that the local existence and uniqueness of solutions is ascertained.

2.5 Existence and stability of the equilibrium points

2.5.1 Disease-free equilibrium

The disease-free equilibrium (DFE) points are steady state solutions that depict the absence of infection in both the human host and black-fly vector populations, i.e, onchocerciasis does not exist in the population. This implies that at onchocerciasis-free equilibrium (E_0), $E_H = I_H = E_T = I_T = E_V = I_V = 0$. Solving the first, fourth and seventh equations of the system (4) we obtain

$$E_0 = \left(\frac{b_1}{Q_1(1-\Phi_1)}, 0, 0, \frac{b_1\alpha}{Q_1Q_3(1-\Phi_1)}, 0, 0, \frac{b_2}{\mu_v}, 0, 0 \right), \quad (10)$$

where

$$Q_1 = \alpha + \mu_h, \quad Q_2 = \alpha + \gamma + \mu_h, \quad Q_3 = \varphi + \mu_h, \quad Q_4 = \rho\gamma + \varphi + \mu_h, \quad Q_5 = \eta + \mu_v, \quad \Phi_1 = \frac{\varphi\alpha}{Q_1Q_3}.$$

2.5.2 Basic reproduction number

The basic reproduction number is defined as the average number of secondary cases of human/vector onchocerciasis infections generated by a typical infected human/vector in an otherwise disease free population [9]. The basic reproduction number (R_0) of our system (4) is computed using the next generation matrix method and is given by

$$R_0 = \sqrt{\mathcal{R}_0} = \sqrt{R_0^h R_0^v}, \quad (11)$$

where

$$R_0^h = \frac{\beta_h \gamma \mu_h^2 (\Phi_3 + \alpha \delta (\alpha \kappa \varphi + Q_2 \rho (Q_1 \kappa + \varphi)))}{b_1 Q_1^2 Q_2 Q_3^2 Q_4 (1 - \Phi_1)^2 (1 - \Phi_2)}, \quad R_0^v = \frac{b_2 \beta_v \eta}{Q_5 \mu_v^2}, \quad \Phi_2 = \frac{\alpha \varphi}{Q_2 Q_4},$$

$$\Phi_3 = Q_3 [\alpha \varphi (\delta + \rho) + Q_1 \alpha \kappa \rho + Q_4 (Q_3 + \alpha \kappa)].$$

The basic reproduction number R_0 , determines whether onchocerciasis dies out or persists in the population. The square root in (11) agrees with the findings of [22]. Note that R_0^v is the contribution of the vector population to the overall infection while R_0^h is the contribution of the human population. The following theorem follows directly from [9].

Theorem 2 *The disease-free equilibrium of the system (4) exists and is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable otherwise.*

2.6 Existence of the disease persistent steady states

Let $S_H^*, E_H^*, I_H^*, S_T^*, E_T^*, I_T^*, S_V^*, E_V^*, I_V^*$ be non-trivial the solutions to the endemic equilibrium points. Setting all the equations of the system (4) to zero and expressing the state variables in terms of the forces of infections λ_h and λ_v , we have

$$\left. \begin{aligned} S_H^* &= \frac{b_1(Q_3 + \delta\lambda_h^*)}{Q_1Q_3(1-\Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*)}, \\ E_H^* &= \frac{b_1\lambda_h^*(\alpha\delta\varphi + Q_4(Q_3 + \delta\lambda_h^*))}{Q_2Q_4(1-\Phi_2)(Q_1Q_3(1-\Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*))}, \\ I_H^* &= \frac{\gamma b_1\lambda_h^*(\delta\lambda_h^*(\alpha\rho\varphi + Q_3Q_4) + Q_2\alpha\delta\rho\varphi + Q_3(\alpha\varphi(\delta + \rho) + Q_3Q_4))}{Q_1Q_2Q_3Q_4(1-\Phi_1)(1-\Phi_2)(Q_1Q_3(1-\Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*))}, \\ S_T^* &= \frac{\alpha b_1}{Q_1Q_3(1-\Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*)}, \\ E_T^* &= \frac{\alpha b_1\lambda_h^*(Q_3 + \delta(Q_2 + \lambda_h^*))}{Q_2Q_4(1-\Phi_2)(Q_1Q_3(1-\Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*))}, \\ I_T^* &= \frac{\alpha b_1\gamma\lambda_h^*(\alpha\delta\varphi + Q_4(\delta\lambda_h^* + Q_3) + \rho Q_1(\delta(\lambda_h^* + Q_2) + Q_3))}{Q_1Q_2Q_3Q_4(1-\Phi_1)(1-\Phi_2)(Q_1Q_3(1-\Phi_1) + \lambda_h^*(Q_1\delta + Q_3 + \delta\lambda_h^*))}, \\ S_V^* &= \frac{b_2}{\lambda_v^* + \mu_v}, \quad E_V^* = \frac{b_2\lambda_v^*}{Q_5(\lambda_v^* + \mu_v)}, \quad I_V^* = \frac{b_2\eta\lambda_v^*}{Q_5\mu_v(\lambda_v^* + \mu_v)}. \end{aligned} \right\} \quad (12)$$

From the results in (12), we have the following two cases describing the existence of the steady states;

Case 1: $\lambda_h^* = \lambda_v^* = 0$.

This corresponds to the disease-free state treated in (10), where there is no infection in the population.

Case 2: $\lambda_h^* \neq \lambda_v^* \neq 0$.

This is the scenario in which there is infection in both the population (hosts and vector populations). We describe this state using the following denotation.

$$E_1 = (S_H^*, E_H^*, I_H^*, S_T^*, E_T^*, I_T^*, S_V^*, E_V^*, I_V^*).$$

Substituting the expressions for the state variables I_V^* , I_H^* and I_T^* in (12) into the expressions for the forces of infection in (2) and (3) then simplifying we obtain the following polynomial.

$$\Psi_2 \lambda_h^{*2} + \Psi_1 \lambda_h^* + \Psi_0 = 0, \quad (13)$$

where

$$\begin{aligned} \Psi_2 &= Q_5 b_1 \delta \mu_v [Q_1 Q_2 Q_3 Q_4 \mu_v (1 - \Phi_1)(1 - \Phi_2) + \beta_v \mu_h \gamma (\alpha \rho (\kappa Q_1 + \varphi) + Q_4 (\alpha \kappa + Q_3))], \\ \Psi_1 &= -[b_2 \gamma \delta \eta \beta_h \mu_h^2 \beta_v (\alpha \rho (\kappa Q_1 + \varphi) + Q_4 (\alpha \kappa + Q_3)) - b_1 Q_5 \mu_v (\gamma \mu_h \beta_v (\alpha^2 \delta \kappa \varphi + \alpha \delta \rho Q_2 (\kappa Q_1 + \varphi) \\ &\quad + Q_3 (\alpha \varphi (\delta + \rho) + \alpha \kappa \rho Q_1 + Q_4 (\alpha \kappa + Q_3))) + Q_1 Q_2 Q_3 Q_4 (1 - \Phi_1)(1 - \Phi_2) (\delta Q_1 + Q_3) \mu_v], \\ \Psi_0 &= b_1 Q_1^2 Q_2 Q_3^2 Q_4 Q_5 \mu_v^2 (1 - \Phi_1)^2 (1 - \Phi_2) [1 - \mathcal{R}_0]. \end{aligned}$$

The existence and the number of endemic equilibria for the system (4) is determined by the existence of, and the number of positive roots of the quadratic equation given in (13). The roots to the quadratic equation (13) can be obtained by the quadratic formula given by

$$(\lambda_h^*)_{1,2} = \frac{-\Psi_1 \pm \sqrt{\Psi_1^2 - 4\Psi_2\Psi_0}}{2\Psi_2}. \quad (14)$$

We note that $\Psi_0 > 0$ if $\mathcal{R}_0 < 1$, $\Psi_0 = 0$ if $\mathcal{R}_0 = 1$ and $\Psi_0 < 0$ if $\mathcal{R}_0 > 1$. If $\Psi_0 < 0$, then $\Delta = \Psi_1^2 - 4\Psi_2\Psi_0 > 0$ and equation (13) has a unique positive solution hence the model system (4) has a unique endemic equilibrium. If $\mathcal{R}_0 < 1$ then $\Psi_0 > 0$ and by adding the conditions $\Psi_1 < 0$ and $\Delta > 0$, we get two positive real equilibria. If $\mathcal{R}_0 = 1$, then $\Psi_0 = 0$ and there is a unique non-zero solution of (13) which is positive if and only if $\Psi_1 < 0$. The following theorem summarizes the existence of the endemic equilibria of the system (4).

Theorem 3 *The system (4)*

1. has no endemic equilibrium if $\mathcal{R}_0 < \mathcal{R}_0^c$ where \mathcal{R}_0^c is referred to as critical \mathcal{R}_0 .
2. has a unique endemic equilibrium in Ω if $\mathcal{R}_0 > 1$.
3. has two endemic equilibria for some parameter values of $\mathcal{R}_0^c < \mathcal{R}_0 < 1$. In this range, one endemic equilibrium and the disease-free equilibrium are locally stable.
4. has one positive equilibrium for $\mathcal{R}_0 = 1$ provided $\Psi_1 < 0$ and $\Delta > 0$, otherwise there is no positive equilibrium.
5. has no endemic equilibrium otherwise.

Proposition 1 *The system (4) has a backward bifurcation at $\mathcal{R}_0 = 1$ if and only if $\Psi_1 < 0$ and $\Delta > 0$.*

Epidemiologically, proposition 1 implies that bringing \mathcal{R}_0 below unity does not suffice for the eradication of onchocerciasis. From the analysis of the existence of the endemic equilibrium, we have established that the system (4) exhibits backward bifurcation when $\mathcal{R}_0 < 1$. The existence of backward bifurcation indicates that in the neighbourhood of 1, for $\mathcal{R}_0 < 1$, a stable disease-free equilibrium coexists with two endemic equilibria, that is, a smaller equilibrium (smaller number of infectious individuals) which is unstable and a larger equilibrium (with a larger number of infectious individuals) which is stable. These two endemic equilibria disappear by saddle-node bifurcation when the basic reproduction \mathcal{R}_0 is decreased below the critical value \mathcal{R}_0^c . In order to achieve an epidemiological goal of disease eradication, \mathcal{R}_0 must be brought below the critical value \mathcal{R}_0^c . To obtain the critical value \mathcal{R}_0^c , we set the discriminant Δ of the polynomial (13) to zero and make \mathcal{R}_0 the subject of the relation. Thus, we have

$$\mathcal{R}_0^c = 1 - \frac{\Psi_1^2}{4\Psi_2 [b_1 Q_1^2 Q_2 Q_3^2 Q_4 Q_5 \mu_v^2 (1 - \Phi_1)^2 (1 - \Phi_2)]}. \quad (15)$$

2.7 Bifurcation analysis

This is a qualitative change in the behaviour of a dynamical system produced by varying a parameter in the equation [29]. Backward bifurcation is an important phenomenon in compartmental epidemiological models. This phenomenon has been observed in numerous disease transmission models [10, 13, 18, 40]. Wang [40] studied backward bifurcation of an epidemic model with treatment. He demonstrated that his model exhibits backward bifurcation behaviour. The existence of such a bifurcation suggests that the basic reproduction number itself is not enough to characterize or decide whether onchocerciasis will prevail or not and if the disease will become endemic also depends on the initial sizes of the involved population. Thus, it is important to identify the backward bifurcations and establish the threshold for that bifurcation. We carry out bifurcation analysis to study the behaviour of the system (4) based on the results in (13) through numerical simulation over chosen parameter values. It is important to note that the existence of bi-stability is not easy to simulate numerically. This is because a small interval of \mathcal{R}_0 is required for the occurrence of backward bifurcation and very small range of parameters has to be chosen. The qualitative backward bifurcation diagram describing the behaviour of $\mathcal{R}_0 = 1$ is presented in Figure 2 where β_h is taken as the bifurcation parameter. The result indicates that in the backward bifurcation, if \mathcal{R}_0 is below unity then the disease control depends on the initial sizes of the various sub-populations of the system (4). However, reducing \mathcal{R}_0 below the saddle-node bifurcation value \mathcal{R}_0^c , may result in disease eradication. This is guaranteed provided that the disease-free equilibrium is globally asymptotically stable. Figure 3 is obtained after increasing the rate of mass administration of ivermectin to 1. The biological interpretation of this is that increasing treatment can lead to disappearance of backward bifurcation curve and in this case lowering \mathcal{R}_0 below one is sufficient to eliminate the disease from the population. So when the rate of mass treatment is high enough we will have a forward bifurcation and lowering \mathcal{R}_0 below unity would be sufficient to make the disease-free equilibrium globally stable.

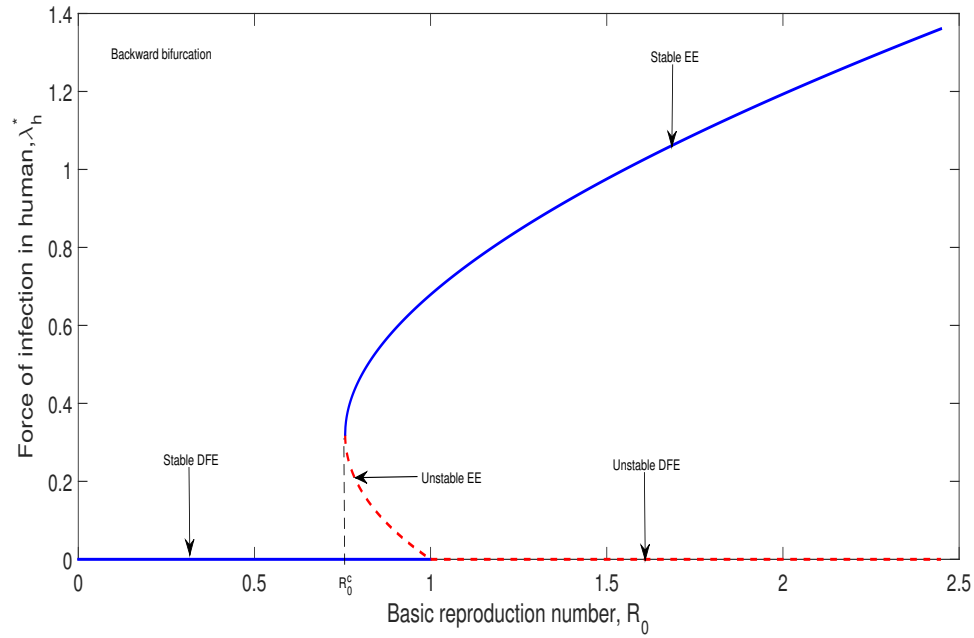


Fig. 2: Variation of the equilibrium level of λ_h^* with β_h showing the backward bifurcation of the system (4). We considered $b_1 = 10, b_2 = 50, \mu_h = 0.000150, \gamma = 0.0097, \beta_v = 0.000127, \mu_v = 0.09800, \eta = 0.0884, \varphi = 0.002, \alpha = 0.40, \kappa = 0.005, \delta = 0.0025, \rho = 0.0013$.

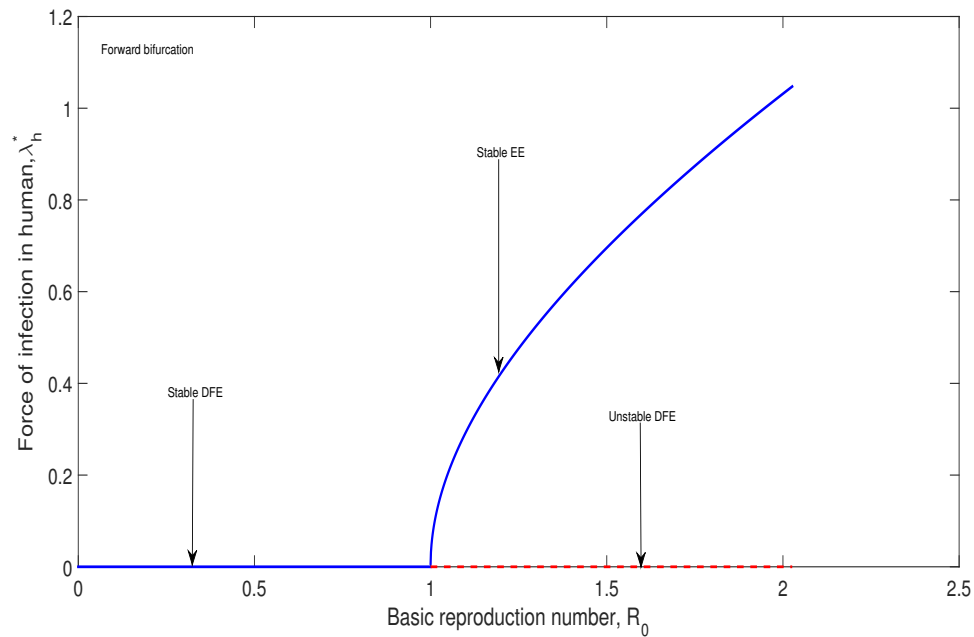


Fig. 3: Description of forward bifurcation of the system (4) for parameter values $\kappa = 0.020, \alpha = 1$ and all other parameters as used in Figure 2.

2.8 Global stability of the disease-free equilibrium

Since the system (4) has two endemic equilibria when $R_0 < \mathcal{R}_0^c$, it implies that the disease-free equilibrium is globally stable if and only if $\mathcal{R}_0 < \mathcal{R}_0^c$. We therefore establish the global stability of the disease-free equilibrium, E_0 using a Lyapunov function for $\mathcal{R}_0 < \mathcal{R}_0^c$.

