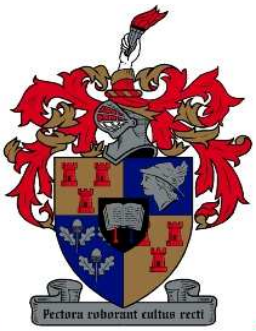

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Modelling the control of tsetse and African trypanosomiasis through application of insecticides on cattle in Southeastern Uganda

Supervisor: Prof. John Hargrove
Co-supervisors: Prof. Joseph Y.T. Mugisha & Prof. Charles Waiswa

by

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Declaration

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and has not previously, in its entirety or in part, been submitted at any university for a degree.

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Damian Kajunguri Date

Abstract

In Uganda, cattle are an important reservoir of *Trypanosoma brucei rhodesiense*, a parasite that causes human African trypanosomiasis or sleeping sickness. We developed mathematical models to examine the transmission of *T. b. rhodesiense* by tsetse vector species, *Glossina fuscipes fuscipes* in a host population that consists of humans, domestic and wild mammals, and reptiles. The models were developed and analysed based on the situation in Tororo district in Southeastern Uganda, where sleeping sickness is endemic and which has a cattle and human population of $40,000$ and $500,000$, respectively. Assuming populations of cattle and humans only, the impact of mass chemoprophylaxis and vector control through insecticide-treated cattle (ITC) is evaluated. Keeping 12% or 82% of the cattle population on insecticides that have an insecticidal killing effect of 100% at all times or trypanocides that have 100% efficacy, respectively, can lead to the control of *T. b. rhodesiense* in both humans and cattle. Optimal control of *T. b. rhodesiense* is shown to be achieved through ITC alone or a combination of chemoprophylaxis and ITC, the former being the cheapest control strategy. Allowing for the waning effect of insecticides and including wildhosts, *T. b. rhodesiense* control can be achieved by keeping 21% or 27% of the cattle population on insecticides through whole-body or restricted application, respectively. Restricting the treatment of insecticides to adult cattle only would require 24% or 33% of the adult cattle population to be kept on insecticides through whole-body or restricted application, respectively, to control *T. b. rhodesiense*. A cost-effectiveness and benefit-cost analysis of using ITC to control *T. b. rhodesiense* show that restricted application of insecticides is a cheaper and more beneficial strategy compared to whole-body treatment. The results of the study show that the restricted application of insecticides on cattle provides a cheap, safe and farmer-based strategy for controlling tsetse and trypanosomiasis.

Opsomming

In Uganda is beeste 'n belangrike reservoir van *Trypanosoma brucei rhodesiense*, 'n parasiet wat tripanosomiase of slaapsiekte in mense veroorsaak. Ons het wiskundige modelle ontwikkel wat die oordrag van *T. b. Rhodesiense* deur tesetse vektor spesies, *Glossina fuscipes fuscipes* in 'n draer populasie wat bestaan uit mense, mak en wilde diere en reptiele, ondersoek. Die modelle was ontwikkel en geanaliseer gebaseer op die oordrag situasie in die Tororo distrik in Suidoostelike Uganda, 'n gebied waar slaapsiekte endemies is en wat 'n populasie van $40,000$ beeste en $500,000$ mense het. Die impak van massa chemoprofilakse en vektor beheer deur insekdoder-behandelde beeste is gevalueer onder die aanname van bees en mens populasies alleenlik. Beheer oor *T. b. Rhodesiense* in beide mense en beeste kan verkry word deur of 12% van die bees populasie te behandel met 'n insekdoder wat 100% effektief is ten alle tye of 82% van die bees populasie te behandel met tripanosiedes wat 100% effektief is. Daar is aangetoon dat optimale beheer van *T. b. Rhodesiense* bereik kan word deur die gebruik van insekdoders alleenlik of 'n kombinasie van insekdoders en chemoprofilakse, hoewel eersgenoemde die goedkoopste strategie is. Wanneer die kwynende effek van insekdoders asook wilde diere as draers in ag geneem word, kan *T. b. Rhodesiense* beheer verkry word deur 21% van beeste se hele liggaam met insekdoders te behandel of 27% gedeeltelik te behandel. As slegs volwasse beeste met insekdoders behandel word, moet 24% se hele liggaam of 33% gedeeltelik behandel word vir beheer van *T. b. Rhodesiense*. 'n Koste-effektiwiteit en voordeel-koste analise van insekdoders as beheermaatstaf vir *T. b. Rhodesiense* toon aan dat gedeeltelike behandeling van die bees se liggaam die goedkoper en meer voordelige strategie is in vergelyking met behandeling van die hele liggaam. Die resultate van die studie wys dat gedeeltelike behandeling van beeste met insekdoders 'n goedkoop, veilige en landbouer-gebaseerde strategie is om tsetse en tripanosomiase te beheer.

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Finally, my sincere appreciation goes to my family and friends at home, who instilled in me the strength and confidence to continue in the way of success, to make my passion and dreams come true.

Contents

1 Introduction **1**

1.1 Background 1

1.2 Epidemiology of African trypanosomiasis in Africa 1

1.3 Epidemiology of African trypanosomiasis in Uganda 4

1.4 Importance of domestic animals and wildlife in the transmission of African trypanosomiasis 6

1.5 Parasite lifecycle and clinical aspects of infection 7

1.6 Control of African trypanosomiasis 8

1.7 Cost-effectiveness analysis of disease control strategies 10

1.8 Benefit-cost analysis of disease control 11

1.9 Integrated Control of Neglected Zoonotic diseases (ICONZ) project 11

1.10 Motivation 12

1.11 Objectives of the study 13

1.12 Outline of this work 13

1.13 Publications 14

2 Literature review **16**

2.1 Modelling the transmission and control of trypanosomiasis 16

2.2 Comparative analysis of the costs, benefits and effectiveness of tsetse and trypanosomiasis control 19

2.3 Conclusion 20

3 Modelling the control of *T. b. rhodesiense* through mass chemoprophylaxis and insecticide-treated cattle 22

3.1 Introduction 22

3.2 Model development and analysis 22

3.2.1 Estimation of the tsetse mortality in the presence of insecticide-treated cattle 25

3.2.2 Effect of mass chemoprophylaxis and ITC on R_0 29

3.2.3 The optimal control problem to minimise the cost of controlling *T. b. rhodesiense* through chemoprophylaxis and ITC 30

3.2.4 Sensitivity analysis 31

3.3 Parameter estimation 37

3.3.1 Demographic parameters 37

3.3.2 Tsetse infection parameters 38

3.3.3 Cattle infection parameters 39

3.3.4 Human infection parameters 39

3.4 Numerical results 39

3.4.1 Estimation of minimum R_{0H} if humans only are susceptible to infection 39

3.4.2 Prevention of an epidemic 40

3.4.3 Optimal control of the disease through chemoprophylaxis and ITC . 46

3.5 Summary 50

4 A multi-host model for the control of tsetse and *T. b. rhodesiense* through insecticide-treated cattle 52

4.1 Introduction 52

4.2 Model development 52

4.2.1 Including insecticide-treated cattle (ITC) in the model 55

4.3 Mathematical analysis 58

4.3.1 Analysis of the multi-host model in the absence of ITC 58

4.3.2 Local stability of the disease-free equilibrium of the one-host *T. b. rhodesiense* transmission model in the absence of ITC 61

4.3.3 The endemic steady states of the multi-host *T. b. rhodesiense* transmission model in the absence of ITC 64

4.3.4 Mathematical analysis of the multi-host model in the presence of ITC 66

4.3.5 Sensitivity analysis of R_{03}^T to parameter values 67

4.3.6 Cost-effectiveness analysis 69

4.4 Numerical results 70

4.4.1 Parameter estimation 71

4.4.2 Importance of cattle and wildlife in the transmission of *T. b. rhodesiense* 74

4.4.3 Application of insecticides to cattle to prevent the transmission . . 76

4.4.4 Effect of insecticide-treated cattle on the tsetse population 80

4.4.5 Cost-effectiveness analysis of the ITC control programme 80

4.5 Summary 83

5 Modelling the control of tsetse and *T. b. rhodesiense* by treating adult cattle only with insecticides 85

5.1 Introduction 85

5.2 Model development 86

5.2.1 Basic reproduction number 88

5.2.2 Benefit-cost analysis 89

5.3 Numerical Results 90

5.3.1 Prevention of the epidemic by treating adult cattle only with insecticides 90

5.3.2 Effect of treating adult cattle only with insecticides on the tsetse population 93

5.3.3 Benefit-cost analysis of the ITC control programme 94

5.4 Summary 95

6 Conclusions and recommendations 97

6.1 Limitations and future work 99

Appendix 101

A Derivation of the tsetse recruitment rate, Λ_V 101

List of Figures

1.1 Distribution of human African trypanosomiasis in sub-Saharan Africa. The black line divides the areas in which *Trypanosoma bruce gambiense* prevails and in which *Trypanosoma brucei rhodesiense* predominates [11]. 2

1.2 Number of reported cases of African trypanosomiasis and population screened, 1939-2004. Data obtained from [55, 76] 3

1.3 The map of Uganda highlighting areas of *T. b. gambiense* and *T. b rhodesiense* transmission for the years 1985, 1995, 2000 and 2005 [26]. 4

1.4 Number of reported cases of African trypanosomiasis in Uganda, 1939-2004. Data obtained from [55, 76] 5

1.5 Number of reported cases of *T. b. rhodesiense* in Uganda compared with all the cases reported in Africa, 1990-2009. Data obtained from [55, 76] . . 6

1.6 The life cycle of African trypanosomiasis. Reproduced from [11] 7

3.1 Flow diagram of the compartmental model of *T. b. rhodesiense* in cattle, human and tsetse populations. λ_C, λ_H, and λ_V are the forces of infection for cattle, humans and tsetse vectors, respectively. 25

3.2 Sensitivity analysis of R_0 with respect to ϕ_C for $\epsilon = 100\%, 90\%, 85\%, 75\%$ and 65% (a), and the control parameters p and ϕ_C for $\epsilon = 100\%$ (b). All the other parameters are given in Table 3.5. 33

3.3 The effect of mass chemoprophylaxis on the basic reproduction number for different values of ϵ and γ_C. The values of γ_C and ϵ were taken to be 0.0055 and 100% in (a) and (b), respectively. 41

3.4 Proportion of cattle kept on trypanocides for different values of ϕ_C. 41

3.5 Mass chemoprophylaxis. (a) incidence and (b) prevalence of *T. b. rhodesiense* in humans. Different proportions of cattle are taken to be kept on chemoprophylactic drugs that provide 100% protection to infection. The recovery rate for infectious cattle g_C is taken to be $g'_C + \phi_C$. 42

3.6 The effect of insecticide-treated cattle on the basic reproduction number. . 43

3.7 Insecticide-treated cattle. (a) incidence and (b) prevalence of *T. b. rhodesiense* in humans for different proportions of cattle assumed to be kept on insecticides. 44

3.8 The effect of combining chemoprophylaxis and insecticide-treated cattle on the basic reproduction number for $\epsilon = 100\%$ (a), and different values of ϵ (b). 45

3.9 Insecticide-treated cattle and mass chemoprophylaxis. (a) incidence and (b) prevalence of *T. b. rhodesiense* in humans. 2.0% of the cattle population is assumed to be kept on insecticides and 3.5% of cattle is treated with trypanocides that provide 100% protection to infection. The recovery rate for infectious cattle g_C is taken to be $g'_C + \phi_C$. 46

3.10 The critical proportions of cattle needed to be kept on insecticides and treated with trypanocides for R_0 to be less than ρ for $\rho = 1$ (a) and $\rho = 0.5$ (b). The cost ratio (CR) refers to the ratio of the daily cost of keeping one cow on insecticides to the cost of treating one cow with trypanocides. $\epsilon = 1$ in all cases and all the other parameters values are given in Table 3.5. . . . 47

3.11 Insecticide-treated cattle and mass chemoprophylaxis. Proportions of cattle required to be treated with either insecticides or trypanocides for $CR = 0.04$ (a) and $CR = 0.12$ (b) . $\epsilon = 1$ in both cases and all the other parameters values are given in Table 3.5. 48

3.12 Insecticide-treated cattle and mass chemoprophylaxis. Total cost for controlling *T. b. rhodesiense* in humans and cattle against the basic reproduction number threshold (ρ) and the time required for controlling the disease in years. $\epsilon = 1$ in all cases and all the other parameters values are given in Table 3.5. 48

4.1 Flow diagram of the compartmental model of *T. b. rhodesiense* in tsetse and a multi-host population that includes treatment of cattle with insecticides. The cattle population that is treated with insecticides is enclosed in a dotted rectangle. λ_i and λ_V are the forces of infection for the host and tsetse vector populations, respectively. 54

4.2 Tsetse mortality estimates for different proportions of cattle treated with insecticides. 56

4.3 Simulation results for the *T. b. rhodesiense* incidence and prevalence in humans in the absence of curative treatment of infectious humans and cattle, and ITC. 73

4.4 *T. b. rhodesiense* infection rates for cattle, human and wildlife host populations. 74

4.5 *T. b. rhodesiense* infection rate in wildlife with different proportions of monitor lizards in the wildlife population 75

4.6 *T. b. rhodesiense* incidence (a) and prevalence (b) in humans for different proportions of monitor lizards in the wildlife population. 76

4.7 The effect of treating cattle with insecticides on the basic reproduction number, R_{03}^T. (a) shows the plot of the basic reproduction number, R_{03}^T with respect to the proportion of cattle treated with insecticides, ψ for $d = 0.04$. (b) and (c) shows the critical proportions of cattle needed to be treated with insecticides for different values of d for whole body and restricted application, respectively. 77

4.8 Proportion of cattle kept on insecticides 78

4.9 Increased tsetse mortality through insecticide-treated cattle (ITC). *T. b. rhodesiense* incidence in humans for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b). 78

4.10 Increased tsetse mortality through insecticide-treated cattle (ITC). *T. b. rhodesiense* prevalence in humans for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b). 79

4.11 Effect of increased tsetse mortality through insecticide-treated cattle on the tsetse population for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b). 80

4.12 The cost of implementing the insecticide-treated cattle (ITC) control programme over time for whole-body (a) and restricted application of insecticides (b) to cattle 81

4.13 The cost-effectiveness ratio per infection avoided of the insecticide-treated cattle (ITC) control programme over time for whole-body (a) and restricted application of insecticides (b) to cattle 82

4.14 The cost-effectiveness ratio per DALY averted of the insecticide-treated cattle (ITC) control programme over time for whole-body (a) and restricted application of icnsectcides (b) to cattle 82

5.1 Flow diagram of the compartmental model of *T. b. rhodesiense* in tsetse, cattle, human and wildlife populations that includes treatment of adult cattle only with insecticides. The adult cattle population that is treated with insecticides is enclosed in a dotted rectangle. λ_i and λ_V are the forces of infection for the host and tsetse vector populations, respectively. 87

5.2 The effect of treating adult cattle only with insecticides on the basic reproduction number, R_A^T. (a) shows the plot of the basic reproduction number, R_A^T with respect to the proportion of adult cattle treated with insecticides, ψ_A for $d = 0.04$. (b) and (c) shows the critical proportions of adult cattle needed to be treated with insecticides for different values of d for whole body and restricted application, respectively. 91

5.3 Proportion of adult cattle kept on insecticides 92

5.4 Increased tsetse mortality through treatment of adult cattle only with insecticides. *T. b. rhodesiense* incidence in humans for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b). . 93

5.5 Increased tsetse mortality through treatment of adult cattle only with insecticides. *T. b. rhodesiense* prevalence in humans for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b). 93

5.6 Effect of increased tsetse mortality through treatment of adult cattle with insecticides on the tsetse population for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b). 94

5.7 The benefit-cost ratio of the ITC control programme through treatment of adult cattle only with insecticides for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b). 95

List of Tables

3.1 The model variables 23

3.2 Definitions of the parameters used in the model 24

3.3 Sensitivity indices of R_0. All parameters were fixed to the values given in Table 3.5, ϕ_C, ϵ and p were taken to be 0.02, 0.5 and 0.05, respectively. . . 32

3.4 Sensitivity indices of the endemic equilibrium with respect to the control parameters considered in the model. All parameters were fixed to the values given in Table 3.5, ϕ_C, ϵ and p were taken to be 0.05, 0.8 and 0, respectively. The tsetse recruitment and mortality rates are evaluated at $p = 0$ and taken to be $\Lambda_V = \Lambda_V(0) = 1,235$ and $\mu_V = \mu_V(0) = 0.03$, respectively, where μ_V is the tsetse natural mortality. 36

3.5 Model parameter value estimates. All time periods are given in days and all rates are instantaneous per capita rates per day. 38

4.1 Definitions of the parameters used in the model 53

4.2 Sensitivity indices of R_{03}^T of the 3-host *T. b. rhodesiense* model with and without insecticide-treated cattle. All parameters were fixed to the values given in Table 4.3, and ψ was taken to be 0.02. 68

4.3 Numerical values for the parameters of the three-host model 72

Chapter 1

Introduction

1.1 Background

Human African trypanosomiasis or sleeping sickness is caused by protozoan parasites of the genus *Trypanosoma* transmitted by tsetse flies (genus *Glossina*). Trypanosomes cause disease in both humans and animals and if left untreated, the disease is fatal [16]. The African trypanosomes pathogenic for humans belong to the species *Trypanosoma brucei*, which has two subspecies: *T. b. gambiense*, which causes the chronic form of the disease in central and west Africa; and *T. b. rhodesiense*, which causes more acute disease in East and Southern Africa (figure 1.1) [8, 11, 13, 47].

1.2 Epidemiology of African trypanosomiasis in Africa

Sleeping sickness is endemic in 37 countries of sub-Saharan Africa (figure 1.1), where there are suitable habitats for its vector, the tsetse fly. A small fraction of the patients in these countries are under surveillance with regular examination, have access to a health centre that can provide diagnostic facilities, or are protected by vector control interventions. The number of reported cases annually is over 10,000 [56]. Over 60 million people live in risk areas and since many of these have poor access to diagnostic and health care facilities, under-reporting is probably high [77, 79].

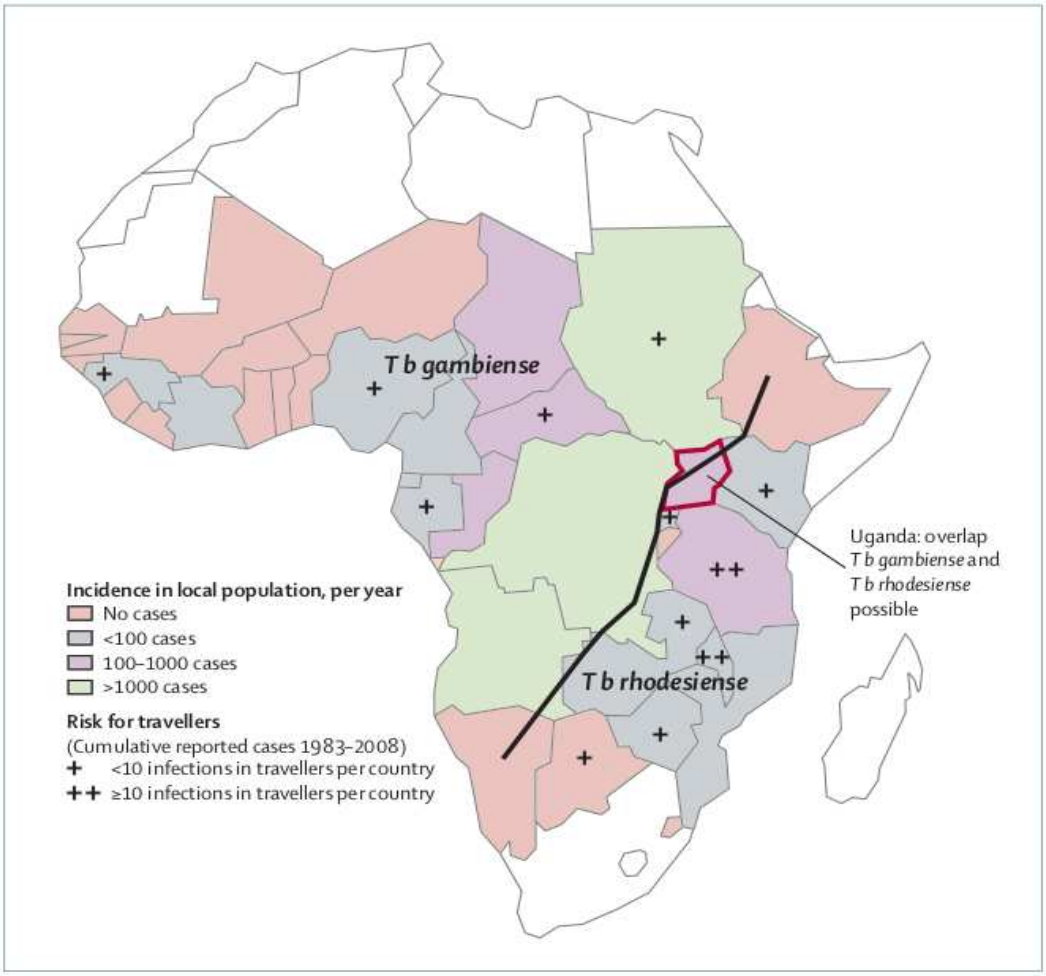


FIG. 1.1. Distribution of human African trypanosomiasis in sub-Saharan Africa. The black line divides the areas in which *Trypanosoma bruce gambiense* prevails and in which *Trypanosoma brucei rhodesiense* predominates [11].

Both human and animal African trypanosomiasis are a major cause of rural underdevelopment in sub-Saharan Africa. Although there are a few cases reported in urban and peri-urban areas, it mainly affects poor and remote rural regions. Infections normally occur in children and adults during activities such as farming, hunting, fishing, or washing clothes [11].

Three severe sleeping sickness epidemics took place in sub-Saharan Africa in the 20^{th} century. The first one took place between 1896 and 1906, and affected mainly Uganda and Congo killing an estimated 800,000 people. The second major epidemic which took place between 1920 and the late 1940s worried the colonial administrators and prompted them to

invest in vector and disease control. The disease was almost eradicated by the early 1960s (figure 1.2). By the mid 1960s most of the trypanosomiasis endemic countries had become independent and this led to the collapse of the surveillance and control activities due to political instability and economic ruin with a disastrous effect on the health services. This resulted in a decline in the number of screened individuals (figure 1.2), since most of the control programmes were stopped. The disease then re-emerged and reached its peak in the late 1990s. This marked the beginning of the third and most recent epidemic in the 20^{th} century in sub- Saharan Africa, mainly affecting Angola, Congo, Southern Sudan and the West Nile district of Uganda [11, 59].

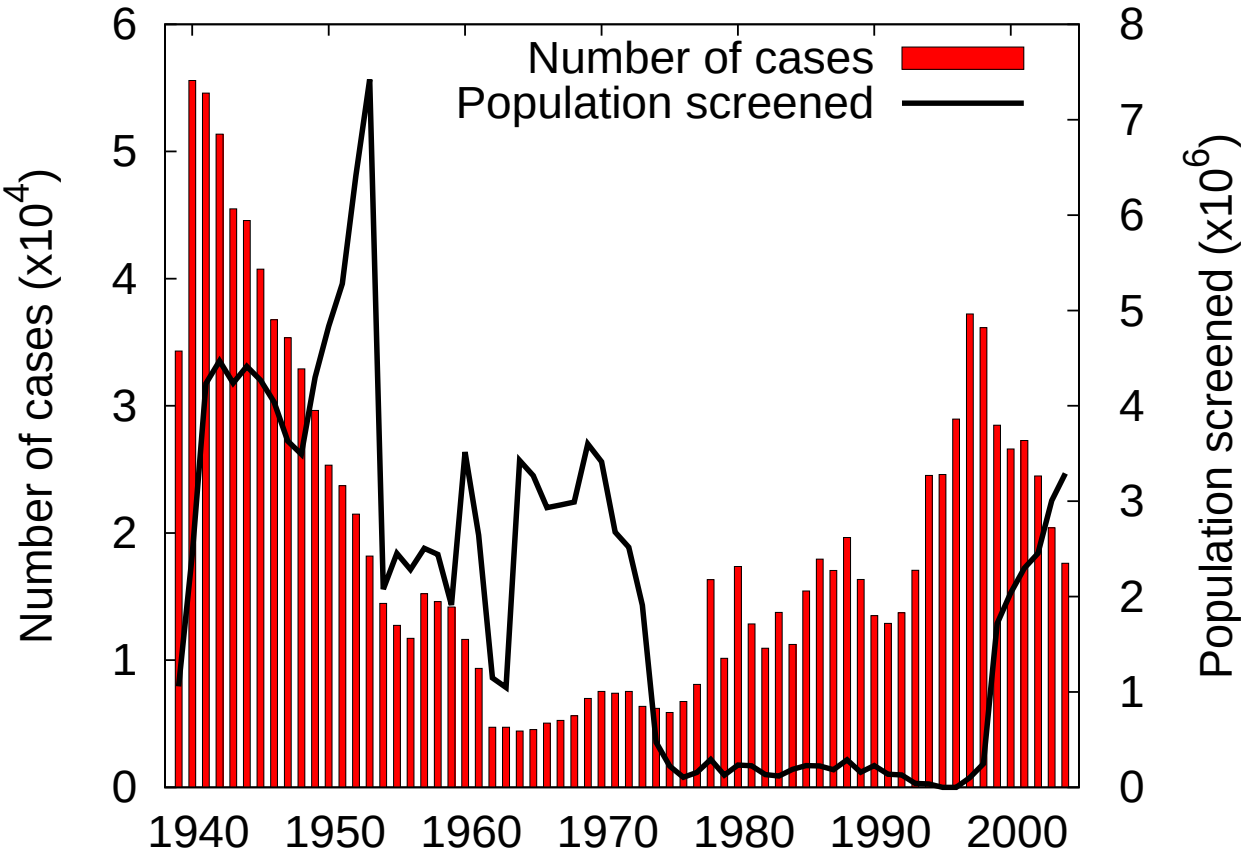


FIG. 1.2. Number of reported cases of African trypanosomiasis and population screened, 1939-2004. Data obtained from [55, 76]

1.3 Epidemiology of African trypanosomiasis in Uganda

In Uganda, African trypanosomiasis threatens the lives of more than 10 million people [58]. Both pathogens of human African trypanosomiasis are present in Uganda, with *T. b. gambiense* in the north-western and West Nile region, and *T. b. rhodesiense* in the Eastern region (figure 1.3). *T. b. rhodesiense* which was originally restricted to districts clustered around the north shore of Lake Victoria and the source of the Nille (Busoga region) has now spread to other districts including Tororo, Busia, Palisa and Mbale. Since 1980, the area affected by *T. b. rhodesiense* in Uganda has increased by a factor of 2.5 and the population at risk of getting the disease doubled [47]. This was observed through increased reporting of new cases of African trypanosomiasis in Uganda during 1977 to 1983. This increased reporting was attributed to the epidemic of *T. b. rhodesiense* sleeping sickness in Busoga (figure 1.4) [76]. Three major outbreaks have been recorded in Southeastern Uganda, with the latest epidemic starting in the 1980s [36, 72].

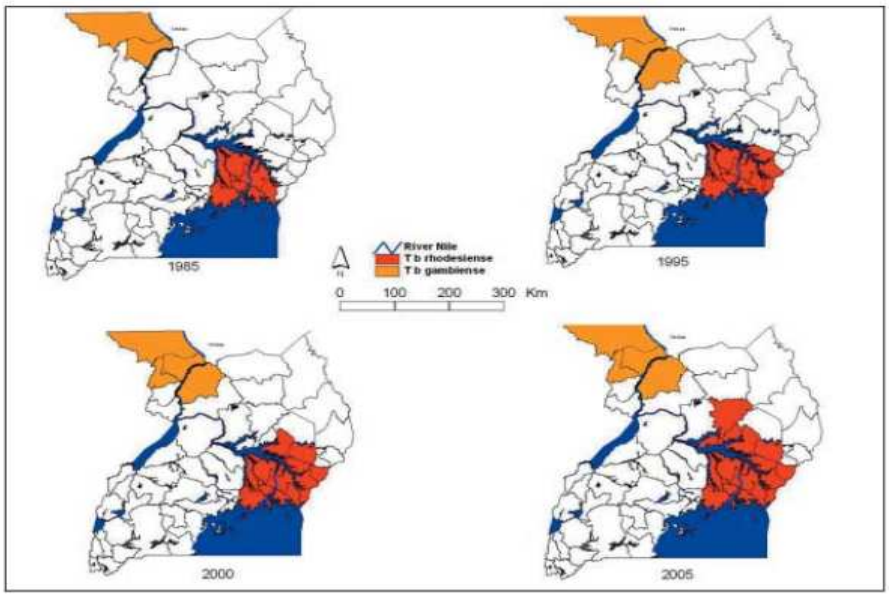


FIG. 1.3. The map of Uganda highlighting areas of *T. b. gambiense* and *T. b rhodesiense* transmission for the years 1985, 1995, 2000 and 2005 [26].

Livestock, in particular cattle is the most important reservoir of *T. b. rhodesiense* [26] in Eastern Uganda. Since the keeping of livestock is an economic and social activity in Eastern Uganda, the risk of transmission of the disease is anticipated to be high [9]. It is estimated

that cattle are kept in numbers of 1-5 cows per family either grazed at homestead or 50-100 animals grazed communally within or near the village borders [81]. Previous studies in Southeastern Uganda reported the prevalence of *T. brucei* species in the domestic cattle population to be 5%, and out of these, 23% being human infective *T. b. rhodesiense*. It has also been reported that a tsetse fly is five times more likely to pick up an infection from a cow than from a human [25].

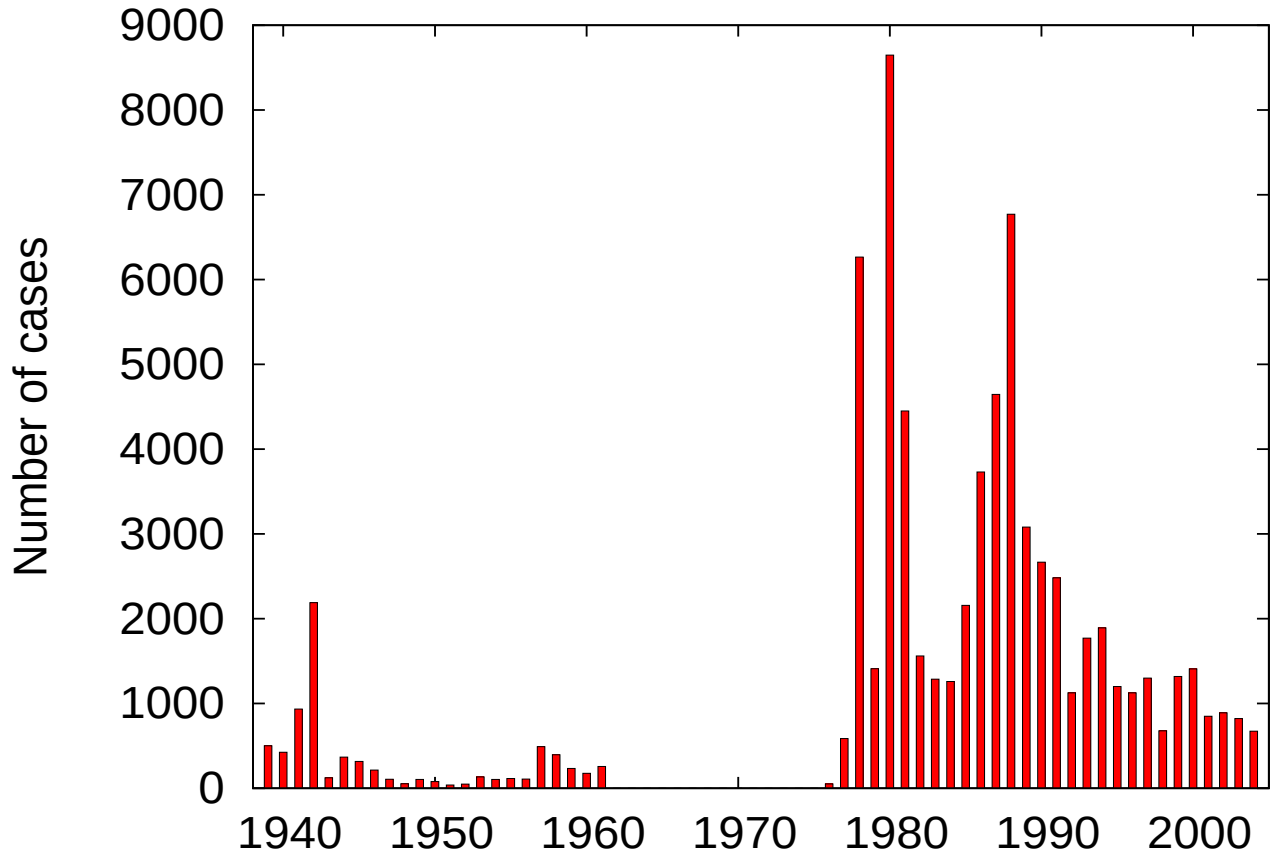


FIG. 1.4. Number of reported cases of African trypanosomiasis in Uganda, 1939-2004. Data obtained from [55, 76]

Movement of infected animals between localities has been seen as a strong factor that influences the transmission of trypanosomiasis in many countries including Uganda. For example, animals were implicated in the transmission of *T. b. rhodesiense* disease during the 1940s epidemic in Busoga, Southeastern Uganda. Cattle restocking was also believed to have led to an outbreak of *T. b. rhodesiense* in 2000 in which 18% of cattle were found

to be carrying the human pathogen [8, 47]. In a study that was done in Tororo District, Uganda, it was established that over 50% of cattle traded in the market were originating from endemic sleeping sickness areas [25]. These studies indicate that there is a need for treating livestock that is to be moved from infected areas, either for restocking or selling, if the disease is to be put under control.

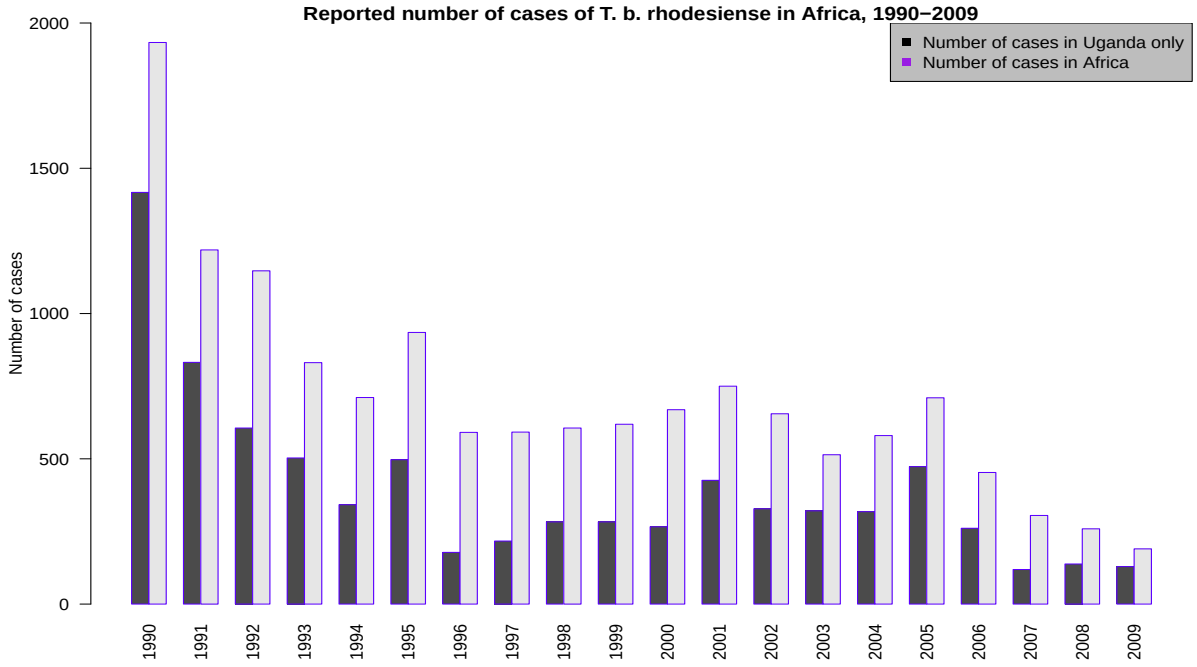


FIG. 1.5. Number of reported cases of *T. b. rhodesiense* in Uganda compared with all the cases reported in Africa, 1990-2009. Data obtained from [55, 76]

1.4 Importance of domestic animals and wildlife in the transmission of African trypanosomiasis

Trypanosomes are multi-host parasites capable of infecting a wide range of domestic and wildlife species, which constitute a reservoir for human infections. In domesticated animals clinical cases have been detected in cattle, water buffalo, sheep, goats, camels, horses, donkeys, alpacas, llamas, pigs, dogs, cats and other species. In wild animals clinical cases have been detected in bushbuck, buffalo, kudo,bushpig, duiker, giraffe, impala, lion, warthog,

waterbuck, zebra and other species [1, 71, 72]. In most parts of Africa, cattle are the main species affected, due to the tsetse feeding preferences and the fact that they can shield other domesticated animals such as goats and pigs from the effects of trypanosomiasis [61].

1.5 Parasite lifecycle and clinical aspects of infection

The parasite that causes human African trypanosomiasis is picked up from the blood of an infected human or domestic or wild animal by a tsetse fly while feeding and undergoes an essential maturation within the vector, resulting in the infectious stage in the salivary glands. Tsetse flies are more likely to pick an infection while having their first meal.

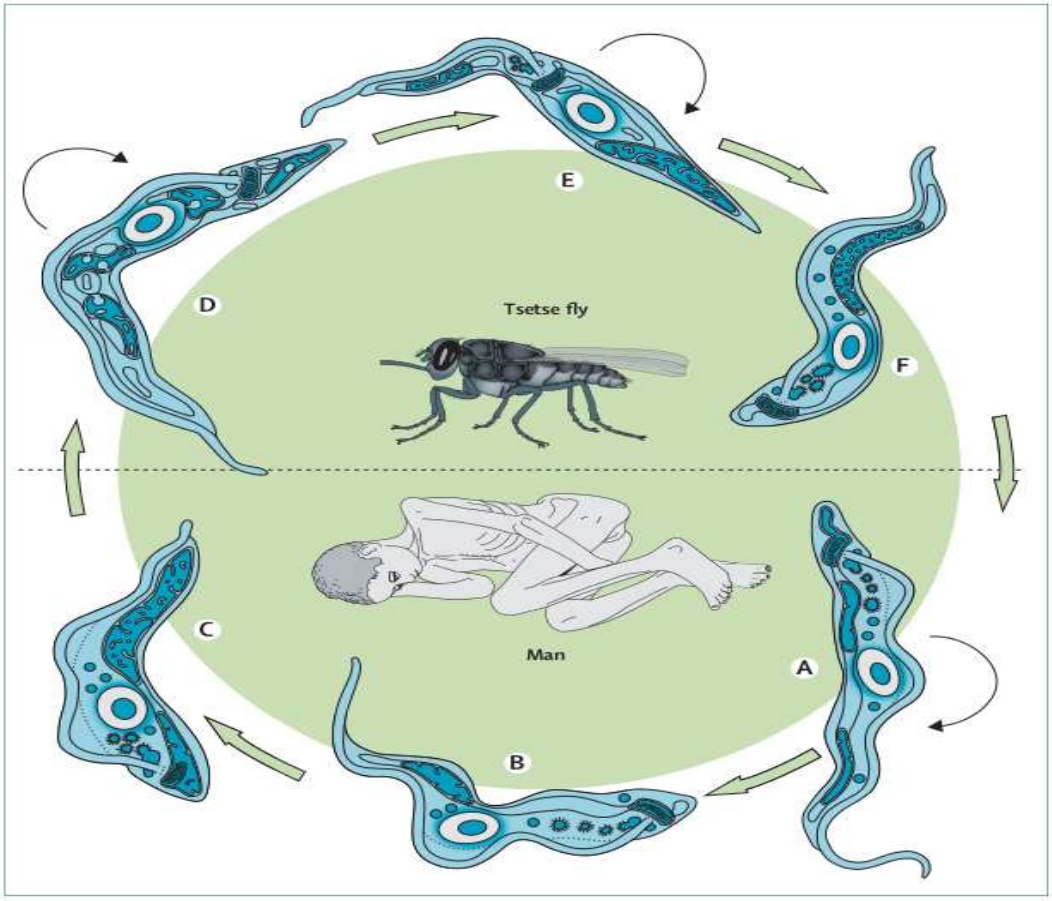


FIG. 1.6. The life cycle of African trypanosomiasis. Reproduced from [11]

Laboratory studies have shown that high infection rates are obtained when flies are induced

to feed from an infected host on the first day of life. Other studies have also shown that infection rates in flies increase with increase in temperature [71]. The parasites are injected into a susceptible human or animal when the infectious vector is feeding. African trypanosomiasis appears in two stages, the first haemolymphatic stage and the second meningoencephalitic stage, which is characterised by the invasion of the central nervous system. For *T. b. gambiense*, infection is characterised by a chronic progressive course, with an estimated average duration of about 3 years, which is evenly divided between the first and second stages. *T. b. rhodesiense* disease is usually acute, and if left untreated death occurs within weeks or months. Figure 1.6 shows the life cycle of African trypanosomiasis in man and tsetse vectors. In man, the bloodstream forms a polymorphism with (A) dividing (black arrows) slender forms, (B) intermediate forms, and (C) stumpy forms. In the tsetse fly vector, the bloodstream forms transform to (D) dividing midgut forms, then to (E) the migrating epimastigote forms, which develop in the salivary glands to (F) the infective metacyclic forms, which are injected during the next blood meal into the mammalian host [11].

1.6 Control of African trypanosomiasis

Currently there are three principal control strategies for tsetse-transmitted trypanosomiasis: trypanocidal drugs (chemotherapy and chemoprophylaxis), trypanotolerant cattle and tsetse control [40, 71]. Treatment of livestock in sub-Saharan Africa with trypanocidal drugs has been hindered by the problem of drug resistance [10, 33] and being expensive for many farmers. Treatment of human sleeping sickness is expensive, normally ranging from US$150 to US$800 per patient. Due to the toxicity of the drugs used for treating *T. b. rhodesiense*, about 5% of the patients die from the side effects of the treatment [80]. Moreover, many patients fail to report to health clinics or present with late stage symptoms [44], so prevention of the disease is a preferable option to reliance on curative treatment.

Based on these observations it has been suggested that controlling the disease by attacking its insect vectors, the tsetse flies (*Glossina ssp*) might be a preferable option [51]. Tsetse control methods include aerial and ground spraying, sterile insect technique, bait tech-

nology, and insecticide-treated cattle. Bait technology and insecticide-treated cattle do little damage to the environment and are very effective if applied properly in appropriate circumstances [33, 67].

Over the last two decades, there has been an increasing emphasis on getting farmers to control tsetse themselves, instead of relying on governments or donor organisations. The only feasible techniques that can be taken up by farmers as self-help schemes are bait methods, and the most cost-effective of these is the application of pyrethroids to cattle in tsetse infested areas. The original protocol for these applications involved the treatment of all the cattle, using the standard "whole-body" dose as recommended for tick control, and applied at intervals of about a month. To be effective, the technique must be applied over an area of at least several hundred square kilometers, necessitating participation by all livestock keepers over relatively large areas [10, 64, 67].

In areas where cattle provide the majority of tsetse blood meals, the use of insecticide-treated cattle provides one of the cheapest, and most effective, methods of controlling human African sleeping sickness. Research has shown, however, that only small areas of the animal need to be treated with the insecticide. Moreover, only the largest animals in any herd need to be treated since tsetse feed preferentially on the legs or belly of large or adult cattle. This leads to a large saving in insecticide costs and reduces the already small problems of insecticide pollution. Finally, this method offers the possibility of controlling ticks and tsetse problems simultaneously and thus, unlike other methods, can be integrated into the farmer's tick control programme and the control programme can be undertaken by the farmers themselves [10, 31].

Insecticide-treated cattle have already been used in a number of countries in sub-Sharan Africa to control tsetse and trypanosomiasis. Some of these countries include Zambia [15], Zimbabwe [62, 64], Tanzania [28, 33], Ethiopia [7, 51], Burkina Faso [5, 6] and Uganda [39, 45]. The degrees of success differ in each of the countries where the control programme was carried out. As pointed by Hargrove *et al*, 2003 [32], the success of insecticide-treated cattle depends on the size and shape of the control areas, and the number and density of treated cattle. If the area treated is small, and is surrounded by a tsetse-infested area, invasion from the untreated area can re-infest all or much of the controlled region [63].

1.7 Cost-effectiveness analysis of disease control strategies

Cost-effectiveness analysis in health care involves identification of all the relevant alternative uses of resources (cost) and the evaluation of the expected health gains derived by putting those resources to use. The aim is to maximise the health benefits per dollar spent (or minimise the cost per unit of health benefit gained). Cost-effectiveness analysis is more useful in comparing broader sets of health policies or interventions to inform health-sector budget allocation decisions [20].

Cost-effectiveness analysis measures effects on both mortality (quantity of life) and morbidity (quality of life) [29, 42]. There are two methods of carrying out a cost-effectiveness analysis that combine the two effects. The quality-adjusted life years (QALY) is the first known method that was developed in the 1970's. In this approach, the incremental effect of the control programme is compared to the status quo option in terms of the extension of life and reduction of time spent in disability. The QALY weights are coded on a scale of one for perfect health and zero for death [17, 52]. More details on the formulation of QALY calculations are given in [52].

The second method of cost-effectiveness analysis which was developed in the early 1990s that also combines morbidity and mortality effects is the Disability-Adjusted Life Year (DALY). This method was initiated by the World Health Organisation and is more commonly used in the context of developing countries. In this method, DALY weights are coded on a scale of zero for perfect health and one for death, which is exactly the opposite of the QALY. The effect of interest in this case is the DALYs avoided, rather than QALYs gained. The DALY differs from the QALY in several aspects. Most importantly, the DALY incorporates an age-weighting function that assigns different weights to life years lived at different ages. The age-weights are lowest for the young and old, and peak at middle age when people are most productive. DALY weights have been constructed from a process of expert elicitation, while QALY weights are derived using a survey-based approach from the general population [17, 29, 42, 52].

In this thesis, the cost-effectiveness analysis is done using the DALY method and the details of DALY calculations are given in section 4.3.6.

1.8 Benefit-cost analysis of disease control

Cost-effectiveness analysis seeks to achieve a given health objective at lowest cost. Benefit-cost analysis, on the other hand, can be used to answer different types of questions of allocative efficiency. Unlike cost-effectiveness analysis, benefit-cost analysis is founded on a branch of economics known as welfare economics, which emphasises the public decisions that impact the economic interests of more than one person. A benefit-cost analysis requires monetising all health impacts by determining consumer's willingness to trade income (or wealth) for the health improvements or a reduction in mortality risk. The proper decision rule is to select projects with the highest net benefits: total social benefits less total social costs. Benefit-cost analysis is intended to be a decision-making aid rather than the sole normative criterion for evaluating a policy or programme[17, 30]. More details on benefit-cost analysis calculations are given in section 5.2.2.

1.9 Integrated Control of Neglected Zoonotic diseases (ICONZ) project

This project aims at improving human health and animal production in sub-Saharan Africa through the control of neglected zoonotic diseases in animals. With 21 partner institutions in Africa and Europe, and 8 case study areas in Africa, ICONZ is tackling eight neglected zoonoses at the moment. These zoonoses include: Anthrax, Bovine Tuberculosis, Brucellosis, Cysticercosis/Neurocysticercosis, Echinococcosis, Leishmaniasis, Rabies and Zoonotic Sleeping Sickness or Human African Trypanosomiasis (HAT).

In Uganda, ICONZ is involved in the control of Human African Trypanosomiasis (HAT) in the Southeastern region, where *T. b. rhodesiense*, the acute form of sleeping sickness is predominant. The case study for this project in Uganda is termed as "work-package" 8. The main objective of this study is to develop cost-effective disease control strategies for zoonotic trypanosomiasis and tick-borne animal diseases in Southeastern Uganda. This study which started in 2010 aims at collecting data for a series of interventions which will be used as input data for epidemiological models. The control activities being done include restricted application of insecticides (RAP) on cattle by treating 0, 25%, 50% and 100%

of village cattle at monthly intervals with and without trypanocidal intervention. The impact of the different intervention strategies will be monitored at monthly intervals and cost-effectiveness analysis will be done.

The work presented in this thesis gives theoretical models for the analysis of the data which is being collected from Tororo district, Southeastern Uganda.

1.10 Motivation

Despite the effort to control African trypanosomiasis and the vector responsible for the spread of *Trypanosoma* parasites, the disease still claims the lives of many people in Africa. The diagnosis of human African trypanosomiasis requires a high degree of training and expertise which is still lacking in sub-Saharan Africa. Its treatment requires a range of drugs that are limited, and only one of them is less than 40 years old. A number of problems are associated with the current therapies which include: resistance to, toxicity and lack of effective diagnostic drugs that are costly and cause adverse reactions [60]. More over, sleeping sickness affects the poorest and most disenfranchised rural communities with the least access to health care [25].

Donors and many African governments have reduced their commitment to tsetse control, leaving operations to local communities and other inexperienced agencies [67]. Affordable control measures are thus needed if epidemics are to be controlled. Treating cattle with insecticides is an increasingly important and cheap means of controlling tsetse flies and can be applied by farmers themselves. This control strategy is more likely to be sustained compared to other complex and expensive strategies such as aerial spraying and sterile insect technique [21, 64]. In this study, we intend to develop mathematical models that can be used to examine, assess and analyse the control of African trypanosomiasis in Southeastern Uganda using the cheapest and most affordable strategies of insecticide-treated cattle.

1.11 Objectives of the study

The aim of this research is to develop mathematical models that can be used to study the dynamics of the transmission and control of tsetse and trypanosomiasis through insecticide-treated cattle in Southeastern Uganda.

The specific objectives of this study are:

(i) To analyse the dynamics of the transmission of trypanosomiasis so as to find conditions necessary for the disease interruption, control and eradication.

(ii) To evaluate the relative contribution of treating cattle with insecticides through whole-body or restricted application on the control of tsetse and trypanosomiasis in Southeastern Uganda.

(iii) To evaluate the proportion of cattle needed to be treated with insecticides in order to significantly reduce the tsetse vector population and trypanosomiasis infection in each of the strategies in Southeastern Uganda.

(iv) To evaluate the cost-effectiveness and benefit-cost analysis of each of the control strategies.

1.12 Outline of this work

In Chapter 2 we give a review of the literature in mathematical modelling of trypanosomiasis, with an emphasis on *T. b. rhodesiense* - the acute form of trypanosomiasis that is prevalent in East Africa. A review of studies done on the cost, benefit and effectiveness of trypanosomiasis control strategies is also given.

In Chapter 3 we give a model for the transmission of *T. b. rhodesiense* by tsetse vectors in human and cattle populations. Mathematical analysis and simulations of the model are given. Optimal control of *T. b. rhodesiense* through mass chemoprophylaxis and ITC is done.

In Chapter 4 we give a model for the transmission of *T. b. rhodesiense* by tsetse vectors in a multi-host population. Mathematical analysis of the model in absence of ITC is given. Numerical analysis of the model in the presence of ITC is also given. A cost-effectiveness analysis to evaluate the costs and effectiveness of controlling *T. b. rhodesiense* is done.

In Chapter 5 we give a model for the control of *T. b. rhodesiense* through treatment of adult cattle only with insecticides. Numerical analysis of the model is given. A benefit-cost analysis to evaluate the benefits and costs of controlling *T. b. rhodesiense* is done.

In Chapter 6, we give a detailed conclusion on our findings.

In the Appendix, we show how the tsetse recruitment rate was derived.

1.13 Publications

This dissertation was built around the following papers and presentations at conferences:

Chapter 3:

- *Modelling the control of Trypanosoma brucei rhodesiense through mass chemoprophylaxis and insecticide-treated cattle*, Damian Kajunguri, John W. Hargrove, Rachid Ouifki, Susan C. Welburn and Paul G. Coleman. To be submitted to *PLOS Neglected Tropical Diseases*.

  The results of this paper were presented by D. Kajunguri at the DVTD/ITM International Colloquium on Zoonoses and Neglected Infectious Diseases of Africa, November 1-4, 2011, Johannesburg, South Africa, in a talk entitled: *A delay differential equation model for the impact of mass chemoprophylaxis and insecticide-treated cattle on the control of T. b. rhodesiense*.

Chapter 4:

- *Modelling the control of tsetse and Trypanosoma brucie rhodesiense in a multi-host population through insecticide-treated cattle*, Damian Kajunguri, John W. Hargrove, Rachid Ouifki, J.Y.T. Mugisha and Susan C. Welburn- in preparation

Part of this paper's results were presented by D. Kajunguri at the the South African and American Mathematical Societies (SAMS/AMS) Congress, November 29 - December 3, 2011, Port Elizabeth, South Africa in a talk entitled: *Cost-effectiveness analysis of cheap and safe strategies for tsetse and sleeping sickness control.*

- *Cost-effectiveness analysis of tsetse and Trypanosoma brucei rhodesiense control through application of insecticides on cattle*, Damian Kajunguri, John W. Hargrove, Rachid Ouifki, J.Y.T. Mugisha and Susan C. Welburn - in preparation.

  The results of this paper were presented by D. Kajunguri at the Society for Mathematical Biology 2012 Annual Meeting & Conference, July 25-28, 2012, Knoxville, Tennessee, USA.

Other publications. The following paper was influential in developing ideas related to the modelling of the control of tsetse and trypanosomiasis using trypanocides or insecticide-treated cattle.

- *Modeling the control of trypanosomiasis using trypanocides or insecticide-treated livestock*, John W. Hargrove, Rachid Ouifki, Damian Kajunguri, Glyn A. Vale and Stephen J. Torr, *PLOS Neglected Tropical Diseases*, 6, e1615.

Chapter 2

Literature review

A number of researchers have developed and analysed mathematical models that endeavour to explain the transmission and control of trypanosomiasis. Research on the costs, benefits and effectiveness of various trypanosomiasis control measures has also been done. We present a literature review of some of the studies that have been done so far. We start by presenting modelling work that has been developed to explain the dynamics of trypanosomiasis transmission and control. We end with a review of studies that have been done to evaluate the costs, benefits and effectiveness of tsetse and trypanosomiasis control.

2.1 Modelling the transmission and control of trypanosomiasis

One of the pioneering works in the modelling of trypanosomiasis was done by Rogers (1988) [50]. His model provides a mathematical framework to describe the vector-borne transmission of trypanosomes between multiple host species. The model assumed constant populations of tsetse flies and hosts and allowed for multiple tsetse, host and trypanosome species. The model was used to study trypanosomiasis in a typical West African village situation, with 300 humans, 50 domestic animals and 500 tsetse flies. The model predicted the equilibrium prevalence of *T. vivax*, *T. congelense* and *T. brucei* to be 47.0%, 45.8% and 28.7%, respectively, in the wild and domestic mammalian hosts, and 24.2%, 3.4% and 0.15% in the tsetse vectors. An equilibrium prevalence of 7.0% of the human-infective *T.*

brucei was also predicted in humans. It was demonstrated that the human infective *T. brucei* could not be maintained by humans hosts alone. This was due to the fact that the contribution to the basic reproduction number from human and animal hosts was 0.11 and 2.54, respectively. Seasonal changes that affect the fly mortality were shown to lead to an effect in both the future population size and infection rate. It was suggested that treating animal reservoirs will achieve a greater reduction in human sleeping sickness than direct treatment of humans alone.

A number of studies on the transmission of trypanosomiasis [16, 40, 72] have been based on the mathematical model developed by Rogers (1988) [50]. Model predictions for the transmission of *T. b. brucei* and *T. b. rhodesiense* in humans and cattle by one tsetse species, *G. f. fuscipies* show that *T. b. rhodesiense* would be 3 and 3.5-fold more prevalent than *T. b. brucei* in the cattle and vector populations, respectively [16]. It was also estimated that the cattle population accounts for approximately 92% of the total *T. b. rhodesiense* transmission potential, and human population contributing only 8% of the total basic reproduction number. Adding the effects of both medical and veterinary interventions, it was shown that keeping about 86% of the cattle population effectively immune to infection interrupts the transmission of *T. b. rhodesiense* and protects the wider human population [72].

Reducing Rogers' model to a one tsetse species, one trypanosome species (*T. congelense*) and one host species (cattle), McDermott and Coleman [40] used the model to evaluate the effects of four control measures on the transmission of trypanosomiasis in cattle. The control measures considered were curative drugs, vector control, use of trypanotolerant cattle and vaccination. Vaccination was taken to be a hopeful future option in the event that vaccines are developed. The results showed that the relative rankings of the effect of control strategies on reducing disease prevalence were: vector control, vaccination, and drug use, in that order. Trypanotolerance was assumed to decrease disease prevalence, but not to influence transmission.

Davis *et al.* (2011) [19] constructed models for the basic reproduction number of *T. b. gambiense* and *T. b. rhodesiense*, the causative agents of the West and East African human sleeping sickness, respectively. The models were used to carry out a global sensitivity analysis based on parameter ranges from the literature, field data and expertise out of

Uganda. For *T. b. gambiense*, the parameter for the proportion of blood meals taken from humans was found to be the most sensitive parameter to the basic reproduction number. The parameter for the proportion of tsetse flies refractory to infection was found to be the second ranked parameter for *T. b. gambiense* and the highest ranked for *T. b. rhodesiense*. The population parameters for tsetse species composition, survival and abundance were also ranked almost as high as the proportion refractory for *T. b. rhodesiense*. The results show the implications of nutritionally stressed tsetse that are more susceptible to trypanosomiasis infection and provides a broad support for control strategies that are aimed at increasing refractoriness in tsetse flies.

Recently, Hargrove *et al.* (2012) [31] generalised Rogers model and developed an R_0 mathematical model that allows tsetse to feed off multiple host species. They identified treatment coverages required to break transmission when host populations consisted of various proportions of wild and domestic mammals, and reptiles that support tsetse but do not harbour trypanosomes. The model was used to compare the control of trypanosomiasis through insecticide-treated cattle or treating cattle with trypanocides that protect against infection. The results show that in areas with few wild animals, where cattle provide most of the tsetse's blood meals, treating cattle with insecticides could be a cheaper and more effective method for breaking transmission of trypanosomiasis. Assuming that tsetse feed only on cattle and humans, about 20% of the cattle need to be sprayed with insecticides to control the disease in humans, whereas 65% would be required to be treated with trypanocides to produce the same effect. Increasing the insecticide or trypanocide coverage to 55% or 100%, respectively, could lead to the control of *T. congelense* in cattle. *T. vivax* can only be controlled if 100% of the cattle population are kept on trypanocides. The results also showed that the presence of wild mammalian hosts lead to an increase in the coverage required and makes the control of *T. congolense* difficult. With insecticide-treated cattle, control of *T. brucei* and *T. congelense* is possible if proportions of non-human bloodmeals from cattle are more than 40% or 70%, respectively.

Mathematical models describing the dynamics of the spread of *T. b. gambiense* were presented in [2, 3, 4, 13]. The effects of tsetse immigration, vector control and detection (followed by treatment) of infected individuals were studied. The vector control strategy was shown to lead to the conrol of the Gambian sleeping sickness if the vector density is decreased by about fifty percent. Detection of sick individuals was found to be more

efficient if there is a long asymptomatic phase (first stage of Gambian sleeping sickness) characteristic of an endemic situation. It was also established that the persistence and/or extension of Gambian sleeping sickness foci could be due either to a continuous reinvasion of infected flies or to slow dynamics.

2.2 Comparative analysis of the costs, benefits and effectiveness of tsetse and trypanosomiasis control

Shaw (1989) [54] made one of the first attempts to analyse the costs and benefits of different trypanosomiasis control strategies, which included vector control, human case finding and treatment. In the economic analysis, a benefit was defined as equivalent to one year's infection avoided due to the control strategy for one person. Using a simple spreadsheet-based economic model, the relative economic performance of vector control versus human case finding and treatment in terms of the cost per benefit unit were compared. The analysis did not include domestic and wild animal populations. Though the results showed that the two control strategies are cost-effective, it was also pointed out that there is need to integrate economic and epidemiological models in order to evaluate control options.

Wahab and Asuming-Bermpong (2007) [69] used a maximum Likelihood-Binary Logit model to estimate the cost of tsetse and treatment of trypanosomiasis and the benefits involved. The model was also used to estimate the extent to which socio-economic characteristics of farmers affect the use of tsetse control techniques in Ghana. Benefits were estimated using gains from effective disease control and revenue from increased cattle production. The cost of the disease was taken to be represented by the level of revenue forgone due to the disease (or revenue gained as a result of the control of the disease). The benefit/cost of the disease was determined by estimating the impact of trypanosomiasis, which consisted of estimates of the prevalence and incidence of infections and the effects of the disease on key livestock production parameters such as mortality, milk yield and draught power. The results showed that farmers will benefit if they invest in control and treatment of trypanosomiasis. The findings suggested that there is potential for farmer's response and participation in tsetse control activities in Northern Ghana. It was recommended that more extension services be provided to livestock farmers to help them derive maximum

benefit from trypanosomiasis control practices.

A number of studies to estimate the cost-effectiveness of trypanosomiasis control were carried out based on the total costs of hospitalization and treatment for the disease. The health outcomes for different control options were rated against each other by looking at the DALYs averted. Studies are few and far between for human African trypanosomiasis, and have tended to focus on *T. b. gambiense* compared to *T. b. rhodesiense*. Shaw and Cattand [53] showed that above a prevalence of 2%, it is more cost-effective to screen and treat *T. b. gambiense* using mobile teams carrying out active surveillance. At lower prevalences, active screening may not be cost-effective in the short term. Lutumba *et al.* [37] estimated the cost-effectiveness of *T. b. gambiense* control programmes in terms of DALYs averted in Buma, Democratic Republic of Congo. In a population of $1,300$, active case finding control programme resulted in $1,408$ DALYs averted, for a cost of US$17 per DALY averted.

For *T. b. rhodesiense*, Fevre *et al.* [26] estimated the burden of the disease during an outbreak in Serere, Uganda. Unique characteristics affecting the burden of *T. b. rhodesiense* such as age, severity, level of under-reporting and duration of hospitalisation were identified and put into consideration in quantifying the burden of Human African Trypanosomiasis (HAT). Early and late stage HAT morbidity were considered differently, and disability weightings were appropriately used for the *T. b. rhodesiense* form of HAT. The results showed that hospital-based interventions alone are cost-effective for HAT control in rural settings in Uganda, with a mean cost per DALY averted (for reported cases) of US$8.50. It was demonstrated that under-reporting accounts for 93% of the DALY estimate of *T. b. rhodesiense*.