Theorem 4 *The disease-free equilibrium E_0 of system (4) is globally asymptotically stable if $\mathcal{R}_0 < \mathcal{R}_0^c$ and unstable otherwise.*

Proof Let $L(E_H, I_H, E_T, I_T, E_V, I_V) = \Phi_4 E_H + \Phi_5 I_H + \Phi_6 E_T + \Phi_7 I_T + \Phi_8 E_V + \Phi_9 I_V$, be a candidate Lyapunov function for some non-negative values of $\Phi_4, \Phi_5, \Phi_6, \Phi_7, \Phi_8$ and Φ_9 . The time derivative of L is given by;

$$\begin{aligned} \dot{L} &= \Phi_4 \dot{E}_H + \Phi_5 \dot{I}_H + \Phi_6 \dot{E}_T + \Phi_7 \dot{I}_T + \Phi_8 \dot{E}_V + \Phi_9 \dot{I}_V, \\ &= \Phi_4 \left(\frac{\beta_h I_V S_H}{N} + \varphi E_T - Q_2 E_H \right) + \Phi_5 (\gamma E_H + \varphi I_T - Q_1 I_H) + \Phi_6 \left(\alpha E_H + \frac{\delta \beta_h I_V S_T}{N} - Q_4 E_T \right) \\ &\quad + \Phi_7 (\alpha I_H + \rho \gamma E_T - Q_3 I_T) + \Phi_8 \left(\frac{\beta_v I_H S_V}{N} + \frac{\kappa \beta_v I_T S_V}{N} - Q_5 E_V \right) + \Phi_9 (\eta E_V - \mu_v I_V), \\ &= (\Phi_5 \gamma + \Phi_6 \alpha - \Phi_4 Q_2) E_H + \left(\Phi_7 \alpha + \Phi_8 \frac{\beta_v b_2 \mu_h}{\mu_v b_1} - \Phi_5 Q_1 \right) I_H + (\Phi_4 \varphi + \Phi_7 \rho \gamma - \Phi_6 Q_4) E_T \\ &\quad + \left(\Phi_5 \varphi + \Phi_8 \frac{\kappa \beta_v b_2 \mu_h}{\mu_v b_1} - \Phi_7 Q_3 \right) I_T + (\Phi_9 \eta - \Phi_8 Q_5) E_V \\ &\quad + \left(\Phi_4 \frac{\beta_h \mu_h}{Q_1 (1 - \Phi_1)} + \Phi_6 \frac{\beta_h \delta \alpha \mu_h}{Q_1 Q_3 (1 - \Phi_1)} - \Phi_9 \mu_v \right) I_V. \end{aligned}$$

Evaluating the coefficients of the suitable Lyapunov function such that the coefficients of I_H, E_T, I_T, E_V , and I_V are equal to zero we obtain

$$\begin{aligned} \Phi_4 &= \frac{Q_1^2 Q_3^2 b_1 (1 - \Phi_1)^2 Q_4 Q_5 \mu_v^2 - \beta_h \beta_v \mu_h^2 b_2 \eta \gamma \alpha \delta \rho (Q_1 \kappa + \varphi)}{Q_1 Q_3 \beta_h b_1 \mu_h \mu_v (1 - \Phi_1) (Q_3 Q_4 + \alpha \varphi \delta)}, & \Phi_5 &= \frac{\beta_v \mu_h b_2 \eta (Q_3 + \alpha \kappa)}{Q_1 Q_3 b_1 \mu_v (1 - \Phi_1)}, \\ \Phi_6 &= \frac{Q_1^2 Q_3^2 (1 - \Phi_1)^2 Q_5 b_1 \mu_v^2 \varphi - Q_3 \beta_h \beta_v b_2 \eta \gamma \rho (Q_1 \kappa + \varphi)}{Q_1 Q_3 \beta_h b_1 \mu_h \mu_v (1 - \Phi_1) (Q_3 Q_4 + \alpha \varphi \delta)}, & \Phi_7 &= \frac{\beta_v \mu_h b_2 \eta (\varphi + Q_1 \kappa)}{Q_1 Q_3 b_1 \mu_v (1 - \Phi_1)}, \\ \Phi_8 &= \eta, & \Phi_9 &= Q_5. \end{aligned}$$

Using these coefficients, the time derivative of the Lyapunov function is given by

$$\dot{L} = \left(\frac{Q_1 Q_2 Q_3 Q_4 Q_5 \mu_v (1 - \Phi_1) (1 - \Phi_2)}{\beta_h \mu_h (Q_3 Q_4 + \alpha \varphi \delta)} \right) [\mathcal{R}_0 - 1] E_H < 0, \quad (16)$$

It follows that $\dot{L} < 0$ for $\mathcal{R}_0 < \mathcal{R}_0^c$ and $\dot{L} = 0$ if and only if $I_H = E_T = I_T = E_V = I_V = 0$. Therefore, L is a Lyapunov function in $\Omega = (S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V, I_V)$. Since, Ω is invariant and attracting, it follows that the largest possible invariant set in $\{(S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V, I_V) \in \Omega : \dot{L} = 0\}$, is the singleton $\{E_f^0\}$. According to La-Salle's invariance principle [19], E_0 is globally attractive. Therefore, the disease-free equilibrium E_0 is globally asymptotically stable when $\mathcal{R}_0 < \mathcal{R}_0^c$. This completes the proof.

In the case of the occurrence of a backward bifurcation in the system (4), the above result shows that in order to eliminate onchocerciasis, the basic reproduction \mathcal{R}_0 must be lower than the threshold \mathcal{R}_0^c which is strictly less than unity.

3 Application of optimal control

3.1 Formulation of optimal control

In this section, we formulate a model framework that minimizes onchocerciasis infection in the human population. In the system (4), the recruitment rates in each susceptible population is modified to include the density effects. Thus, the density dependent factors for the recruitment rates are $b_1(N)$ for the host population and $b_2(V)$ for the vector population. Personal protection efforts through wearing insect repellents

such as N,N-Diethyl-meta-toluamide (DEET) on exposed skin, wearing long sleeves and long pants during the day when black-flies bite, and wearing permethrin-treated clothing minimizes or eliminates black-fly-human contacts [32]. Insecticide spraying with larvicide and adulticide ensures that the breeding sites of the black-flies are minimized. We thus define some linear control functions $u_i(t)$ such that $u_i(t) = 1, i = 1, 2, 3$. It is important to note that controls are fully effective when $u_i(t) = 1$ and not effective control when $u_i(t) = 0$. The forces of infection λ_h and λ_v corresponding to human population and vector population respectively are reduced by factor $(1 - u_1)$, where $u_1(t)$ measures the level of successful exposure prevention efforts. The control $u_1(t)$ represents the use of alternative prevention measures to minimize or eliminate the black-fly-human contacts. Such measures include the use of insect repellents, wearing protective coats and long sleeves and wearing permethrin-treated clothing amongst other. The mass administration of ivermectin as a control is modelled by u_2 . The factor u_2 can be viewed as the coverage of ivermectin. The factor $u_3(t)$, represents the level of larvicide and adulticide use for the elimination of black-flies from the breeding sites. This implies that the reproduction rate of the black-fly population is reduced by a factor of $(1 - u_3(t))$. We assume that, larvicidal spraying increases the mortality rate of the black-flies at a rate proportional to the control factor $u_3(t)$. It is further assumed that the per capita mortality rate of the vector is $r_0 u_3(t)$, where $0 \leq r_0 \leq 1$ is the proportion of effective adulticide spraying. Taking into account the assumptions and extensions made above, we therefore find the most effective strategy that reduces the onchocerciasis infection in the population at a minimum cost. Using bounded lebesgue measurable control, the objective functional to be minimized is given by

$$J(u_1, u_2, u_3) = \int_0^T (A_1 E_H + A_2 I_H + A_3 V + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2)) dt \quad (17)$$

subject to the state system given in (4). The dynamics of the control that minimizes the objective functional $J(u_1, u_2, u_3)$ is given by

$$\left. \begin{aligned} \dot{S}_H &= b_1 N + \varphi S_T - \lambda_h S_H (1 - u_1) - (u_2 \alpha + \mu_h) S_H, \\ \dot{E}_H &= \lambda_h S_H (1 - u_1) + \varphi E_T - (u_2 \alpha + \gamma + \mu_h) E_H, \\ \dot{I}_H &= \gamma E_H + \varphi I_T - (u_2 \alpha + \mu_h) I_H, \\ \dot{S}_T &= u_2 \alpha S_H - \delta \lambda_h S_T (1 - u_1) - (\varphi + \mu_h) S_T, \\ \dot{E}_T &= u_2 \alpha E_H + \delta \lambda_h S_T (1 - u_1) - (\rho \gamma + \varphi + \mu_h) E_T, \\ \dot{I}_T &= u_2 \alpha I_H + \delta \gamma E_T - (\varphi + \mu_h) I_T, \\ \dot{S}_V &= b_2 V (1 - u_3) - \lambda_v S_V (1 - u_1) - \mu_v S_V - r_0 u_3 S_V, \\ \dot{E}_V &= \lambda_v S_V (1 - u_1) - (\eta + \mu_v) E_V - r_0 u_3 E_V, \\ \dot{I}_V &= \eta E_V - \mu_v I_V - r_0 u_3 I_V, \end{aligned} \right\} \quad (18)$$

with the following initial conditions

$$S_H(0) \geq 0, E_H(0) \geq 0, I_H(0) \geq 0, S_T(0) \geq 0, E_T(0) \geq 0, I_T(0) \geq 0, S_V(0) \geq 0, E_V(0) \geq 0, I_V(0) \geq 0. \quad (19)$$

We endeavour to minimize the exposed and infectious human populations (E_H, I_H), the black-fly population and the cost of implementing the control by use of possible minimum variables $u_i, i = 1, 2, 3$. This functional includes the number of exposed, infectious and the total number of black-fly populations, respectively, as well as the social costs related to the resources needed for personal protection $\frac{1}{2} B_1 u_1^2$, the coverage of ivermectin $\frac{1}{2} B_2 u_2^2$ and spraying of larvicide and adulticide operations $\frac{1}{2} B_3 u_3^2$. This implies that we are minimizing the number of exposed, infectious human and susceptible, exposed and infectious black-fly populations as well as the cost based on the implementation of the control functions. The quantities A_1 and A_2 represent the cost associated with minimizing the exposed and infected human population respectively while A_3 represent the cost associated with minimizing total black-fly population. The quantity T is the time period of intervention. The quantities B_1, B_2 and B_3 represent the weight constants for personal protection, the coverage of ivermectin and spraying of larvicide and adulticide operations. According to [17, 31] the costs associated with $A_1 E_H, A_2 I_H$ and $A_3 V$ are linear while the cost control functions $\frac{1}{2} B_1 u_1^2, \frac{1}{2} B_2 u_2^2$ and $\frac{1}{2} B_3 u_3^2$ should be non-linear and take the quadratic form. We assume that the costs of implementation of the control policies are proportional to the square of the corresponding control function. We seek to minimize

the objective functional over the given time interval $[0, T]$. In particular, the aim of the optimal control problem is to seek optimal control functions $(u_1^*(t), u_2^*(t), u_3^*(t))$ such that

$$J(u_1^*, u_2^*, u_3^*(t)) = \min_{\mathbf{U}} J(u_1, u_2, u_3), \quad (20)$$

where $\mathbf{U} = \{u_1, u_2, u_3 | 0 \leq u_i(t) \leq 1, i = 1, 2, 3\}$ is the control set and is Lebesgue measurable. Pontryagin's Maximum Principle is used to solve this optimal control problem and the derivation of the necessary conditions. First we prove the existence of an optimal control for the system (18) and then derive the optimality system.

3.2 Existence of control problem

In order to find the optimal solution, we first find the Lagrangian and Hamiltonian for the optimal control problem (17) and (18). The Lagrangian of the optimal control problem is given by

$$L = A_1 E_H + A_2 I_H + A_3 V + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2). \quad (21)$$

We seek for the Lagrangian minimum value. In order to accomplish this, we define the Hamiltonian, H for the control problem. This is given by

$$\left. \begin{aligned} H &= L(E_H, I_H, V, u_1, u_2, u_3) + \lambda_1 \dot{S}_H + \lambda_2 \dot{E}_H + \lambda_3 \dot{I}_H + \lambda_4 \dot{S}_T + \lambda_5 \dot{E}_T + \lambda_6 \dot{I}_T + \lambda_7 \dot{S}_V + \lambda_8 \dot{E}_V + \lambda_9 \dot{I}_V, \\ &= A_1 E_H + A_2 I_H + A_3 V + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2) \\ &\quad + \lambda_1 [b_1 N + \varphi S_T - \lambda_h S_H (1 - u_1) - (u_2 \alpha + \mu_h) S_H] \\ &\quad + \lambda_2 [\lambda_h S_H (1 - u_1) + \varphi E_T - (u_2 \alpha + \gamma + \mu_h) E_H] + \lambda_3 [\gamma E_H + \varphi I_T - (u_2 \alpha + \mu_h) I_H] \\ &\quad + \lambda_4 [u_2 \alpha S_H - \delta \lambda_h S_T (1 - u_1) - (\varphi + \mu_h) S_T] + \lambda_5 [u_2 \alpha E_H + \delta \lambda_h S_T (1 - u_1) - (\rho \gamma + \varphi + \mu_h) E_T] \\ &\quad + \lambda_6 [u_2 \alpha I_H + \delta \gamma E_T - (\varphi + \mu_h) I_T] + \lambda_7 [b_2 N_V (1 - u_3) - \lambda_v S_V (1 - u_1) - \mu_v S_V - r_0 u_3 S_V] \\ &\quad + \lambda_8 [\lambda_v S_V (1 - u_1) - (\eta + \mu_v) E_V - r_0 u_3 E_V] + \lambda_9 [\eta E_V - \mu_v I_V - r_0 u_3 I_V]. \end{aligned} \right\} \quad (22)$$

Theorem 5 *There exists an optimal control $u^* = (u_1^*, u_2^*, u_3^*) \in \mathbf{U}$ such that*

$$J(u_1^*, u_2^*, u_3^*) = \min_{(u_1, u_2, u_3) \in \mathbf{U}} J(u_1, u_2, u_3), \quad (23)$$

subject to the control system (18) with the initial conditions (19).

Proof We prove the existence of the optimal problem following the results in [12, 23]. It is clear that the system of equations given by (18) is bounded and the state variables are non-negative. In this minimizing problem, the control set \mathbf{U} is convex and closed by definition. The optimal system is bounded which determines the compactness needed for the existence of the optimal control. The integrand in the objective functional, $A_1 E_H + A_2 I_H + A_3 V + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2)$, is clearly convex on the control set \mathbf{U} . Moreover, we can easily see that, there exists, $\beta > 1$ and positive numbers c_1, c_2 satisfying

$$J(u_1, u_2, u_3) \geq c_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{\beta}{2}} - c_2, \quad (24)$$

because, the state variables are bounded. This completes the proof.

3.3 Optimality of the system

In order to find the optimal solution, we employ Pontryagin's Maximum Principle [34] to the Hamiltonian (22), such that if (x, u) is an optimal solution of an optimal control problem, then there exists a non-trivial vector $\lambda = (\lambda_1, \lambda_2, \dots, \lambda_n)$ satisfying the following inequalities.

$$\frac{dx}{dt} = \frac{\partial H(t, x, u, \lambda)}{\partial \lambda}, \quad 0 = \frac{\partial H(t, x, u, \lambda)}{\partial u}, \quad \lambda' = -\frac{\partial H(t, x, u, \lambda)}{\partial x}. \quad (25)$$

We, now derive the necessary conditions to the Hamiltonian in (22) that optimal control functions and corresponding states must satisfy.

Theorem 6 Let $S_H^*, E_H^*, I_H^*, S_T^*, E_T^*, I_T^*, S_V^*, E_V^*$ and I_V^* be the solutions of the corresponding optimal control problem (17)-(18) associated with the optimal control variables (u_1^*, u_2^*, u_3^*) . Then, there exists adjoint variables $\lambda_i, i = 1, 2, \dots, 9$ satisfying

$$\left. \begin{aligned} \frac{d\lambda_1(t)}{dt} &= \frac{\beta_h}{N}(\lambda_1 - \lambda_2)(1 - u_1)I_V + (\lambda_1 - \lambda_4)u_2\alpha + \lambda_1\mu_h, \\ \frac{d\lambda_2(t)}{dt} &= (\lambda_2 - \lambda_3)\gamma + (\lambda_2 - \lambda_5)u_2\alpha + \lambda_2\mu_h - A_1, \\ \frac{d\lambda_3(t)}{dt} &= (\lambda_3 - \lambda_6)u_2\alpha + \frac{\beta_v}{N}(\lambda_7 - \lambda_8)(1 - u_1)S_V + \lambda_3\mu_h - A_2, \\ \frac{d\lambda_4(t)}{dt} &= \frac{\delta\beta_h}{N}(\lambda_4 - \lambda_5)I_V(1 - u_1) + (\lambda_4 - \lambda_1)\varphi + \lambda_4\mu_h, \\ \frac{d\lambda_5(t)}{dt} &= (\lambda_5 - \lambda_2)\varphi + (\lambda_5 - \lambda_6)\rho\gamma + \lambda_5\mu_h, \\ \frac{d\lambda_6(t)}{dt} &= (\lambda_6 - \lambda_3)\varphi + \lambda_6\mu_h + \frac{\beta_v\kappa}{N}(\lambda_7 - \lambda_8)S_V(1 - u_1), \\ \frac{d\lambda_7(t)}{dt} &= -b_2\lambda_7(1 - u_3) + \frac{\beta_v}{N}(\lambda_7 - \lambda_8)(1 - u_1)(I_H + \kappa I_T) + \lambda_7\mu_v + \lambda_7r_0u_3 - A_3, \\ \frac{d\lambda_8(t)}{dt} &= -b_2\lambda_7(1 - u_3) + (\lambda_8 - \lambda_9)\eta + \lambda_8\mu_v + \lambda_8r_0u_3 - A_3, \\ \frac{d\lambda_9(t)}{dt} &= -b_2\lambda_7(1 - u_3) + \frac{\beta_h}{N}(\lambda_1 - \lambda_2)(1 - u_1)S_H + \frac{\delta\beta_h}{N}(\lambda_4 - \lambda_5)(1 - u_1)S_T + \lambda_9\mu_v + \lambda_9r_0u_3 - A_3, \end{aligned} \right\} \quad (26)$$

with transversality conditions (or boundary conditions)

$$\lambda_i(T) = 0, i = 1, 2, \dots, 9, \quad (27)$$

expressed as

$$u_i^* = \begin{cases} 0 & \text{if } u_i \leq 0, \\ u_i & \text{if } 0 < u_i < 1, \\ 1 & \text{if } u_i \geq 1. \end{cases} \quad (28)$$

In addition, the control functions u_1^*, u_2^* and u_3^* are represented by

$$u_1^* = \max \left\{ \min \left\{ \frac{\beta_h(\lambda_2 - \lambda_1)I_V^*S_H^* + \delta\beta_h(\lambda_4 - \lambda_5)I_V^*S_T^* + \beta_v(\lambda_8 - \lambda_7)(I_H^* + \kappa I_T^*)S_V^*}{NB_1}, 1 \right\}, 0 \right\}, \quad (29)$$

$$u_2^* = \max \left\{ \min \left\{ \frac{\alpha[(\lambda_1 - \lambda_4)S_H^* + (\lambda_2 - \lambda_5)E_H^* + (\lambda_3 - \lambda_6)I_H^*]}{B_2}, 1 \right\}, 0 \right\}, \quad (30)$$

$$u_3^* = \max \left\{ \min \left\{ \frac{\lambda_7b_2V^* + r_0(\lambda_7S_V^* + \lambda_8E_V^* + \lambda_9I_V^*)}{B_3}, 1 \right\}, 0 \right\}. \quad (31)$$

Proof To determine the adjoint equations and the transversality conditions, we minimize the Hamiltonian H with respect to the controls (u_1^*, u_2^*, u_3^*) at the optimal control functions. Setting $S_H(t) = S_H^*(t)$, $E_H(t) = E_H^*(t)$, $I_H(t) = I_H^*(t)$, $S_T(t) = S_T^*(t)$, $E_T(t) = E_T^*(t)$, $I_T(t) = I_T^*(t)$, $S_V(t) = S_V^*(t)$, $E_V(t) = E_V^*(t)$ and $I_V(t) = I_V^*(t)$ and differentiating the Hamiltonian (22) with respect to $S_H, E_H, I_H, S_T, E_T, I_T, S_V, E_V$ and I_V , respectively, we obtain (26). Solving the equations

$$\frac{\partial H}{\partial u_1} = 0, \quad \frac{\partial H}{\partial u_2} = 0, \quad \frac{\partial H}{\partial u_3} = 0, \quad (32)$$

on the interior of the control set using the optimality conditions and the property of the control set \mathbf{U} , we derive (29)-(31). Due to the fact that the state and the adjoint functions are bounded and the Lipschitz structure of the ordinary differential equations, we obtain the uniqueness of the optimal control. This completes the proof.