2.3 Conclusion

An understanding of the pathogenesis and epidemiology of trypanosomiasis are essential in the development of mathematical models that can predict the dynamics for the transmission of the disease. In this Chapter we have reviewed some of the mathematical models used to describe the transmission dynamics of trypanosomiasis. But the model assumptions, the number of parameters and equations used differ, and few of them have been

validated by experimental data. We acknowledge the limitations of data for parameter estimation. This has an impact of limiting the use of the mathematical models in real life scenarios. The following observations were made:

- It was noticed that most mathematical models describe the transmission dynamics of *Trypanosoma brucei gambiense*: little modelling work on *Trypanosoma brucei rhodesiense* has been done. It was also noticed that most studies on the economic burden of HAT were focused on *T. b. gambiense* rather than *T. b. rhodesiense*.
- Most of the modelling work on trypanosomiasis is based on the basic reproduction number analysis. This implies that the analysis is mainly focused on the transmission of trypanosomiasis, giving less or no information on the prevalence, incidence and progress of the disease over time.
- Mathematical models have been used to identify the role of the animal reservoir in the transmission and control of trypanosomiasis. Some of the findings indicate that interventions aimed at controlling the trypanosome parasite in the animal reservoir might lead to a greater reduction in human sleeping sickness compared to direct treatment of humans alone [16, 50].

Chapter 3

Modelling the control of *T. b. rhodesiense* through mass chemoprophylaxis and insecticide-treated cattle

3.1 Introduction

In this Chapter, we develop a simple mathematical model that describes the dynamics of the transmission of *Trypanosoma brucei rhodesiense* in humans, cattle and tsetse populations. The model is an extension of the model developed by Rogers (1988) [50] describing the transmission of *Trypanosoma brucei* parasites by tsetse vector species between two host populations, to include the effects of veterinary and tsetse control interventions [72].

3.2 Model development and analysis

We consider the scenario in which a population of *G. f. fuscipes* tsetse flies, N_V, transmits *T. b. rhodesiense* parasites between populations of humans, N_H, and cattle, N_C. Tsetse flies feed at a rate a per day so that each fly takes a new blood meal on average every $\frac{1}{a}$ days. Vectors are assumed to feed on humans and cattle at random, but with a fixed preference taking a proportion f_H of all meals from humans and the remainder $f_C = (1 - f_H)$ of meals

from cattle. Thus, tsetse flies feed on humans at a rate $a_H = af_H$ per day and on cattle at a rate $a_C = af_C$ per day, with $a = a_H + a_C$ [72]. The human and cattle populations are each divided into three classes, susceptible, infectious and recovered, whereas the tsetse population is divided into two classes, susceptible and infectious. We define time delays T_H, T_C and T_V representing the incubation period in humans, cattle and tsetse vectors, respectively. This means that infections are caused by infectious groups that were infected T_H, T_C and T_V units of time earlier, respectively. A proportion, p and ϕ_C, of the cattle population are assumed to be kept on insecticides and treated with trypanocides per day, respectively, to control *T. b. rhodesiense*. The tsetse mortality, $\mu_V(p)$, is taken to depend on the proportion, p, of cattle that is kept on insecticides. Due to the short life span of tsetse flies and the effect of insecticide-treated cattle we assume that a proportion $e^{-\mu_V(p)T_V}$ of infected flies will survive the incubation period, T_V [31, 50].

TABLE. 3.1. The model variables

Variable	definition
S_H	Susceptible human population
I_H	Infectious human population
R_H	Recovered human population
S_C	Susceptible cattle population
P_C	Cattle population on treatment with trypanocides
I_C	Infectious cattle population
R_C	Recovered cattle
S_V	Susceptible tsetse population
I_V	Infectious tsetse population

We assume a constant tsetse birth rate B_V. Only newly emerged flies (known as tenerals) feeding in the first t days of adult life (where $t < \frac{1}{a}$) are susceptible to *T. b. rhodesiense* infection [16, 31, 50]. The number of newly born flies that survive and have not fed in one unit of time (that is, between $t-1$ and t) is given by

$$\Lambda_V(p) = B_V \int_{t-1}^{t} e^{-(a+\mu_V(p))(t-s)} ds = \frac{B_V}{(a+\mu_V(p))}(1 - e^{-(a+\mu_V(p))}), \tag{3.1}$$

where a is the tsetse feeding rate and $\mu_V(p)$ is the tsetse mortality which depends on the proportion of cattle, p, kept on insecticides. The probability of a susceptible teneral fly acquiring infection is assumed to be α; for tsetse flies older than $t = \frac{1}{a}$ days, the probability of acquiring infection is zero. It takes a total of T_V days from acquiring trypanosomes for

TABLE. 3.2. Definitions of the parameters used in the model

Parameter	**Definition**	**Parameter**	**Definition**
Λ_H	Recruitment rate for humans	g_C	Recovery rate of infected cattle
f_H	Proportion of tsetse blood meals from humans	μ_C	Cattle natural mortality rate
a_H	Tsetse-human biting rate	ν_C	Rate of loss of immunity in recovered cattle
μ_H	Human natural mortality rate	T_C	Incubation period for cattle
g_H	Recovery rate of infected humans	ϕ_C	Proportion of cattle treated with trypanocides per day
β_H	Probability of infected fly bite producing an infection in humans	ϵ	Protection provided to cattle by trypanocides towards *T. b. rhodesiense* infection (or efficacy of trypanocides)
ν_H	Rate of loss of immunity in recovered humans	γ_C	Rate of loss of chemoprophylactic immunity
T_H	Incubation period for humans	p	Proportion of cattle kept on insecticides
σ_H	Mortality rate of infected humans	B_V	Tsetse birth rate
Λ_C	Recruitment rate for cattle	$\Lambda_V(p)$	Recruitment rate for tsetse flies
f_C	Proportion of tsetse blood meals from cattle	$\mu_V(p)$	Tsetse mortality rate
a_C	Tsetse-cattle biting rate	T_V	Incubation period for tsetse flies
β_C	Probability of infected fly bite producing an infection in cattle	α	Probability of the first infected blood meal giving rise to infection in tsetse flies
σ_C	Mortality rate of infected cattle	a	Tsetse feeding rate

the parasites to mature so that the fly becomes infectious. Infected tsetse flies are assumed to die of natural causes only.

We assume a constant recruitment rate Λ_C and Λ_H for cattle and humans, respectively, which is through birth and emigration. Following the bite of an infectious tsetse fly, the probability of susceptible cattle and humans becoming infected is β_C and β_H, respectively. Infectious cattle and humans are assumed to recover at a rate g_C and g_H, respectively. Cattle are treated with trypanocidal drugs with efficacy of ϵ at a rate ϕ_C. Susceptible and infectious cattle move to compartment P_C and R_C, respectively, after chemoprophylactic

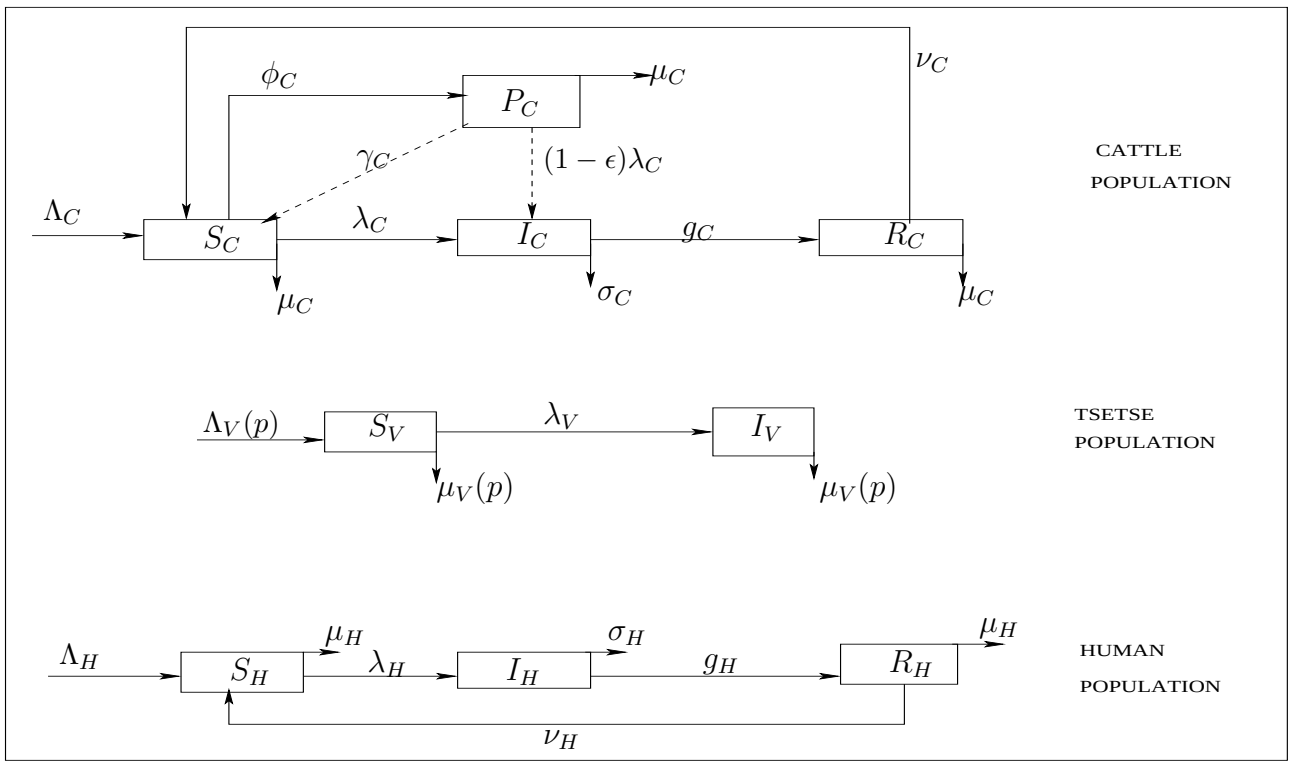


FIG. 3.1. Flow diagram of the compartmental model of *T. b. rhodesiense* in cattle, human and tsetse populations. λ_C, λ_H, and λ_V are the forces of infection for cattle, humans and tsetse vectors, respectively.

treatment. In the presence of treatment, it is implied that $g_C = g'_C + \phi_C$, where g'_C is the self-recovery rate of infectious cattle. Recovered cattle and humans lose their immunity after a period of $\frac{1}{\nu_C}$ and $\frac{1}{\nu_H}$, respectively, and become susceptible again. The flows between the different states (compartments) of the model are clearly shown in figure 3.1. The summary of model variables is given in Table 3.1. Table 3.2 shows the model parameters and their definitions.

3.2.1 Estimation of the tsetse mortality in the presence of insecticide-treated cattle

Hargrove *et al.* (2012) [31] made the first attempt to estimate the tsetse mortality in the presence of ITC using the knowledge of probability theory and we adopt their method in this thesis. If the probability that a tsetse fly survives a feed on a host is q_1 and the

probability of surviving a non-feeding day is q_2, then a fly survives the feeding cycle of f days, where $f = \frac{1}{a}$ with a probability

$$S_f = q_1 q_2^f. \tag{3.2}$$

The daily mortality rate is calculated from $\mu_V = -\ln(S_f)/f$. Setting the parameters to $q_1 = 0.96$ and $q_2 = 0.98$ as in [31], we obtain $\mu_V = 0.03$, which is the natural mortality that was assumed in [16, 50]. The survival probability in equation (3.2) can be re-written as

$$S_f = f_C q_1 q_2^f + (1 - f_C) q_1 q_2^f,$$

where f_C is the probability that a fly feeds on cattle (which is equal to the proportion of blood meals a tsetse fly takes from cattle) and $1 - f_C$ is the probability that a fly feeds on a non-cattle host. If the proportion of cattle treated with insecticides is p, then the probability of a fly surviving a feeding cycle is now given by

$$S_f = (1 - p) f_C q_1 q_2^f + (1 - f_C) q_1 q_2^f.$$

Thus, the tsetse mortality as a function of the proportion of cattle treated with insecticides, p, can be obtained as

$$\mu_V(p) = -\ln[(1 - p) f_C q_1 q_2^f + (1 - f_C) q_1 q_2^f]/f. \tag{3.3}$$

We thus have the following differential equations which describe the transmission dynamics

of *T. b. rhodesiense* in cattle, human and tsetse populations.

$$\frac{d}{dt}S_H = \Lambda_H + \nu_H R_H - \mu_H S_H - \lambda_H(t-T_H)S_H(t-T_H), \tag{3.4}$$

$$\frac{d}{dt}I_H = \lambda_H(t-T_H)S_H(t-T_H) - (g_H+\sigma_H)I_H, \tag{3.5}$$

$$\frac{d}{dt}R_H = g_H I_H - (\mu_H+\nu_H)R_H, \tag{3.6}$$

$$\frac{d}{dt}S_C = \Lambda_C + \nu_C R_C + \gamma_C P_C - (\mu_C+\phi_C)S_C - \lambda_C(t-T_C)S_C(t-T_C), \tag{3.7}$$

$$\frac{d}{dt}P_C = \phi_C(S_C+I_C+R_C) - (\mu_C+\gamma_C)P_C - (1-\epsilon)\lambda_C(t-T_C)P_C(t-T_C), \tag{3.8}$$

$$\frac{d}{dt}I_C = \lambda_C(t-T_C)[(1-\epsilon)P_C(t-T_C) + S_C(t-T_C)] - (\phi_C+g_C+\sigma_C)I_C, \tag{3.9}$$

$$\frac{d}{dt}R_C = g_C I_C - (\phi_C+\mu_C+\nu_C)R_C, \tag{3.10}$$

$$\frac{d}{dt}S_V = \Lambda_V(p) - e^{-\mu_V(p)T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V(p)S_V, \tag{3.11}$$

$$\frac{d}{dt}I_V = e^{-\mu_V(p)T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V(p)I_V, \tag{3.12}$$

where

$$\begin{aligned}
\lambda_H(t) &= a_H\beta_H I_V(t)/N_H(t) \\
\lambda_C(t) &= a_C\beta_C I_V(t)/N_C(t) \quad \text{and} \\
\lambda_V(t) &= \alpha[a_H I_H(t)/N_H(t) + a_C I_C(t)/N_C(t)].
\end{aligned}$$

The total population sizes can be determined by $N_H = S_H + I_H + R_H$, $N_C = S_C + P_C + I_C + R_C$ and $N_V = S_V + I_V$ or from the differential equations

$$\frac{d}{dt}N_H = \Lambda_H - \mu_H N_H - (\sigma_H - \mu_H)I_H, \tag{3.13}$$

$$\frac{d}{dt}N_C = \Lambda_C - \mu_C N_C - (\sigma_C - \mu_C)I_C, \tag{3.14}$$

$$\frac{d}{dt}N_V = \Lambda_V(p) - \mu_V(p)N_V. \tag{3.15}$$

By using standard results of well possedness, one can prove that the model (3.4-3.12) is well posed in the region

$$\chi = \left\{(S_H, I_H, R_H, S_C, P_C, I_C, R_C, S_V, I_V) \in \mathbb{R}^9_+ : N_H \leq \frac{\Lambda_H}{\mu_H}, N_C \leq \frac{\Lambda_C}{\mu_C}, N_V \leq \frac{\Lambda_V(p)}{\mu_V(p)}\right\}.$$

Because of the presence of a delay term in the first equation of this model (and the models in Chapters 4 and 5), the classical proofs of its well possedness do not apply. Although, mathematically, this is an important point that should be further investigated. In this thesis, we focus more on the epidemiological properties of the model where this is not a serious issue.

Basic reproduction number, R_0

The basic reproduction number, R_0, is the average number of infectious cases an individual would generate during his/her infectious period in a population that is wholly susceptible. In this case, the basic reproduction number is defined as the average number of *T. b. rhodesiense* cases that an infectious cattle or human or tsetse fly would generate in a totally susceptible population of humans, cattle and tsetse flies. If $R_0 > 1$, then the disease may emerge in one of the populations. However, if $R_0 < 1$, then the disease-free equilibrium is locally asymptotically stable [66]. Model system (3.4-3.12) has a disease-free equilibrium given by,

$$E_0 = \left(\frac{\Lambda_H}{\mu_H}, 0, 0, \frac{\Lambda_C(\mu_C+\gamma_C)}{\mu_C(\mu_C+\gamma_C+\phi_C)}, \frac{\phi_C\Lambda_C}{\mu_C(\mu_C+\gamma_C+\phi_C)}, 0, 0, \frac{\Lambda_V(p)}{\mu_V(p)}, 0\right).$$

Using the next generation operator method described in [66], we obtain the matrices F (for the new infections) and V (for the transition terms) as

$$F = \begin{pmatrix} 0 & 0 & a_H\beta_H \\ 0 & 0 & \frac{a_C\beta_C(\mu_C+\gamma_C+(1-\epsilon)\phi_C)}{\mu_C+\gamma_C+\phi_C} \\ \frac{e^{-\mu_V(p)T_V}\alpha a_H\mu_H\Lambda_V(p)}{\Lambda_H\mu_V(p)} & \frac{e^{-\mu_V(p)T_V}\alpha a_C\mu_C\Lambda_V(p)}{\Lambda_C\mu_V(p)} & 0 \end{pmatrix}$$

$$\text{and} \quad V = \begin{pmatrix} g_H+\sigma_H & 0 & 0 & \\ 0 & g_C+\sigma_C & 0 & \\ 0 & & 0 & \mu_V(p) \end{pmatrix},$$

respectively. It follows that the basic reproduction number, denoted by R_0, is given by

$$\rho(FV^{-1}) = \sqrt{R_{0H}^2 + R_{0C}^2}, \tag{3.16}$$

where ρ is the spectral radius (dominant eigenvalue in magnitude) of the next generation matrix FV^{-1},

$$R_{0H} = \sqrt{\frac{e^{-\mu_V(p)T_V}\Lambda_V(p)\alpha a_H^2 \mu_H \beta_H}{\mu_V^2(p)\Lambda_H(g_H+\sigma_H)}} \tag{3.17}$$

is the human-vector basic reproduction number and

$$R_{0C} = \sqrt{\frac{e^{-\mu_V(p)T_V}\Lambda_V(p)\alpha a_C^2 \mu_C \beta_C (1-\epsilon\pi_C)}{\mu_V^2(p)\Lambda_C(g_C+\sigma_C)}}, \tag{3.18}$$

is the cattle-vector reproduction number, with $\pi_C = \frac{\phi_C}{(\phi_C+\mu_C+\gamma_C)}$ and $(1-\epsilon\pi_C) > 0$. The expressions of R_{0H} and R_{0C} are similar to the one obtained by Rogers (1988) [50] for constant populations of humans, cattle and flies (except for the square roots, and the term $(1-\epsilon\pi_C)$ which is due to treatment of cattle with trypanocides). The square root in the expressions of R_{0H} and R_{0C} arises from the fact that two generations are required for an infected vector or host to reproduce itself [66]. Note that in the derivation and analysis of R_0, we are taking $g_C = g'_C$. A case where $g_C = g'_C + \phi_C$ will be considered in numerical simulations given in Section 3.4.

3.2.2 Effect of mass chemoprophylaxis and ITC on R_0

From [66] we know that the disease-free equilibrium is locally asymptotically stable if and only if $R_0 < 1$, that is

$$\left(\epsilon\tilde{R}_{0C}^2(p) - (\tilde{R}_0^2(p)-1)\right)\phi_C > (\tilde{R}_0^2(p)-1)(\mu_C+\gamma_C), \tag{3.19}$$

where $\tilde{R}_0^2(p) = \frac{e^{-\mu_V(p)T_V}\Lambda_V(p)\alpha}{\mu_V^2(p)}(A_H + A_C)$ and $\tilde{R}_{0C}^2(p) = \frac{e^{-\mu_V(p)T_V}\Lambda_V(p)\alpha}{\mu_V^2(p)}A_C$, with $A_C = \frac{a_C^2\mu_C\beta_C}{\Lambda_C(g_C+\sigma_C)}$ and $A_H = \frac{a_H^2\mu_H\beta_H}{\Lambda_H(g_H+\sigma_H)}$. Note that $\tilde{R}_0(p)$ (resp. $\tilde{R}_{0C}(p)$) is the basic reproductive number, in the presence of ITC only, of the total population (resp. cattle population).

Thus, we have the the following result

Proposition 1

1. *If $\tilde{R}_0(p) < 1$, then there is no need for chemoprophylaxis as the disease will be eradicated with ITC only.*

2. If $\tilde{R}_0(p) > 1$, then eradication is possible provided that

$$\begin{cases} \epsilon > \dfrac{(\tilde{R}_0^2(p) - 1)}{\tilde{R}_{0C}^2(p)} \\ \\ \phi_C > \dfrac{(\tilde{R}_0^2(p) - 1)(\mu_C + \gamma_C)}{\epsilon \tilde{R}_{0C}^2(p) - (\tilde{R}_0^2(p) - 1)}. \end{cases}$$

A simple differentiation of $\tilde{R}_0(p)$ shows that it is a decreasing function of p. This implies that

i). If $\tilde{R}_0(0) < 1$ (the basic reproductive number without ITC or prophylaxis), then $\tilde{R}_0(p) < 1$ for each $p \in [0, 1]$

ii). If $\tilde{R}_0(1) > 1$, then $\tilde{R}_0(p) > 1$ for each $p \in [0, 1]$

iii). If $\tilde{R}_0(0) < 1 < \tilde{R}_0(1)$, then there exists a unique $p_0 \in [0, 1]$ such that $\tilde{R}_0(p_0) = 1$, $\tilde{R}_0(p) > 1$ for $p \in [0, p_0)$ and $\tilde{R}_0(p) < 1$ for $p \in (p_0, 1]$.

3.2.3 The optimal control problem to minimise the cost of controlling *T. b. rhodesiense* through chemoprophylaxis and ITC

If we assume that the cost of treating one cow with trypanocides is C_1 and the daily cost of keeping one cow on insecticides is given by C_2, then the optimal control problem can be defined by

$$J(\phi_C, p) = C_1\phi_C + C_2 p, \tag{3.20}$$

where $J(\phi_C, p)$ is the total daily cost of treating a proportion ϕ_C of cattle with trypanocides and keeping a proportion p of cattle on insecticides. In proposition 1, we proved that *T. b. rhodesiense* control through ITC and chemoprophylaxis is possible provided that $\epsilon > \dfrac{(\tilde{R}_0^2(p) - 1)}{\tilde{R}_{0C}^2(p)}$ and $\phi_C > \dfrac{(\tilde{R}_0^2(p) - 1)(\mu_C + \gamma_C)}{\epsilon \tilde{R}_{0C}^2(p) - (\tilde{R}_0^2(p) - 1)}$. Numerical simulations show that optimal control of *T. b. rhodesiense* for $R_0 < 1$ and close to 1 can be achieved at a long period of time (40 years for ITC only, and 95 years for ITC and chemoprophylaxis), which is very hard to be maintained. To solve this problem of disease control over a long period of time,

we seek $R_0 < \rho$, where ρ is any value in $[0, 1)$ and small enough for *T. b. rhodesiense* eradication within a short period of time. Taking $R_0 = \rho$, and using proposition 1, we obtain $\phi_C = \dfrac{(\tilde{R}_0^2(p) - \rho)(\mu_C + \gamma_C)}{\epsilon \tilde{R}_{0C}^2(p) - (\tilde{R}_0^2(p) - \rho)}; = \Phi_C(p)$. Substituting for ϕ_C in equation (3.20), gives an expression in terms of p only, given by

$$J(p) = C_1 \Phi_C(p) + C_2 p. \tag{3.21}$$

The objective is to minimise the daily cost of combined intervention for $R_0 < \rho$. Numerical simulations suggest that $\Phi_C(p)$ (and therefore $J(p)$) is convex. Therefore, the value of p, p^*, for which $J(p)$ is minimum can be obtained by solving $J'(p^*) = 0$, that is, $\Phi'_C(p^*) = -CR$, where $CR = \frac{C_2}{C_1}$. The corresponding value of ϕ_C is given by $\phi_C^* = \Phi_C(p^*)$.

3.2.4 Sensitivity analysis

To determine how best one can reduce the burden of *T. b. rhodesiense* in both humans and cattle, it is necessary to know the relative importance of the different factors responsible for the control of the disease. This is done by determining input parameters that contribute the most output variability. We apply the method in [14] to calculate the forward sensitivity index of a variable to a parameter, which is the ratio of the relative change in the variable to the relative change in the parameter. Following [14], the sensitivity index of a variable X with respect to a parameter μ is given by

$$\Upsilon_\mu^X = \frac{\partial X}{\partial \mu} \frac{\mu}{X}. \tag{3.22}$$

Sensitivity indices of R_0

The sensitivity index measures the relative change in a state variable that results from a relative change in a parameter [14]. For our model we calculate the sensitivity indices of the basic reproductive number, R_0, with respect to all the parameters. Since we have an explicit formula for R_0, we derive analytical expressions for the sensitivity of R_0 using equation (3.22). For example, the sensitivity indices of R_0 with respect to the control parameters ϕ_C and p considered in the model are

$$\Upsilon_{\phi_C}^{R_0} = \frac{-(\epsilon a_C^2 \beta_C \Lambda_H (g_H + \sigma_H)\mu_C(\gamma_C + \mu_C) + a_H^2 \beta_H \Lambda_C (g_C + \sigma_C)\mu_H)\phi_C}{2(\gamma_C + \mu_C + \phi_C)(a_H^2 \beta_H \Lambda_C (g_C + \sigma_C)\mu_H + a_C^2 \beta_C \Lambda_H (g_H + \sigma_H)\mu_C(\gamma - C + \mu_C + (1-\epsilon)\phi_C))},$$

$$\Upsilon_p^{R_0} = -\frac{pf_C}{2d(1-pf_C)}\left[1 + T_V - \frac{2d}{\ln((1-pf_C)q_1 q_2^d)} - \frac{d}{\ln((1-pf_C)q_1 q_2^d) - d(a_H + a_C)} - \frac{1}{1 - ((1-pf_C)q_1 q_2^d)^{\frac{1}{d}} e^{-(a_C + a_H)}}\right]. \tag{3.23}$$

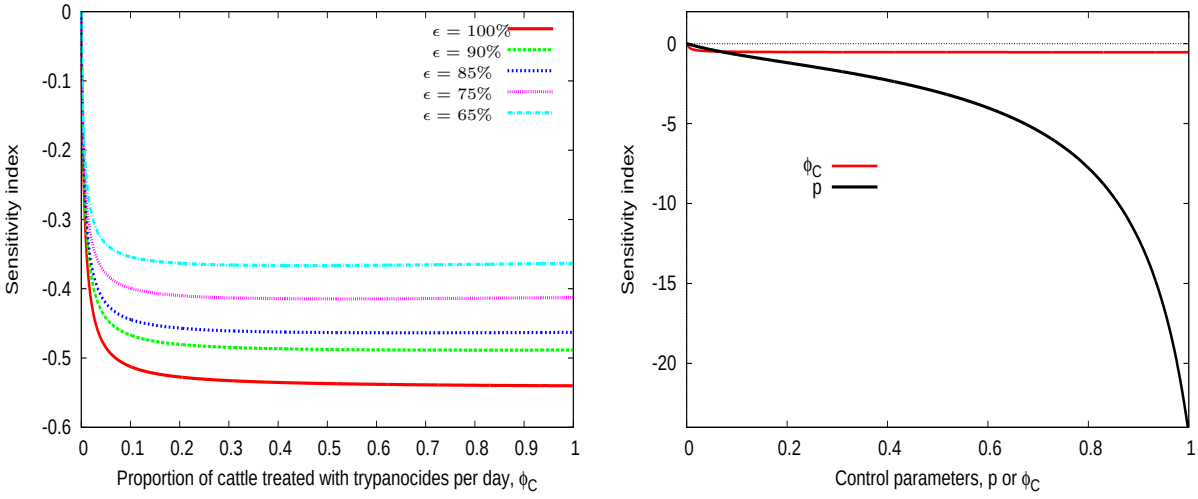
TABLE. 3.3. Sensitivity indices of R_0. All parameters were fixed to the values given in Table 3.5, ϕ_C, ϵ and p were taken to be 0.02, 0.5 and 0.05, respectively.

Parameter	Sensitivity index	Parameter	Sensitivity index
a_C	+0.8965	σ_C	-0.2583
Λ_V	+0.500	ϕ_C	-0.0879
α	+0.500	γ_C	+0.0572
μ_C	+0.4807	a_H	+0.0440
β_C	+0.4750	β_H	+0.0250
Λ_C	-0.4750	Λ_H	-0.0250
p	-0.3898	μ_H	+0.0250
T_V	-0.3773	g_H	-0.0194
g_C	-0.3167	σ_H	-0.0056
ϵ	-0.2960		

Table 3.3 gives the sensitivity indices of R_0 with respect to all parameters in the model. A negative sensitivity index means that an increase in the value of the parameter would lead to a decrease in R_0. On the other hand, a positive sensitivity index means that an increase in the parameter value would lead to an increase in R_0. R_0 is most sensitive to the tsetse-cattle biting rate, a_C, followed by the tsetse recruitment rate, Λ_V, and the probability of the first infected blood meal giving rise to infection in tsetse vectors, α. Other important parameters are the cattle natural mortality rate, μ_C, and the probability of an infected fly bite causing infection in cattle, β_C. Since $\Upsilon_{a_C}^{R_0} = +0.8965$, increasing (or decreasing) a_C by 10% increases (or decreases) R_0 by 8.965%. Similarly, since $\Upsilon_{B_V}^{R_0} = +0.500$, increasing (or decreasing) B_V by 10% increases (or decreases) R_0 by 5.0%. This implies that reducing the tsetse birth rate and tsetse-cattle biting rate have a significant effect on disease transmission.

Since we are interested in chemoprophylaxis and control of the tsetse vector to prevent *T. b.*

rhodesiense in humans, we focus on the sensitivity analysis of R_0 with respect to ϕ_C and p, whose expressions are given in (3.23). We notice that chemoprophylaxis treatment depends on the protection, ϵ, provided by the drugs given to cattle. By fixing all the parameters, except ϕ_C and ϵ, we show in figure 3.2(a) how the sensitivity of R_0 with respect to ϕ_C changes for different values of ϵ. It can be seen that the higher the protection, the more sensitive R_0 is to ϕ_C and vice versa. The sensitivity index of R_0 with respect to ϕ_C reduces rapidly and becomes almost constant for large values of ϕ_C. This is because cattle are assumed to be treated with trypanocides once a month. For instance, treating 50% of the cattle population per day for 2 days is equivalent to treating 100% per day in one month. Thus, the effect of treating larger proportions of cattle with trypanocides on R_0 is almost the same.



(a) (b)

FIG. 3.2. Sensitivity analysis of R_0 with respect to ϕ_C for $\epsilon = 100\%, 90\%, 85\%, 75\%$ and 65% (a), and the control parameters p and ϕ_C for $\epsilon = 100\%$ (b). All the other parameters are given in Table 3.5.

Figure 3.2 (b) shows the plots of the sensitivity indices of R_0 with respect to ϕ_C, and p for $(\phi_C, p) \in [0, 1]$. From the plots, it can be seen that for values of p and ϕ_C less than 0.065, R_0 is more sensitive to ϕ_C. However, as the values of p and ϕ_C increases, R_0 becomes more sensitive to p as compared to ϕ_C. The results show that keeping a significant proportion of cattle on insecticides has a greater impact in reducing the transmission of *T. b. rhodesiense* in both humans and cattle. This effect is due to the fact that insecticides reduce the tsetse

vector population which are responsible for the transmission of the disease as compared to trypanocides which have no effect of the tsetse population.

Sensitivity analysis of the endemic equilibrium

Sensitivity indices of the reproduction number, R_0, show how crucial a parameter is to the disease transmission. To know how crucial the parameter is to the prevalence of the disease, we need to find the sensitivity indices of the endemic equilibrium. When $R_0 > 1$, system (3.4-3.12) has an endemic equilibrium $E^* = (S_H^*, I_H^*, R_H^*, S_C^*, P_C^*, I_C^*, R_C^*, S_V^*, I_V^*)$. For our case, we are unable to get explicit expressions for the endemic equilibrium and therefore we use numerical simulations to obtain the endemic equilibrium point. Using the parameter values in Table 3.5, with ϕ_C and ϵ fixed at 0.05 and 0.8, respectively, we obtain

$$E^* = (72673, 5875, 82, 189, 143, 3632, 44, 33231, 8635). \tag{3.24}$$

Let

$$\left.\begin{aligned} h_1(x_1^*(\mu), x_2^*(\mu), \ldots, x_n^*(\mu), \mu) &= 0, \\ \vdots \qquad\qquad\qquad\qquad & \vdots \quad \vdots \\ h_n(x_1^*(\mu), x_2^*(\mu), \ldots, x_n^*(\mu), \mu) &= 0, \end{aligned}\right\} \tag{3.25}$$

denote the system (3.4-3.12) at the endemic equilibrium, with $n = 9$, $(x_1^*(\mu), \ldots, x_n^*(\mu))$ being the endemic equilibrium point and μ representing any parameter in Table 3.5. To find the sensitivity index of a variable x_i^* with respect to the parameter μ, we need to evaluate $\dfrac{\partial x_i^*}{\partial \mu}$. Taking the derivative of system (3.25) with respect to μ, we obtain

$$\begin{aligned} \frac{\partial h_1}{\partial x_1^*}\frac{\partial x_1^*}{\partial \mu} + \cdots + \frac{\partial h_1}{\partial x_n^*}\frac{\partial x_n^*}{\partial \mu} + \frac{\partial h_1}{\partial \mu} &= 0, \\ \vdots \qquad\qquad\qquad\qquad & \vdots \\ \frac{\partial h_n}{\partial x_1^*}\frac{\partial x_1^*}{\partial \mu} + \cdots + \frac{\partial h_n}{\partial x_n^*}\frac{\partial x_n^*}{\partial \mu} + \frac{\partial h_n}{\partial \mu} &= 0. \end{aligned}$$

This implies that

$$\begin{pmatrix} \frac{\partial h_1}{\partial x_1^*} & \cdots & \frac{\partial h_1}{\partial x_n^*} \\ & \vdots & \\ \frac{\partial h_n}{\partial x_1^*} & \cdots & \frac{\partial h_n}{\partial x_n^*} \end{pmatrix} \begin{pmatrix} \frac{\partial x_1^*}{\partial \mu} \\ \vdots \\ \frac{\partial x_n^*}{\partial \mu} \end{pmatrix} = - \begin{pmatrix} \frac{\partial h_1}{\partial \mu} \\ \vdots \\ \frac{\partial h_n}{\partial \mu} \end{pmatrix},$$

which can be written as

$$J\delta = -h', \quad \text{where} \quad J = \begin{pmatrix} \frac{\partial h_1}{\partial x_1^*} & \cdots & \frac{\partial h_1}{\partial x_n^*} \\ & \vdots & \\ \frac{\partial h_n}{\partial x_1^*} & \cdots & \frac{\partial h_n}{\partial x_n^*} \end{pmatrix}, \quad \delta = \begin{pmatrix} \frac{\partial x_1^*}{\partial \mu} \\ \vdots \\ \frac{\partial x_n^*}{\partial \mu} \end{pmatrix} \quad \text{and} \quad h' = \begin{pmatrix} \frac{\partial h_1}{\partial \mu} \\ \vdots \\ \frac{\partial h_n}{\partial \mu} \end{pmatrix}.$$

Since J is calculated at the stable equilibrium point, it is invertible. Therefore

$$\delta = -J^{-1}h'. \tag{3.26}$$

Let $\Upsilon_\mu^{x_i^*}$ be the sensitivity index of variable x_i^* with respect to the parameter μ. This implies that

$$\Upsilon_\mu^{x_i^*} = \frac{\partial x_i^*}{\partial \mu} \frac{\mu}{x_i^*} = \delta_i \frac{\mu}{x_i^*}.$$

$$\text{Thus, } \Upsilon_\mu^{x^*} = \begin{pmatrix} \frac{\mu}{x_1^*} & 0 & \dots & 0 \\ 0 & \frac{\mu}{x_2^*} & \dots & 0 \\ \vdots & \vdots & & \vdots \\ 0 & 0 & \dots & \frac{\mu}{x_n^*} \end{pmatrix} \begin{pmatrix} \delta_1 \\ \delta_2 \\ \vdots \\ \delta_n \end{pmatrix}.$$

Substituting for δ from equation 3.26, we obtain the following proposition

Proposition 2 *The vector sensitivity index of system (3.4) at the endemic equilibrium is given by*

$$\Upsilon_\mu^{x^*} = -MJ^{-1}h', \tag{3.27}$$

$$\text{where} \quad M = \begin{pmatrix} \frac{\mu}{x_1^*} & 0 & \dots & 0 \\ 0 & \frac{\mu}{x_2^*} & \dots & 0 \\ \vdots & \vdots & & \vdots \\ 0 & 0 & \dots & \frac{\mu}{x_n^*} \end{pmatrix}.$$

From the endemic equilibrium point given in equation (3.24), we obtain the sensitivity indices for the endemic equilibrium with respect to all the parameters given in Table 3.4.

TABLE. 3.4. Sensitivity indices of the endemic equilibrium with respect to the control parameters considered in the model. All parameters were fixed to the values given in Table 3.5, ϕ_C, ϵ and p were taken to be 0.05, 0.8 and 0, respectively. The tsetse recruitment and mortality rates are evaluated at $p = 0$ and taken to be $\Lambda_V = \Lambda_V(0) = 1,235$ and $\mu_V = \mu_V(0) = 0.03$, respectively, where μ_V is the tsetse natural mortality.

Parameter	S_H^*	I_H^*	R_H^*	S_C^*	P_C^*	I_C^*	R_C^*	S_V^*	I_V^*
μ_V	+9.0615	-1.5410	-1.5410	+2.2534	+4.6062	-0.0273	-0.0273	-0.6507	-2.3443
Λ_V	-4.4010	+0.7484	+0.7484	-1.0943	-2.2369	+0.0133	+0.0133	+0.9640	+1.1385
α	-3.4930	+0.5940	+0.5940	-0.8686	-1.7756	+0.0105	+0.0105	-0.2348	+0.9037
a_C	-3.8638	+0.6571	+0.6571	-1.9221	-3.9289	+0.0233	+0.0233	-0.2597	+0.9996
ϕ_C	+0.0947	-0.0161	-0.0161	-0.0888	+0.9581	-0.0030	-0.0030	+0.0064	-0.0245
ϵ	+0.5103	-0.0868	-0.0868	+0.2770	+4.1643	-0.0163	-0.0163	+0.0343	-0.1320
g_H	+3.113	-0.5296	+0.4704	+0.0257	+0.0525	-0.0003	-0.0003	+0.0069	-0.0267
g_C	+0.2526	-0.0430	-0.0430	+0.7800	+0.9052	-0.0081	+0.9919	+0.0170	-0.0653
T_V	+1.8862	-0.3208	-0.3208	+0.4691	+0.9588	-0.0057	-0.0057	+0.1268	-0.4880
a_H	-4.0298	+0.6853	+0.6853	-0.0409	-0.0836	+0.0004	+0.0004	-0.0011	+0.0425
β_H	-3.9981	+0.6799	+0.6799	-0.0330	-0.0474	+0.0004	+0.0004	-0.0089	+0.0343
Λ_H	+4.9980	+0.3201	+0.3201	+0.0330	+0.0674	-0.0004	-0.0004	+0.0089	-0.0343
σ_C	-0.2933	+0.0499	+0.0499	-1.6613	-2.7068	-0.9812	-0.9812	-0.0197	+0.0759
σ_H	-3.3823	-0.4246	-0.4246	-0.0209	-0.0426	+0.0025	+0.0025	-0.0056	+0.0217
β_C	-0.4025	+0.0685	+0.0685	-1.0613	-2.1695	+0.0129	+0.0129	-0.0271	+0.1041
Λ_C	+0.4026	-0.0685	-0.0685	+2.0613	+3.1695	+0.9871	+0.9871	+0.0271	-0.1041
μ_C	-0.0045	+0.0008	+0.0008	-0.0186	-0.0377	-0.0092	-0.0097	-0.0003	+0.0011
μ_H	-0.7273	+0.0466	-0.0466	-0.0048	-0.0098	+0.0001	+0.0001	-0.0013	+0.0050
γ_C	-0.0079	+0.0013	+0.0013	+0.0074	-0.0074	+0.0003	+0.0003	-0.0005	+0.0020
ν_C	-0.0416	+0.0071	0.0071	-0.0186	-0.0392	+0.0013	-0.9981	-0.0028	+0.0108
ν_H	-0.0034	+0.0008	-0.9991	-0.0000	-0.0000	+0.0000	+0.0000	-0.0000	+0.0000

Note that in this case we are looking at the proportion of cattle treated with trypanocides per day, ϕ_C, since the total cattle population at the endemic equilibrium is different from the one obtained at the disease-free equilibrium. The state variable I_V^* is most sensitive to μ_V followed by Λ_V, a_C, α and T_V. The state variable I_C^* is most sensitive to Λ_C, followed by σ_C, μ_V, a_C and ϵ. The state variable I_H^* is most sensitive to μ_V followed by Λ_V, a_H, β_H and a_C. The intuitive explanation of the sensitivity results of the endemic equilibrium point is that, increase in the disease prevalence (which is determined by I_C^* and I_H^*) will lead to a decrease in the cattle and human populations because of the mortality rate σ_C and σ_H of infected cattle and humans, respectively. Reducing the disease prevalence will lead to an increase in the cattle and human populations since the mortality will be reduced. Increasing the tsetse mortality, μ_V, will not only reduce the tsetse population but also the

number of infectious cattle and humans, and hence increase the total cattle and human populations. Increasing μ_V by 1% would approximately reduce I_H^*, I_C^* and I_V^* by 1.5410%, 0.0273% and 2.3443%, respectively. The intuitive explanations agree with the signs of the sensitivity indices of the endemic equilibrium with respect to all the parameters given in Table 3.4.

3.3 Parameter estimation

Empirical observations were collected from published literature for each of the model parameter values in the model (3.4-3.12). Parameter values were selected to be most applicable to the transmission of *T. b. rhodesiense* by *G. f. fuscipes* as in Tororo district, Southeastern Uganda. We give details of how each parameter was chosen.

3.3.1 Demographic parameters

The human and cattle natural mortality was taken to be $\mu_H = 0.000055$ and $\mu_C = 0.00055$ per day as in [21], corresponding to a life expectancy of 50 and 5 years, respectively. The life expectancy of humans in Uganda is estimated at 48 and 57 years for males and females, respectively [78]. The birth rate Λ_H for humans was chosen to attain a total population at the disease-free equilibrium ($S_H = \frac{\Lambda_H}{\mu_H}$) of $500,000$ [78] corresponding to the number of people in Tororo district, Uganda and this gives $\Lambda_H = 27.5$ per day. Using the same technique for cattle, we obtain $\Lambda_C = 22.0$ per day for a total cattle population of $40,000$ [65] (the number of cattle in Tororo district, Uganda) at the disease-free equilibrium.

The tsetse mortality in the absence of ITC, $\mu_V(0)$, was taken to be 0.03 per day as in [16, 40, 50], corresponding to an average life expectancy of 33 days. The tsetse birth rate was taken to be $B_V = 1,440$ per day to attain a tsetse to cattle ratio of 1.2 [19] at the disease-free equilibrium. The number of teneral tsetse flies, $\Lambda_V(p)$, that are susceptible to infection is obtained from equation (3.1).

TABLE. 3.5. Model parameter value estimates. All time periods are given in days and all rates are instantaneous per capita rates per day.

Parameter	Tsetse population			Human population			Cattle population		
Tsetse birth rate	B_V	1,440	[19]	-	-	-	-	-	-
Recruitment rate	$\Lambda_V(p)$	varying	-	Λ_H	27.5	[78]	Λ_C	22.0	[65]
Natural mortality	μ_V	0.03	[50]	μ_H	0.000055	[78]	μ_C	0.00055	[78]
Mortality of infected hosts	-	-	-	σ_H	0.004	[19]	σ_C	0.006	[19]
Tsetse feeding cycle	$\frac{1}{a}$	4	[16]	-	-	-	-	-	-
Proportion of tsetse blood meal	-	-	-	f_H	0.1	[19]	f_C	$1-f_H$	-
Biting rate	-	-	-	a_H	af_H	-	a_C	af_C	-
Probability of the first infected meal giving rise to infection in tsetse flies	α	0.065	[50]	-	-	-	-	-	-
Probability of infected fly bite producing infection in hosts	-	-	-	β_H	0.53	[23]	β_C	0.62	[50]
Incubation period	T_V	18.0	[18]	T_H	10.0	[16, 18]	T_C	7.0	[16, 18]
Recovery rate in infectious hosts	-	-	-	g_H	0.014	[19]	g'_C	0.012	[19]
Duration of immunity in recovered hosts	-	-	-	$\frac{1}{\nu_H}$	1.0	[16]	$\frac{1}{\nu_C}$	1.0	[16]
Proportion of cattle treated with trypanocides/day	-	-	-	-	-	-	ϕ_C	varying	-
Proportion of cattle kept on trypanocides	-	-	-	-	-	-	π	varying	-
Protection provided by chemoprophylactic treatment	-	-	-	-	-	-	ϵ	varying	-
Average duration of chemoprophylactic immunity	-	-	-	-	-	-	$\frac{1}{\gamma_C}$	180	[10]
Proportion of cattle treated kept on insecticides	-	-	-	-	-	-	p	varying	-
Cost of treating one cow with trypanocides	-	-	-	-	-	-	C_1	\$0.5	[48]
Daily cost of treating one cow with insecticides using the spraying method/traditional pour-on formulation method	-	-	-	-	-	-	C_2	\$0.02/\$0.06	[10, 24]

3.3.2 Tsetse infection parameters

The probability of the first blood meal leads to infection in tsetse flies was taken to be 0.065 as in [16, 31, 50]. The incubation period in tsetse flies, T_V, was taken to be 25 days in [31, 50], 18 days in [16], $16-20$ days in [19]. We take this value to be 18 days as in [16, 19]. The proportion of tsetse blood meals from humans, f_H, was taken to be $0.02-0.23$ in [19], 0.3 in [31, 50]. For our case, we take this value to be 0.1 as in [19]. The proportion of tsetse blood meals from cattle, f_C, is taken to be $1-f_H$, since we are assuming that tsetse can take blood meals from either cattle or humans.

3.3.3 Cattle infection parameters

The probability that an infected fly bite leads to infection in cattle was taken to be $\beta_C = 0.62$ as in [16, 31, 50] and the incubation period taken to be $T_C = 7.0$ days as in [16]. The mortality and self-recovery rates of infectious cattle were taken to be $\sigma'_C = 0.006$ and $g_C = 0.012$, respectively, to give a period of infectiousness of 55 days as in [19].

3.3.4 Human infection parameters

The probability that an infected fly bite results into infection in humans was taken to be $\beta_H = 0.53$ as in [16] and the incubation period taken to be $T_H = 10.0$ days as in [16]. The mortality and self-recovery rates of infectious humans were taken to be $\sigma_H = 0.004$ and $g_H = 0.014$, respectively, to give a period of infectiousness of 55 days as in [19].

3.4 Numerical results

With all the parameters having been fixed or estimated (Table 3.5), we look at the numerical results following from the mathematical model (3.4-3.12). The numerical results with fixed parameters show that in the absence of any medical or veterinary treatment, $R_0 \simeq 2.59$. This value is in the same range with 2.65 and 3 obtained in [50] and [31], respectively, for *T. brucei* species in humans and cattle.

3.4.1 Estimation of minimum R_{0H} if humans only are susceptible to infection

The value of R_{0H} is 0.10 which is close to 0.11 that was obtained in [31, 50] and 0.34 obtained in [72]. The value of R_{0H} being less than one means that the human population would be unable to sustain the transmission and that cattle are crucial to the long-term maintenance of *T. b. rhodesiense* infection. This result leads to the same conclusion as the one stated in [50, 72].

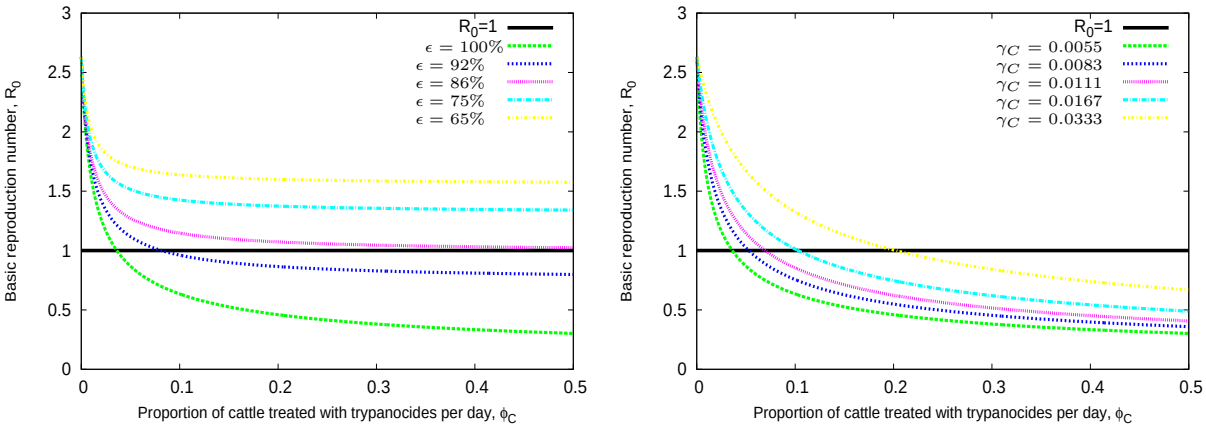
3.4.2 Prevention of an epidemic

Currently the fight against *T. b. rhodesiense* is based on three principal control strategies: trypanocidal drugs (chemotherapy and chemoprophylaxis), trypanotolerant cattle and tsetse control (insecticidal spraying, insecticidal targets, insecticide-treated cattle, traps, and the sterile insect technique). Chemotherapy is used for both humans and livestock while chemoprophylaxis is only used for livestock. The use of trypanotolerant cattle was shown to decrease the disease prevalence, but has no influence on the transmission of trypanosomiasis [40]. We thus concentrate on the study of the effectiveness of two of the control measures, that is, chemoprophylaxis and insecticide-treated cattle on the control of *T. b. rhodesiense*. We are also interested in the extent to which the control measures should be applied if the epidemic is to be eliminated. The results are shown to reflect the situation in Tororo district, Southeastern, Uganda.

Mass chemoprophylaxis

The effects of veterinary interventions on the transmission of human infective trypanosomes may be investigated through the parameter, ϕ_C, which gives the rate at which the cattle population are treated with trypanocides. We confine our arguments to treatment of cattle with trypanocidal drugs that afford chemoprophylactic protection, ϵ, against infection. If $\epsilon = 1$, then for those animals under chemoprophylaxis, the probability of an infectious fly bite producing an infection $\beta_C = 0$. This control measure reduces the infection rate in both cattle and tsetse flies, and hence protects humans from being infected [72]. Due to this protection, we expect the incidence and infection rate in humans to reduce with time.

Figure 3.3 shows the critical proportion of cattle that needs to be treated with trypanocides for R_0 to be less than one, for different levels of protection, ϵ, and rate of loss of immunity, γ_C, provided trypanocides. The results from the graph show that for $\gamma_C = 0.0055$, treating 3.5% of the cattle population per day with trypanocides that have an efficacy of 100% can reduce R_0 to less than one and hence lead to disease control. The results also show that the proportion of cattle required to be treated with trypanocides increases with a decrease or increase in the efficacy or rate of loss of protection provided by trypanocides, respectively.



(a) (b)

FIG. 3.3. The effect of mass chemoprophylaxis on the basic reproduction number for different values of ϵ and γ_C. The values of γ_C and ϵ were taken to be 0.0055 and 100% in (a) and (b), respectively.

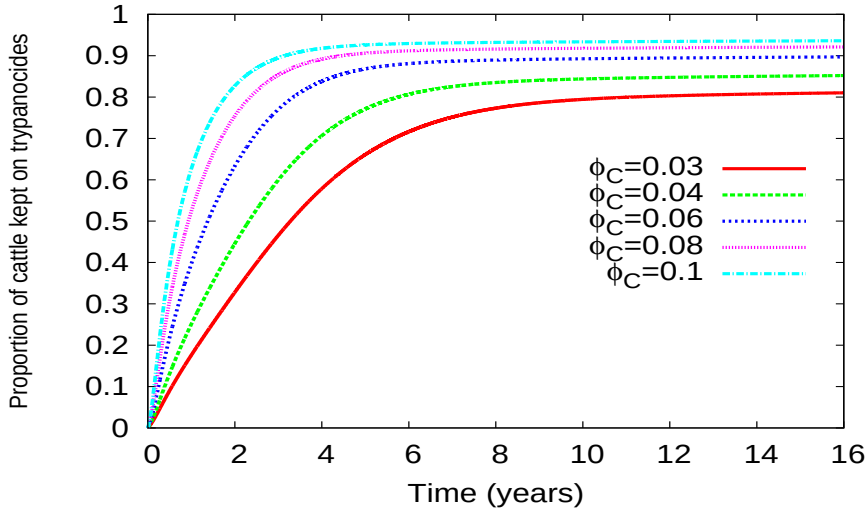
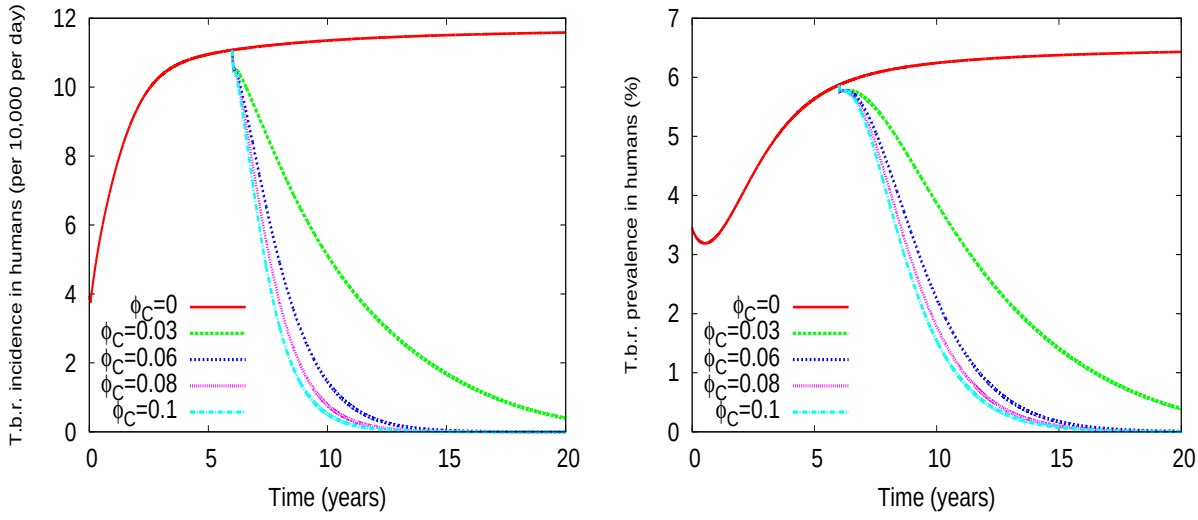


FIG. 3.4. Proportion of cattle kept on trypanocides for different values of ϕ_C.

To obtain the proportion of cattle that need to be kept on trypanocides, model (3.4-3.12) was solved in python and run up to when it reached a steady state. Figure 3.4 shows the proportion of cattle kept on trypanocides for different proportions of cattle treated with trypanocides per day, ϕ_C. The results show that treating 3.0% or 4.0% per day corresponds to keeping 80% or 85% of the cattle population on trypanocides, respectively. The results also show that the critical proportion of 3.5% required to be treated per day for R_0 to be

less than one is equivalent to keeping 82% of the cattle population on trypanocides. This value is close to 86% that was obtained in [72].



(a) (b)

FIG. 3.5. Mass chemoprophylaxis. (a) incidence and (b) prevalence of *T. b. rhodesiense* in humans. Different proportions of cattle are taken to be kept on chemoprophylactic drugs that provide 100% protection to infection. The recovery rate for infectious cattle g_C is taken to be $g'_C + \phi_C$.

Figure 3.5 shows the effect of treating different proportions of cattle with chemoprophylactic drugs on the incidence and prevalence of *T. b. rhodesiense* in humans. The results show that the *T. b. rhodesiense* incidence and prevalence in humans decrease monotonically as the proportion of cattle treated with trypanocides increases. Though the results show that trypanocides have an effect on *T. b. rhodesiense*, its impact on the long-term protection against trypanosomiasis is not clear. Since trypanocides have no effect on mortality, abundance and age structure of the vector population, it has been pointed out that it is difficult to use mass treatment of cattle with trypanocides to control *T. b. rhodesiense* in humans [31].

Insecticide-treated cattle

Insecticide-treated cattle (ITC) is regarded as one of the cheapest method for controlling tsetse and trypanosomiasis in Africa. The use of insecticide-treated cattle to control

trypanosomiasis is an attractive method which can be maintained by farmers in rural areas [10, 67]. We assume that each fly that bites or touches an animal that is treated with insecticides dies within a few hours. With this control measure, the density of the tsetse population is expected to decline with time, thus reducing the transmission of trypanosomiasis in both cattle and humans. The effects of insecticide-treated cattle on the transmission of *T. b. rhodesiense* can be investigated through the parameter, p, which gives the proportion of cattle kept on insecticides.

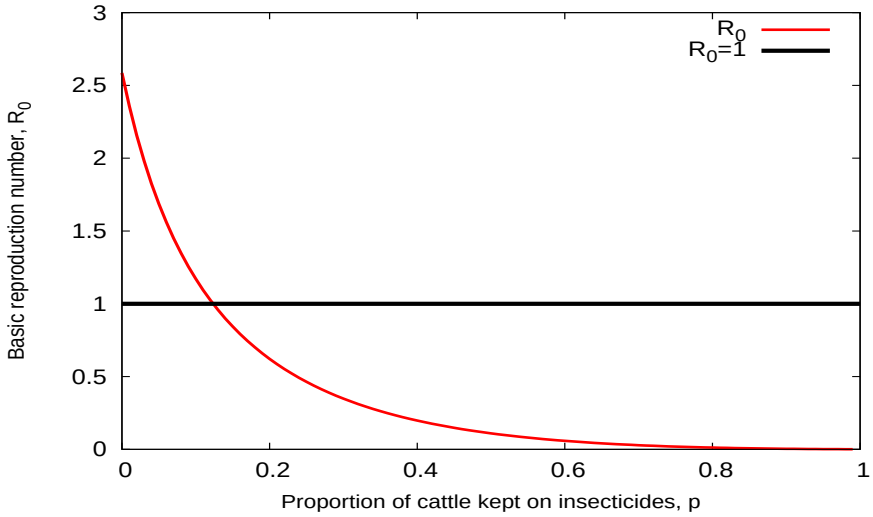
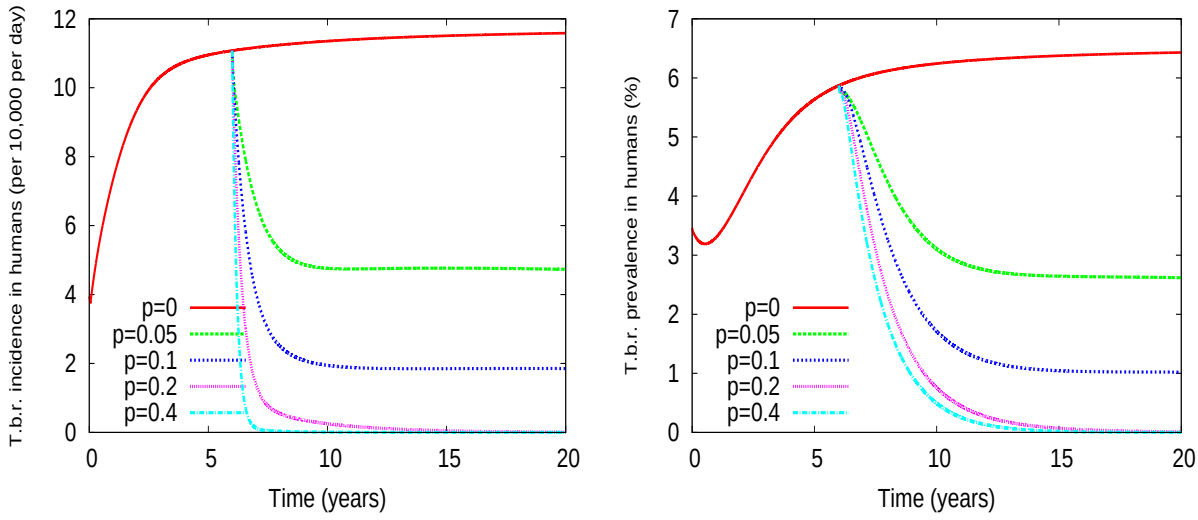


FIG. 3.6. The effect of insecticide-treated cattle on the basic reproduction number.

Figure 3.6 shows the critical proportion of cattle that needs to be kept on insecticide treatment for R_0 to be less than one. The results show that keeping 12% of the cattle population on insecticides could lead to R_0 less than one and hence control the *T. b. rhodesiense* epidemic in humans and cattle. This value is less than the 20% that was obtained in [31]. This is due to the fact that we considered a model where the tsetse population declines as a result of the insecticide treatment of cattle as opposed to the one in [31] which is a constant population model.

Figure 3.7 shows the effect of keeping different proportions of cattle on insecticides on the incidence and prevalence of *T. b. rhodesiense* in humans. The results show that there is a decrease in incidence and prevalence of *T. b. rhodesiense* in humans. The same results were obtained in [31, 40], where tsetse control was found to have an impact on trypanosomiasis.



(a) (b)

FIG. 3.7. Insecticide-treated cattle. (a) incidence and (b) prevalence of *T. b. rhodesiense* in humans for different proportions of cattle assumed to be kept on insecticides.

Mass chemoprophylaxis and insecticide-treated cattle (ITC)

We now consider the possibility of eradicating the human disease through a combination of chemoprophylaxis and ITC. Figure 3.8 (a) shows the critical proportion of cattle that needs to be treated with trypanocides per day and/or kept on insecticides for the basic reproduction number, R_0, to be less than one.