The formulas (29)-(31) for u^* are the characteristics of the optimal control. The optimal control are found by solving the optimality system, that consists of the state system (18), the adjoint system (26), the initial conditions (19), boundary conditions (27) and the characteristic of the optimal control (29)-(31). In order to solve the optimality system, we use the initial and transversality conditions alongside the characterization of the optimal control (u_1^*, u_2^*, u_3^*) given in (29)-(31). Furthermore, the second derivative of the Lagrangian with respect to u_1, u_2 and u_3 , respectively, are positive indicating that the optimal control problem is minimum at controls u_1^*, u_2^* and u_3^* . We thus obtain the optimal control through numerical simulation.

4 Numerical simulation

In this section, we discuss the numerical solutions of the optimality system (18) and the corresponding optimal control strategies. In order to solve the optimality system we employ the standard two-boundary point method described in [20]. In our numerical simulations, we first start by solving the state equations (18) using Runge-Kutta forth order forward in time with a guess for the controls over simulated time. Based on the transversality conditions (27), the adjoint equations are solved by backward method. The time varying control values are found by entering the calculated values of the state and adjoint variables in the characterization of optimal controls (29)-(31). Convex combination is used to update the control values. In this case, the average of the new and old control values is taken. The convergence is acquired when the values of the variables in the new iteration and the previous iteration are insignificantly close.

4.1 Parameter estimation

In this section, we consider average parameter values that encompass features of onchocerciasis disease including rate of infection, incubation period, length of infections period in the vector and host populations. Although estimates of some parameters are given in Table 1, here we give additional explanation and description of some of the parameters based on available literature and with reference to Ghana which is one of the onchocerciasis endemic countries.

1. The average birthrate in Ghana was estimated to be 31.09 births/1,000 population in 2015 and 30.60 births/1,000 population in 2014 according to the World Fact Book by Central Intelligence Agency [37] and Ghana Statistical Service report on Demographic and Health Survey [14] respectively. Thus, the recruitment rate is estimated from the range $0.0000819 \leq b_1 \leq 0.000108$ per day.
2. The natural human death rate is estimated based on average life of 50-70 years in accordance to Central Intelligence Agency and 2014 demographic data released by Ghana Statistical Service estimates of life expectancy at birth respectively [14, 37]. The black-fly death rate is estimated based on the average life span lasting for 2-3 weeks, to as long as 85 days [11, 30].
3. It takes $\frac{3}{4}$ to 2 years for the worm to mature and release enough microfilariae to be detectable in the skin of the human host [21, 28, 35]. Therefore, a reasonable estimate of the incubation rate γ is $0.00137 \leq \gamma \leq 0.00365$ per day. On the other hand, the average incubation period in the black-fly is 1-2 weeks [21, 33, 35]. Thus, a reasonable value for η is $0.0714 \leq \eta \leq 0.1667$ per day.
4. The modification parameters (κ , δ and ρ) have been estimated to be between 0 and 1 due to the reduced ability of individuals to cause infections following ivermectin treatment.
5. The rate of protection following mass administration of ivermectin α is estimated to be between 0% and 100%.
6. We balance the host populations and control functions by arbitrarily choosing weight constant values $A_1 = A_2 = A_3 = 1$, $B_1 = 20, B_2 = 20, B_3 = 20$ in the objective functional (17). These weight parameters determine the importance of variables in the objective functional [20]. The estimate for rate constant r_0 is given as 0.06.

For illustration purpose, we consider the parameter estimates in Table 1 with the following initial conditions;

$$\begin{aligned} S_H(0) = 16200, \quad E_H(0) = 1500, \quad I_H(0) = 100, \quad S_T(0) = 2000, \quad E_T(0) = 300, \\ I_T(0) = 10, \quad S_V(0) = 2500, \quad E_V(0) = 250, \quad I_V(0) = 10. \end{aligned}$$

In the simulation, we consider the treatment rate as the protection rate upon the mass administration of ivermectin.

Table 1: Parameters used for numerical simulation. The rates are given per day.

Parameter	Description	Range	Point value	Source
b_1	Human recruitment rate	0.0000819-0.001085	0.001	Estimated
μ_h	Death rate of the human	0.0000391-0.0000548	0.000052	[14,37]
β_h	The rate of transmission of the disease from black-fly to human	0.0-0.02	0.00214	Estimated
γ	Transfer rate from E_H to I_H class	0.00137-0.00365	0.0023	[21,28,35]
α	Ivermectin treatment rate	0-1.0	0.0165	[41]
φ	Waning rate of ivermectin	0.01-0.1	0.0013	[39]
κ	Modification parameter	0.00-1.0	0.002	Estimated
ρ	Modification parameter	0.0-0.1.0	0.012	Estimated
δ	Modification parameter	0.00-1.0	0.001	Estimated
b_2	Vector recruitment rate	0.0177-0.0871	0.0643	Estimated
β_v	The rate of transmission of the disease from human to black-fly	0.0-0.02	0.00104	Estimated
η	Transfer rate from E_V to I_V class	0.0714-0.1667	0.074	[21,33,35]
μ_v	Death rate of the black-fly	0.0118-0.0714	0.065	[11,30]

4.2 Sensitivity analysis

Sensitivity analysis is introduced to study the strength of the basic reproduction number for the model parameters. Due to the unavailability of data, uniform distribution is used for the set of parameters in Table 1 peaked at the median. Tornado plot for the normalised sensitivity index for different parameters is given in Fig. 4. If the sensitivity index is positive, then R_0 increases along with increasing value of the parameter. On the other hand, if the sensitivity index is negative, then R_0 decreasing with the increasing value of the parameter. The transmission contact rates in human and the vector have the greatest effect on the disease transmission. The results in Fig. 4 indicate that the basic reproduction number increases with increase in the transmission contact rate in both the human (host) and the vector whereas the basic reproduction number decreases with increase in the vector death rate. The results therefore suggest that if the transmission of onchocerciasis in both the vector and the human (host) can be reduced and the vector death rate increased, then the disease can be easily controlled. On the other hand, Fig. 5 shows that an increase in both κ and δ increases R_0 . Thus, the effectiveness of ivermectin in the treatment of onchocerciasis is critical in eliminating new cases of infections in the treated population.

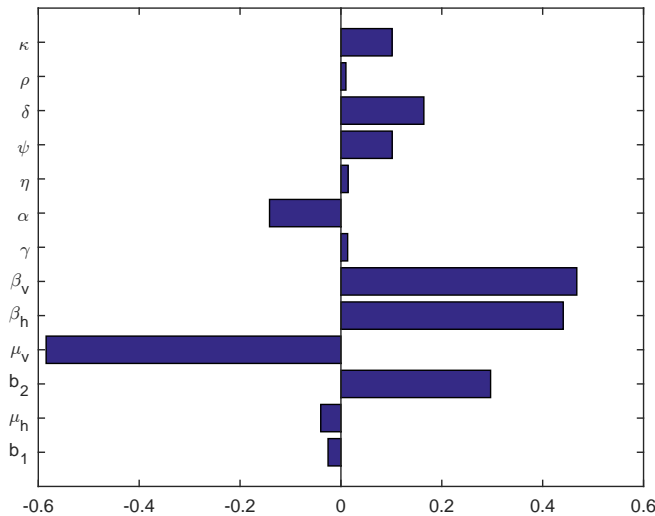


Fig. 4: Tornado plots of partial rank correlation coefficients (PRCCs) of the parameters that influence R_0 for the input parameters using the values in Table 1. Parameters with $\text{PRCC} > 0$ increases R_0 when they are increased whereas parameters with $\text{PRCC} < 0$ decreases R_0 when they are increased.

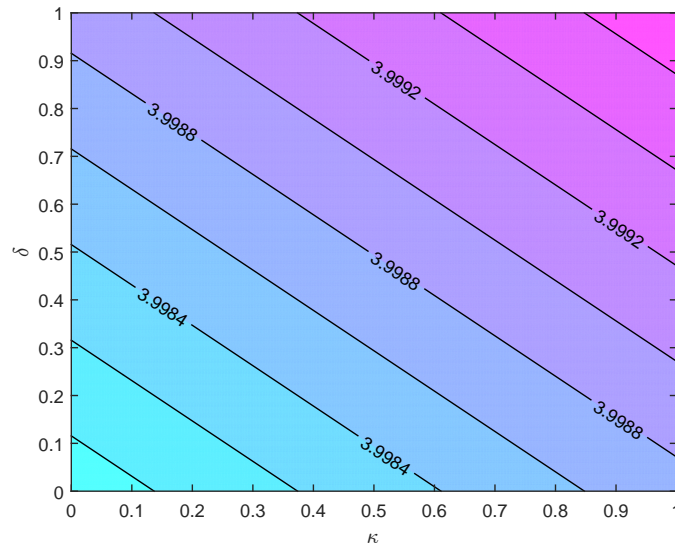


Fig. 5: Contour plot showing the effect of modification parameters δ and κ on R_0 .

4.3 Simulation results

Fig. 6, represents the population of susceptible, exposed, infected individuals (human) in two systems, (4) without control and (18) with control. The red line denotes the population of individuals in the system (4) without control while the blue dotted line denotes the population of individuals in the system (18) with control. Onchocerciasis infection is shown to be contained much earlier in time when appropriate and aggressive optimal controls are applied to the onchocerciasis epidemic. Part (a) of Fig. 6 reveals that without controls, the susceptible human (hosts) population not on ivermectin gets depleted at a higher rate due to unchecked transmission. However, with controls, more individuals stay in the susceptible class. In addition, part (b) of Fig. 6 shows that more susceptible individuals stay protected with ivermectin when there is control as compared to when there is no control. Part (c) and (e) of Fig. 6 show that the populations of exposed and infected individuals with control are more decreased than the individuals without control. The results suggest that much less time is taken to clear onchocerciasis disease when optimal control measures are applied than without controls. Fig. 7 reveals that the population of the susceptible vector with optimal control is more sharply decreased while the population without control grows and settles at endemic state. The population of susceptible vector with control decreases to zero. We observe in Fig. 7 (b) and (c) that the exposed and infected vector without control rise during the initial stages of epidemic followed by a decrease then remains at endemic stage. However, in the presence of control we observe a decrease which ends at onchocerciasis free stage. The results illustrate the importance of control in the reduction of onchocerciasis infection in the population. Fig. 8 shows the evolution of the control profiles over time. The results show that the controls u_1, u_2^* and u_3^* all start at the upper bound. However, the first and third controls, u_1 and u_3^* , decline after about 100 days and vanish in the 250th day. The control profile u_2 maintains its upper bound and vanishes when the epidemics ends. This can be explained by the fact that in the treatment of onchocerciasis with ivermectin, the drug is administered for the entire period corresponding with the lifespan of filarial adult worms. The simulation shows that a lot more emphasis should be put in reducing the contact that results into onchocerciasis infection. More emphasis should be put on vector eradication that poses danger on the continuous spread of the disease. We suggest that treatment services should be patient specific, proper, efficient and timely.

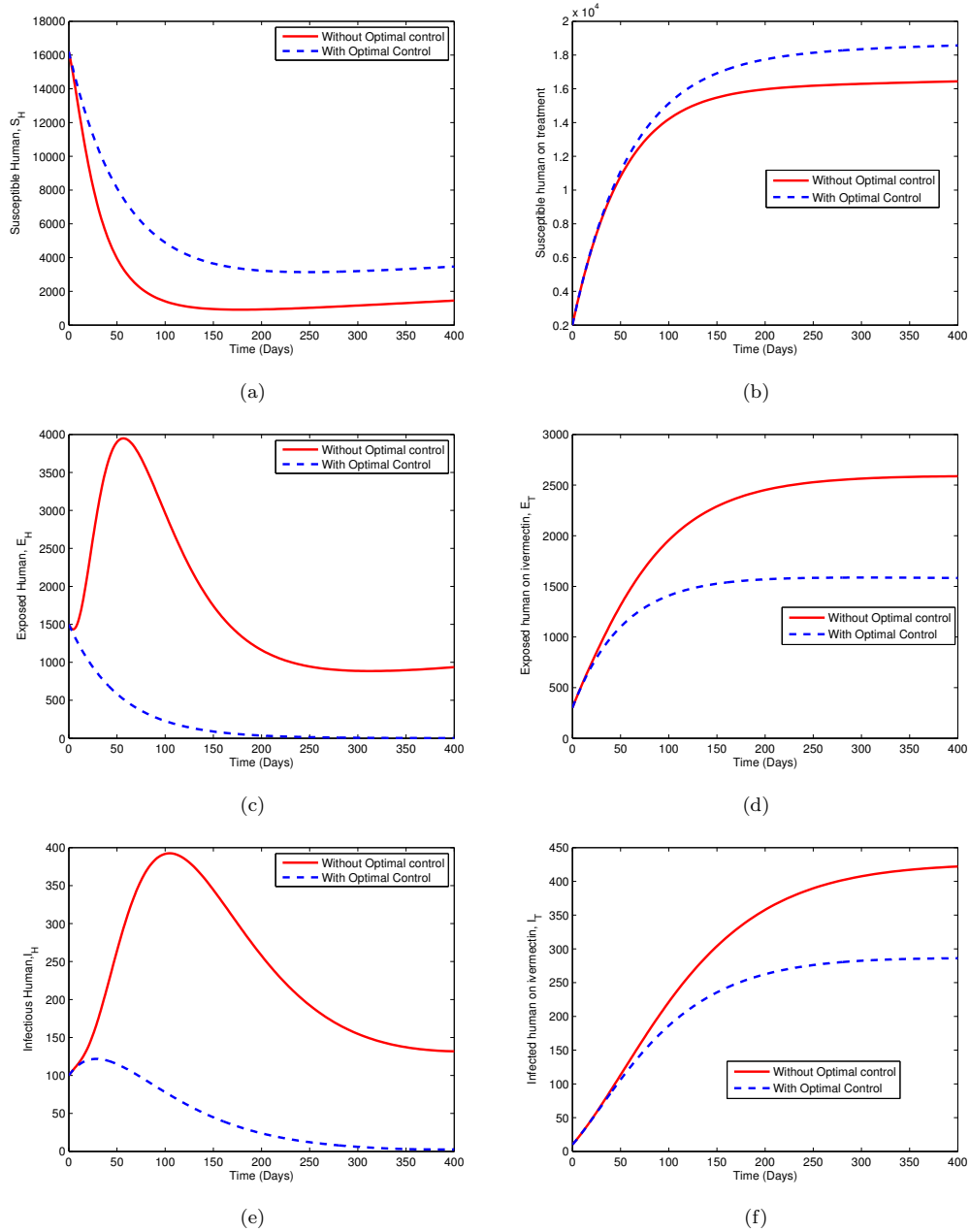


Fig. 6: The plot represents population of susceptible not on ivermectin, exposed not on ivermectin, infected not on ivermectin, susceptible on ivermectin, exposed on ivermectin and infected on ivermectin human host both with control (blue dotted line) and without control (red line).

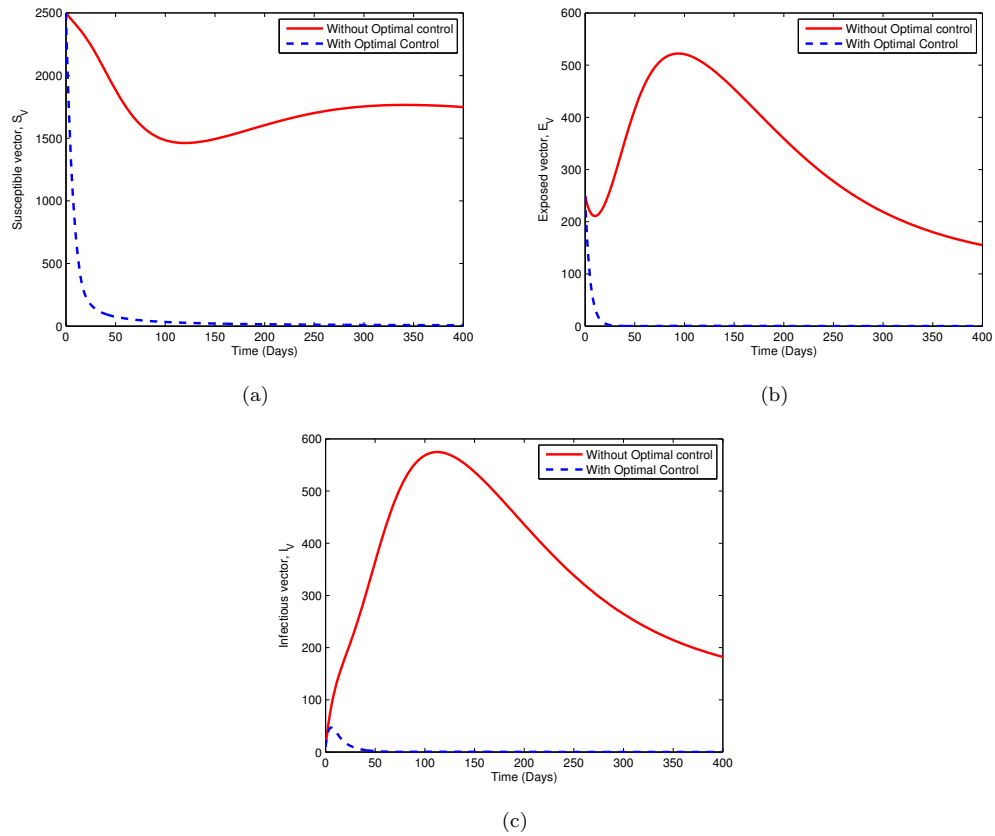


Fig. 7: The plot represents population of susceptible, exposed and infected vector both with control (blue dotted line) and without control (red line).

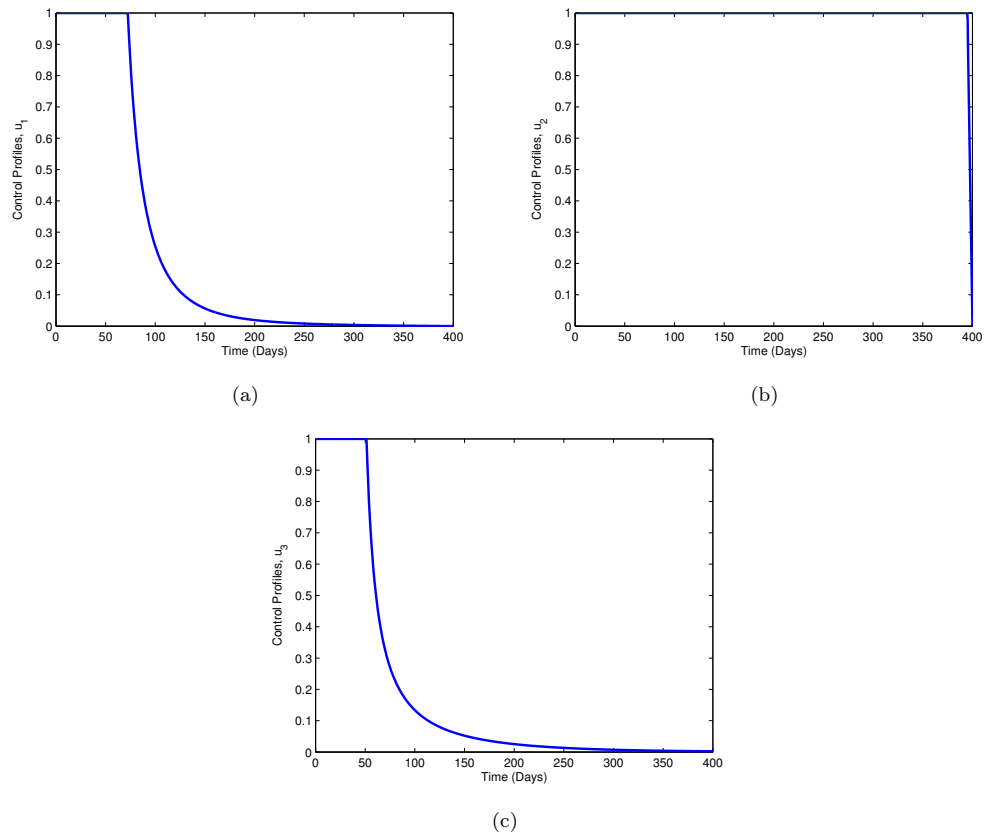


Fig. 8: Profiles of personal protection control u_1 , the treatment efficiency control u_2 and insecticide u_3 .

5 Conclusion

In this paper, a deterministic model for onchocerciasis disease dynamics that incorporates compartment with treatment was developed. The model was extended to account for density dependent parameters and control functions to assess the impact of control measures using optimal control techniques with important epidemiological features. The model properties and stability analysis were examined. We have shown that there exist multiple endemic equilibrium when the basic reproduction is less than unity. The model is shown to exhibit backward bifurcation implying that $R_0 < 1$ is not sufficient to eliminate the disease from the population and hence we need another threshold parameter less than one and R_0 should be reduced below this threshold to eliminate the disease from the population. This behaviour has been shown using the bifurcation diagram. In addition, it is established that the rate of mass administration of ivermectin plays an important role in the occurrence of backward bifurcation. An increase in the rate of mass administration of ivermectin results in the forward bifurcation and in this case reducing R_0 below 1 becomes sufficient to eliminate the disease from the population.

We also determined the cost effective strategies for combating the spread of onchocerciasis infection in the population. By application of Pontryagin's Maximum Principle, we performed the optimal analysis of the non-autonomous control model considering three controls, one for black-fly-reduction strategies and the other two for personal (human) protection and the coverage of ivermectin respectively. In addition, we minimised the exposed and infectious hosts as well as the total vector population by using the three control variables. We have investigated the dynamics by an efficient numerical scheme based on optimal control to identify the best strategy of onchocerciasis control. A comparison between optimal control system and system without control is presented. It is easy to see that the optimal control system has desirable impact on the reduction of the number of exposed and infected humans (hosts) and the vector population. The results indicate that treatment with ivermectin remains the most effective and recommended methodology to control onchocerciasis disease. In addition, application of vector control can produce more desirable results and enhance the disease eradication. Thus, the results support the hypothesis that preventive practices are very efficient in reducing the incidence of exposed and infectious hosts as well as the vector.

As with many models, the model presented in this article should be treated with circumspection because of the difficulty in the estimation of model parameters. The weights on cost considered in this paper are mainly for illustration. More realistic results can be obtained if data on the costs of the implementation of control strategies are available. Despite these shortcomings, the model still provides some useful insights into the control of onchocerciasis through the implementation of the discussed control measures. Note that the same model could be used to investigate the emergence of drug resistance in the treatment of onchocerciasis with ivermectin. The model can also be used to investigate the impulsive effect of mass administration of ivermectin in the treatment of onchocerciasis.

In summary, the fight to eradicate onchocerciasis from the population depends on the mass administration of ivermectin as well as vector control. The elimination of black-fly is critical in eliminating new infections that may result due to human-blackfly contact. Therefore, the model discussed here is much suitable for onchocerciasis and it can readily be extended to incorporate climatic conditions on the transmission of this disease.

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Modelling the impact of mass administration of ivermectin in the treatment of onchocerciasis (river blindness)

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Abstract

Onchocerciasis (river blindness) is a disease spread from blackflies to humans that causes chronic morbidity in sub-Saharan Africa. Treatment occurs through twice-yearly mass administration of ivermectin, a drug that is effective in the short term but which wanes quickly. We used a system of impulsive differential equations to model both fixed and non-fixed administration of ivermectin. In the absence of treatment, we determined the threshold for eradication R_0 but showed that the disease is unlikely to be eradicated without extremely low transmission levels or strong vector control. If treatment is included, then treatment at fixed intervals can control but not eradicate the disease. Treatment at non-fixed intervals may produce bursts of infection. Six-monthly mass administration can only lead to significant reduction of onchocerciasis if human-vector contact is sufficiently reduced and vector-control programs are implemented.

Keywords: Onchocerciasis, river blindness, ivermectin, mathematical model, impulsive differential equations.

1. Introduction

Onchocerciasis (also known as river blindness) is a neglected tropical disease caused by the filarial worms *Onchocerca volvulus* in human hosts [1]. The disease is transmitted by the blackfly (*Simulium damnosum*) [2]. *Simulium* breeds close to oxygen-rich flowing streams and rivers in inter-tropical zones [3, 4]. Onchocerciasis-endemic areas thus tend to include the most agriculturally fertile land available. The migration and deaths of microfilariae damage surrounding tissue or organs, causing intense itching and disfigurement; ocular degeneration and blindness occur when microfilariae migrate to the eyes [4]

The infection of onchocerciasis begins at the third larvae stage in the human host after the vector's blood meal. The larvae develop into adult filariae in the subcutaneous tissues from which microfilariae migrate throughout the body, predominantly within the skin [5]. This produces an intense itching of the skin

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and a chronic dermatitis that leads to skin atrophy and depigmentation [6]. The migration of microfilariae through the anterior and posterior segments of the eye precipitates inflammatory reactions that may lead to loss of vision and sometimes blindness [4, 7].

Various onchocerciasis control strategies have achieved dramatic success in reducing onchocerciasis transmission [8, 9]. The strategies have employed both the use of larvicide spraying at blackfly breeding sites and the periodic mass drug administration of ivermectin to affected human populations. The control programmes have been spearheaded by three international programmes: the Onchocerciasis Control Program (OCP), the Onchocerciasis Elimination Programme in the Americas (OEPA) and the African Program for Onchocerciasis Control (APOC). Transmission of onchocerciasis was interrupted in Guatemala and in several hyper-endemic foci of Mali and Senegal following six-monthly mass administration of ivermectin [10]. In 2014, Columbia and Ecuador were declared free of onchocerciasis following the implementation of the control strategies for decades by the WHO [11].

A number of epidemiological models have been formulated and mathematically analysed to describe the behaviour of onchocerciasis in the population. Mapocha and Thieme [7] developed a model to account for both human and bovine onchocerciasis. They considered cross-reactive immunity in response to inoculation of cattle by larvae. They showed that if parasites are wasted on the “wrong” hosts, then the reproduction number is lowered, while cross-reactive immunity can lead to classical competition phenomena. Basáñez and Ricárdez-Esquinca [12, 13] developed a model to describe the population biology and control of human onchocerciasis. Their aim was to evaluate various interventions combining the removal of adult worms (nodulectomy) and the microfilaricidal and sterilizing effects of ivermectin. They derived a threshold condition for disease control involving the vector biting rate and the basic reproduction number. They estimated that the annual biting rate for the *Simulium onchraceum s.l* is 7665 bites per person per year. This is the minimum below which human onchocerciasis would be unable to become endemic in Central America since the basic reproduction number, R_0 , would be less than unity. They recommended that if the worm is sterilised and the vector population is condensed, then the epidemic could be restricted. In Africa, several field studies have achieved significant reduction in the transmission of infection by repeated annual mass treatment with ivermectin [14, 15, 16]. Alley *et al.* [17] used a microsimulation model to examine the possibility of switching treatment from the microfilaricide ivermectin to a hypothetical macrofilaricide. They showed that elimination was possible using a macrofilaricide, but that high coverage levels were critical. Filipe *et al.* [18] developed an age- and sex-structured model for intensity of infection with parasite regulation within humans and vectors. They showed that heterogeneous age and sex exposure could explain location-specific infection patterns of onchocerciasis. Poolman and Galvani [19] incorporated host heterogeneity into a model in order to evaluate intervention strategies targeting specific populations for treatment with ivermectin. They found that targeted allocation of ivermectin in a highly heterogeneous population could

reduce the public-health burden of onchocerciasis using 20–25% of the doses of untargeted allocation.

Mass administration of ivermectin is the main strategy used in the control of onchocerciasis in sub-Saharan Africa [9, 20]. Mass treatment with ivermectin was initially carried out annually. However, a change in strategy to six-monthly mass treatment was adopted to increase the probability of disease eradication [9, 21]. Although substantial epidemiological work has been done on the study of onchocerciasis transmission dynamics, few mathematical models have been developed. Our aim is to examine the effects of mass administration of ivermectin using a mathematical model of impulsive differential equations. The model focuses on the effect of fixed and non-fixed mass administration of ivermectin in the treatment of onchocerciasis to account for the reduction of infection of onchocerciasis in the human population. Thus, we endeavour to address the following research questions: 1. Can we determine the critical threshold for the proportion of individuals with onchocerciasis that will reduce the infection of the onchocerciasis in the population? 2. Can mass administration of ivermectin eradicate onchocerciasis? 3. Does control of onchocerciasis depend on administration occurring at fixed times?

2. The mathematical model

2.1. Model formulation

We develop a model to better understand the transmission dynamics of onchocerciasis and its treatment. We consider a habitat with two interacting populations. The two populations are humans (hosts) and blackflies (vectors). The total human population is partitioned into six compartments: the susceptible human compartment, S_H , referring to individuals not infected with onchocerciasis but who are at risk of infection; the exposed compartment, E_H , referring to the individuals that have been exposed to onchocerciasis through bites; the infectious compartment, I_H , referring to individuals with onchocerciasis infection; susceptible humans undergoing ivermectin treatment, S_T ; exposed humans undergoing ivermectin treatment, E_T ; and the infectious humans undergoing ivermectin treatment, I_T . The blackfly population is partitioned into three compartments: susceptible vectors, S_V , referring to blackflies that have not picked up microfilariae but are at risk of picking up microfilariae during a blood meal; the exposed vector compartment, E_V , referring to blackflies that have picked up microfilariae from an infected human during blood meal; and the infective vector compartment, I_V .

The total human and vector populations at any given time, t , are respectively given by;

$$N(t) = S_H(t) + E_H(t) + I_H(t) + S_T(t) + E_T(t) + I_T(t), \quad V(t) = S_V(t) + E_V(t) + I_V(t). \quad (1)$$

We assume that the transmission of onchocerciasis in susceptible hosts is only through contact with an infectious vector. We also assume that susceptible vectors become infectious as a result of contact with infectious hosts during a blood meal. The population under study is assumed to be large enough to be

modelled deterministically. The recruitment of new susceptible individuals and susceptible vectors is given by b_1 and b_2 respectively. Assuming β is the black-fly biting rate, that is, the average number of bites per black-fly per unit, the rate of infection per susceptible black-fly can be represented by

$$\lambda_v(t) = \frac{q\beta(I_H + \kappa I_T)}{N}, \quad (2)$$

where q is the transmission probability from infectious human to black-flies and κ is the modification parameter which measures the relative ability of individuals in class I_T to cause new infections relative to those in compartment I_H . We assume here that the individuals under treatment have a slightly lower probability to initiate new infections, thus, $0 \leq \kappa \leq 1$. Assuming that the total number of bites made by black-flies equals to the number of bites received by humans, then the average number of bites per human receives per unit time is $\frac{\beta V}{N}$. Assuming that the transmission probability per bite from infectious black-flies to human is p , the rate of infection per susceptible human is given by

$$\lambda_h(t) = \frac{p\beta V}{N} \frac{I_V}{V} = \frac{p\beta I_V}{N}. \quad (3)$$

We then introduce $\beta_h = p\beta$ and $\beta_v = q\beta$ parameters to simplify the infection rates per susceptible human and vector respectively. Individuals in class E_H progress to the infectious class I_H at rate γ . Individuals undergoing ivermectin treatment in class S_T acquire infection at the rate $\delta\lambda_h$, where δ defines the reduced effect of infection of the susceptible individuals as a result of treatment. Individuals in class E_T progress to the infectious treated class I_T at the rate $\rho\gamma$, where ρ is the reduced effect of progression to class I_T as a result of treatment. Immediately following treatment, infection in the human population is assumed to be reduced by some proportion α . This therefore results in a system of impulsive differential equations [22, 23]. Individuals undergoing treatment will relapse due to waning of the drug at the rate φ . We include natural mortality rates given by μ_h and μ_v for the human and vector populations respectively.

We further assume that individuals under treatment have no immunity to the disease upon treatment. In addition, we assume that infected vectors and human do not recover from the infection during the modelling time. The dynamics in the host and vector populations are represented in the schematic diagram in Figure 1.

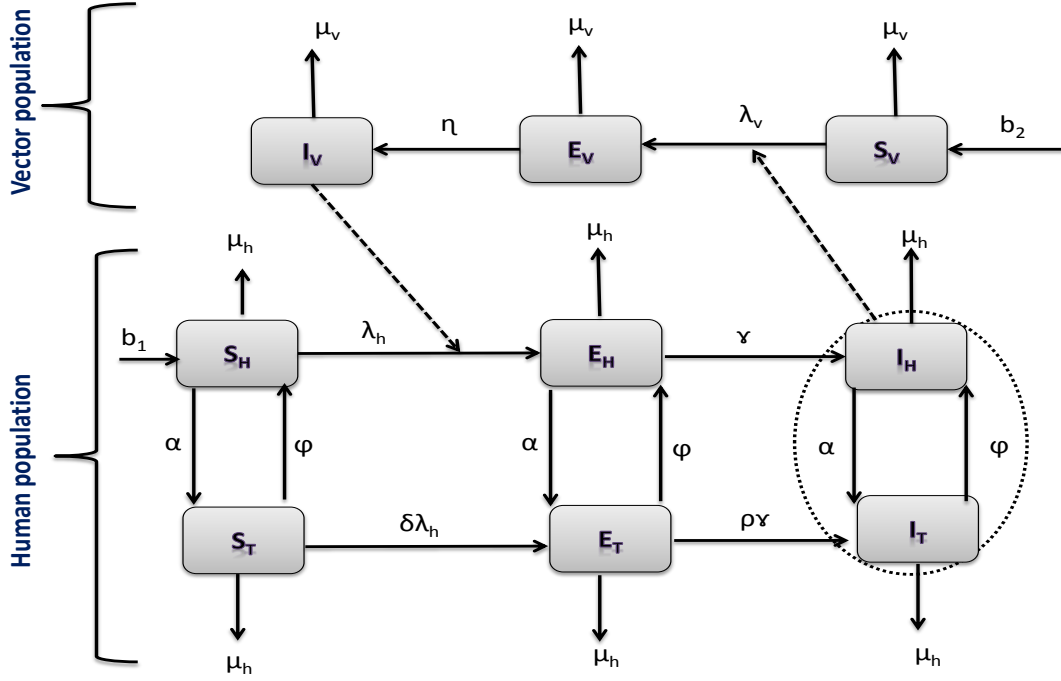


Fig. 1: A compartmental representation of the epidemics and treatment of onchocerciasis.

2.2. Model equations

The following system of nonlinear ordinary differential equations, with nonnegative initial conditions, describes the dynamics of onchocerciasis epidemics:

$$\left. \begin{aligned}
 \dot{S}_H &= b_1 + \varphi S_T - \frac{\beta_h I_V S_H}{N} - \mu_h S_H, \\
 \dot{E}_H &= \frac{\beta_h I_V S_H}{N} + \varphi E_T - (\gamma + \mu_h) E_H, \\
 \dot{I}_H &= \gamma E_H + \varphi I_T - \mu_h I_H, \\
 \dot{S}_T &= -\frac{\delta \beta_h I_V S_T}{N} - (\varphi + \mu_h) S_T, \\
 \dot{E}_T &= \frac{\delta \beta_h I_V S_T}{N} - (\rho \gamma + \varphi + \mu_h) E_T, \\
 \dot{I}_T &= \rho \gamma E_T - (\varphi + \mu_h) I_T, \\
 \dot{S}_V &= b_2 - \frac{\beta_v I_H S_V}{N} - \frac{\kappa \beta_v I_T S_V}{N} - \mu_v S_V, \\
 \dot{E}_V &= \frac{\beta_v I_H S_V}{N} + \frac{\kappa \beta_v I_T S_V}{N} - (\eta + \mu_v) E_V, \\
 \dot{I}_V &= \eta E_V - \mu_v I_V.
 \end{aligned} \right\} t \neq t_k, \quad (4)$$

subject to the following initial conditions:

$$S_H(0) > 0, E_H(0) > 0, I_H(0) > 0, S_T(0) > 0, E_T(0) > 0, I_T(0) > 0, S_V(0) > 0, E_V(0) > 0, I_V(0) > 0. \quad (5)$$

The impulsive conditions are

$$\left. \begin{aligned} \Delta S_H &= -\alpha S_H, & \Delta E_H &= -\alpha E_H, & \Delta I_H &= -\alpha I_H, \\ \Delta S_T &= +\alpha S_H, & \Delta E_T &= +\alpha E_H, & \Delta I_T &= +\alpha I_H, \end{aligned} \right\}, \quad t = t_k. \quad (6)$$

Treatment may occur at either fixed or non-fixed intervals.