The results from the graph show that keeping about 12% of the cattle population on insecticides only, or treating about 3.5% of the cattle population per day with trypanocides (that have an efficacy of 100%) only, can reduce R_0 to less than one, and hence eradicate *T. b. rhodesiense* disease in both humans and cattle. It has already been shown that treating 3.5% per day is equivalent to keeping 82% of the cattle population on trypanocides. The control of *T. b. rhodesiense* through chemoprophylaxis largely depends on the efficacy of trypanocides, ϵ, which is the level of protection provided to cattle against the infection when bitten by an infectious fly. Results for different levels of protection provided by trypanocides are given in figure 3.8 (b). For high values of ϵ, disease eradication can be achieved by either treating cattle with trypanocides only or treating small proportions of cattle with trypanocides and insecticides. For low values of ϵ disease eradication can be achieved by either treating 12% of the cattle population with insecticides only or treating

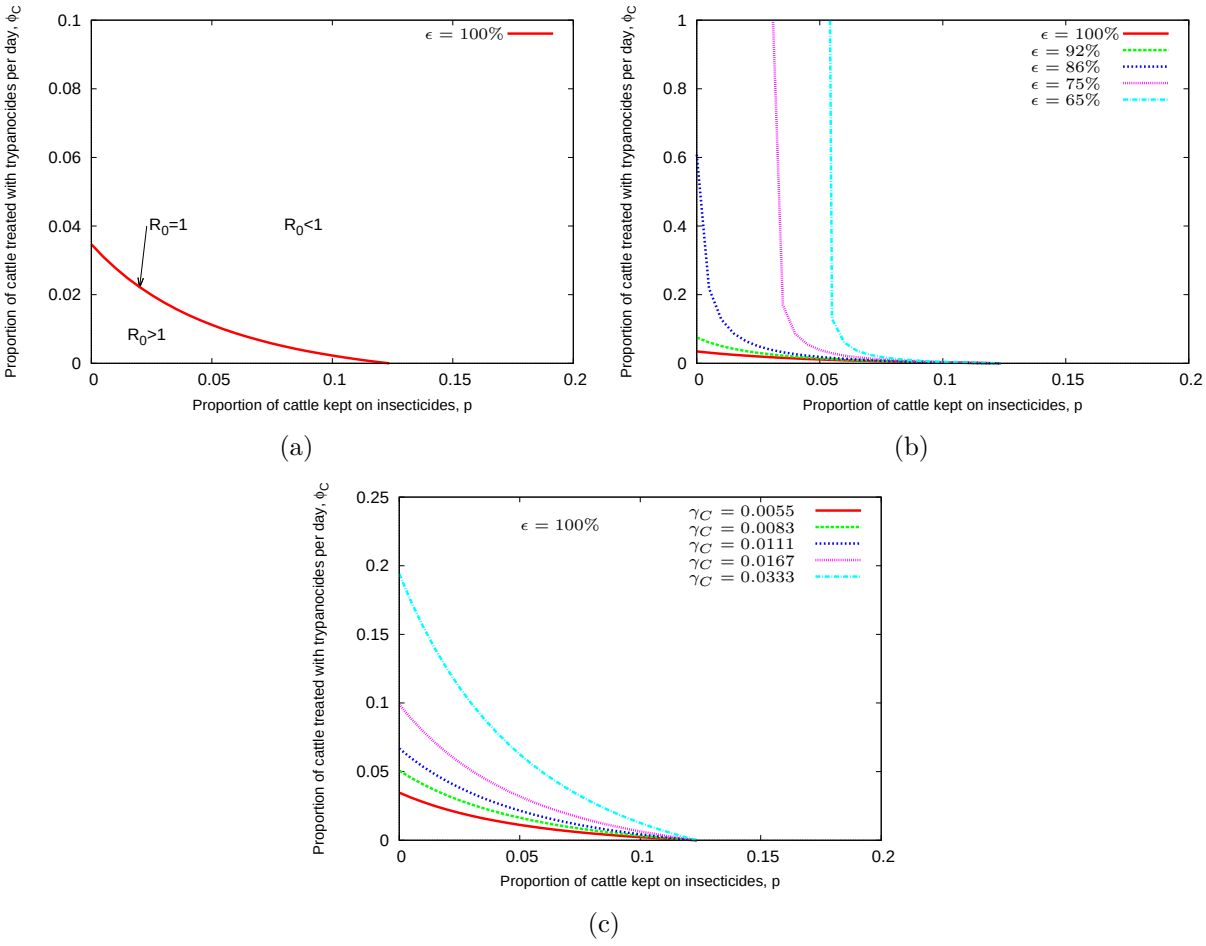
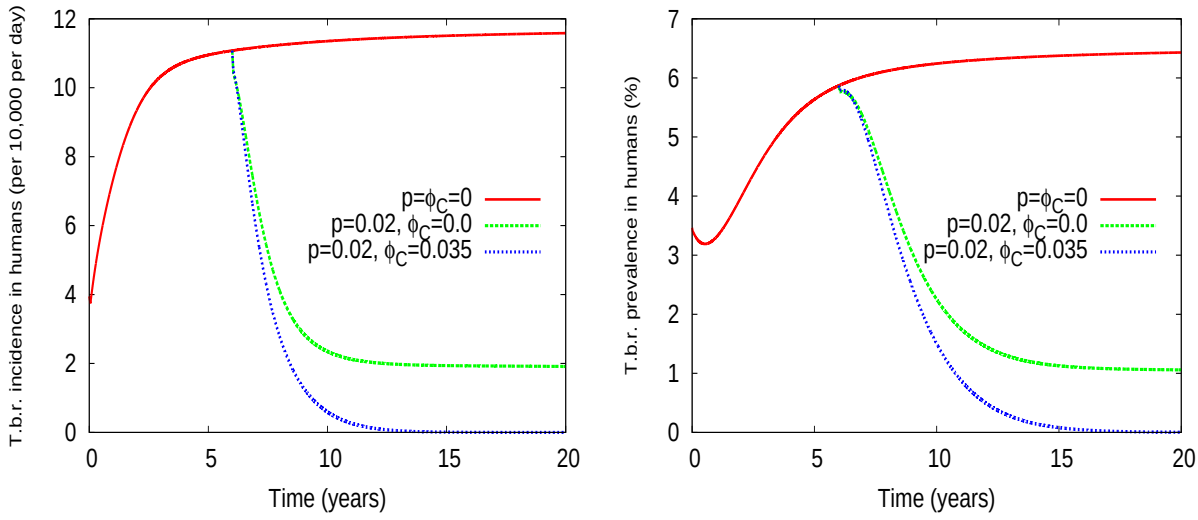


FIG. 3.8. The effect of combining chemoprophylaxis and insecticide-treated cattle on the basic reproduction number for $\epsilon = 100\%$ (a), and different values of ϵ (b).

less that 12% of cattle with insecticides and a higher proportion of cattle with trypanocides. It can also be noticed that for all values of ϵ, some combinations of p and ϕ_C can not lead to disease control. Disease control is only possible if the values of p and ϕ_C lie in the region where $R_0 < 1$ as shown in figure 3.8 (a).

Numerical results for the impact of combining chemoprophylaxis and ITC on the incidence and prevalence of *T. b. rhodesiense* in humans are shown in figure 3.9. The results show the benefit of treating 3.5% of the cattle population with trypanocides per day (or keeping 82% of the cattle population on trypanocides) in addition to keeping 2.0% of cattle on insecticides in reducing the incidence (a) and prevalence (b) of *T. b. rhodesiense* in humans.



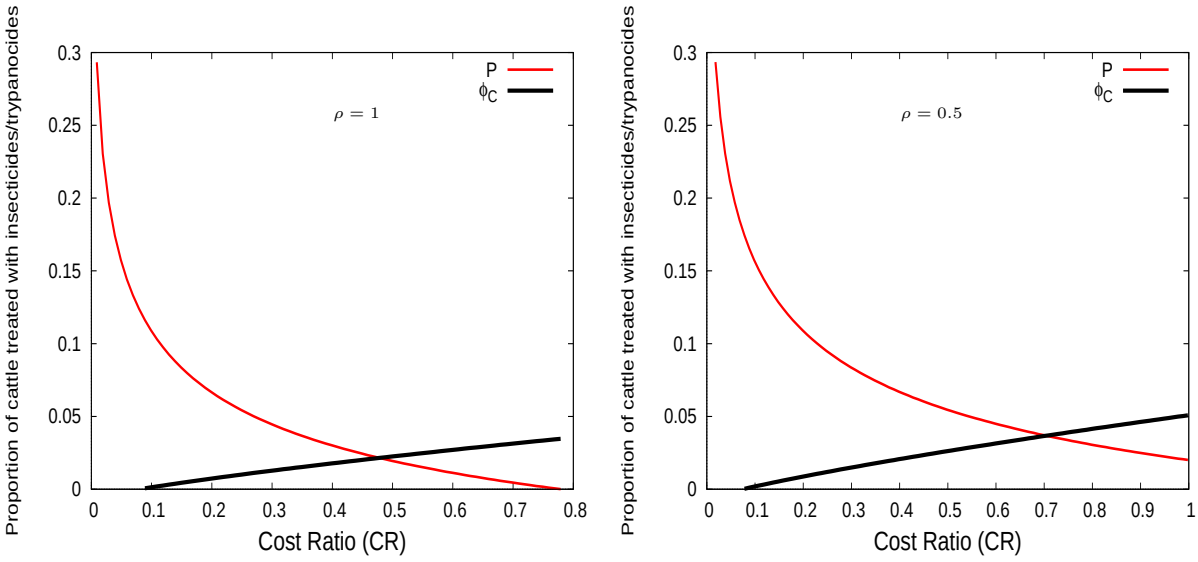
(a) (b)

FIG. 3.9. Insecticide-treated cattle and mass chemoprophylaxis. (a) incidence and (b) prevalence of *T. b. rhodesiense* in humans. 2.0% of the cattle population is assumed to be kept on insecticides and 3.5% of cattle is treated with trypanocides that provide 100% protection to infection. The recovery rate for infectious cattle g_C is taken to be $g'_C + \phi_C$.

3.4.3 Optimal control of the disease through chemoprophylaxis and ITC

Controlling the disease by combining the two control options can be done by treating a proportion, ϕ_C of cattle with trypanocides per day and keeping a proportion, p of cattle on insecticides. Any combination of values of ϕ_C and p picked from the region where $R_0 < 1$ (figure 3.8 (a)) will lead to disease control. The question is, what values of ϕ_C and p do we need in order to control the disease at minimum cost? To answer this question, an optimal control problem for controlling the disease at a minimal cost is carried out (see section 3.2.3 for the details). The results for the combinations of proportions of cattle treated with insecticides, p, and trypanocides, ϕ_C, with their corresponding cost ratio (CR) are given in figure 3.10. CR$<$ 1 means that treating a cow with insecticides is cheaper than treating with trypanocides. On the other hand, CR$>$ 1, implies that treating with trypanocides is cheaper than treating with insecticides.

Numerical results for optimal control show that for all values of ρ, $\phi_C \geq 0$ when the cost ratio, $CR \geq 0.08$. Thus, for the cost ratio less than 0.08, optimal control of *T. b.*



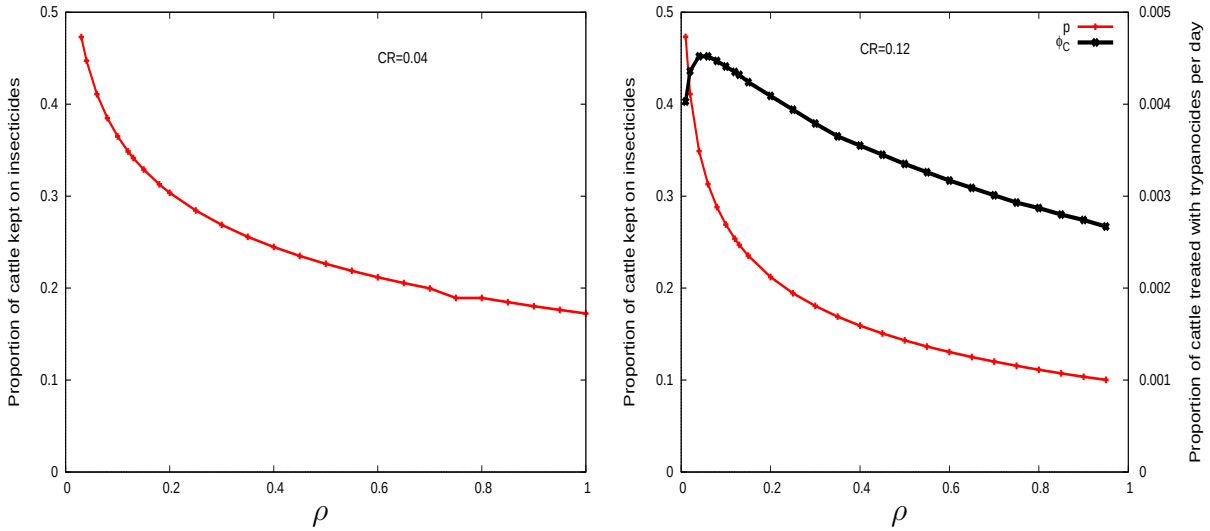
(a) (b)

FIG. 3.10. The critical proportions of cattle needed to be kept on insecticides and treated with trypanocides for R_0 to be less than ρ for $\rho = 1$ (a) and $\rho = 0.5$ (b). The cost ratio (CR) refers to the ratio of the daily cost of keeping one cow on insecticides to the cost of treating one cow with trypanocides. $\epsilon = 1$ in all cases and all the other parameters values are given in Table 3.5.

rhodesiense can be achieved by ITC only, and for $CR > 0.08$, optimal control can be achieved through a combination of ITC and chemoprophylaxis. The results in figure 3.10 (a) show that for $\rho = 1$, the cost ratio (CR) less than 0.48, implies that ϕ_C must be less than p for the disease to be controlled at a minimum cost. As the cost ratio exceeds 0.48, then ϕ_C must be greater than p for disease control at a minimal cost. The same explanation applies to case $\rho = 0.5$ shown in figure 3.10 (b).

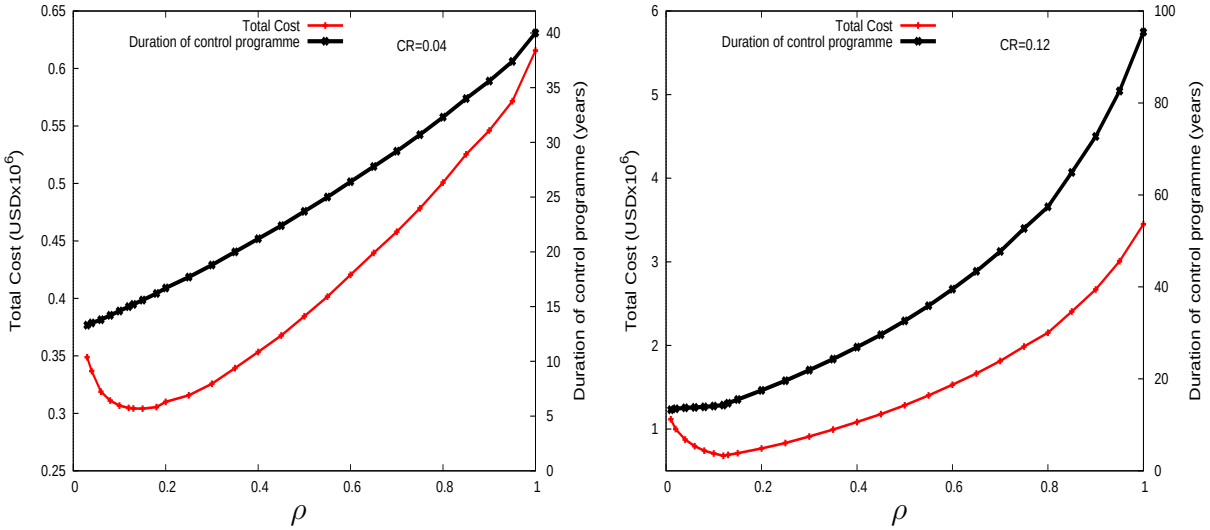
Figure 3.11 (a) shows the proportions of cattle required to be kept on insecticides for different values of the basic reproduction number threshold, ρ, for optimal control when $CR = 0.04$. The proportion, p decreases with the increase in ρ. The proportions of cattle required to be kept on insecticides and treated with trypanocides when $CR = 0.12$ for optimal control are shown in figure 3.11 (b). Both values of p and ϕ_C decrease with the increase in ρ.

Figure 3.12 shows the total cost for controlling *T. b. rhodesiense* in humans and cattle for different values of the basic reproduction number threshold ρ and cost ratio CR. Two optimal control scenarios are considered; that is, where $CR < 0.08$ and $CR > 0.08$ corre-



(a) (b)

FIG. 3.11. Insecticide-treated cattle and mass chemoprophylaxis. Proportions of cattle required to be treated with either insecticides or trypanocides for $CR = 0.04$ (a) and $CR = 0.12$ (b) . $\epsilon = 1$ in both cases and all the other parameters values are given in Table 3.5.



(a) (b)

FIG. 3.12. Insecticide-treated cattle and mass chemoprophylaxis. Total cost for controlling *T. b. rhodesiense* in humans and cattle against the basic reproduction number threshold (ρ) and the time required for controlling the disease in years. $\epsilon = 1$ in all cases and all the other parameters values are given in Table 3.5.

sponding to disease control through ITC only, and ITC and chemoprophylaxis, respectively. For the first optimal control scenario, we take the cost for treating one cow daily with insecticides as $C_2 = \$7.0/365 \simeq \$0.02$ as in [10, 24]. Taking the cost of treating one cow with trypanocides to be $C_1 = \$0.5$ as in [48] gives a cost ratio, $CR = 0.04$. This scenario corresponds to a case where cattle are treated with insecticides by using the spraying method [10]. The total cost for each proportion, p, of cattle that is kept on insecticides is obtained from $C_2 p \int_0^T N_C(t)dt$, where T is the duration of the control programme in days. The value of T for each proportion, p was obtained by running model (3.4-3.12) starting with the endemic equilibrium point obtained in the absence of any control measure as the initial condition up to when I_H, I_C and I_V are all less than one. For low values of ρ, the disease can be eradicated after a short period of time at a relatively higher cost. As ρ increases, the total cost for disease control decreases to a minimal value and then increases as values of ρ gets close to 1. The minimal total cost for disease control over a short period of time was estimated as $\$304,081$ for $\rho = 0.1$ and $T = 15.5$ years. The minimal total cost for this scenario is obtained by keeping 33% of the cattle population on insecticide treatment. Results of this scenario are shown in figure 3.12 (a).

In the second optimal control scenario, we take the daily cost of keeping one cow on insecticides as $C_2 = \$22.5/365 \simeq \$0.06$ as in [24]. Taking the cost of treating one cow with trypanocides to be $C_1 = 0.5$ gives a cost ratio, $CR = 0.12$. This scenario corresponds to a case where cattle is treated with insecticides by using the traditional pour-on formulation [24]. The total cost for scenario is calculated in same way as in the first scenario. The total cost for each combination of proportions of cattle treated with insecticides and trypanocides is obtained from $C_1\phi_C \int_0^T [S_C(t) + I_C(t)]dt + C_2 p \int_0^T N_C(t)dt$, where T is the duration of the control programme in days. The value of T is obtained by running model (3.4-3.12) starting with the endemic equilibrium point as in the first scenario. The optimal cost for this scenario was estimated to be $\$680,615$ for $\rho = 0.12$ and $T = 14.3$ years. The minimal total cost for the second scenario is obtained by treating 0.44% of the cattle with trypanocides per day (or keeping 14% of the cattle population on trypanocides) that provide 100% protection against *T. b. rhodesiense* infection and keeping 25% of the cattle population on ITC.

3.5 Summary

In this Chapter, we discussed the impact of treating cattle with chemoprophylactic drugs that provide considerable protection against infection, and tsetse control through insecticide-treated cattle (ITC) on the control of *T. b. rhodesiense* in humans and cattle. We used a mathematical model that assumes that tsetse flies only feed on either cattle or humans. An analytical expression of the basic reproduction number, R_0 of the model was obtained. Sensitivity analysis of the basic reproduction number, R_0 was carried out to determine the relative importance of each parameter to *T. b. rhodesiense* disease transmission. The sensitivity results of R_0 show that it is more sensitive to the tsetse-cattle biting rate, a_C, followed by the tsetse recruitment rate, Λ_V, and the probability of the first blood meal leading to infection in tsetse flies, α. A sensitivity analysis of R_0 with respect to the control parameters, ϕ_C and p was carried out to find which parameter has a higher impact on R_0 for each parameter in the range 0 to 1. The analysis suggests that vector control through ITC is more effective than chemoprophylaxis in reducing the transmission of *T. b. rhodesiense*.

Sensitivity analysis of the endemic equilibrium, E^*, was carried out to determine the relative importance of each parameter to *T. b. rhodesiense* disease prevalence. The sensitivity results of E^* show that the tsetse population variable states, S_V^* and I_V^*, are more sensitive to μ_V and Λ_V. The infectious human population variable state, I_H^*, is more sensitive to μ_V followed by Λ_V, a_H, β_H and a_C. The infectious cattle population variable state, I_C^*, is more sensitive to Λ_C followed by σ_C, μ_V, a_C and ϵ. The analysis suggests that treatment of infected humans and cattle combined with vector control are effective in reducing the prevalence of *T. b. rhodesiense*.

Numerical analysis of the model in terms of disease control through insecticide-treated cattle and chemoprophylaxis, shows that keeping about 12% or 82% of the cattle population on insecticides or trypanocides that have an efficacy of 100%, respectively, can reduce R_0 to less than one, a condition necessary for *T. b. rhodesiense* control. However, controlling the disease at $R_0 = 1$ requires the programme to be run for a long period of time. For the disease to be controlled in a short period of time, the proportions of cattle kept on insecticides or trypanocides need to be greater than 12% and 82%, respectively. A combination of proportions of cattle treated with insecticides and trypanocides that reduce R_0 to less

than ρ, where $\rho \in [0, 1)$ is the basic reproduction number threshold, were shown to lead to disease control. Optimal proportions of cattle needed to be treated with insecticides and trypanocides (to achieve disease control at a minimum cost) were also obtained for different cost ratios, where the cost ratio (CR) is taken to be the ratio of the daily cost of treating an animal with insecticides to the cost of treating the one animal with trypanocides. With, CR=0.04, optimal control can be achieved through ITC only by keeping 33% of the cattle population on insecticides for 15.5 years at a cost of about $\$300,000$. Taking $CR = 0.12$, requires a combination of ITC and chemoprophylaxis to achieve optimal control. Keeping 25% and 14% of the cattle population on insecticides and trypanocides that have an efficacy of 100% for 14.3 years lead to optimal control of *T. b. rhodesiense* in Tororo district, Uganda at a cost of about $\$680,000$.

Chapter 4

A multi-host model for the control of tsetse and *T. b. rhodesiense* through insecticide-treated cattle

4.1 Introduction

In this Chapter, we develop a simple model that describes the dynamics of the transmission of *Trypanosoma brucei rhodesiense* in a multi-host and tsetse vector populations. This is an extension of the model given in Chapter 3 to include more hosts in the presence of insecticide-treated cattle (ITC) only. We focus on the impact of a number of hosts, especially wild hosts and monitor lizards which can not be treated with either insecticides or trypanocides on the transmission of *T. b. rhodesiense*. We also focus on the control of *T. b. rhodesiense* through treatment of cattle with insecticides in the presence of wild hosts. Two methods of application of insecticides to cattle are considered, that is, whole-body and restricted application. A cost-effectiveness analysis is carried out to evaluate the costs and effectiveness of the two methods of application of insecticides.

4.2 Model development

We present a mathematical model that describes the transmission of *T. b. rhodesiense* by the tsetse vector species to a multi-host population of n different hosts. Tsetse flies feed at

a rate a per day so that each fly takes a new blood meal on average every $\frac{1}{a}$ days. Tsetse vectors are assumed to feed from the n hosts at random, but with a fixed preference taking a proportion f_i of its blood meals from the i^{th} host, where $\sum_i f_i = 1$ and $i = 1, 2, \ldots, n$. Thus, tsetse flies feed from each host at rates $a_i = af_i$ per day, with $a = \sum_i a_i$. Each host population is divided into three classes, susceptible (S_i), infectious (I_i) and recovered (R_i), whereas the tsetse population is divided into two classes, susceptible (S_V) and infectious (I_V). We take a time delay T_i and T_V representing the incubation period in the host and tsetse vector populations, respectively. This means that infections are caused by infectious groups that were infected T_i and T_V units of time earlier, respectively.

TABLE. 4.1. Definitions of the parameters used in the model

Parameter	**Definition**
Λ_i	Recruitment rate for host i
Λ_V	Recruitment rate for tsetse flies
μ_V	Tsetse natural mortality
m_V	Tsetse mortality in the presence of ITC
μ_i	Natural mortality for host i
a_i	Tsetse-host biting rate
β_i	Probability of infected fly bite producing an infection in host i
α_i	Probability of the first infected blood meal from host i giving rise to infection in tsetse flies
σ_i	Mortality rate of infected host i
g_i	Recovery rate of infected host i
ν_i	Rate of loss of immunity in recovered hosts i
T_V	Incubation period for tsetse flies
T_i	Incubation period for host i
ψ	Proportion of cattle treated with insecticides per day
d	Rate of loss of insecticidal killing effect

We assume that a vector infection only occurs during the first blood meal because teneral flies are the ones that become infected [3, 50]. We obtain the daily recruitment rate, Λ_V for susceptible tsetse flies which is composed of flies that survive and have not fed in one unit of time (that is, between $t-1$ and t) from

$$\Lambda_V = B_V \int_{t-1}^{t} e^{-\int_s^t (a+m_V(p(\xi)))d\xi} ds = B_V \int_0^1 e^{-\int_{-u}^0 (a+m_V(p(t+x)))dx} du, \tag{4.1}$$

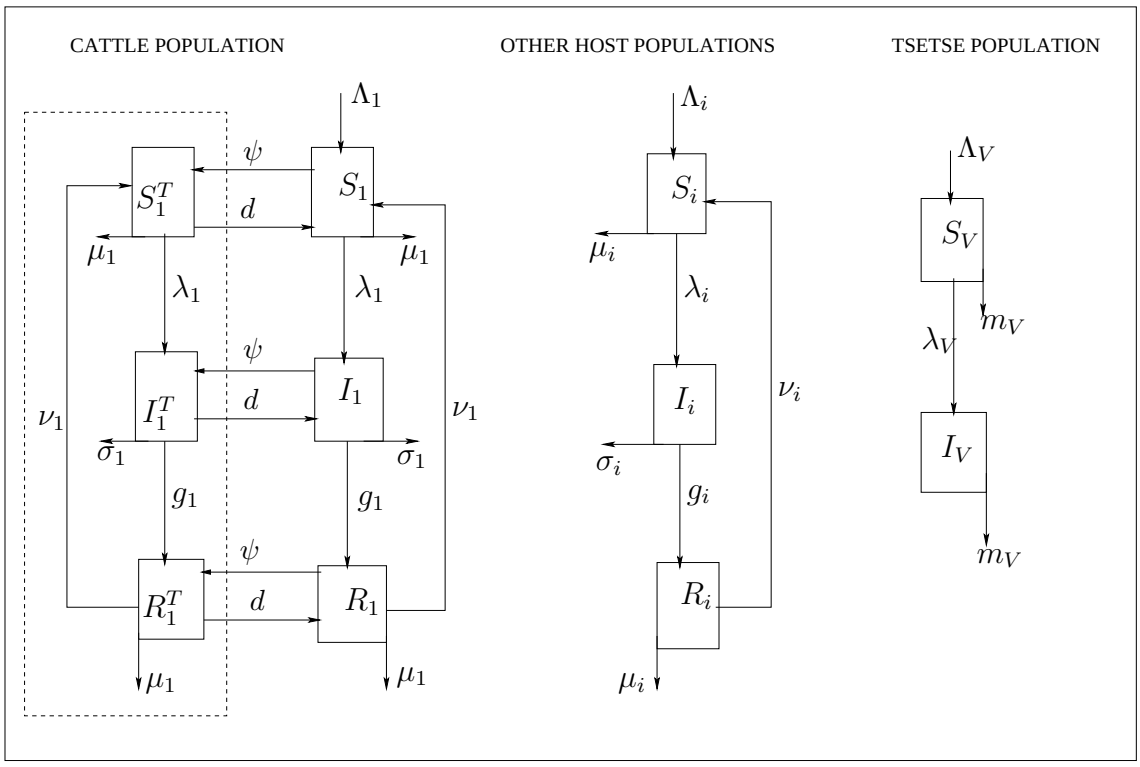


FIG. 4.1. Flow diagram of the compartmental model of *T. b. rhodesiense* in tsetse and a multi-host population that includes treatment of cattle with insecticides. The cattle population that is treated with insecticides is enclosed in a dotted rectangle. λ_i and λ_V are the forces of infection for the host and tsetse vector populations, respectively.

where B_V is the constant birth rate for the tsetse population, a is the tsetse feeding rate, $m_V(p(t+x))$ is the tsetse mortality which depends on the proportion of cattle, $p(t+x)$, that is on ITC, and $u \in [0,1]$. The solution of equation (4.1) is given in the Appendix. Susceptible flies get infected after biting an infectious host with a probability α_i. Due to the short life span of tsetse flies and the effect of insecticide-treated cattle we assume that a proportion $e^{-m_V(p(t))T_V}$ of infected flies will survive the incubation period, T_V [31, 50]. An actively infected vector never suffers from sleeping sickness but just transmits the trypanosome parasites and once it is infected it remains infective for life [50]. This means that vectors can only die due to natural mortality or insecticides if they bite a treated animal.

We assume a constant recruitment rate Λ_i for each host which is through birth and emigration. Following the bite of an infectious tsetse fly, the probability of a susceptible host

becoming infected is β_i. Infectious hosts are assumed to recover at a rate g_i. Recovered hosts lose their immunity at a rate ν_i and become susceptible again. A schematic representation of the *T. b. rhodesiense* transmission model in a multi-host population is shown in figure 4.1. Table 4.1 shows the model parameters and their definitions.

4.2.1 Including insecticide-treated cattle (ITC) in the model

To include ITC in the model, we split the cattle population from the rest of $(n-1)$ host populations as shown in figure 4.1. The cattle population is assumed to be treated with insecticides at a rate ψ per day, thus moving to the treated classes, S_1^T, I_1^T and R_1^T. The insecticide effect is assumed to be maximum on the day of application and it reduces with time, lasting on average for $\frac{1}{d}$ days. The value of $\frac{1}{d}$ will depend mainly on the type of insecticide formulation used, as well as the method of application. The insecticides applied to cattle are not repellents [68], and therefore, do not prevent tsetse from biting cattle. However, each fly that bites or touches an animal that is treated with insecticides is assumed to die within a few hours. We thus assume that cattle treated with insecticide get infected with trypanosomiasis when bitten by infectious tsetse flies with a probability, β_1, which is equal to that of untreated cattle. After infection, treated cattle progress to the infectious class, I_1^T, from which they can either die of the disease or recover at a rate g_1. The recovery and loss of immunity rates for treated and untreated cattle are taken to be the same. Each cow in the treated compartments S_1^T, I_1^T and R_1^T returns to S_1, I_1 and R_1, respectively, at a rate d, after the insecticides have lost their killing effect.