3. System without impulses

3.1. Well-posedness

System (4) describes a human–vector population, so it is therefore necessary to prove that the solutions of system (4) with nonnegative initial conditions remain nonnegative for all time $t \geq 0$ and are bounded in the region

$$\Omega = \left\{ (S_H, E_H, I_H, S_T, E_T, I_T) \in \mathbb{R}_+^6 : N \leq \frac{b_1}{\mu_h}, \quad (S_V, E_V, I_V) \in \mathbb{R}_+^3 : V \leq \frac{b_2}{\mu_v} \right\}. \quad (7)$$

Theorem 3.2. *Let $S_H \geq 0, E_H \geq 0, I_H \geq 0, S_T \geq 0, E_T \geq 0, I_T \geq 0, S_V \geq 0, E_V \geq 0, I_V \geq 0$. Then the solutions $S_H(t), E_H(t), I_H(t), S_T(t), E_T(t), I_T(t), S_V(t), E_V(t), I_V(t)$ of the system (4) are positive for all $t \geq 0$. In addition, the region Ω is positively invariant, and all solutions starting in Ω approach, enter or stay in Ω .*

Proof. Let $t^* = \sup\{t > 0 : S_H(t) > 0, E_H(t) > 0, I_H(t) > 0, S_T(t) > 0, E_T(t) > 0, I_T(t) > 0, S_V(t) > 0, E_V(t) > 0, I_V(t) > 0\}$. Thus $t^* \geq 0$. Then, from the first equation of our system (4), we obtain

$$\begin{aligned} \dot{S}_H &= b_1 + \varphi S_T - \frac{\beta_h I_V S_H}{N} - \mu_h S_H \geq -(\lambda_h + \mu_h) S_H, \\ S_H(t^*) &\geq S_H(0) \exp \left\{ - \left(\int_0^{t^*} \lambda_h(m) dm + \mu_h t^* \right) \right\}. \end{aligned}$$

Similarly, one can show that $E_H \geq 0, I_H \geq 0, S_T \geq 0, E_T \geq 0, I_T \geq 0, S_V \geq 0, E_V \geq 0, I_V \geq 0$. This completes the proof for positivity.

The total population of the humans N and that of the vector population V is governed by

$$\dot{N} = b_1 - \mu_h N, \quad \dot{V} = b_2 - \mu_v V. \quad (8)$$

Hence

$$\limsup_{t \rightarrow \infty} N \leq \frac{b_1}{\mu_h} \quad \text{and} \quad \limsup_{t \rightarrow \infty} V \leq \frac{b_2}{\mu_v}. \quad (9)$$

Therefore $N(t)$ and $V(t)$ are bounded and the domain of biological significance is positively invariant and attracting. Thus all solutions starting in Ω remain in Ω . \square

3.3. Maximal solution

Next we overestimate the number of infectious individuals in the population. From the system (4), we have established that the total human (host) population is bounded above by $\frac{b_1}{\mu_h}$. Thus, from the fifth equation of the system (4) we have

$$\frac{dE_T}{dt} = \frac{\delta\beta_h I_V S_T}{N} - (\rho\gamma + \varphi + \mu_h)E_T.$$

If we bound S_T by the total human population and I_V by the total vector population, we have

$$\frac{dE_T}{dt} \leq \frac{\delta\beta_h b_2}{\mu_v} - (\rho\gamma + \varphi + \mu_h)E_T. \quad (10)$$

Solving the inequality in (10), we obtain

$$E_T \leq \frac{\delta\beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} + \left[E_T(0) - \frac{\delta\beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} \right] e^{-(\rho\gamma + \varphi + \mu_h)t}. \quad (11)$$

As t approaches infinity, then the solution in (11) is bounded by

$$E_T \leq \frac{\delta\beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)}. \quad (12)$$

Substituting the expression in (12) into the sixth equation of the system (4), we have

$$\frac{dI_T}{dt} \leq \frac{\delta\beta_h \rho\gamma b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} - (\varphi + \mu_h)I_T,$$

whose solution can be expressed as

$$I_T \leq \frac{\delta\beta_h \rho\gamma b_2}{\mu_v(\varphi + \mu_h)(\rho\gamma + \varphi + \mu_h)}. \quad (13)$$

Using the solutions obtained in (12) and (13) in the second and third equations in the system (4) respectively, we have

$$E_H \leq \left[\frac{\beta_h b_2}{\mu_v} + \frac{\delta\varphi\beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} \right], \quad (14)$$

$$I_H \leq \gamma \left[\frac{\beta_h b_2}{\mu_v} + \frac{\delta\varphi\beta_h b_2}{\mu_v(\rho\gamma + \varphi + \mu_h)} \right] + \varphi \left[\frac{\delta\beta_h \rho\gamma b_2}{\mu_v(\varphi + \mu_h)(\rho\gamma + \varphi + \mu_h)} \right]. \quad (15)$$

The significance of these inequalities is that they overestimate the number of people with onchocerciasis in the population without necessarily solving the original systems of the differential equations. We will make use of these overestimates shortly.

3.4. Stability of the model equilibria

3.4.1. Disease-free equilibria

The disease-free equilibrium (DFE) for the system without impulses is given by

$$E_0 = (\hat{S}_H, \hat{E}_H, \hat{I}_H, \hat{S}_T, \hat{E}_T, \hat{I}_T, \hat{S}_V, \hat{E}_V, \hat{I}_V) = \left(\frac{b_1}{\mu_h}, 0, 0, 0, 0, 0, \frac{b_2}{\mu_v}, 0, 0 \right). \quad (16)$$

3.4.2. The basic reproduction number

The basic reproduction number for the system (4) is obtained using the next-generation method described in [24]. It is given by

$$R_0 = \sqrt{\mathcal{R}_0} = \sqrt{\frac{b_2\gamma\eta\beta_h\beta_v}{b_1\mu_v^2(\gamma + \mu_h)(\eta + \mu_v)}}.$$

Note that this expression is a threshold, not necessarily the average number of secondary infections [25].

Theorem 3.5. *The disease-free equilibrium, E_0 , given in (16) of the system (4) is globally stable if $\mathcal{R}_0 < 1$ otherwise unstable.*

Proof. Let $V = \theta_1 E_H + \theta_2 I_H + \theta_3 E_T + \theta_4 I_T + \theta_5 E_V + \theta_6 I_V$ be a candidate Lyapunov function. The constants θ_i for $i = 1, 2, 3, 4, 5, 6$ are nonnegative. We can find the constants θ_i such that the Lyapunov candidate is positive definite. The derivative of the Lyapunov function is given by

$$\begin{aligned} \frac{dV}{dt} &= \theta_1 \frac{dE_H}{dt} + \theta_2 \frac{dI_H}{dt} + \theta_3 \frac{dE_T}{dt} + \theta_4 \frac{dI_T}{dt} + \theta_5 \frac{dE_V}{dt} + \theta_6 \frac{dI_V}{dt}, \\ &= \theta_1 \left[\frac{\beta_h I_V S_H}{N} + \varphi E_T - Q_1 E_H \right] + \theta_2 [\gamma E_H + \varphi I_T - \mu_h I_H] + \theta_3 \left[\frac{\delta \beta_h I_V S_T}{N} - Q_3 E_T \right] + \theta_4 [\rho \gamma E_T - Q_2 I_T] \\ &\quad + \theta_5 \left[\frac{\beta_v I_H S_V}{N} + \frac{\kappa \beta_v I_T S_V}{N} - Q_4 E_V \right] + \theta_6 [\eta E_V - \mu_v I_V], \\ &= [\theta_2 \gamma - \theta_1 Q_1] E_H + \left[\frac{\theta_5 \mu_h b_2 \beta_v}{\mu_v b_1} - \theta_2 \mu_h \right] I_H + [\theta_1 \varphi + \theta_4 \rho \gamma - \theta_3 Q_3] E_T + \left[\theta_2 \varphi + \frac{\theta_5 \kappa \beta_v \mu_h b_2}{\mu_v b_1} - \theta_4 Q_2 \right] I_T \\ &\quad + [\theta_6 \eta - \theta_5 Q_4] E_V + [\theta_1 \beta_h - \theta_6 \mu_v] I_V, \end{aligned}$$

where

$$Q_1 = \gamma + \mu_h, \quad Q_2 = \varphi + \mu_h, \quad Q_3 = \rho \gamma + \varphi + \mu_h, \quad Q_4 = \eta + \mu_v.$$

Setting the coefficients to I_H, E_T, I_T, E_V and I_V to zero, we obtain

$$\begin{aligned} \theta_1 &= \frac{Q_4 \mu_v}{\beta_h}, \quad \theta_2 = \frac{b_2 \beta_v \eta}{b_1 \mu_v}, \quad \theta_3 = \frac{b_2 \eta \kappa \rho \gamma \mu_h \beta_v}{b_1 Q_2 Q_3 \mu_v} + \frac{b_2 \eta \rho \gamma \varphi \beta_v}{b_1 Q_2 Q_3 \mu_v} + \frac{Q_4 \varphi \mu_v}{Q_3 \beta_h}, \quad \theta_4 = \frac{b_2 \beta_v \eta (\kappa \mu_h + \varphi)}{Q_2 b_1 \mu_v}, \\ \theta_5 &= \eta, \quad \theta_6 = Q_4. \end{aligned} \tag{17}$$

We then use the coefficients obtained in (17) into the candidate Lyapunov function. The derivative of the resulting Lyapunov function becomes

$$\frac{dV}{dt} = \frac{Q_1 Q_4 \mu_v}{\beta_h} [\mathcal{R}_0 - 1]. \tag{18}$$

We note that, whenever $\mathcal{R}_0 < 1$, then $\frac{dV}{dt} < 0$. Therefore, by LaSalle's Invariance principle [26], the disease-free equilibrium is globally stable whenever $\mathcal{R}_0 < 1$. \square

3.5.1. Endemic equilibrium

The endemic equilibrium point, E_1 , is found by equating the right-hand of the system (4) to zero. Expressing all the variables in terms of I_H , we get

$$S_H^* = b_1 \left(\frac{1}{\mu_h} - \frac{b_2 \eta \beta_h I_H^* \beta_v}{b_1 Q_4 \mu_v (b_1 \mu_v + \mu_h I_H^* \beta_v) + b_2 \eta \beta_h \mu_h I_H^* \beta_v} \right), E_H^* = \frac{b_1 b_2 \eta \beta_h \mu_h I_H^* \beta_v}{Q_1 (b_1 Q_4 \mu_v (b_1 \mu_v + \mu_h I_H^* \beta_v) + b_2 \eta \beta_h \mu_h I_H^* \beta_v)},$$

$$S_T^* = E_T^* = I_T^* = 0, \quad S_V^* = \frac{b_1 b_2}{\beta_v \mu_h I_H^* + b_1 \mu_v}, \quad E_V^* = \frac{b_2 \beta_v \mu_h I_H^*}{Q_4 (\beta_v \mu_h I_H^* + b_1 \mu_v)}, \quad I_V^* = \frac{b_2 \beta_v \mu_h \eta I_H^*}{Q_4 \mu_v (\beta_v \mu_h I_H^* + b_1 \mu_v)}.$$

After some algebraic manipulations, we either have $I_H^* = 0$ or

$$I_H^* = \frac{Q_1 Q_4 b_1^2 \mu_v^2}{Q_1 \beta_v \mu_h (b_2 \beta_h \eta + Q_4 b_1 \mu_v)} [\mathcal{R}_0 - 1]. \quad (19)$$

The case where $I_H^* = 0$, gives the disease-free equilibrium, treated earlier. From expression (19), one sees that when $\mathcal{R}_0 < 1$, then $I_H^* < 0$, implying that the system (4) has no positive solution. However, when $\mathcal{R}_0 > 1$, then $I_H^* > 0$ and a unique endemic equilibrium exists.

Theorem 3.6. *If $\mathcal{R}_0 > 0$, then E_0 is unstable and the unique endemic equilibrium E_1 is locally asymptotically stable in the interior of the feasible region Ω .*

Proof. The stability and the direction of bifurcation $\mathcal{R}_0 = 1$ of the endemic equilibrium is proved by the direct use of the Center Manifold Theory (CMT) as described in [27]. We avoid re-stating the theorem and adopting notations as described in [27], we compute the values of \mathbf{a} and \mathbf{b} whose signs determine local dynamics of the model (4). The basic reproduction of the system (4) is established to be

$$\mathcal{R}_0 = \frac{b_2 \gamma \eta \beta_h \beta_v}{b_1 \mu_v^2 (\gamma + \mu_h) (\eta + \mu_v)}. \quad (20)$$

Suppose, we choose $\theta = \beta_h$ as the bifurcation parameter so that when $\mathcal{R}_0 = 1$, we have

$$\theta = \frac{b_1 \mu_v^2 (\gamma + \mu_h) (\eta + \mu_v)}{b_2 \gamma \eta \beta_v} \quad (21)$$

In order to apply the Center Manifold Theory (CMT), it is necessary to make the following changes to the state variables, we let $S_H = x_1, E_H = x_2, I_H = x_3, S_T = x_4, E_T = x_5, I_T = x_6, S_V = x_7, E_V = x_8, I_V = x_9$. The system (4) can now be written in the form $\frac{df}{dx} = f(x)$, where $x = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9)$. The system

(4) therefore becomes

$$\left. \begin{aligned} \dot{x}_1 &= b_1 + \varphi x_4 - \frac{\beta_h x_9 x_1}{N} - \mu_h x_1, \\ \dot{x}_2 &= \frac{\beta_h x_9 x_1}{N} + \varphi x_5 - Q_1 x_2, \\ \dot{x}_3 &= \gamma x_2 + \varphi x_6 - \mu_h x_3, \\ \dot{x}_4 &= -\frac{\delta \beta_h x_9 x_4}{N} - Q_2 x_4, \\ \dot{x}_5 &= \frac{\delta \beta_h x_9 x_4}{N} - Q_3 x_5, \\ \dot{x}_6 &= \rho \gamma x_5 - Q_2 x_6, \\ \dot{x}_7 &= b_2 - \frac{\beta_v x_3 x_7}{N} - \frac{\kappa \beta_v x_6 x_7}{N} - \mu_v x_7, \\ \dot{x}_8 &= \frac{\beta_v x_3 x_7}{N} + \frac{\kappa \beta_v x_6 x_7}{N} - Q_4 x_8, \\ \dot{x}_9 &= \eta x_8 - \mu_v x_9. \end{aligned} \right\} \quad (22)$$

The system (22) with the bifurcation point θ , has a simple zero eigenvalue. Thus, it enables us to use the Center Manifold Theory to analyse the stability of the system (22) near $\beta_h = \theta$. Therefore a right eigenvector w associated with zero eigenvalue has components

$$\begin{aligned} w_1 &= -\frac{b_1 \mu_v^2 (\gamma + \mu_h) (\eta + \mu_v)}{b_2 \gamma \eta \mu_h \beta_v}, & w_2 &= \frac{b_1 \mu_v^2 (\eta + \mu_v)}{b_2 \gamma \eta \beta_v}, & w_3 &= \frac{b_1 \mu_v^2 (\eta + \mu_v)}{b_2 \eta \mu_h \beta_v}, \\ w_4 &= w_5 = w_6 = 0, & w_7 &= -\frac{(\eta + \mu_v)}{\eta}, & w_8 &= \frac{\mu_v}{\eta}, & w_9 &= 1. \end{aligned} \quad (23)$$

Similarly, the corresponding left eigenvector v associated with zero eigenvalue has components

$$\begin{aligned} v_1 &= v_4 = v_7 = 0, & v_2 &= 1, & v_3 &= \frac{Q_1}{\gamma}, & v_5 &= \frac{Q_1 \kappa \beta_v \rho \gamma \mu_h + \beta_v \varphi (\gamma (\rho \gamma + \varphi) + \mu_h (\gamma + \rho \gamma))}{Q_2 Q_3 \beta_v \gamma}, \\ v_6 &= \frac{Q_1 \beta_v (\kappa \mu_h + \varphi)}{Q_2 \beta_v \gamma}, & v_8 &= \frac{Q_1 b_1 \mu_v}{b_2 \beta_v \gamma}, & v_9 &= \frac{Q_1 Q_4 b_1 \mu_v}{b_2 \beta_v \eta \gamma}. \end{aligned} \quad (24)$$

We now compute \mathbf{a} and \mathbf{b} as outlined in [27]. From the system (22), the non-zero partial derivatives of $f(x)$ associated with \mathbf{a} are given by

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_9} = \frac{\theta \mu_h}{b_1}, \quad \frac{\partial^2 f_8}{\partial x_3 \partial x_7} = \frac{\beta_v \mu_h}{b_1}, \quad \frac{\partial^2 f_8}{\partial x_6 \partial x_7} = \frac{\kappa \beta_v \mu_h}{b_1}. \quad (25)$$

Thus, the expression for \mathbf{a} is given by

$$\begin{aligned} \mathbf{a} &= v_2 w_1 w_9 \frac{\partial^2 f_2}{\partial x_1 \partial x_9} + v_8 w_3 w_7 \frac{\partial^2 f_8}{\partial x_3 \partial x_7} + v_8 w_6 w_7 \frac{\partial^2 f_8}{\partial x_6 \partial x_7}, \\ &= -\left(\frac{b_1 \mu_v^3 (\gamma + \mu_h) (\eta + \mu_v)^2 (\mu_v (\gamma + \mu_h) + \gamma \kappa \beta_v)}{b_2^2 \gamma^2 \eta^2 \beta_v^2} \right) < 0. \end{aligned} \quad (26)$$

We finally compute the value of \mathbf{b} . The non-zero partial derivatives of $f(x)$ associated with b is given by

$$\frac{\partial^2 f_2}{\partial x_9 \partial \theta} = 1. \quad (27)$$

Therefore the expression for \mathbf{b} is given by

$$\mathbf{b} = v_2 w_9 \frac{\partial^2 f_2}{\partial x_9 \partial \theta} = 1 > 0. \quad (28)$$

Since, $\mathbf{a} < 0$ and $\mathbf{b} > 0$, we conclude from item (iv) of Center Manifold Theorem [27] that the established endemic equilibrium E_1 is locally asymptotically stable for $\mathcal{R}_0 > 1$ and there exists a positive unstable equilibrium. This completes the proof. \square

4. Model with impulses

In this section, we present and analyse the system with pulse treatment of onchocerciasis with ivermectin. Treatment occurs every six months. We therefore first examine the case of fixed times t_k , with individuals treated at rate α . This results in system of impulsive differential equations [22, 23, 28]. The administration of ivermectin is thus approximated by an instantaneous change.