Let p be the proportion of cattle treated with insecticides. The daily tsetse mortality can be obtained from the expression

$$\mu_V(p) = -\ln[(1-p)f_C q_1 q_2^f + (1-f_C)q_1 q_2^f]/f. \tag{4.2}$$

which is derived in Chapter 3, Subsection 3.2.1, where q_1 is the probability that a tsetse fly survives a feed on a host, q_2 is the probability that a fly survives a non-feeding day, f is the tsetse feeding cycle in days, f_C is the probability that a tsetse fly feeds on cattle and $p = \frac{(S_1^T+I_1^T+R_1^T)}{N_1}$. We notice that expression (4.2) does not allow for the waning effect of insecticides since it assumes constant tsetse survival probabilities and takes the insecticidal killing effect to be 100% at all times. The expression also assumes that cattle are treated

with insecticides through the whole-body treatment strategy and does not cater for the different ITC application strategies. To allow for the waning effect of insecticides and cater for different strategies of insecticide application, we take the daily tsetse mortality in the presence of ITC to be given by

$$m_V = \mu_V + a_1 m \frac{(S_1^T + I_1^T + R_1^T)}{N_1}, \tag{4.3}$$

where μ_V is the tsetse natural mortality rate, and

$$a_1 m \frac{(S_1^T + I_1^T + R_1^T)}{N_1},$$

is the tsetse mortality incremental factor which is a function of the tsetse-cattle biting rate, a_1, the proportion of cattle treated with insecticides, $\frac{(S_1^T+I_1^T+R_1^T)}{N_1}$, and the tsetse additional mortality (or average knock down) due to the insecticides, m. The value of m is assumed to depend on the area of the animal covered by insecticides (e.g. whole-body (WB) treatment or restricted application (RAP) of insecticides), formulation of the insecticides as well as the duration of insecticide application. For the same formulation and duration of insecticide application, m is considered to be higher for whole-body treatment compared to restricted application of insecticides [64]. Figure 4.2 shows the tsetse mortality obtained from expressions (4.2) and (4.3) for different values of the proportion of cattle treated with insecticides, p, and different ITC application strategies.

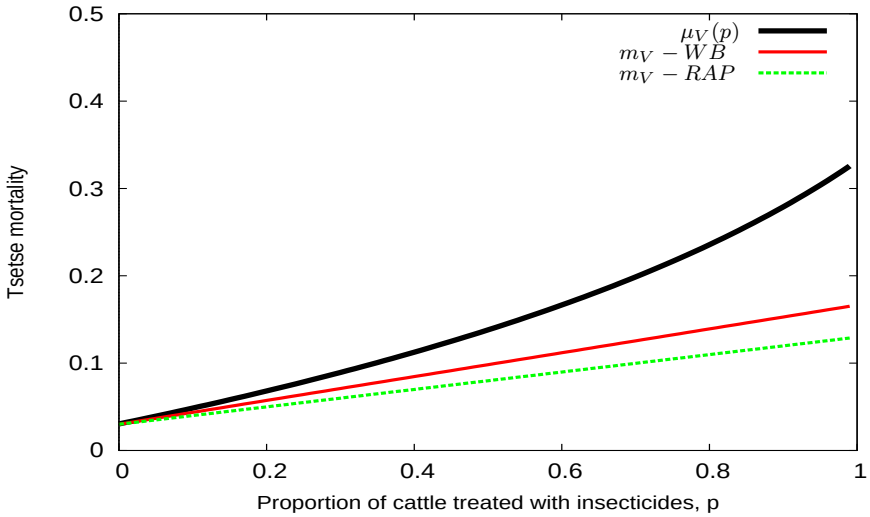


FIG. 4.2. Tsetse mortality estimates for different proportions of cattle treated with insecticides.

The results from figure 4.2 show that for small proportions of cattle treated with insecticides, the two expressions give almost the same estimates for the tsetse mortality. The tsetse mortality estimates obtained by expression (4.2) are significantly higher than those obtained by expression (4.3) for values of $p > 20\%$. The deviation in the mortality estimates is due to the fact that the waning effect of insecticides is not taken into account in expression (4.2). The results also show a small difference in the tsetse mortality estimates obtained by ITC through whole-body (WB) treatment and restricted application (RAP) of insecticides to cattle.

The equations for the model are given by,

$$\begin{aligned}
\frac{d}{dt}S_1 &= \Lambda_1 + \nu_1 R_1 + dS_1^T - (\psi + \mu_1)S_1 - \lambda_1(t-T_1)S_1(t-T_1),\\
\frac{d}{dt}I_1 &= \lambda_1(t-T_1)S_1(t-T_1) + dI_1^T - (\psi + g_1 + \sigma_1)I_1,\\
\frac{d}{dt}R_1 &= g_1 I_1 + dR_1^T - (\psi + \mu_1 + \nu_1)R_1,\\
\frac{d}{dt}S_1^T &= \psi S_1 + \nu_1 R_1^T - (\mu_1 + d)S_1^T - \lambda_1(t-T_1)S_1^T(t-T_1),\\
\frac{d}{dt}I_1^T &= \psi I_1 + \lambda_1(t-T_1)S_1^T(t-T_1) - (d + g_1 + \sigma_1)I_1^T,\\
\frac{d}{dt}R_1^T &= \psi R_1 + g_1 I_1^T - (d + \mu_1 + \nu_1)R_1^T,\\
\frac{d}{dt}S_i &= \Lambda_i + \nu_i R_i - \mu_i S_i - \lambda_i(t-T_i)S_i(t-T_i),\\
\frac{d}{dt}I_i &= \lambda_i(t-T_i)S_i(t-T_i) - (g_i + \sigma_i)I_i,\\
\frac{d}{dt}R_i &= g_i I_i - (\mu_i + \nu_i)R_i,\\
\frac{d}{dt}S_V &= \Lambda_V - e^{-m_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - m_V S_V,\\
\frac{d}{dt}I_V &= e^{-m_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - m_V I_V,
\end{aligned} \tag{4.4}$$

where $\lambda_1(t) = \frac{a_1\beta_1 I_V(t)}{N_1(t)}$, $\lambda_i(t) = \frac{a_i\beta_i I_V(t)}{N_i(t)}$, $\lambda_V(t) = \alpha_1 a_1 \frac{(I_1(t)+I_1^T(t))}{N_1(t)} + \sum_i \frac{\alpha_i a_i I_i(t)}{N_i(t)}$ and $i = 2, 3, \ldots, n$. The total population sizes N_1 (for cattle hosts), N_i (for non-cattle hosts) and N_V (for tsetse vectors) can be determined by $S_1 + I_1 + R_1 + S_1^T + I_1^T + R_1^T = N_1$, $S_i + I_i + R_i = N_i$ and $S_V + I_V = N_V$, respectively. All variables and parameters in the model (4.4) are considered to be positive and the model lies in the region

$$\Gamma^T = \left\{ (S_1, I_1, R_1, S_1^T, I_1^T, R_1^T, S_i, I_i, R_i, S_V, I_V) \in \mathbb{R}_+^{3n+8} : N_1 \leq \frac{\Lambda_1}{\mu_1}, N_i \leq \frac{\Lambda_i}{\mu_i}, N_V \leq \frac{\Lambda_V}{m_V} \right\},$$

where $i = 2, 3, \ldots, n$.

4.3 Mathematical analysis

Before carrying out the mathematical analysis of the whole model it is enlightening to consider its sub-model. We are able to gain insights into the dynamics of the whole model by considering smaller models. We consider firstly, the multi-host model in the absence of insecticide-treated cattle (ITC), by setting $S_1^T = I_1^T = R_1^T = 0$. Secondly, we consider the whole model. Qualitative analysis of some models is not tractable and we resort to simulations to obtain insights into the dynamics of such model.

4.3.1 Analysis of the multi-host model in the absence of ITC

In the absence of treatment of cattle with insecticides, the recruitment rate, Λ_V reduces to

$$\Lambda_V = B_V \int_0^1 e^{-\int_{-u}^{0}(a+\mu_V)dx} du = \frac{B_V}{(a+\mu_V)}(1 - e^{-(a+\mu_V)}).$$

Model (4.4) also reduces to

$$\begin{aligned}
\frac{d}{dt}S_i &= \Lambda_i + \nu_i R_i - \mu_i S_i - \lambda_i(t-T_i)S_i(t-T_i), && (4.5)\\
\frac{d}{dt}I_i &= \lambda_i(t-T_i)S_i(t-T_i) - (g_i+\sigma_i)I_i, && (4.6)\\
\frac{d}{dt}R_i &= g_i I_i - (\mu_i+\nu_i)R_i, && (4.7)\\
\frac{d}{dt}S_V &= \Lambda_V - e^{-\mu_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V S_V, && (4.8)\\
\frac{d}{dt}I_V &= e^{-\mu_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V I_V, && (4.9)
\end{aligned}$$

where $\lambda_i(t) = \frac{a_i\beta_i I_V(t)}{N_i(t)}$, $\lambda_V(t) = \sum_i \frac{\alpha_i a_i I_i(t)}{N_i(t)}$ and $i = 1, 2, \ldots, n$. The total population sizes N_i (for each host) and N_V can be determined by $S_i + I_i + R_i = N_i$ and $S_V + I_V = N_V$ or from the differential equations

$$\begin{aligned}
\frac{d}{dt}N_i &= \Lambda_i - \mu_i N_i - (\sigma_i - \mu_i)I_i, && (4.10)\\
\frac{d}{dt}N_V &= \Lambda_V - \mu_V N_V, && (4.11)
\end{aligned}$$

that are derived by adding equations (4.5-4.7) for each host population and (4.8-4.9) for the tsetse population. All variables and parameters in the model (4.5-4.9) are considered to be positive and the model lies in the region

$$\Gamma = \left\{ (S_i, I_i, R_i, S_V, I_V) \in \mathbb{R}_+^{3n+2} : N_i \leq \frac{\Lambda_i}{\mu_i}, N_V \leq \frac{\Lambda_V}{m_V} \right\}.$$

Basic reproduction number, R_{0n}

The expression of the basic reproduction number is derived by using the next generation method developed in [66] . Model system (4.5-4.9) has a disease-free equilibrium given by

$$E_0 = \left(\frac{\Lambda_1}{\mu_1}, 0, 0, \ldots, \frac{\Lambda_n}{\mu_n}, 0, 0, \frac{\Lambda_V}{\mu_V}, 0 \right).$$

Following [66], we obtain the matrices F (for the new infections) and V (for the transition terms) as

$$F = \begin{pmatrix} 0 & 0 & \ldots & 0 & a_1\beta_1 \\ 0 & 0 & \ldots & 0 & a_2\beta_2 \\ \vdots & \vdots & \ldots & \vdots & \vdots \\ 0 & 0 & \ldots & 0 & a_n\beta_n \\ \frac{e^{-\mu_V T_V}\alpha_1 a_1 \mu_1 \Lambda_V}{\Lambda_1 \mu_V} & \frac{e^{-\mu_V T_V}\alpha_2 a_2 \mu_2 \Lambda_V}{\Lambda_2 \mu_V} & \ldots & \frac{e^{-\mu_V T_V}\alpha_n a_n \mu_n \Lambda_V}{\Lambda_n \mu_V} & 0 \end{pmatrix}$$

$$\text{and} \quad V = \begin{pmatrix} g_1 + \sigma_1 & 0 & \ldots & 0 & 0 \\ 0 & g_2 + \sigma_2 & \ldots & 0 & 0 \\ \vdots & \vdots & \ldots & \vdots & \vdots \\ 0 & 0 & \ldots & g_n + \sigma_n & 0 \\ 0 & 0 & \ldots & 0 & \mu_V \end{pmatrix},$$

respectively. To obtain the expression for the basic reproduction number, R_{0n}, we need to find the eigenvalues of the matrix FV^{-1}. First, we observe that V is a diagonal matrix and its inverse is obtained by replacing each element in the diagonal with its reciprocal. Thus,

$$V^{-1} = \begin{pmatrix} \frac{1}{g_1+\sigma_1} & 0 & \dots & 0 & 0 \\ 0 & \frac{1}{g_2+\sigma_2} & \dots & 0 & 0 \\ \vdots & \vdots & \dots & \vdots & \vdots \\ 0 & 0 & \dots & \frac{1}{g_n+\sigma_n} & 0 \\ 0 & 0 & \dots & 0 & \frac{1}{\mu_V} \end{pmatrix} \quad \text{and}$$

$$FV^{-1} = \begin{pmatrix} 0 & 0 & \dots & 0 & \frac{a_1\beta_1}{\mu_V} \\ 0 & 0 & \dots & 0 & \frac{a_2\beta_2}{\mu_V} \\ \vdots & \vdots & \dots & \vdots & \vdots \\ 0 & 0 & \dots & 0 & \frac{a_n\beta_n}{\mu_V} \\ \frac{e^{-\mu_V T_V}\alpha_1 a_1 \mu_1 \Lambda_V}{\Lambda_1 \mu_V (g_1+\sigma_1)} & \frac{e^{-\mu_V T_V}\alpha_2 a_2 \mu_2 \Lambda_V}{\Lambda_2 \mu_V (g_2+\sigma_2)} & \dots & \frac{e^{-\mu_V T_V}\alpha_n a_n \mu_n \Lambda_V}{\Lambda_n \mu_V (g_n+\sigma_n)} & 0 \end{pmatrix}.$$

The eigenvalues of matrix, FV^{-1} are given by the roots of the following characteristic polynomial

$$P_{n+1} = \begin{vmatrix} -\lambda & 0 & \dots & 0 & \frac{a_1\beta_1}{\mu_V} \\ 0 & -\lambda & \dots & 0 & \frac{a_2\beta_2}{\mu_V} \\ \vdots & \vdots & \dots & \vdots & \vdots \\ 0 & 0 & \dots & -\lambda & \frac{a_n\beta_n}{\mu_V} \\ \frac{e^{-\mu_V T_V}\alpha_1 a_1 \mu_1 \Lambda_V}{\Lambda_1 \mu_V (g_1+\sigma_1)} & \frac{e^{-\mu_V T_V}\alpha_2 a_2 \mu_2 \Lambda_V}{\Lambda_2 \mu_V (g_2+\sigma_2)} & \dots & \frac{e^{-\mu_V T_V}\alpha_n a_n \mu_n \Lambda_V}{\Lambda_n \mu_V (g_n+\sigma_n)} & -\lambda \end{vmatrix}.$$

We have

$$P_{n+1} = -\lambda \begin{vmatrix} -\lambda & 0 & \dots & 0 & \frac{a_1\beta_1}{\mu_V} \\ 0 & -\lambda & \dots & 0 & \frac{a_2\beta_2}{\mu_V} \\ \vdots & \vdots & \dots & \vdots & \vdots \\ 0 & 0 & \dots & -\lambda & \frac{a_{n-1}\beta_{n-1}}{\mu_V} \\ \frac{e^{-\mu_V T_V}\alpha_1 a_1 \mu_1 \Lambda_V}{\Lambda_1 \mu_V (g_1+\sigma_1)} & \frac{e^{-\mu_V T_V}\alpha_2 a_2 \mu_2 \Lambda_V}{\Lambda_2 \mu_V (g_2+\sigma_2)} & \dots & \frac{e^{-\mu_V T_V}\alpha_{n-1} a_{n-1} \mu_{n-1} \Lambda_V}{B_{n-1} \mu_V (g_{n-1}+\sigma_{n-1})} & -\lambda \end{vmatrix} -$$

$$\frac{e^{-\mu_V T_V}\alpha_n a_n \mu_n \Lambda_V}{\Lambda_n \mu_V (g_n+\sigma_n)} \begin{vmatrix} -\lambda & 0 & \dots & 0 & \frac{a_1\beta_1}{\mu_V} \\ 0 & -\lambda & \dots & 0 & \frac{a_2\beta_2}{\mu_V} \\ \vdots & \vdots & \dots & \vdots & \vdots \\ 0 & 0 & \dots & -\lambda & \frac{a_{n-1}\beta_{n-1}}{\mu_V} \\ 0 & 0 & \dots & 0 & \frac{a_n\beta_n}{\mu_V} \end{vmatrix}.$$

This implies that,

$$\begin{aligned} P_{n+1} &= -\lambda P_n - \frac{e^{-\mu_V T_V}\alpha_n a_n^2 \mu_n \beta_n \Lambda_V}{\Lambda_n \mu_V^2 \left(g_n + \sigma_n\right)}(-\lambda)^{n-1}, \\ &= (-\lambda)^2 p_{n-1} - \left(\frac{e^{-\mu_V T_V}\alpha_{n-1} a_{n-1}^2 \mu_{n-1} \beta_{n-1} \Lambda_V}{B_{n-1}\mu_V^2 (g_{n-1} + \sigma_{n-1})} + \frac{e^{-\mu_V T_V}\alpha_n a_n^2 \mu_n \beta_n \Lambda_V}{\Lambda_n \mu_V^2 (g_n + \sigma_n)}\right)(-\lambda)^{n-1}, \end{aligned}$$

from which we deduce that

$$P_{n+1} = (-\lambda)^{n-1}\left(\lambda^2 - \sum_{i=1}^{n} \frac{e^{-\mu_V T_V}\alpha_i a_i^2 \mu_i \beta_i \Lambda_V}{\Lambda_i \mu_V^2 (g_i + \sigma_i)}\right).$$

By solving $P_{n+1} = 0$, we have

$$\lambda = 0 \quad \text{or} \quad \lambda = \sqrt{\sum_{i=1}^{n} \frac{e^{-\mu_V T_V}\alpha_i a_i^2 \mu_i \beta_i \Lambda_V}{\Lambda_i \mu_V^2 (g_i + \sigma_i)}}.$$

Thus, the basic reproduction number, R_{0n}, which is given by the spectral radius of the next generation matrix FV^{-1}, is

$$R_{0n} = \sqrt{\sum_{i=1}^{n} \frac{e^{-\mu_V T_V}\alpha_i a_i^2 \mu_i \beta_i \Lambda_V}{\Lambda_i \mu_V^2 (g_i + \sigma_i)}}. \tag{4.12}$$

This is the net number of secondary infections arising from one infectious index case in an otherwise disease-free equilibrium (DFE). The square root arises due to the fact that two generations are required for an infected tsetse fly or host to reproduce itself [66]. If R_{0n} is greater than 1, the disease-free equilibrium is unstable and we are in the presence of an endemic equilibrium, where the disease can invade and persist. However, if R_{0n} is smaller than 1, then the disease-free equilibrium is stable, and the disease dies out.

4.3.2 Local stability of the disease-free equilibrium of the one-host *T. b. rhodesiense* transmission model in the absence of ITC

In this subsection, we study the local stability of the disease-free equilibrium of the one-host *T. b. rhodesiense* transmission model with time delay in the absence of insecticide-treated

cattle. In a case where there is one host population, system (4.5-4.9) reduces to,

$$\begin{aligned}
\frac{d}{dt}S_1 &= \Lambda_1 + \nu_1 R_1 - \mu_1 S_1 - \lambda_1(t-T_1)S_1(t-T_1),\\
\frac{d}{dt}I_1 &= \lambda_1(t-T_1)S_1(t-T_1) - (g_1+\sigma_1)I_1,\\
\frac{d}{dt}R_1 &= g_1 I_1 - (\mu_1+\nu_1)R_1,\\
\frac{d}{dt}S_V &= \Lambda_V - e^{-\mu_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V S_V,\\
\frac{d}{dt}I_V &= e^{-\mu_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - \mu_V I_V,
\end{aligned} \tag{4.13}$$

where $\lambda_1(t) = \frac{a_1\beta_1 I_V(t)}{N_1(t)}$ and $\lambda_V(t) = \frac{\alpha_1 a_1 I_1(t)}{N_1(t)}$ are the forces of infection for the host and tsetse populations, respectively. System (4.13) satisfy the initial conditions: $S_1(\theta) = S_1^0, I_1(\theta) = I_1^0, R_1(\theta) = R_1^0, S_V(\theta) = S_V^0, I_V(\theta) = I_V^0$, for $\theta \in [-\tau, 0]$, where $\tau = \max(T_1, T_V)$. The respective total host and tsetse population sizes can be determined by $N_1 = S_1 + I_1 + R_1$ and $N_V = S_V + I_V$ or from the differential equations

$$N_1' = \Lambda_1 - \mu_1 N_1 - (\sigma_1 - \mu_1)I_1 \quad \text{and} \quad N_V' = \Lambda_V - \mu_V N_V,$$

which are derived by adding the equations in system (4.13). We study system (4.13) in the region

$$\Gamma_1 = \left\{(S_1, I_1, R_1, S_V, I_V) \in \mathbb{R}_+^5 : 0 \le S_1 + I_1 \le \frac{\Lambda_1}{\mu_1}, 0 \le I_V \le \frac{\Lambda_V}{\mu_V}, S_1 \ge 0, I_1 \ge 0\right\},$$

where $\mathbb{R}_+^5$ denotes the non-negative cone of $\mathbb{R}^5$ including its lower dimensional faces. We denote the boundary and interior of Γ_1 by $\partial\Gamma_1$ and $\dot{\Gamma}_1$, respectively. System (4.13) has a disease-free equilibrium $E_{01} = (\frac{\Lambda_1}{\mu_1}, 0, 0, \frac{\Lambda_V}{\mu_V}, 0)$. An explicit expression for the basic reproduction number of system (4.13) can be obtained from equation (4.12) for $n = 1$ as $R_{01} = \sqrt{\frac{e^{-\mu_V T_V}\alpha_1 a_1 \mu_1 \beta_1 \Lambda_V}{\Lambda_1 \mu_V^2 (g_1+\sigma_1)}}$.

We consider the local stability of the disease-free equilibrium, E_{01}, in two cases, that is, when $R_{01} < 1$ and when $R_{01} > 1$.

Theorem 3 *The disease-free equilibrium, E_{01}, of the one-host T. b. rhodesiense transmission model with time delay in the absence of ITC is locally asymptotically stable in Γ_1 if $R_{01} < 1$ and unstable if $R_{01} > 1$.*

Proof. Linearising system (4.13) around the disease-free equilibrium, $E_{01} = (\frac{\Lambda_1}{\mu_1}, 0, 0, \frac{\Lambda_V}{\mu_V}, 0)$, we obtain three negative eigenvalues; $-(\nu_1 + \mu_1), -\mu_1$ and $-\mu_V$, and the following characteristic equation whose solutions (real or complex) give the remaining eigenvalues:

$$\lambda^2 + (\mu_V + g_1 + \sigma_1)\lambda - \mu_V(g_1 + \sigma_1)\left[(R_{01})^2 e^{-\lambda(T_1+T_V)} - 1\right] = 0. \tag{4.14}$$

For $T_1 = T_V = 0$, equation (4.14) will have only roots with negative real parts if $R_{01} < 1$ and the disease-free equilibrium will be locally stable, according to the Routh-Hurwitz criterion. Otherwise, equation (4.14) will have one positive root if $R_{01} > 1$ and E_{01} is unstable.

For $T_1 = 0$ and $T_V \neq 0$, we first consider the case when $R_{01} > 1$ and arrange equation (4.14) in the form

$$\lambda^2 + (\mu_V + g_1 + \sigma_1)\lambda = \mu_V(g_1 + \sigma_1)\left[(R_{01})^2 e^{-\lambda T_V} - 1\right]. \tag{4.15}$$

Let $F(\lambda)$ and $G(\lambda)$ denote the left-hand and right-hand sides of equation (4.15), respectively. It is clear that $F(\lambda)$ is an increasing function of λ, for $\lambda \in \mathbb{R}$, with $F(0) = 0$ and $\lim_{\lambda\to\infty} F(\lambda) = \infty$. The function $G(\lambda)$ is a decreasing function of λ, $\lambda \in \mathbb{R}$, and $G(0) = \mu_V(g_1 + \sigma_1)\left[(R_{01})^2 - 1\right] > 0$. Thus, the two functions must intersect for some $\lambda^* > 0$. Hence (4.15) has a positive real solution for $R_{01} > 1$ and the disease-free equilibrium is unstable.

Moving to the case $R_{01} < 1$, we notice that $F(\lambda)$ is still an increasing function of λ. $G(\lambda)$ is also a decreasing function of λ, with $G(0) = \mu_V(g_1+\sigma_1)\left[(R_{01})^2 - 1\right] < 0$. Thus, equation (4.15) has no positive real roots. If equation (4.15) is to have positive real roots, they must be complex and should have been obtained from a pair of complex conjugate roots that cross the imaginary axis. So, we need to show that these roots do not exist for E_{01} to be stable. Assume that $\lambda = i\omega$, for $\omega > 0$. Substituting for λ in equation (4.15), we obtain

$$-\omega^2 + i(\mu_V + g_1 + \sigma_1)\omega - \mu_V(g_1 + \sigma_1)\left[(R_{01})^2(\cos(\omega T_V) - i\sin(\omega T_V)) - 1\right] = 0$$

Separating the real and imaginary parts, we have the following system of equations

$$\begin{aligned} -\omega^2 + \mu_V(g_1 + \sigma_1) &= \mu_V(g_1 + \sigma_1)(R_{01})^2\cos(\omega T_V), \\ (\mu_V + g_1 + \sigma_1)\omega &= -\mu_V(g_1 + \sigma_1)(R_{01})^2\sin(\omega T_V). \end{aligned}$$

Adding the above equations together and using the trigonometric identity, $\cos^2(\omega T_V) + \sin^2(\omega T_V) = 1$, we obtain the following four degree equation in ω

$$\omega^4 + (\mu_V^2 + (g_1 + \sigma_1)^2)\omega^2 + \mu_V^2(g_1 + \sigma_1)^2(1 - (R_{01})^4) = 0. \tag{4.16}$$

To reduce this fourth order equation to a quadratic equation, we let $z = \omega^2$, and the resulting equation in terms of z is

$$z^2 + (\mu_V^2 + (g_1 + \sigma_1)^2)z + \mu_V^2(g_1 + \sigma_1)^2(1 - (R_{01})^4) = 0. \tag{4.17}$$

It is clear that for $R_{01} < 1$, equation (4.17) does not have positive real roots which leads to the conclusion that there is no ω such that $\lambda = i\omega$ is a solution of (4.15). In a similar way, it can be shown that there are no positive real roots for cases $T_1 \neq 0$ and $T_V = 0$, and for the general case when $T_1 \neq 0$ and $T_V \neq 0$. Therefore, the real parts of all eigenvalues of the characteristic equation (4.14) are negative for all values of the time delay $T_1 \geq 0$ and $T_V \geq 0$. Thus, the disease-free equilibrium, E_{01}, is locally asymptotically stable for $R_{01} < 1$ and unstable for $R_{01} > 1$. This completes the proof of the theorem. □

4.3.3 The endemic steady states of the multi-host *T. b. rhodesiense* transmission model in the absence of ITC

Assuming that $R_{0n} > 1$, we can now focus on the existence and uniqueness of the endemic equilibrium. An endemic equilibrium is a time-independent solution of system (4.5-4.9). Since a time-independent solution has the same values at time t as at time $t - \tau$, where τ is the time delay, the solution of the endemic equilibrium of system (4.5-4.9) can be obtained by considering the system without time delay. Let

$$\lambda_i^* = \frac{a_i \beta_i I_V^*}{N_i^*} \quad \text{and} \quad \lambda_V^* = \sum_{i=1}^{n} \frac{\alpha_i a_i I_i^*}{N_i^*} \tag{4.18}$$

be the respective forces of infection for the host and tsetse vector populations. Further, let the endemic steady state of model (4.5-4.9) be given by $E^* = (S_i^*, I_i^*, R_i^*, S_V^*, I_V^*)$. Solving the equations (4.5-4.9) at the steady state gives

$$\begin{aligned} I_i^* &= \frac{B_i \lambda_i^*}{D_i \lambda_i^* + F_i}, \quad R_i^* = \frac{g_i I_i^*}{\mu_i + \nu_i}, \quad S_i^* = \frac{\Lambda_i + \nu_i R_i}{\mu_i + \lambda_i^*}, \quad N_i^* = \frac{G_i \lambda_i^* + H_i}{D_i \lambda_i^* + F_i} \\ I_V^* &= \frac{A\Lambda_V \lambda_V^*}{\mu_V(A\lambda_V^* + \mu_V)}, \quad S_V^* = \frac{\Lambda_V}{A\lambda_V^* + \mu_V}, \quad N_V^* = \frac{\Lambda_V}{\mu_V}, \end{aligned} \tag{4.19}$$

where $B_i = \Lambda_i(\mu_i+\nu_i)$, $D_i = g_i\mu_i+\sigma_i(\mu_i+\nu_i)$, $F_i = \mu_i(\nu_i+\mu_i)(g_i+\sigma_i)$, $G_i = \Lambda_i(g_i+\nu_i+\mu_i)$, $H_i = \Lambda_i(\nu_i+\mu_i)(g_i+\sigma_i)$ and $A = e^{-\mu_V T_V}$.

Substituting for I_V^*, I_i^* and N_i^* in equation (4.18) and solving, we obtain the endemic equilibrium in terms of λ_i^* as

$$\lambda_i^*(G_i\lambda_i^*+H_i)\mu_V^2 + A\Big(\lambda_i^*(G_i\lambda_i^*+H_i)\mu_V - a_i\beta_i\Lambda_V(D_i\lambda_i^*+F_i)\Big)\sum_{i=1}^{n}[\frac{\alpha_i a_i B_i\lambda_i^*}{G_i\lambda_i^*+H_i}] = 0. \quad (4.20)$$

Considering a case where the transmission of *T. b. rhodesiense* is occurring between the tsetse vector species and one host population (that is, $n = 1$), equation (4.20) becomes

$$\lambda_1^*(G_1\lambda_1^*+H_1)\mu_V^2 + A\Big(\lambda_1^*(G_1\lambda_1^*+H_1)\mu_V - a_1\beta_1\Lambda_V(D_1\lambda_1^*+F_1)\Big)(\frac{\alpha_1 a_1 B_1\lambda_1^*}{G_1\lambda_1^*+H_1}) = 0. \quad (4.21)$$

Simplifying equation (4.21), we obtain a non-zero equilibria for model (4.5-4.9) for a special case when $n = 1$ as

$$\lambda_1^*\Big(a_0(\lambda_1^*)^2 + b_0\lambda_1^* + c_0\Big) = 0, \quad (4.22)$$

where $a_0 = G_1\mu_V(A\alpha_1 a_1 B_1 + G_1\mu_V)$, $b_0 = AH_1\alpha_1 a_1 B_1\mu_V + 2H_1G_1\mu_V^2 - A\alpha_1 a_1^2\Lambda_V B_1 D_1\beta_1$ and $c_0 = \Lambda_1\mu_V^2(g_1+\sigma_1)(1-(R_{01})^2)$.

Thus, the positive endemic equilibria of model (4.5-4.9) for the special case when $n = 1$ is obtained by solving equation (4.22) and substituting the results of λ_1^* into expressions (4.19). It can be seen that a_0 is always positive and c_0 is positive (negative) if R_{01} is less than (greater than) one, respectively. Thus, the following result is obtained

Theorem 4 *The one-host T. b. rhodesiense transmission model with time delay in the absence of ITC has:*

(i) a unique endemic equilibrium if $c_0 < 0 \Longleftrightarrow R_{01} > 1$*;*

(ii) a unique endemic equilibrium if $b_0 < 0$ *and* $C_0 = 0$ *or* $b_0^2 - 4a_0c_0 = 0$*;*

(iii) two endemic equilibria if $c_0 > 0, b_0 < 0$ *and* $b_0^2 - 4a_0c_0 > 0$*;*

(iv) no endemic equilibrium otherwise.

The computation of the endemic equilibria for the cases where $n > 1$ leads to polynomials whose degree is more than three, which are difficult to analyse analytically. We thus resort to numerical results which are given in Section 4.4.