4.1. General solution

Here, we overestimate the number of people infected with onchocerciasis in the population. Suppose the maximal number of individuals infected with onchocerciasis is given by inequality (15). Then the one-dimensional impulsive differential equation given by

$$\begin{aligned} \frac{dI_H}{dt} &= \gamma \left[\frac{\beta_h b_2}{\mu_v} + \frac{\delta \varphi \beta_h b_2}{\mu_v (\rho \gamma + \varphi + \mu_h)} \right] + \varphi \left[\frac{\delta \beta_h \rho \gamma b_2}{\mu_v (\varphi + \mu_h) (\rho \gamma + \varphi + \mu_h)} \right] - \mu_h I_H, \quad t \neq t_k, \\ \Delta I_H &= -\alpha I_H, \quad t = t_k, \end{aligned} \quad (29)$$

overestimates the number of infected individuals.

Letting $I = I_H$ for notational simplicity, from (29) we have

$$\begin{aligned} I^+ - I^- &= -\alpha I, \\ I^+ &= (1 - \alpha) I^-. \end{aligned}$$

Let $Q_5 = \beta_h b_2 \gamma [\delta \rho \varphi + Q_2 (\delta \varphi + Q_3)]$ and denote $I_k^+ = I(t_k^+)$ and $I_k^- = I(t_k^-)$. Here, $I(t_k^-)$ is the population proportion of infected individuals immediately before the impulse and $I(t_k^+)$ is the value immediately after the impulse. Hence, for a single impulsive cycle $t_k \leq t \leq t_k + 1$, we have

$$\begin{aligned} I'(t) + \mu_h I(t) &= \frac{Q_5}{Q_2 Q_3 \mu_v}, \\ \frac{d}{dt} (e^{\mu_h t} I) &= \frac{Q_5}{Q_2 Q_3 \mu_v} (e^{\mu_h t} I), \\ e^{\mu_h t} I(t) - e^{\mu_h t_k} I(t_k^+) &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} e^{\mu_h t} - \frac{Q_5}{Q_2 Q_3 \mu_h^2 \mu_v} e^{\mu_h t_k}, \\ I(t) &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} (1 - e^{\mu_h (t_k - t)}) + I(t_k^+) e^{\mu_h (t_k - t)}. \end{aligned}$$

It therefore follows that

$$\begin{aligned} I_{k+1}^- &= \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) \left(1 - e^{\mu_h(t_{k+1}-t_k)} \right) + I_k^+ e^{\mu_h(t_{k+1}-t_k)}, \\ &= \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) \left(1 - e^{-\mu_h(t_{k+1}-t_k)} \right) + (1-\alpha) I_k^- \left(e^{-\mu_h(t_{k+1}-t_k)} \right). \end{aligned} \quad (30)$$

The solution obtained in (30) at the impulse points satisfies

$$\begin{aligned} I_1^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v}, & I_1^+ &= (1-\alpha) \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right), \\ I_2^- &= (1-\alpha) \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) e^{-\mu_h(t_2-t_1)} + \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) \left(1 - e^{\mu_h(t_2-t_1)} \right), \\ I_2^+ &= (1-\alpha) I_2^- = (1-\alpha)^2 \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) e^{-\mu_h(t_2-t_1)} + (1-\alpha) \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) \left(1 - e^{\mu_h(t_2-t_1)} \right), \\ I_3^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left((1-\alpha)^2 e^{-\mu_h(t_3-t_1)} + (1-\alpha) e^{-\mu_h(t_3-t_2)} + 1 - (1-\alpha) e^{-\mu_h(t_3-t_1)} - e^{-\mu_h(t_3-t_2)} \right), \\ I_3^+ &= (1-\alpha) I_3^- = \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left((1-\alpha)^3 e^{-\mu_h(t_3-t_1)} + (1-\alpha)^2 e^{-\mu_h(t_3-t_2)} + (1-\alpha) - (1-\alpha)^2 e^{-\mu_h(t_3-t_1)} \right. \\ &\quad \left. - (1-\alpha) e^{-\mu_h(t_3-t_2)} \right), \\ I_4^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left((1-\alpha)^3 e^{-\mu_h(t_4-t_1)} + (1-\alpha)^2 e^{-\mu_h(t_4-t_2)} + (1-\alpha) e^{-\mu_h(t_4-t_3)} + 1 - (1-\alpha)^2 e^{-\mu_h(t_4-t_1)} \right. \\ &\quad \left. - (1-\alpha) e^{-\mu_h(t_4-t_2)} - e^{-\mu_h(t_4-t_3)} \right), & I_4^+ &= (1-\alpha) I_4^-. \end{aligned}$$

Thus, the general solution becomes

$$\begin{aligned} I_n^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left((1-\alpha)^{(n-1)} e^{-\mu_h(t_n-t_1)} + (1-\alpha)^{(n-2)} e^{-\mu_h(t_n-t_2)} + \dots + (1-\alpha) e^{-\mu_h(t_n-t_{n-1})} \right. \\ &\quad \left. + 1 - (1-\alpha)^{(n-2)} e^{-\mu_h(t_n-t_1)} - (1-\alpha)^{(n-3)} e^{-\mu_h(t_n-t_2)} - \dots - e^{-\mu_h(t_n-t_{n-1})} \right). \end{aligned} \quad (31)$$

The general solution obtained in (31) defines the maximal number of people with onchocerciasis immediately before the mass treatment with ivermectin. This solution depends on the human and vector recruitment rates, the human-vector transmission contact rate, the incubation period in the human, the waning rate of ivermectin, human and vector death rates, treatment times and the treatment effectiveness. A similar approach can be employed to calculate the maximal number of latently infected individuals using the overestimate obtained in (14). For fixed mass administration of ivermectin, (31) does not depend on time.

4.2. Fixed administration of ivermectin

For a fixed time period $\tau = t_{n+1} - t_n$, we have

$$\begin{aligned} I_n^- &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 + (1-\alpha) e^{\mu_h \tau} + (1-\alpha)^2 e^{-2\mu_h \tau} + \dots + (1-\alpha)^{(n-1)} e^{-\mu_h(n-1)\tau} \right. \\ &\quad \left. - e^{-\mu_h \tau} \left(1 + (1-\alpha) e^{-\mu_h \tau} + \dots + (1-\alpha)^{(n-2)} e^{-\mu_h(n-2)\tau} \right) \right), \\ &= \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(\frac{1 - (1-\alpha)^n e^{\mu_h n \tau}}{1 - (1-\alpha) e^{\mu_h \tau}} - \frac{1 - (1-\alpha)^{(n-1)} e^{-\mu_h(n-1)\tau}}{1 - (1-\alpha) e^{-\mu_h \tau}} e^{-\mu_h \tau} \right). \end{aligned}$$

Thus

$$\lim_{n \rightarrow \infty} I_n^- = \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(\frac{1}{1 - (1 - \alpha) e^{-\mu_h \tau}} - \frac{1}{1 - (1 - \alpha) e^{-\mu_h \tau}} e^{-\mu_h \tau} \right) = \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(\frac{1 - e^{-\mu_h \tau}}{1 - (1 - \alpha) e^{-\mu_h \tau}} \right). \quad (32)$$

The solution obtained in (32) is the maximum population of the infected individuals. Note that

$$\lim_{\substack{\tau \rightarrow 0 \\ n \rightarrow \infty}} I_n^- = 0,$$

implying that the total number of infected humans shrinks to zero as the frequency of mass treatment with ivermectin increases (although note that the impulsive assumptions would break down in this limit). In order to keep the infected individuals under a threshold \hat{I} , we have

$$\hat{I} < \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(\frac{1 - e^{-\mu_h \tau}}{1 - (1 - \alpha) e^{-\mu_h \tau}} \right),$$

which implies that

$$\tau < \frac{1}{\mu_h} \ln \left[\frac{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v (1 - \alpha)}{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v} \right] = \tau_{\max}(\alpha). \quad (33)$$

The expression in (33) gives the maximum period of mass administration of ivermectin in the population to keep the infection of onchocerciasis below \hat{I} . If we restrict τ to $0 \leq \tau < \tau_{\max}$, then the disease can be controlled below the threshold \hat{I} (but not necessarily eradicated).

4.3. Non-fixed administration of ivermectin

In this section, we consider a situation in which the mass administration of ivermectin is carried out at non-fixed times. However, this would require that the entire history of ivermectin administration is known, which is unlikely to be the case. Thus, we will assume that ivermectin treatment occurring more than two events previously has a negligible effect on the number of currently treated individuals. That is,

$$e^{-\mu_h(t_n - t_k)} \approx 0 \text{ for } k > 2.$$

It then follows from (30) that

$$\begin{aligned} I_n^- &< \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - e^{-\mu_h(t_n - t_{n-1})} \right), \\ I_{n+1}^- &< \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - e^{-\mu_h(t_n - t_{n-1})} \right) + (1 - \alpha) I_n^- e^{-\mu_h(t_n - t_{n-1})}, \\ &< \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - e^{-\mu_h(t_{n+1} - t_n)} \right) + (1 - \alpha) \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - \alpha e^{-\mu_h(t_n - t_{n-1})} \right) e^{-\mu_h(t_{n+1} - t_n)}. \end{aligned}$$

The above inequality can be approximated as

$$\hat{I} \equiv \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - e^{-\mu_h(t_{n+1} - t_n)} \right) + (1 - \alpha) \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \left(1 - \alpha e^{-\mu_h(t_n - t_{n-1})} \right) e^{-\mu_h(t_{n+1} - t_n)}. \quad (34)$$

The expression in (34) gives the number of infected humans that will be below \hat{I} based on knowing the two previous mass administration times. Then the "next best" mass treatment with ivermectin satisfies the following:

$$\begin{aligned} \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} (1 + (1 - \alpha)) - \hat{I} &= e^{-\mu_h(t_{n+1} - t_n)} \left(\frac{Q_5}{Q_2 Q_3 \mu_h \mu_v} \right) (1 + \alpha(1 - \alpha) e^{-\mu_h(t_{n+1} - t_n)}), \\ e^{-\mu_h(t_{n+1} - t_n)} &= \frac{2 - \alpha - Q_5 / Q_2 Q_3 \mu_h \mu_v}{1 + \alpha(1 - \alpha) e^{-\mu_h(t_{n+1} - t_n)}}, \\ t_{n+1} &= t_n - \frac{1}{\mu_h} \ln \left(\frac{2 - \alpha - Q_5 / Q_2 Q_3 \mu_h \mu_v}{1 + \alpha(1 - \alpha) e^{-\mu_h(t_{n+1} - t_n)}} \right). \end{aligned}$$

Next we compare fixed and non-fixed mass treatment with ivermectin. Assuming that the mass treatment times in the non-fixed case are constant, $\hat{\tau}$, then from (33), we have

$$\hat{\tau} = \frac{1}{\mu_h} \ln \left(\frac{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v (1 - \alpha)}{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v} \right), \quad (35)$$

$$\hat{\tau}|_{\alpha=0} = \frac{1}{\mu_h} \ln \left(\frac{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v}{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v} \right) = 0, \quad (36)$$

$$\hat{\tau}|_{\alpha=1} = \frac{1}{\mu_h} \ln \left(\frac{Q_5}{Q_5 - \hat{I} Q_2 Q_3 \mu_h \mu_v} \right). \quad (37)$$

If there is no impulse, then from (29), we have $\lim_{t \rightarrow \infty} I = \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v}$. Thus, we can assume that $\hat{I} = \frac{Q_5}{Q_2 Q_3 \mu_h \mu_v}$.

Hence,

$$0 < 1 - \frac{Q_2 Q_3 \mu_h \mu_v \hat{I}}{Q_5} < 1, \quad (38)$$

therefore, $\hat{\tau}|_{\alpha=1} > 0$. Assuming that non-fixed mass treatment with ivermectin occurs indefinitely and further letting $\tau_{\max} \equiv t_{n+1} - t_n = t_n - t_{n-1}$, then the minimum treatment effectiveness satisfies

$$\tau_{\max} = \frac{1}{\mu_h} \ln \left(\frac{2 - \alpha - \hat{I} Q_2 Q_3 \mu_h \mu_v / Q_5}{1 + \alpha(1 - \alpha) e^{-\mu_h \tau_{\max}}} \right). \quad (39)$$

If $\tau_{\max} = 0$, then it follows that (39) becomes

$$\begin{aligned} \frac{1}{\mu_h} \ln \left(\frac{2 - \alpha - \hat{I} Q_2 Q_3 \mu_h \mu_v / Q_5}{1 + \alpha(1 - \alpha)} \right) &= 0, \\ 2 - \alpha - \hat{I} \frac{Q_2 Q_3 \mu_h \mu_v}{Q_5} &= 1 + \alpha(1 - \alpha), \\ \alpha &= 1 \pm \sqrt{\frac{Q_2 Q_3 \mu_h \mu_v}{Q_5}}. \end{aligned}$$

The larger root exceeds 1 and hence can be discounted. It follows that the smaller root $\alpha_0 = 1 - \sqrt{\frac{Q_2 Q_3 \mu_h \mu_v}{Q_5}}$, satisfies $0 < \alpha_0 < 1$ as stated in (38). This implies that the mass treatment is only effective in the range $\alpha_0 < \alpha \leq 1$.

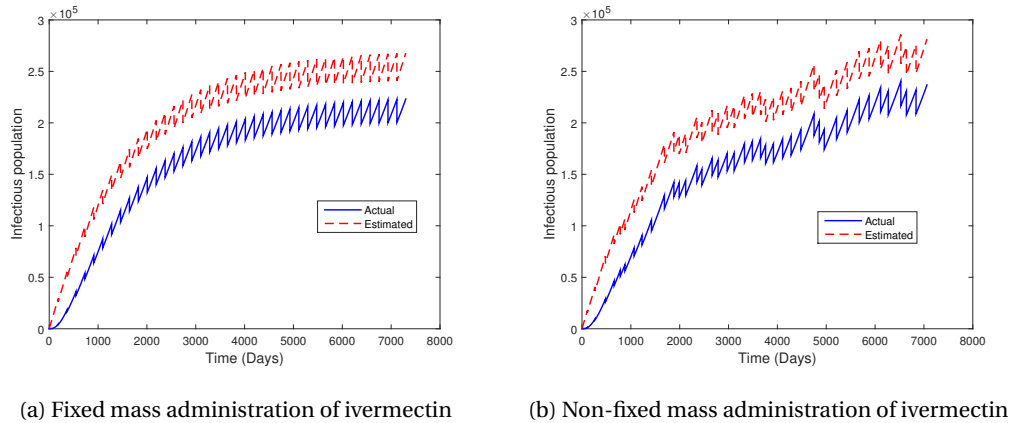


Fig. 2: Comparison of the actual infected individuals and the estimated infected individuals.

5. Numerical simulations

In this section, we carry out parameter estimation, sensitivity analysis of the model parameters and numerical simulations for system (4) to demonstrate the theoretical results. The simulations are performed using the fourth order Runge–Kutta scheme in Matlab 2014a with the set of parameter values given in Table 1. We consider the parameters in realistic ranges with guidance from past literature on onchocerciasis epidemics in Ghana.

5.1. Parameter estimation

We consider average parameter values that encompass features of onchocerciasis disease including the rate of infection, the incubation period and the length of infections period in the vector and host populations. Although estimates of some parameters are given in Table 1, here we give additional explanations and descriptions of some of the parameters.

1. The average birthrate in Ghana was estimated to be 31.09 births/1,000 population in 2015 and 30.60 births/1,000 population in 2014 according to the World Fact Book by Central Intelligence Agency [29] and Ghana Statistical Service report on Demographic and Health Survey [30] respectively. Owing to unchecked immigration, the recruitment rate is therefore estimated to be in the range $(0.0000819 \leq b_1 \leq 0.00108)N$ per day.
2. The natural human death rate is estimated based on average life of 50–70 years in accordance with Central Intelligence Agency data and 2014 demographic data released by Ghana Statistical Service estimates of life expectancy at birth [29, 30]. The average blackfly lifespan is 2–3 weeks [20, 31].
3. It takes $\frac{3}{4}$ to 2 years for the worm to mature and release enough microfilariae to be detectable in the skin of the human host [20, 32, 33, 34]. Therefore a reasonable estimate of the incubation rate γ is

$0.00137 \leq \gamma \leq 0.00365$ per day. On the other hand, the average incubation period in the blackfly is 1–2 weeks [20, 33, 34, 35]. Thus, a reasonable value for η is $0.0714 \leq \eta \leq 0.1667$ per day.

4. The modification parameters (κ, δ and ρ) are strictly between 0 and 1 due to the reduced ability of individuals to cause infections following ivermectin treatment.
5. The mass administration rate α is estimated to be between 0% and 100%.

For illustration purpose, we consider the parameter values estimates given in Table 1 with $N = 200,000$ and $V = 10,000$.

Table 1: Estimated parameter values in the model for onchocerciasis case. The rates are given per day.

Parameter	Definition	Range	Point value (assumed)	Source
b_1	Human recruitment rate	0.0000819–0.001085	0.00009/N	Estimated
μ_h	Death rate of humans	0.0000391–0.0000548	0.000052	[29, 30]
β_h	The rate of transmission of the disease from blackflies to humans	0–0.01	0.00198	Assumed
γ	Transfer rate from E_H to I_H class	0.00137–0.00365	0.00139	[20, 32, 33, 34]
α	Ivermectin treatment rate	0–1	[0.1, 0.65]	[9, 36]
φ	Waning rate of ivermectin	0.01–0.1	0.0015	[36]
κ	Modification parameter	0–1	0.0083	Assumed
ρ	Modification parameter	0–0.1	0.001	Assumed
δ	Modification parameter	0–1	0.002	Assumed
b_2	Vector recruitment rate	0.0214–0.4	0.144/V	Assumed
β_v	The rate of transmission of the disease from humans to blackflies	0–0.01	0.00079	Assumed
η	Transfer rate from E_V to I_V class	0.0714–0.1667	0.078	[20, 33, 34, 35]
μ_v	Death rate of blackflies	0.0118–0.0714	0.068	[20, 31]

5.2. Sensitivity analysis

Sensitivity analysis is the study of how uncertainty in the output of a system can be apportioned to different sources of uncertainty in the model input [37, 38]. It is a technique for systematically varying model inputs and determining their effect on the model output. We perform sensitivity analysis in order to investigate the contribution of vital parameters on the model dynamics, specifically to establish the parameters that have significant influence on the onchocerciasis dynamics. We use Latin Hypercube Sampling (LHS), a stratified Monte Carlo sampling scheme applicable to many parameters from a multidimensional distribution [37, 38]. It allows for simultaneous determination of an unbiased estimate of the model output for a given

set of model input. We perform the sensitivity analysis by computing the Partial Rank Correlation Coefficients (PRCCs) for each parameter value, sampled by the LHS scheme [39]. Parameters with positive PRCCs will increase R_0 when they are increased, whereas parameters with negative PRCCs will decrease R_0 when they are increased. The outcome is the reproduction number R_0 derived from the theoretical model. We determine PRCCs with 1000 simulations per run to determine parameters that have a significant influence on R_0 .

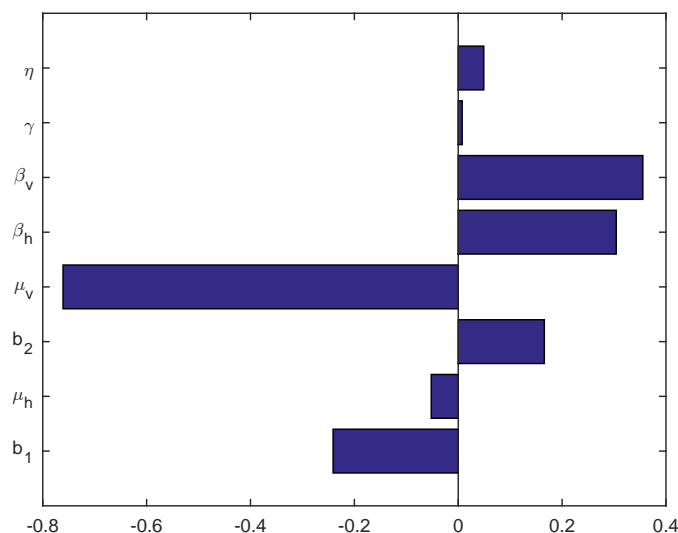


Fig. 3: Tornado plots of partial rank correlation coefficients (PRCCs) of the parameters that influence R_0 for the input parameters using the values in Table 1. Parameters with $\text{PRCC} > 0$ increase R_0 when they are increased whereas parameters with $\text{PRCC} < 0$ decrease R_0 when they are increased.

The PRCCs results in Figure 3 illustrate the degree of the effect that each parameter has on the outcome. The three parameters with the most influence on R_0 are the transmission contact rate in humans, β_h , the vector transmission contact rate, β_v , and the vector death rate μ_v .

Figure 4 displays 1000 Monte Carlo simulations for the input parameters with the most effect on the basic reproduction number. Scatter plots show that R_0 is monotone increasing with increasing values of β_h and β_v and monotone decreasing with increasing vector mortality rate, μ_v . However, R_0 is only guaranteed to be less than unity when the human–vector and vector–human contact rates are sufficiently small. These results also suggest that, even if vector death rate is extremely high, eradication is not possible.

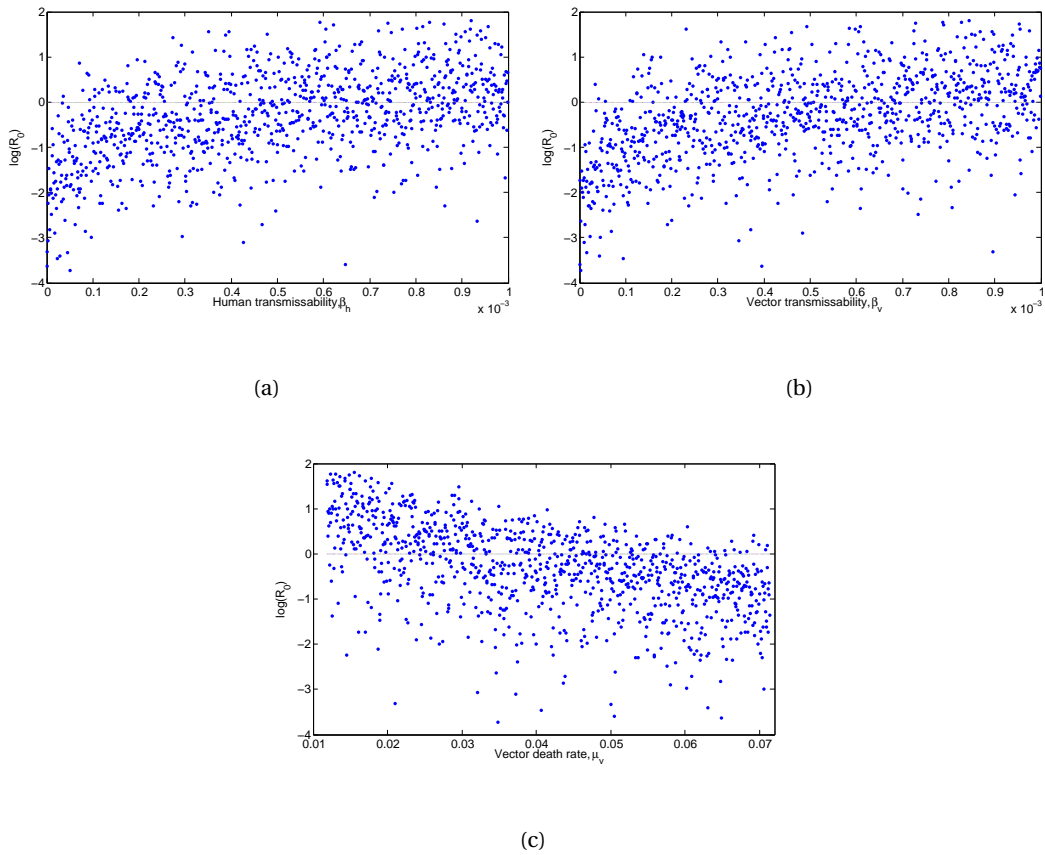


Fig. 4: The Monte Carlo simulations for the three parameters with the greatest influence on the R_0 : the transmission contact rate in humans, the transmission contact rate in the vector and the vector death rate for the input parameters using the values in Table 1 and 1000 simulations per run. Eradication is only possible if the transmissibilities are extremely small or if the vector death rate is extremely high.

In order to gain more insight into the three parameters with the greatest influence on the basic reproduction number, R_0 , all other parameters were fixed at their sample values. A surface plot for $R_0 = 1$ is shown in Figure 5.

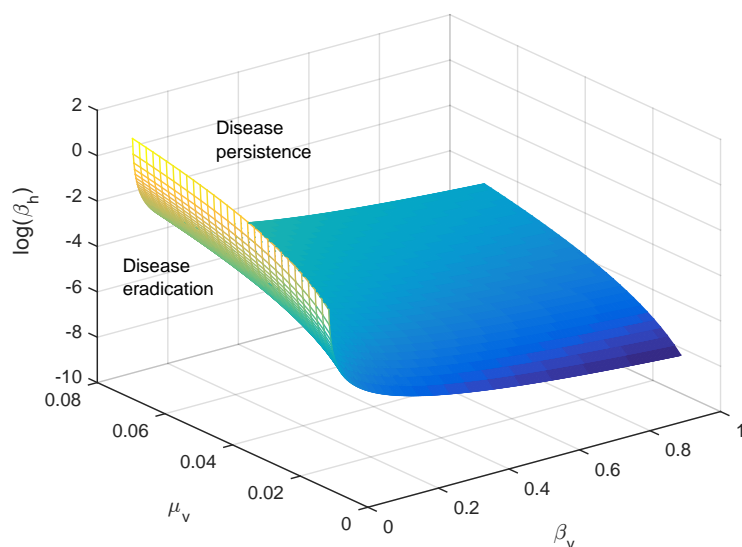


Fig. 5: Eradication threshold for the three parameters with the greatest influence on R_0 .

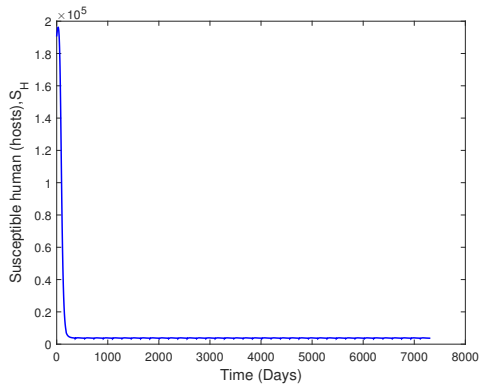
5.3. Simulation results

The results presented in this section demonstrate the dynamics of onchocerciasis for the system (4) obtained using Matlab ODE45 solver, which employs simultaneously the fourth and fifth order Runge–Kutta schemes. Unless otherwise stated, parameters are as stated in Table 1. We give results of system (4) with impulses for both the cases when $R_0 < 1$ and when $R_0 > 1$ as shown in Figures 8–11 and Figures 6–7, respectively. In addition, we numerically make a comparison between fixed and non-fixed mass administration of ivermectin in the treatment of onchocerciasis. In order to illustrate the effectiveness of ivermectin, we vary the reduction rate (α) for both the cases of R_0 .

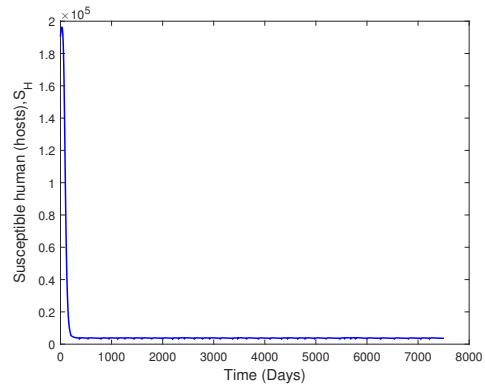
First, we examine the behaviour of the system (4) when the basic reproduction number, R_0 , is greater than unity for the fixed and non-fixed mass administration of ivermectin. It is seen in Figure 6 that when the effectiveness of ivermectin is low, that is, $\alpha = 0.10$, the disease spreads in the population. However, the results in Figure 7 show that the endemicity of the disease is reduced when the effectiveness rate of mass administration of ivermectin is increased. We also observe that fixed mass administration yields a better outcome compared to non-fixed mass administration.

We then examine the case when the basic reproduction number is below unity for both the fixed and non-fixed mass administration of ivermectin. We examine two cases of $R_0 < 1$: when R_0 is close to unity and where R_0 is significantly less than unity. We observe in Figure 8 that when R_0 is less than but close to one, the disease may persist in the population when the value of α is small. However an increment in the value of α moves the system towards a disease-free state, but there is no eradication. This is shown in Figure 9 with $\alpha = 0.65$. The results in Figure 10 show the dynamics of the population under both fixed and non-fixed mass administration of ivermectin at $\alpha = 0.1$ keeping the interval $\tau = 182.5$ days (6 monthly

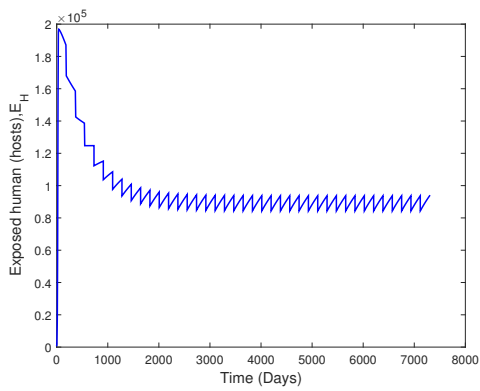
interval) for fixed mass administration. We observe that the system with impulses attains its disease-free state, suggesting that onchocerciasis dies out. These results are consistent with theorem (3.5). However, when the ivermectin effectiveness is increased, the system attains the disease free equilibrium much faster as shown in Figure 11.



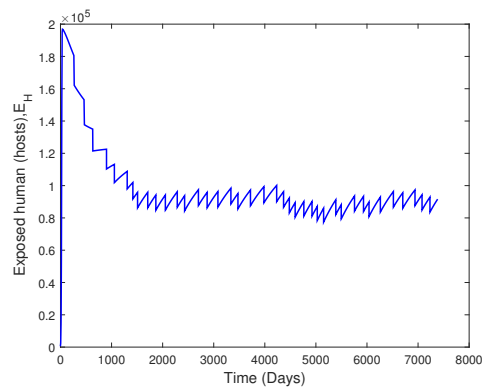
(a) Fixed



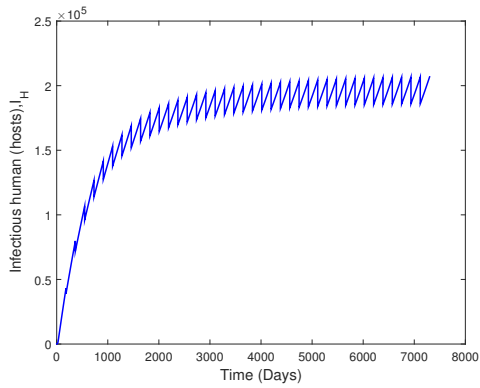
(b) Non-fixed



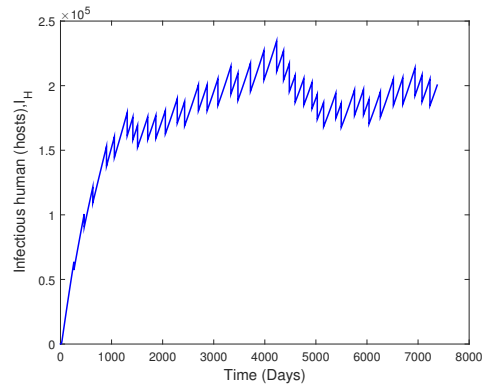
(c) Fixed



(d) Non-fixed

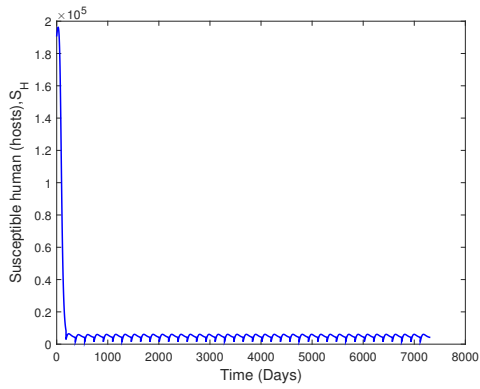


(e) Fixed

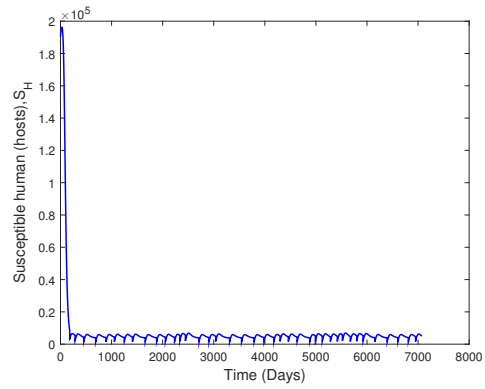


(f) Non-fixed

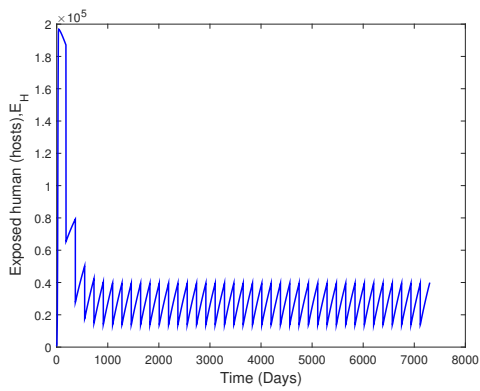
Fig. 6: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.10, R_0 = 1.2412, b_1 = 0.0009, b_2 = 0.35, \beta_h = 0.00562, \beta_v = 0.00243, \varphi = 0.025, \mu_v = 0.012$.



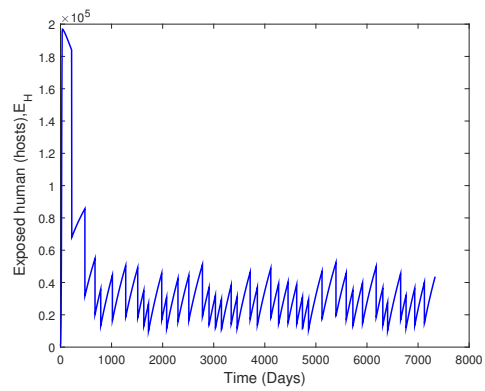
(a) Fixed



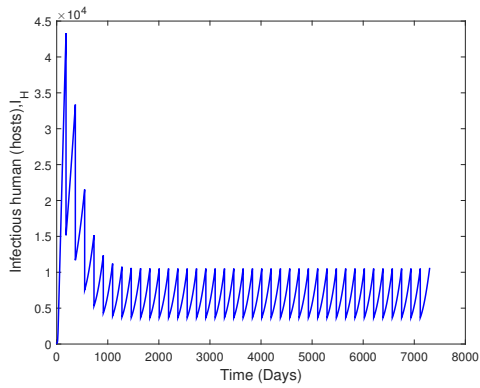
(b) Non-fixed



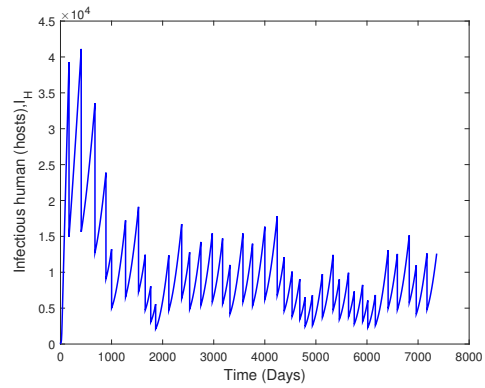
(c) Fixed



(d) Non-fixed

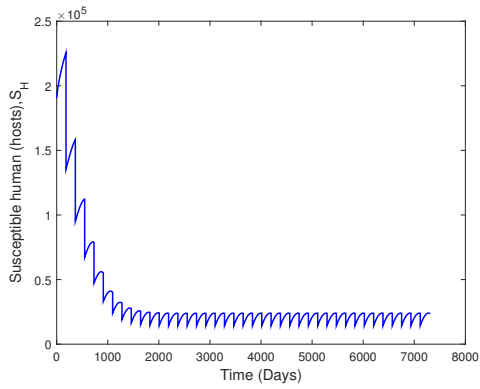


(e) Fixed

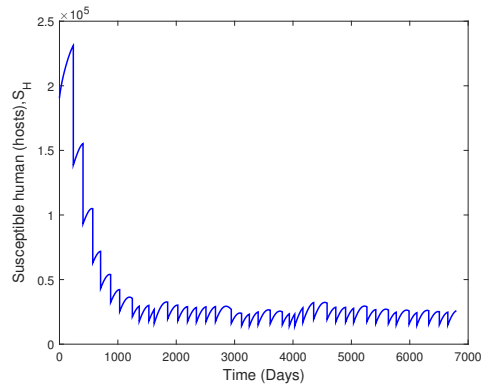


(f) Non-fixed

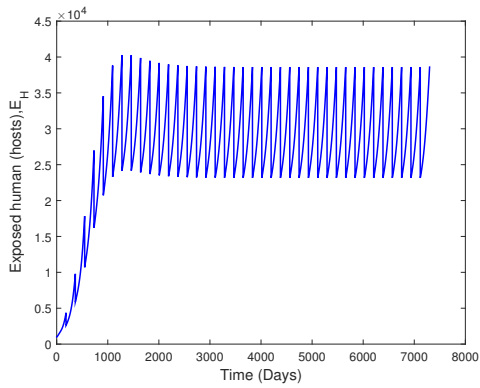
Fig. 7: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.65$, $R_0 = 1.2412$, $b_1 = 0.0009$, $b_2 = 0.35$, $\beta_h = 0.00562$, $\beta_v = 0.00243$, $\varphi = 0.025$, $\mu_v = 0.012$. Note that increasing α improves the outcome but does not lead to eradication.