4.3.4 Mathematical analysis of the multi-host model in the presence of ITC

After taking insecticide-treated cattle (ITC) into consideration we obtain the new model which is schematically represented by figure 4.1 and given by system (4.4). The disease-free equilibrium of the model is given by

$$E_0^T = (\frac{\Lambda_1(1-\pi)}{\mu_1}, 0, 0, \frac{\Lambda_1\pi}{\mu_1}, 0, 0, \frac{\Lambda_2}{\mu_2}, 0, 0, \ldots, \frac{\Lambda_n}{\mu_n}, 0, 0, \frac{\tilde{\Lambda}_V}{\tilde{m}_V}, 0),$$

where $\pi = \frac{\psi}{\psi+d+\mu_1}$ and $\tilde{m}_V = \mu_V + a_1 m\pi$. The expression for $\tilde{\Lambda}_V$ is given by equation (A.11) in the Appendix. Using the notation used in [66], we obtain the following expressions of F and V.

$$F = \begin{pmatrix} 0 & 0 & 0 & \ldots & 0 & a_1\beta_1(1-\pi) \\ 0 & 0 & 0 & \ldots & 0 & a_1\beta_1\pi \\ 0 & 0 & 0 & \ldots & 0 & a_2\beta_2 \\ \vdots & \vdots & \vdots & \ldots & \vdots & \vdots \\ 0 & 0 & 0 & \ldots & 0 & a_n\beta_n \\ \frac{e^{-\tilde{m}_V T_V}\alpha_1 a_1\mu_1\tilde{\Lambda}_V}{\Lambda_1\tilde{m}_V} & \frac{e^{-\tilde{m}_V T_V}\alpha_1 a_1\mu_1\tilde{\Lambda}_V}{\Lambda_1\tilde{m}_V} & \frac{e^{-\tilde{m}_V T_V}\alpha_2 a_2\mu_2\tilde{\Lambda}_V}{\Lambda_2\tilde{m}_V} & \ldots & \frac{e^{-\tilde{m}_V T_V}\alpha_n a_n\mu_n\tilde{\Lambda}_V}{\Lambda_n\tilde{m}_V} & 0 \end{pmatrix}$$

$$\text{and} \quad V = \begin{pmatrix} \psi+g_1+\sigma_1 & -d & 0 & \ldots & 0 & 0 \\ -\psi & d+g_1+\sigma_1 & 0 & \ldots & 0 & 0 \\ 0 & 0 & g_2+\sigma_2 & \ldots & 0 & 0 \\ \vdots & \vdots & \vdots & \ldots & \vdots & \vdots \\ 0 & 0 & 0 & \ldots & g_n+\sigma_n & 0 \\ 0 & 0 & 0 & \ldots & 0 & \tilde{m}_V \end{pmatrix},$$

respectively. Using the method in Subsection 4.3.1, the basic reproduction number for the multi-host model in the presence of insecticide-treated cattle is obtained as the spectral

radius of the next generation matrix, FV^{-1}, and is given by

$$R_{0n}^{T} = \sqrt{\frac{e^{-\tilde{m}_V T_V}\tilde{\Lambda}_V}{\tilde{m}_V^2}\sum_{i=1}^{n}\frac{\alpha_i a_i^2 \beta_i \mu_i}{\Lambda_i(g_i+\sigma_i)}}. \tag{4.23}$$

R_{0n}^{T} gives the expected number of secondary cases produced in a completely susceptible population, by a typical infective host or tsetse fly in the presence of insecticide-treated cattle. If $R_{0n}^{T} > 1$, then the disease may emerge in one of the populations. However, if $R_{0n} < 1$, then the disease-free equilibrium is locally asymptotically stable [66]. Notice that when $\pi = 0$, equation (4.23) reduces to (4.12).

For our study, we consider a special case where the host population is limited to three texa, that is, cattle, humans and wildlife as in [19]. Studies on trypanosomiasis infection in East Africa show that cattle are an important reservoir for *T. b. rhodesiense*. The importance of wildlife in the transmission of trypanosomiasis has also been identified in most parts of sub-Saharan Africa [16, 26, 71, 72]. For the case where $n = 3$, the basic reproduction number can be obtained from equation (4.23) as

$$R_{03}^{T} = \sqrt{\frac{e^{-\tilde{m}_V T_V}\tilde{\Lambda}_V}{\tilde{m}_V^2}\left\{\frac{\alpha_1 a_1^2 \beta_1 \mu_1}{\Lambda_1(g_1+\sigma_1)} + \frac{\alpha_2 a_2^2 \beta_2 \mu_2}{\Lambda_2(g_2+\sigma_2)} + \frac{\alpha_3 a_3^2 \beta_3 \mu_3}{\Lambda_3(g_3+\sigma_3)}\right\}}. \tag{4.24}$$

4.3.5 Sensitivity analysis of R_{03}^{T} to parameter values

R_{03}^{T} is determined by several parameters, and therefore, it is necessary to investigate the sensitivity of R_{03}^{T} to each parameter. As in Chapter 3, this can be determined by calculating the sensitivity index of R_{03}^{T} with respect to each parameter. The definition shows that the sensitivity of a variable X with respect to a parameter μ is given by

$$\Upsilon_{\mu}^{X} = \frac{\partial X}{\partial \mu}\frac{\mu}{X}. \tag{4.25}$$

The definition shows that the sensitivity index measures the relative change in X for a small relative change in the parameter μ. A negative sensitivity index means that an increase in the value of the parameter would lead to a decrease in the variable X. On the other hand, a positive sensitivity index means that an increase in the parameter value would lead to

an increase in the variable X. By using this definition, we obtain the sensitivity indices of R_{03}^T with respect to all parameters. The results are given in Table 4.2.

TABLE. 4.2. Sensitivity indices of R_{03}^T of the 3-host *T. b. rhodesiense* model with and without insecticide-treated cattle. All parameters were fixed to the values given in Table 4.3, and ψ was taken to be 0.02.

Without ITC				**With ITC (RAP case)**			
Parameter	Sensitivity index	Parameter	Sensitivity index	Parameter	Sensitivity index	Parameter	Sensitivity index
μ_V	-1.2772			m	-0.8278	Λ_3	-0.1973
a_1	+0.5626	g_3	-0.1184	μ_V	-0.7537	β_3	+0.1973
B_V	+0.500	σ_1	+0.0906	T_V	-0.5665	μ_3	+0.1973
a_3	+0.3927	σ_3	-0.0789	ψ	-0.5543	g_3	-0.1184
α_1	+0.0.3022	a_2	-0.0049	d	+0.5468	σ_1	-0.0906
β_1	+0.0.3022	μ_2	+0.0005	B_V	+0.5000	σ_3	-0.0789
Λ_1	-0.3022	β_2	+0.0005	a_3	+0.3828	a_2	+0.0049
μ_1	+0.0.3022	α_2	+0.0005	μ_1	+0.3097	β_2	+0.0005
T_V	-0.2700	Λ_2	-0.0005	α_1	+0.3022	α_2	+0.0005
g_1	-0.2115	g_2	-0.0004	β_1	+0.3022	Λ_2	-0.0005
α_3	+0.1973	σ_2	-0.0001	Λ_1	-0.3022	μ_2	+0.0005
β_3	+0.1973			a_1	-0.2649	g_2	-0.0004
Λ_3	-0.1973			g_1	-0.2115	σ_2	-0.0001
μ_3	+0.1973			α_3	+0.1973		

The sensitivity analysis shows that the parameter that has a greater impact on the basic reproduction number in the absence of ITC is the tsetse natural mortality, μ_V. Other important parameters are the tsetse-cattle biting rate, a_1, and the tsetse birth rate, B_V. In the presence of insecticide-treated cattle (ITC), the basic reproduction number, R_{03}^T, is most sensitive to the parameter for the additional tsetse mortality (or average tsetse knock down), m. Other important parameters are the tsetse natural mortality, μ_V, proportion of cattle with insecticides treated per day, ψ, and the rate of loss of the insecticidal effect, d. It can also be noticed that the sensitivity index for R_{03}^T with respect to the tsetse-cattle biting rate, a_1, is positive and negative in the absence and presence of ITC, respectively. This is because, in the absence of ITC, increased tsetse biting on cattle leads to an increase in *T. b. rhodesiense* infection rate and hence an increase in the basic reproduction number. Conversely, in the presence of ITC, increased tsetse biting on cattle lead to increased

tsetse death rate, which results in a decrease in the tsetse density, hence reducing the *T. b. rhodesiense* infection rate and the basic reproduction number.

4.3.6 Cost-effectiveness analysis

We use the cost-effectiveness ratio to analyse the effectiveness of the ITC control programme. The cost-effectiveness ratio is the ratio of the net costs to the net benefit. We investigate the effectiveness, and thus the cost-effectiveness of insecticide-treated cattle on the human population by looking at human infections avoided or DALYs (disability-adjusted life years) averted over time. Let C_T be cost of treating one cow with insecticides once. The net cost of the control programme over a period of T years can be obtained from

$$\int_0^T C_T\psi(S_1(t)+I_1(t)+R_1(t))e^{-rt}dt, \tag{4.26}$$

where $\psi(S_1(t)+I_1(t)+R_1(t))$ is the number of cattle treated with insecticides per day and r is the discount rate. Let φ^* be the initial *T. b. rhodesiense* incidence at the start of the treatment programme, which is assumed to start at the endemic equilibrium point in the absence of treatment. The cost-effectiveness ratio per infection avoided in humans is given by

$$CER = \frac{\int_0^T C_T\psi(S_1(t)+I_1(t)+R_1(t))e^{-rt}dt}{\int_0^T[\varphi^*-\varphi(t)]e^{-rt}dt}, \tag{4.27}$$

where $\varphi(t)$ is the incidence of human infection at time t and r is the discount rate [20].

DALYs measure the difference between a current situation and an ideal situation where everyone lives in perfect health up to the age of the standard life expectancy. The DALY combines the measure of time lived with disability and the time lost due to premature death:

$$DALY = YLL + YLD, \tag{4.28}$$

where YLL is the years of life lost due to premature mortality and YLD is the years lived with disability. The values of YLL and YLD for a single death and each human case,

respectively, were calculated using the following formulae

$$YLL = \frac{KCe^{r\tilde{a_1}}}{(b+r)^2}\left\{e^{-(r+b)(L_1+\tilde{a_1})}[-(r+b)(L_1+\tilde{a_1})-1] - e^{-(r+b)\tilde{a_1}}[-(r+b)\tilde{a_1}-1]\right\} + \frac{1-K}{r}(1-e^{-rL_1}) \tag{4.29}$$

and

$$YLD = DW\frac{KCe^{r\tilde{a_2}}}{(b+r)^2}\left\{e^{-(r+b)(L_2+\tilde{a_2})}[-(r+b)(L_2+\tilde{a_2})-1] - e^{-(r+b)\tilde{a_2}}[-(r+b)\tilde{a_2}-1]\right\} + DW\left(\frac{1-K}{r}\right)(1-e^{-rL_2}), \tag{4.30}$$

where DW is the disability weight ($DW = 1$ for premature death, $DW = 0$ for perfect health), r is the discount rate, K is the age-weighting modulation constant, b is the age-weighting constant, C is the adjustment constant for age-weights, $\tilde{a_1}$ is the age at the onset of the disease, L_1 is the duration of disability, $\tilde{a_2}$ is the age at death and L_2 is the standard life expectancy at age of deaths (years) [29, 42]. We calculate the DALYs averted through insecticide-treated cattle from

$$DALYs\_\text{Averted} = YLL\int_0^T [H^* - H(t)]e^{-rt}dt + YLD\int_0^T [\varphi^* - \varphi(t)]e^{-rt}dt, \tag{4.31}$$

where H^* and $H(t)$ is the estimated number of humans dying per day due to *T. b. rhodesiense* at the beginning of the intervention and at time t, respectively. The first and second term of equation (4.31) gives the DALYs averted due to death and infections avoided, respectively. Since there is no treatment of infectious cases, DALYs are taken to be averted through human infection and death avoided. Thus, the cost-effectiveness ratio per DALY averted is given by [20]

$$CER = \frac{\int_0^T C_T\psi(S_1(t)+I_1(t)+R_1(t))e^{-rt}dt}{DALYs\_\text{Averted}}. \tag{4.32}$$

4.4 Numerical results

In this Section, we limit our study to only three host populations; humans, cattle and wildlife as in [19]. Studies on trypanosomiasis infection in East Africa show that cattle are an important reservoir for *T. b. rhodesiense*. The importance of wildlife in the transmission of trypanosomiasis has also been identified in most parts of sub-Saharan Africa [16, 26, 71, 72].

4.4.1 Parameter estimation

Most of the parameters were discussed in fully in Chapter 3, Section 3.3 and we are using the same parameter values. In this Subsection we give a discussion of how the wildlife and cost-effectiveness analysis related parameters are estimated. Since we are considering three host species, the proportion of tsetse blood meals are considered to be $f_1 = 0.7$ from cattle [31, 50], $f_2 = 0.1$ from humans [19] and $f_3 = 0.2$ from wildlife hosts.

Wildlife infection parameters

The wildlife natural mortality was assumed to be $\mu_3 = 0.00025$ giving a life expectancy of 10 years and the birth rate was assumed to be $\Lambda_3 = 1.25$, giving a total population of $5,000$ at the disease-free equilibrium and a tsetse-wildlife ratio of 9.6 [19]. The probability of an infected fly bite producing infection in wildlife and the incubation period were assumed to be the same as for cattle, that is, $\beta_3 = 0.62$ and $T_3 = 7.0$ days, respectively. The mortality rate of infected wildhosts was taken to be $\mu_3 = 0.008$ [19]. The recovery rate and rate of loss of immunity in recovered wildhosts were also assumed to be same as for cattle hosts and taken to be $g_3 = 0.012$ and $\nu_3 = 1.0$, respectively.

Insecticide-treated cattle parameters

The average tsetse knockdown due to insecticides was shown to depend on the type of insecticides and formulations in [68]. In a study done in Zimbabwe, the average knockdown was shown to be $77 - 86\%$ with deltamethrin, 74% with alphacypermethrin and 59% with cyfluthrin. These knockdowns were estimated in a period of $5 - 24$ days in hot months and $24 - 55$ days at cooler seasons. For our study, we take an average knockdown of 78% for whole-body treatment of cattle with insecticides, with insecticides applied at an interval of 28 days (4 weeks). With restricted application of insecticides, we take the average knockdown to be 57% [64].

TABLE. 4.3. Numerical values for the parameters of the three-host model

Host population parameters						
	Host 1 (Cattle)		Host 2 (Humans)		Host 3 (Wildlife)	
Recruitment rate	Λ_1 22.0	[78]	Λ_2 27.5	[65]	Λ_3 1.25.0	[19]
Natural mortality	μ_1 0.00055	[78]	μ_2 0.000055	[78]	μ_3 0.00025	[19]
Proportion of blood tsetse meal	f_1 0.7	[31, 50]	f_2 0.10	[19]	f_3 $(1-f_1-f_2)$	-
Biting rate	a_1 af_1	-	a_2 af_2	-	a_3 af_3	-
Probability of infected fly producing infection	β_1 0.62	[50]	β_2 0.53	[16]	β_3 0.62	[50]
Incubation period	T_1 7.0	[16]	T_2 10.0	[16]	T_3 7.0	[16]
Mortality of infected hosts	σ_1 0.006	[19]	σ_2 0.004	[19]	σ_3 0.008	[19]
Recovery rate	g_1 0.014	[19, 50]	g_2 0.012	[19]	g_3 0.002	[19]
Duration of immunity in recovered hosts	$\frac{1}{\nu_1}$ 1.0	[16]	$\frac{1}{\nu_2}$ 1.0	[16]	$\frac{1}{\nu_3}$ 1.0	[16]
Probability of first blood meal giving rise to infection in tsetse flies	α_1 0.065	[16, 50]	α_2 0.065	[16, 50]	α_3 0.065	[50]
Tsetse population parameters						
Tsetse birth rate	B_V 1,440	[19]				
Recruitment rate	Λ_V Varying	-				
Natural mortality	μ_V 0.03	[50]				
Feeding cycle	$\frac{1}{a}$ 4.0	[16, 19]				
Incubation period	T_V 18.0	[16, 19]				
Insecticide-treated cattle (ITC) parameters						
	Whole-body (WB)		Restricted application (RAP)			
Proportion of cattle treated with insecticides per day, ψ	Varying	-	Varying	-		
Average duration of treatment, $\frac{1}{d}$	4 weeks	[64]	4 weeks	[64]		
Tsetse additional mortality due to insecticides, m	0.78	[64]	0.57	[64]		
Cost of treating one cow with insecticides once, C_T	\$0.58	[10, 24]	\$0.125	[10, 24]		
Cost-effectiveness analysis parameters						
Disability weight DW	0.35	[38]				
Discount rate r	0.03	[27, 38]				
Age-weighting modulation constant K	1	[42]				
Adjustment constant for age-weights C	0.162431	[42]				
Age-weighting constant b	0.04	[42]				
Age at the onset of disease $\tilde{a_1}$	25 years	Assumed				
Age at death $\tilde{a_2}$	26 years	Assumed				
Duration of disability L_1	100 days	[27]				
Standard life expectancy at age of death L_2	24 years	[27]				

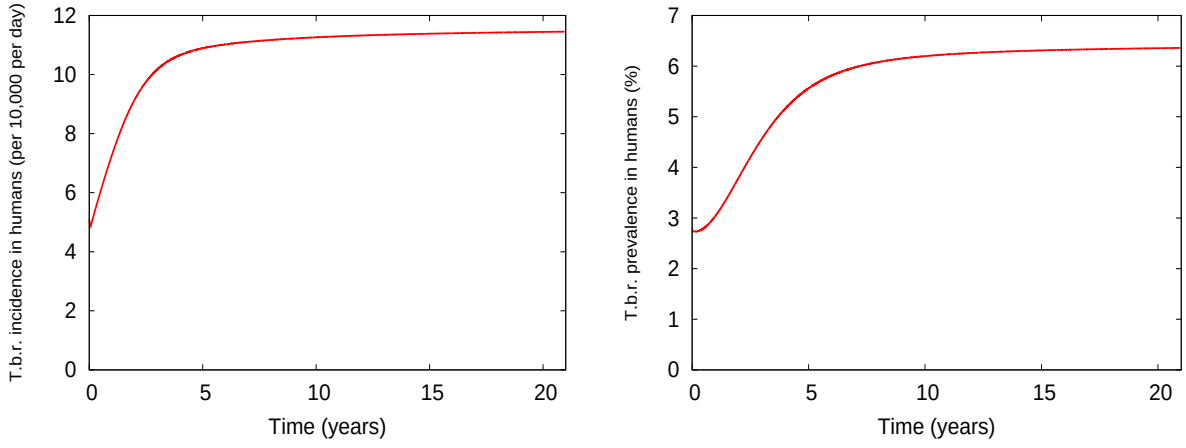
Cost-effectiveness analysis parameters

We take the cost of treating one cow with insecticides to be \$7.0/12 $\simeq$ 0.58 and \$1.5/12 $\simeq$ 0.125 per treatment for whole-body and restricted application of insecticides, respectively [10, 24]. The cost is assumed to include the unit cost of insecticides applied on one cow per

treatment and wages paid to administer the application of insecticides. It is assumed that each cow is treated with insecticides once a month [67]. The total cost for each strategy will depend on the proportion of cattle treated and the number of times each cow is treated.

The disability weighting constant, DW, was taken to be 0.21 and 0.81 for early and late stages of *T. b. rhodesiense*, respectively in [27]. Since we are not classifying the stages of infection, we use a disability weighting of 0.35 as in [38]. The discount rate was taken to be 3% as in [27, 38]. The age of onset of disease $\tilde{a_1}$ was assumed to be 25 years which is the mid-value of the life expectancy in Uganda. The rest of the parameters were taken from [27, 42] as shown in Table 4.3.

With all the parameters fixed or estimated (Table 4.3), we look at the numerical results following from the model (4.5-4.9) for $n = 3$. In the absence of insecticide-treated cattle (ITC), the basic reproduction number, R_{03}, for the case when the number of hosts is limited to three, can be obtained from equation (4.12). First, the disease-free steady state is given by $\Lambda_1 = 40,000$, $\Lambda_2 = 500,000$ and $\Lambda_3 = 5,000$ for cattle, humans and wildlife populations, respectively. In the absence of ITC , we obtain $R_{03} = 2.5$. This value is close to 2.59 obtained in Chapter 3 for *T. brucei* species in humans and cattle. Davis *et al.* [19] did a global sensitivity analysis for African sleeping sickness by considering three host texa; humans, livestock and wildlife, and they obtained a basic reproduction number that lies in the range $0.097 - 4.955$ for *T. b. rhodesiense*.



(a) (b)

FIG. 4.3. Simulation results for the *T. b. rhodesiense* incidence and prevalence in humans in the absence of curative treatment of infectious humans and cattle, and ITC.

Figure 4.3 shows the plot for *T. b. rhodesiense* incidence and prevalence in humans in the absence of insecticide-treated cattle (ITC) and human treatment. The graph shows that in the absence of any intervention, the human incidence and prevalence could be as high as 11 per 10,000 per day and 6%, respectively.

4.4.2 Importance of cattle and wildlife in the transmission of *T. b. rhodesiense*

The importance of animals (cattle and wildlife) to the transmission of *T. b. rhodesiense* can be demonstrated by looking at the infection rates of the different hosts as shown in figure 4.4. With 20% and 70% (Table 4.3) of the tsetse blood meals coming from wildlife

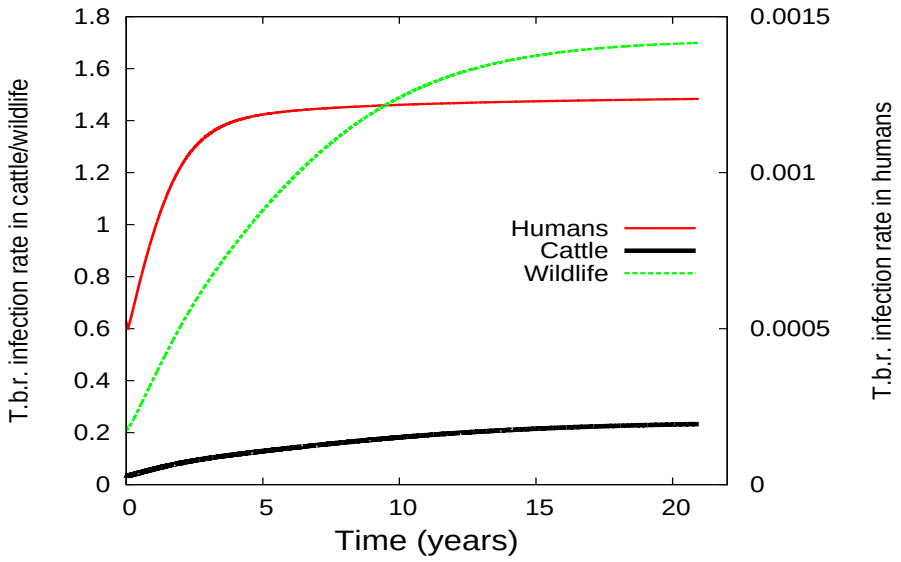


FIG. 4.4. *T. b. rhodesiense* infection rates for cattle, human and wildlife host populations.

and cattle hosts, respectively, the infection rate in the wildlife population can be as high as 1.6 per day. The human infection rate is very low compared to the cattle and wildlife infection rates. The results are in agreement with the sensitivity analysis results, where the tsetse-cattle and tsetse-wildlife biting rates are among the four parameters that the basic reproduction number is highly sensitive to.

Including monitor lizards in the wildlife-host population

Monitor lizards, *varanus niloticus* are part of the wild vertebrate host population that provide a great proportion of blood meals to tsetse flies and do not get infected with trypanosomiasis when bitten by an infected tsetse fly. A study on host and feeding preference of tsetse flies (*G. f. fuscipes*) along Lake Victoria shores, Kenya, where humans, livestock and monitor lizards are the predominant hosts showed that $73-98\%$ of *G. f. fuscipes* fed on monitor lizards irrespective of host prevalence, season and location [41]. Other studies on tsetse feeding preferences carried out in Southeastern Uganda, showed that 22% of *G. f. fuscipes* fed on monitor lizards [71].

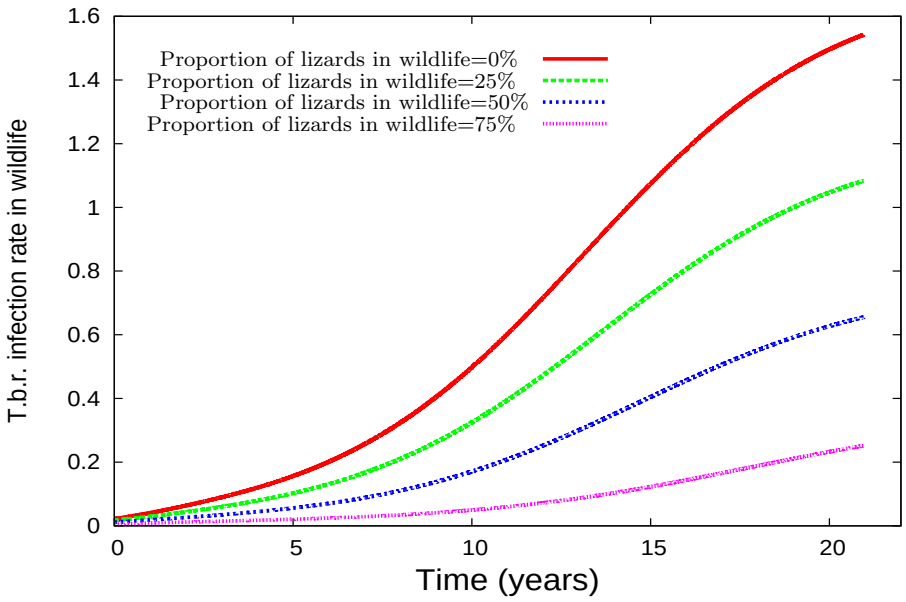


FIG. 4.5. *T. b. rhodesiense* infection rate in wildlife with different proportions of monitor lizards in the wildlife population

Including monitor lizards in the wild vertebrate host population leads to a change in the dynamics of the disease. In this case a proportion of tsetse blood meals are taken from hosts that neither suffer from nor transmit trypanosomiasis [31]. As the proportion of monitor lizards in the wildlife population increases, the infection rate in the wildlife host reduces (figure 4.5). With 50% of the wildlife hosts being monitor lizards, the infection rate in wildhosts can be as low as 0.6 per day. This leads to the reduction in the prevalence and incidence estimates in both host and tsetse populations. Figure 4.6 shows the human prevalence and incidence for different proportions of monitor lizards in the wild vertebrate

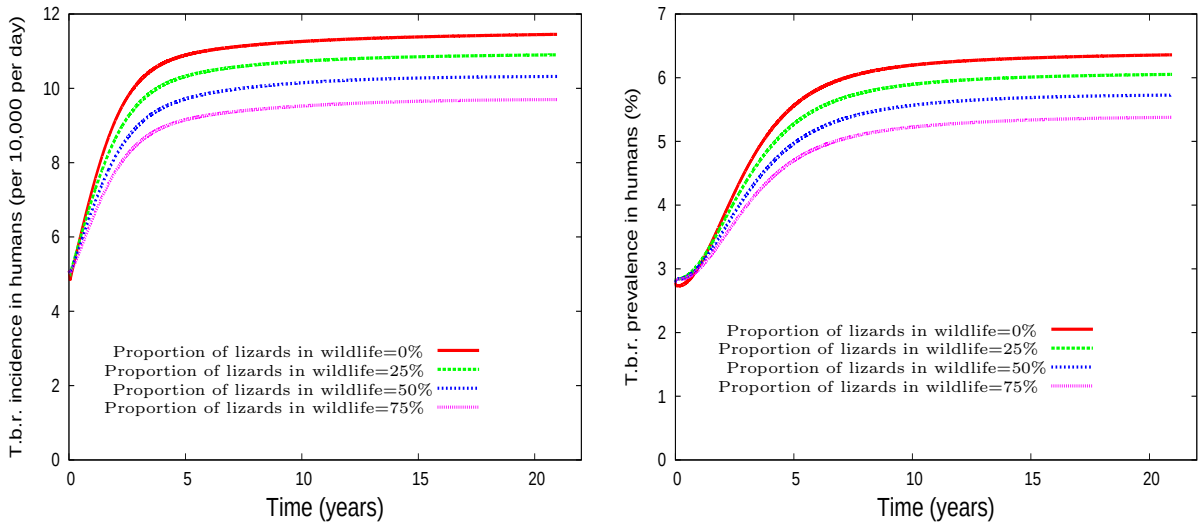


FIG. 4.6. *T. b. rhodesiense* incidence (a) and prevalence (b) in humans for different proportions of monitor lizards in the wildlife population.

host population. The results show that the human incidence and prevalence of *T. b. rhodesiense* reduces with an increase in the proportion of monitor lizards in the wildlife host population. The results reflect a situation where monitor lizards are part of the wildlife hosts that are assumed to provide a proportion of 20% of tsetse blood meals. A situation where monitor lizards are part of wildlife hosts that provide more than 20% of the tsetse blood meals, or form a unique host population which can provide more than 20% of the tsetse blood meals would imply that the results given in figure 4.5 and 4.6 are an underestimate of the real situation.

4.4.3 Application of insecticides to cattle to prevent the transmission

In this subsection, we investigate the impact of insecticide-treated cattle (ITC) on the *T. b. rhodesiense* transmission potential (R_{03}^T) and human incidence for different scenarios of cattle treatment coverage. We proceed to analyse the critical proportion ψ of cattle required to be treated with insecticides for R_{03}^T to be less than one. The critical proportion can easily be derived by setting $R_{03}^T = 1$ and solving for ψ.

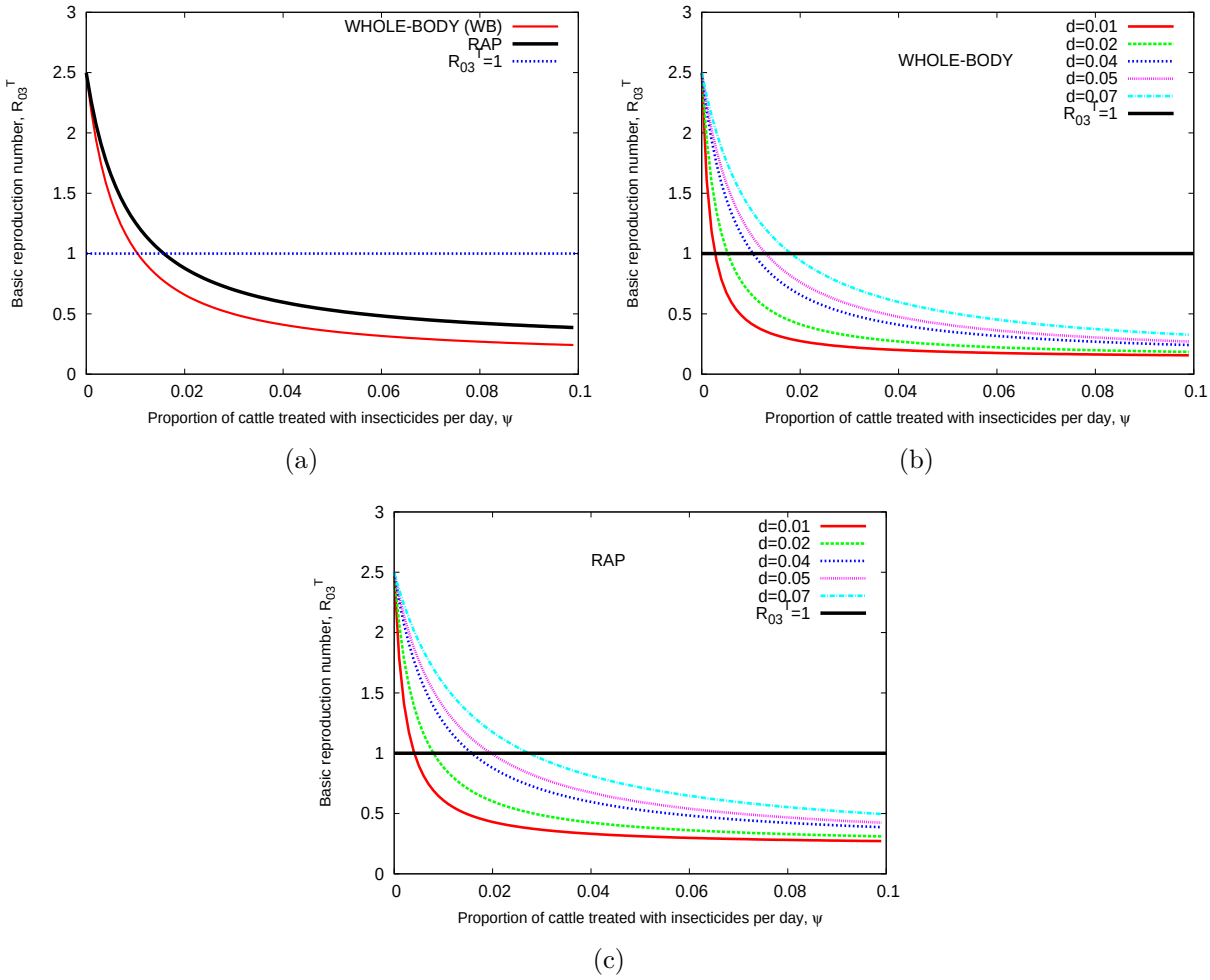


FIG. 4.7. The effect of treating cattle with insecticides on the basic reproduction number, R_{03}^T. (a) shows the plot of the basic reproduction number, R_{03}^T with respect to the proportion of cattle treated with insecticides, ψ for $d = 0.04$. (b) and (c) shows the critical proportions of cattle needed to be treated with insecticides for different values of d for whole body and restricted application, respectively.