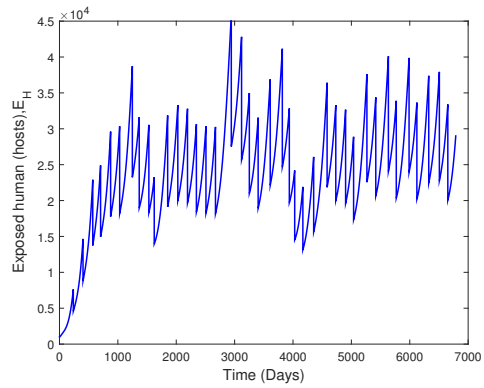
(a) Fixed



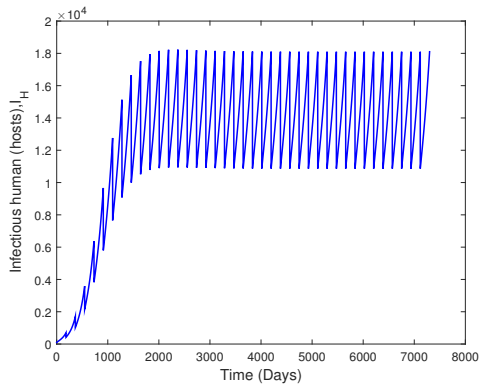
(b) Non-fixed



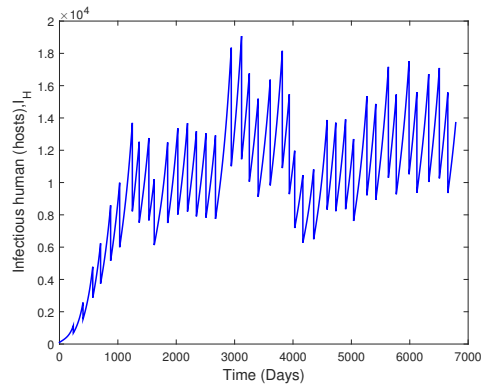
(c) Fixed



(d) Non-fixed



(e) Fixed



(f) Non-fixed

Fig. 8: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.10, R_0 = 0.9352, b_1 = 0.0009, b_2 = 0.35, \beta_h = 0.00443, \varphi = 0.025, \beta_v = 0.00175, \mu_v = 0.012$. Non-fixed administration may produce lower overall numbers of infected individuals, but the outcome is not predictable.

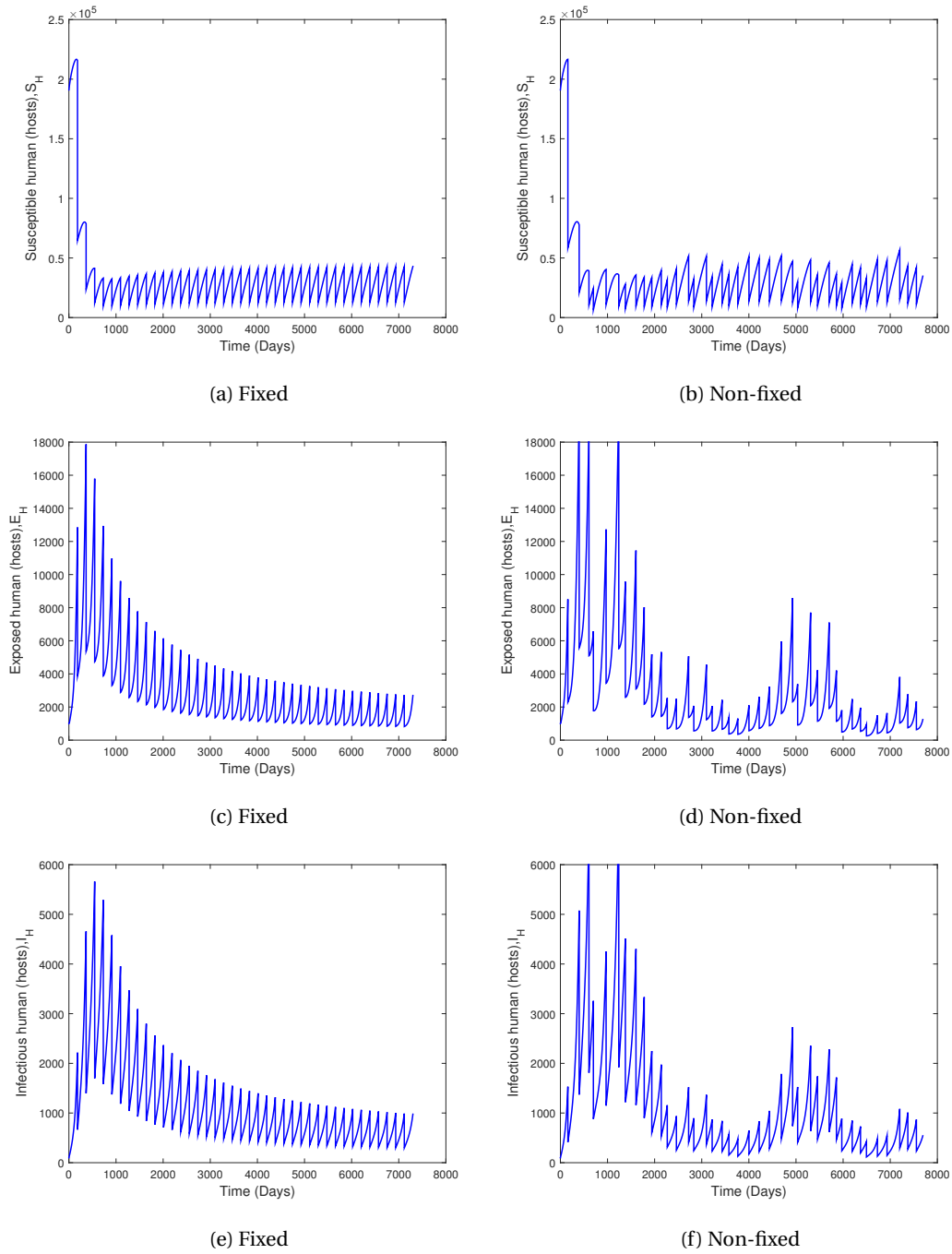
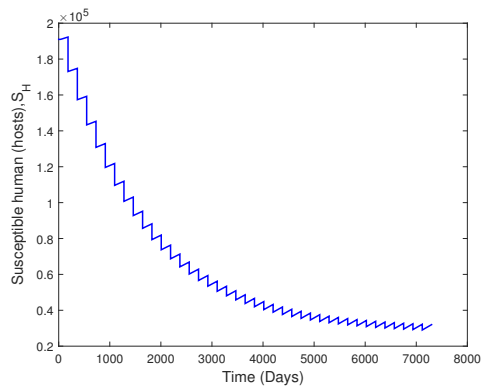
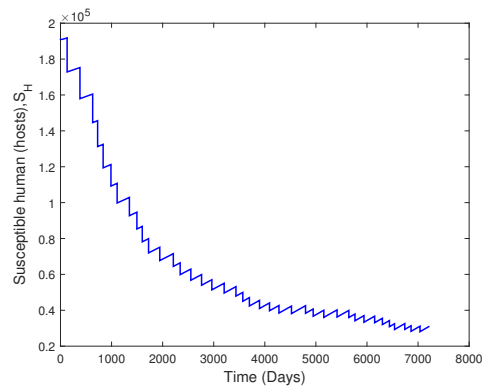


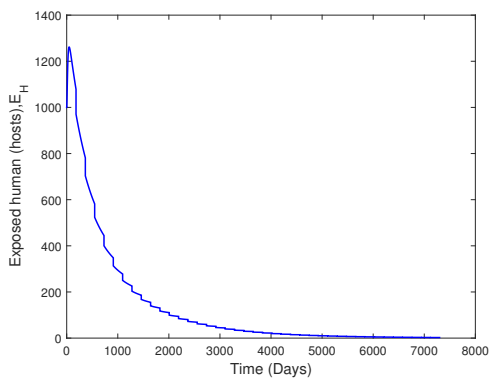
Fig. 9: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.65, R_0 = 0.9352, b_1 = 0.0009, b_2 = 0.35, \beta_h = 0.00443, \varphi = 0.025, \beta_v = 0.00175, \mu_v = 0.012$. Non-fixed administration may produces bursts of infection, even if the disease would be otherwise kept at low levels.



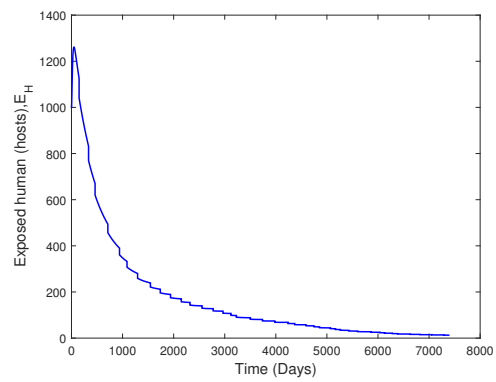
(a) Fixed



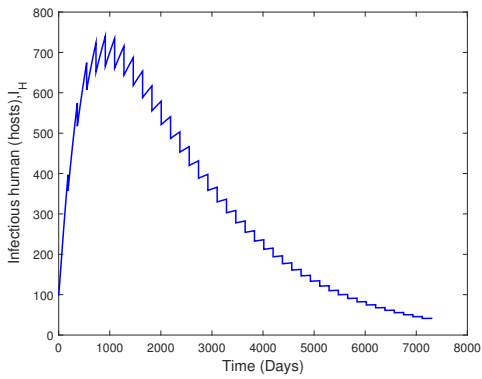
(b) Non-fixed



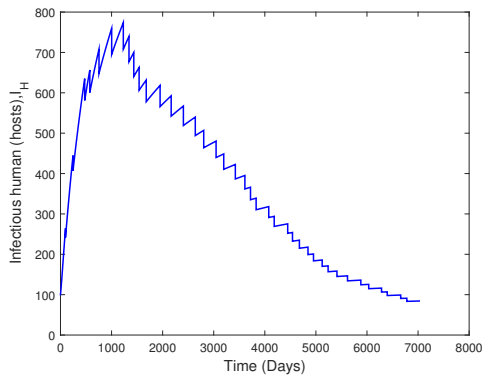
(c) Fixed



(d) Non-fixed

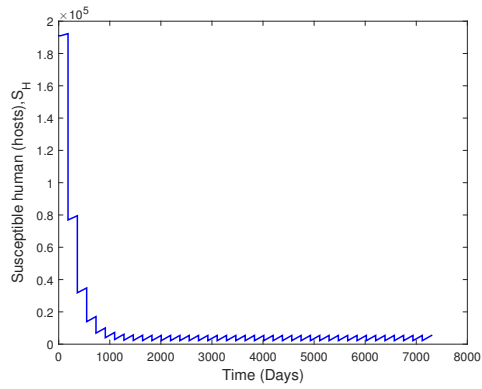


(e) Fixed

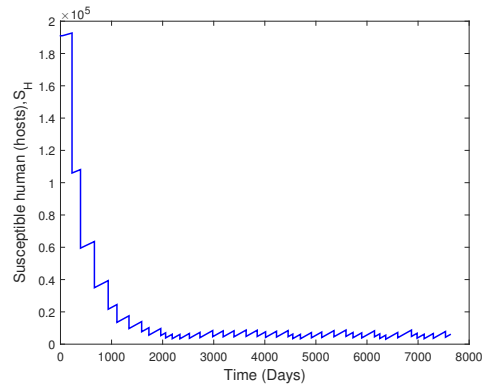


(f) Non-fixed

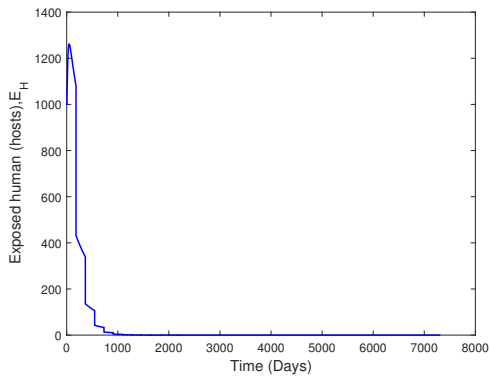
Fig. 10: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.1, R_0 = 0.1181$ using parameter values in Table 1. Note that non-fixed administration may have a delaying or preventative effect on eradication.



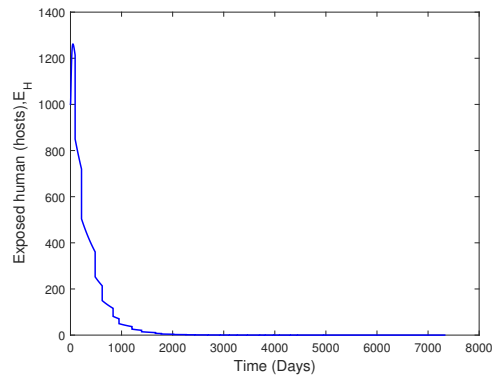
(a) Fixed



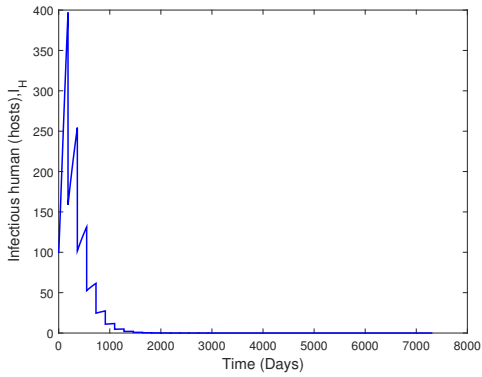
(b) Non-fixed



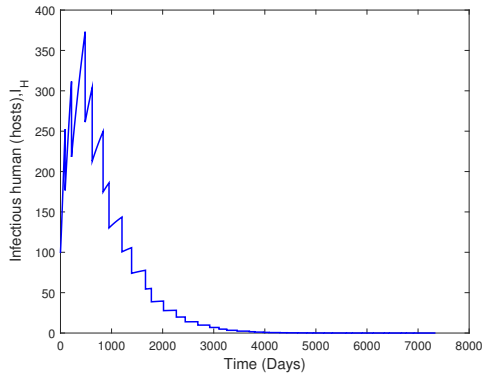
(c) Fixed



(d) Non-fixed



(e) Fixed



(f) Non-fixed

Fig. 11: System behaviour for fixed and non-fixed mass administration of ivermectin with $\alpha = 0.65$, $R_0 = 0.1181$ using parameter values in Table 1. Increasing α hastens eradication, in both the fixed and non-fixed case.

6. Conclusion

Onchocerciasis is one of the neglected tropical diseases that is still to be eradicated. In connection with the WHO's plan of onchocerciasis elimination, mass administration of ivermectin is the most efficient approach towards this effort. This is spearheaded by APOC in sub-Saharan Africa where the disease is endemic. In order to investigate the effectiveness of ivermectin in the control of onchocerciasis, we formulated a deterministic model that captures the dynamics of this disease in humans and blackflies. The analysis of the model without pulse mass administration of ivermectin shows that, the disease-free state exists and is stable if $R_0 < 1$. On the other hand, if $R_0 > 1$, the disease-free state loses its stability and the system tends towards the endemic state.

We have provided the estimates for the necessary frequency and strength of mass administration of ivermectin. We may conclude that the disease can be controlled through mass administration with needed frequency and high strength of ivermectin. Furthermore, our results suggest that reducing human-vector contact can be one way of reducing but not eradicating onchocerciasis from the population. This can be done by implementing personal protection practices such as wearing insect repellent, wearing long sleeves and long pants during the day when blackflies bite. In addition, application of insecticides can be effective in reducing the presence of vector in the environment.

We have observed from our numerical results that the eradication of onchocerciasis is possible with tolerable regularity of mass administration of ivermectin provided the basic reproduction number is kept (far) below unity. We can conclude that, in the presence of mass administration of ivermectin with six month intervals, the disease can be controlled. Furthermore, if the frequency of mass administration is increased, the system moves towards a better outcome. Our modelling results show that mass administration of ivermectin at regular interval is an effective method of onchocerciasis eradication if other parameters can be sufficiently controlled.

The model presented in this paper has a number of limitations. Mass administration of ivermectin is assumed to occur instantaneously. However, in reality, there is usually a small delay as mass treatment reaches its maximum coverage. It is important to note that the delays do not affect the impulsive assumptions, provided the time interval of mass administration of ivermectin is significantly larger than the instantaneous approximation. Unavailability of experiential data poses a challenge for model verification. Despite the shortcomings, the model still provides some useful insights into the control of onchocerciasis through the implementation of regular mass administration of ivermectin in conjunction with transmission reduction and the implementation of vector-control measures.

Acknowledgment

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