The results in figure 4.7 (b) show that in areas where vectors feed predominantly on cattle, treating about 1.1% or 1.6% of the cattle population with insecticides through whole-body or restricted application of insecticides, respectively, can potentially reduce $R_{03}^T < 1$, and therefore, lead to the control of *T. b. rhodesiense*. The duration of treatment with insecticides was taken to be $\frac{1}{d} = 4$ weeks, which is the same as the duration of the waning of the insecticidal effect. The proportion required to be treated with insecticides decreases with the increase in the duration, $\frac{1}{d}$, of the killing effect provided by insecticides, and vice versa for both treatment strategies. For example, reducing the duration of the killing

effect provided by insecticides from 4 weeks to 3 weeks, implies that 1.3% and 2.0% of the cattle population need to be treated with insecticides through whole-body or restricted application, respectively, for $R_{03}^{T} < 1$. Results for the proportion of cattle required to be treated with insecticides for different values of d are shown in figure 4.9 (b) and (c) for whole-body and restricted application, respectively.

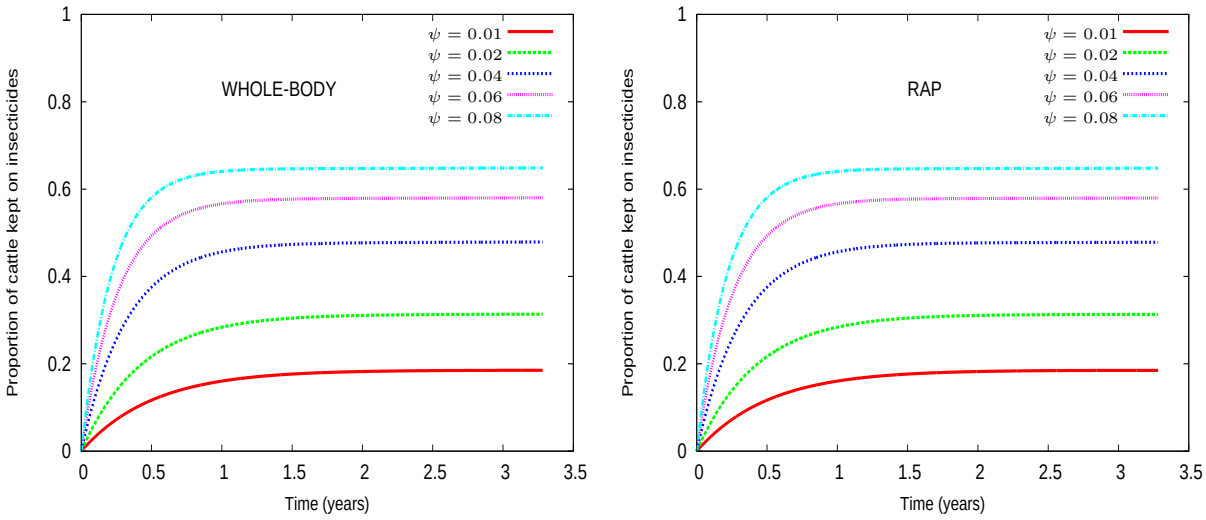
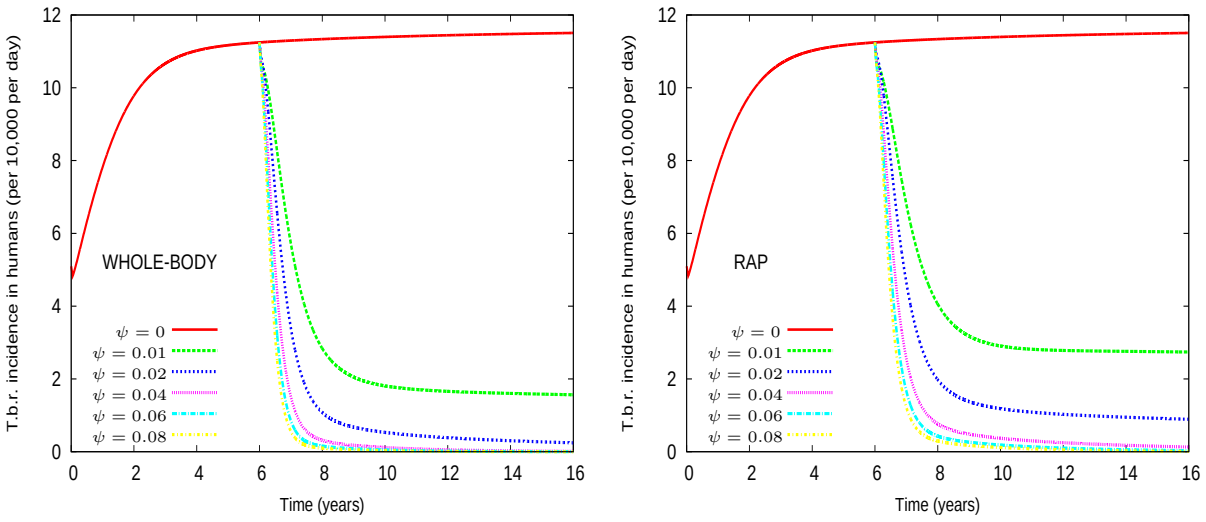
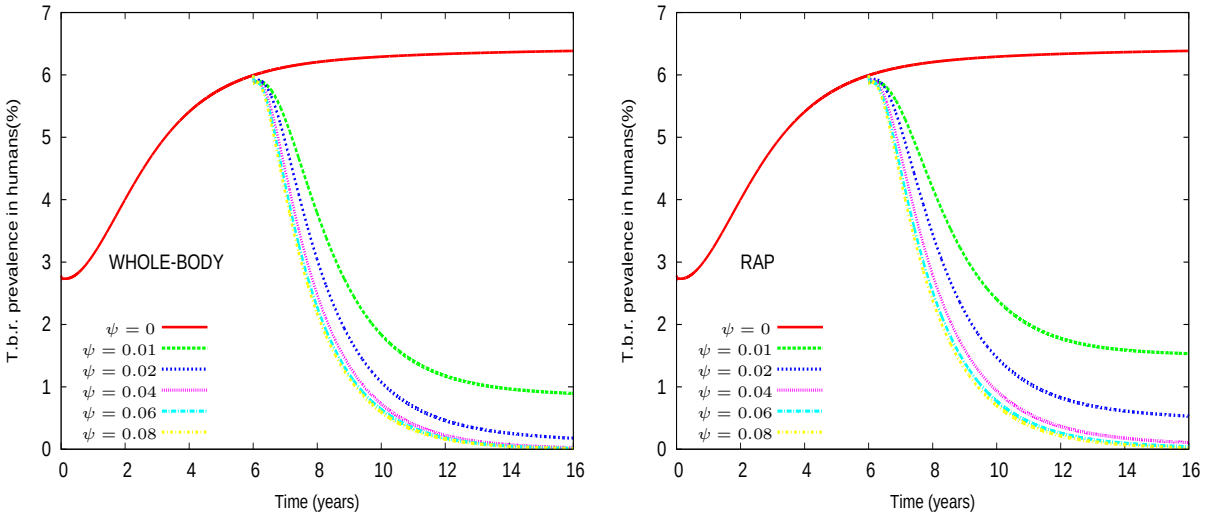


FIG. 4.8. Proportion of cattle kept on insecticides



(a) (b)

FIG. 4.9. Increased tsetse mortality through insecticide-treated cattle (ITC). *T. b. rhodesiense* incidence in humans for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b).



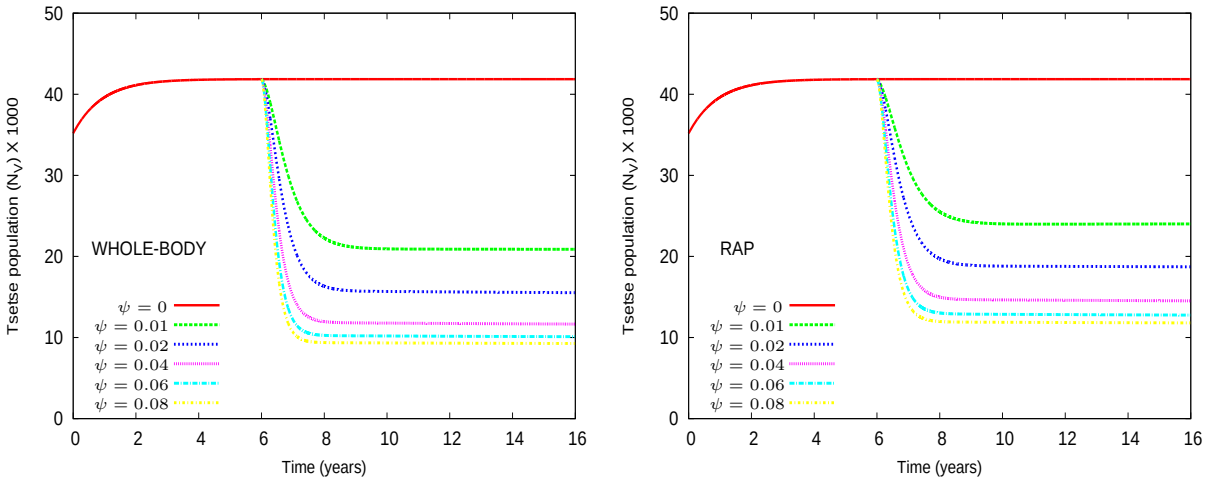
(a) (b)

FIG. 4.10. Increased tsetse mortality through insecticide-treated cattle (ITC). *T. b. rhodesiense* prevalence in humans for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b).

The results for the proportions of cattle kept on insecticides were obtained by running model (4.4) up to a steady state and are shown in figure 4.8. The results show that the critical proportions of 1.1% or 1.6% required to be treated with insecticides per day through whole-body or restricted application for R_{03}^T to be less than one are equivalent to keeping 21.0% or 27.0% of the cattle population on insecticides, respectively. Figure 4.9 and 4.10 show the impact of ITC on the incidence and prevalence of *T. b. rhodesiense* in humans for both strategies. In both strategies, there is a significant decrease in the prevalence and incidence of *T. b. rhodesiense* in humans. The results are shown for the proportion of cattle treated with insecticides per day, ψ, taken to be $0, 0.01, 0.02, 0.04, 0.06$ and 0.08 for both strategies. The results are also shown for the case where different proportions of cattle are treated with insecticides in the presence of wildlife hosts, and without taking monitor lizards to be part of the wildhost population. On the other hand, if monitor lizards were taken to be part of the wildlife host population, then the control of *T. b. rhodesiense* would be achieved by treating a smaller proportion of cattle compared to the one estimated in the results shown in figure 4.7– 4.10.

4.4.4 Effect of insecticide-treated cattle on the tsetse population

Figure 4.11 shows the impact of ITC on the tsetse population for both strategies. The results show that there is a significant decrease in the tsetse population in both strategies. The tsetse population can only be kept constant in the presence of ITC if the increased mortality is balanced by an increase in birth and/or immigration. The results shown in figure 4.11 reflects the situation where birth is the predominant source of replacements. If immigration is the predominant source of replacements, then older flies which are above the average age of being infected with trypanosomes are coming in the population. In this case the results shown in figure 4.11 would be an under-estimate of the situation. Generally, where insecticide-treated cattle is used, either against closed populations of tsetse or on a sufficiently large scale that immigration of tsetse flies is limited at sites far from the boundary, the expectation is that the fly population will decrease [31].



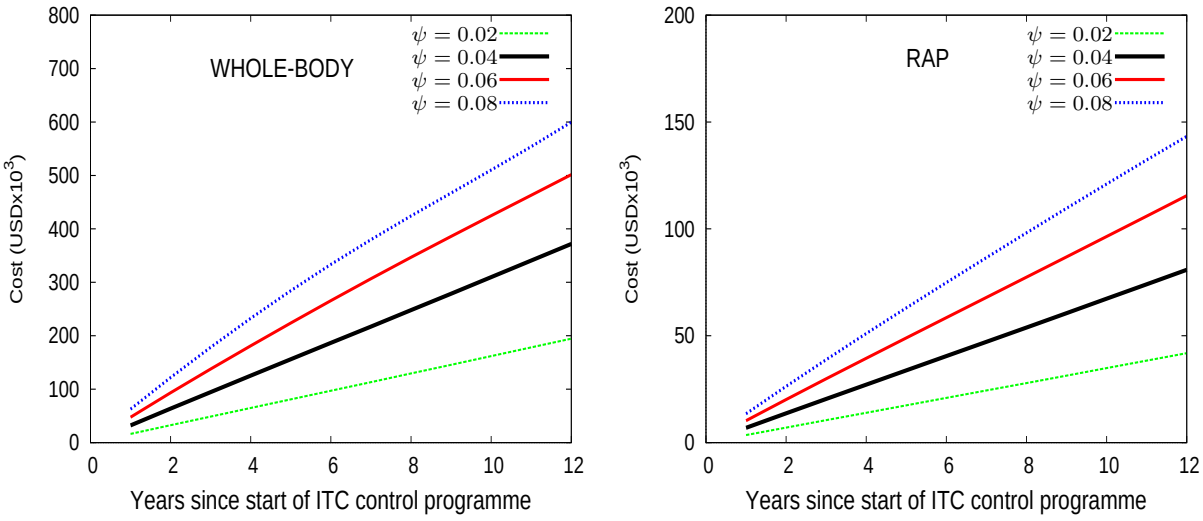
(a) (b)

FIG. 4.11. Effect of increased tsetse mortality through insecticide-treated cattle on the tsetse population for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b).

4.4.5 Cost-effectiveness analysis of the ITC control programme

In this subsection, we look at the cost and cost-effectiveness of implementing insecticide-treated cattle (ITC) as one of sleeping sickness control programmes. We assume that

there is no other intervention apart from treating cattle with insecticides once a month. Due to treatment of cattle with insecticides, the mortality of tsetse vectors is expected to increase with an increase in the proportion of cattle treated. It is assumed that application of insecticides to cattle is started at the endemic equilibrium point and thus the initial conditions are the endemic equilibrium numbers of the classes considered in the model in the absence of ITC or any other intervention. The incidence obtained after the ITC control measure is compared with the predicted incidence in the absence of vector control.



(a) (b)

FIG. 4.12. The cost of implementing the insecticide-treated cattle (ITC) control programme over time for whole-body (a) and restricted application of insecticides (b) to cattle

Taking an example of Tororo district, Uganda which has a total cattle population of $40,000$ [65], and taking the cost of treating one cow to be US$0.58 or US$0.125 using the whole-body strategy or restricted application of insecticides, respectively, we obtained the estimated yearly costs for running the control programme given in figure 4.12. The results show the discounted total cost for running the ITC control programme over time (years) for each of the control strategies. The total cost increases with an increase in the proportion of cattle treated with insecticides. Other studies have also shown that restricted application of insecticides to cattle, leads to a $60-99\%$ reduction in the amount of insecticides used, uses cheaper spray formulations, and has a reduced affect on the environmental impact [10, 63, 72].

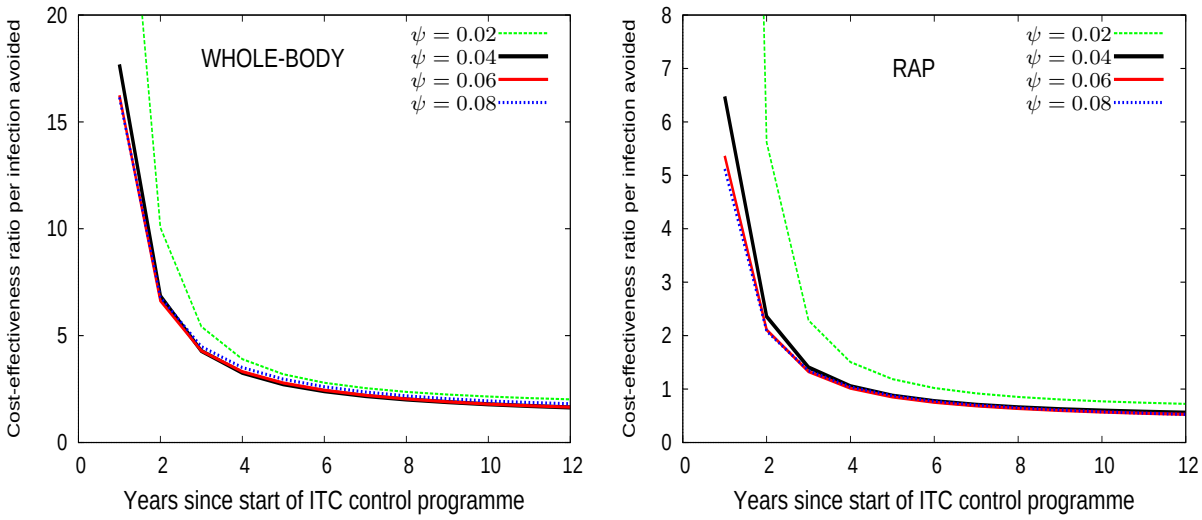


FIG. 4.13. The cost-effectiveness ratio per infection avoided of the insecticide-treated cattle (ITC) control programme over time for whole-body (a) and restricted application of insecticides (b) to cattle

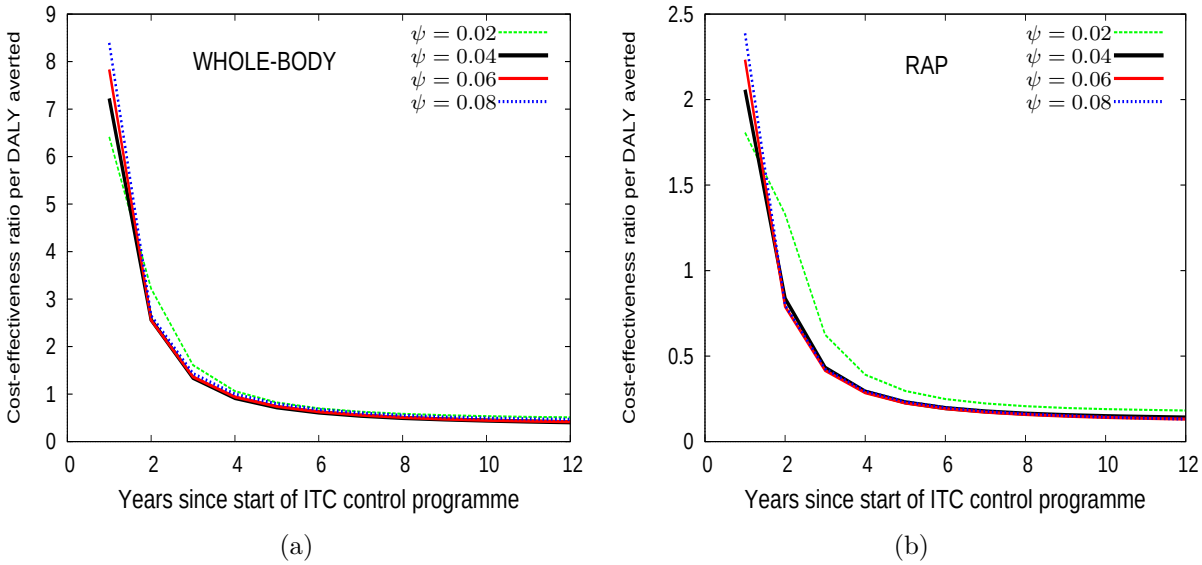


FIG. 4.14. The cost-effectiveness ratio per DALY averted of the insecticide-treated cattle (ITC) control programme over time for whole-body (a) and restricted application of icnsectcides (b) to cattle

Figure 4.13 and 4.14 give the discounted cost-effectiveness ratio per infection avoided and DALYs averted, respectively, in humans for the two control strategies of insecticide-treated

cattle for different proportions of cattle. The results show how the cost-effectiveness ratios vary for each individual year for the two ITC control strategies. The results show that for each control strategy the cost-effectiveness ratio decreases with time since the start of the insecticide treatment and drops to a value of about \$1.8 or \$0.65 per infection avoided for whole-body or restricted application, respectively, after 12 years. In terms of DALYs averted, the cost-effectiveness ratio reduces to a values of about \$0.5 or \$0.15 per DALY averted for whole-body or restricted application, respectively, after 12 years. The ITC control programme has almost the same cost-effectiveness ratio for different values of ψ if it is run for a period of less than 15 years. However, if the control programme is run for many years, the cost-effectiveness ratio increases with an increase in the proportion of cattle that is treated with insecticides per day, ψ (results not shown). The results do not include the benefits arising due to cattle infections avoided. If these benefits are included then the cost-effectiveness ratios would be less than the ones estimated in figures 4.13 and 4.14. Previous studies on the cost-effectiveness of controlling trypanosomiasis show that costs of US\$150 per DALY averted and US\$25 per DALY averted are attractive and highly attractive, respectively. Hospital-based interventions for the control of *T. b. rhodesiense* in Uganda were shown to cost US\$8.5 per DALY averted [26]. Our results show that the control of *T. b. rhodesiense* can be achieved by treating a small proportion of cattle with insecticides at a cost of less than US\$1 per DALY averted.

4.5 Summary

In this Chapter, we developed a mathematical model that describes the transmission dynamics of *T. b. rhodesiense* by tsetse vectors in a multi-host population. A proportion, ψ, of the cattle population is taken to be treated with insecticides per day to control tsetse and trypanosomiasis through increased tsetse mortality. An analytical expression was obtained for the basic reproduction number, R_{0n} and R_{0n}^T of the model in the absence and presence of ITC. Local stability of the model in the absence of ITC is shown for the case when $n = 1$.

By limiting the number of host taxa to three, that is, humans, cattle and wildlife, the impact of monitor lizards on the transmission of *T. b. rhodesiense* was studied. Numerical

results show that an increase in the proportion of monitor lizards in the wild vertebrate population leads to a decrease in the *T. b. rhodesiense* transmission rate. This in turn leads to a decrease in the incidence and prevalence of *T. b. rhodesiense* in both host and tsetse vector populations. The model was then used to study the application of insecticides to cattle to control *T. b. rhodesiense* in humans. Two strategies of insecticide-treated cattle are considered; whole-body treatment and restricted application of insecticides on cattle. Both strategies have a positive impact on the control of tsetse and trypanosomiasis in humans. Cost-effectiveness analysis of the ITC control measure was carried out and restricted application of insecticides was found to be more cost-effective than whole-body treatment of cattle with insecticides.

Chapter 5

Modelling the control of tsetse and *T. b. rhodesiense* by treating adult cattle only with insecticides

5.1 Introduction

In this Chapter, we consider an age-structured model for the cattle population by separating young and adult cattle. We limit the treatment of insecticides to adult cattle only. It is known that tsetse feed preferentially on large adult cattle. The studies carried out in the field to observe the landing behaviour of tsetse show that $67 - 98\%$ of the tsetse land on the belly and legs, particularly the front legs of adult cattle. The studies show no significant difference within tsetse species [64]. Concentrating on the insecticidal treatment of adult cattle should lead to improved results in terms of tsetse mortality per insecticide consumption. This strategy also reduces on the insecticide costs and can be affordable to most farmers in Uganda. We focus on the control of *T. b. rhodesiense* in cattle, humans and wildlife through treating adult cattle with insecticides. We consider two strategies of insecticide-treated cattle as in the previous chapter, that is, whole-body and restricted application of insecticides on cattle. We also carry out a benefit-cost analysis to evaluate the benefits and costs of each method of application of insecticides to cattle.

5.2 Model development

The model describes the transmission of *T. b. rhodesiense* by tsetse vectors in cattle, human and wildlife hosts. The cattle population is categorised as either young or adult and we use superscripts Y or A, respectively, to differentiate between the two categories. The young and adult cattle are assumed to be $0-3$ and $4-10$ years of age. We assume a constant birth rate Λ_1 for young cattle and a progression rate κ from the young cattle compartments to the adult cattle compartments. Each host population is divided into three classes, susceptible (S_i), infectious (I_i) and recovered (R_i), whereas the tsetse population is divided into two classes, susceptible (S_V) and infectious (I_V). The transmission dynamics of *T. b. rhodesiense* in both cattle, humans, wildlife and tsetse vectors are exactly the same as the ones discussed in the previous Chapter. The schematic representation of the model is shown in figure 5.1.

The total population of young and adult cattle is given by $N_1^Y = S_1^Y + I_1^Y + R_1^Y$ and $N_1^A = S_1^A + I_1^A + R_1^A + S_1^T + I_1^T + R_1^T$, respectively, and the total cattle population is given by $N_1 = N_1^Y + N_1^A$. When tsetse flies try to feed on adult cattle that is treated with insecticides, their mortality will be increased by a factor

$$a_1^A m \frac{(S_1^T + I_1^T + R_1^T)}{N_1^A},$$

which is a function of the tsetse-adult cattle biting rate, a_1^A, the proportion of adult cattle treated with insecticides, $\frac{(S_1^T+I_1^T+R_1^T)}{N_1^A}$, and the tsetse additional mortality due to insecticides, m. Thus, the tsetse mortality will be given by

$$m_V = \mu_V + a_1^A m \frac{(S_1^T + I_1^T + R_1^T)}{N_1^A}, \tag{5.1}$$

where μ_V is the tsetse natural mortality rate.

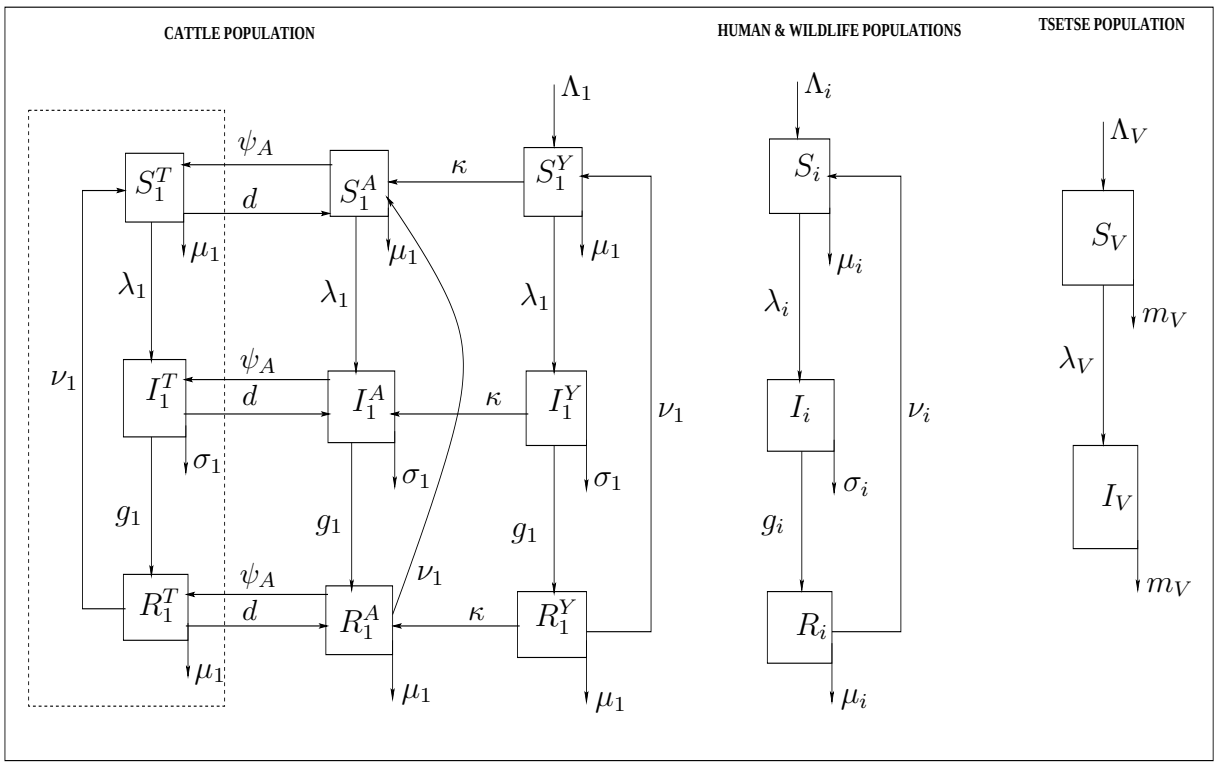


FIG. 5.1. Flow diagram of the compartmental model of *T. b. rhodesiense* in tsetse, cattle, human and wildlife populations that includes treatment of adult cattle only with insecticides. The adult cattle population that is treated with insecticides is enclosed in a dotted rectangle. λ_i and λ_V are the forces of infection for the host and tsetse vector populations, respectively.

The equations for the model are given by

$$
\begin{aligned}
\frac{d}{dt}S_1^Y &= \Lambda_1 + \nu_1 R_1^Y - (\mu_1+\kappa)S_1^Y - \lambda_1^Y(t-T_1)S_1^Y(t-T_1),\\
\frac{d}{dt}I_1^Y &= \lambda_1^Y(t-T_1)S_1^Y(t-T_1) - (\kappa+g_1+\sigma_1)I_1^Y,\\
\frac{d}{dt}R_1^Y &= g_1 I_1^Y - (\kappa+\mu_1+\nu_1)R_1^Y,\\
\frac{d}{dt}S_1^A &= \kappa S_1^Y + \nu R_1^A + dS_1^T - (\psi_A+\mu_1)S_1^A - \lambda_1^A(t-T_1)S_1^A(t-T_1),\\
\frac{d}{dt}I_1^A &= \kappa I_1^Y + \lambda_1^A(t-T_1)S_1^A(t-T_1) + dI_1^T - (\psi_A+g_1+\sigma_1)I_1^A,\\
\frac{d}{dt}R_1^A &= \kappa R_1^Y + g_1 I_1^A + dR_1^T - (\psi_A+\nu_1+\mu_1)R_1^A,\\
\frac{d}{dt}S_1^T &= \psi_A S_1^A + \nu_1 R_1^T - (\mu_1+d)S_1^T - \lambda_1^A(t-T_1)S_1^T(t-T_1),\\
\frac{d}{dt}I_1^T &= \psi_A I_1^A + \lambda_1^A(t-T_1)S_1^T(t-T_1) - (d+g_1+\sigma_1)I_1^T,\\
\frac{d}{dt}R_1^T &= \psi_A R_1^A + g_1 I_1^T - (d+\mu_1+\nu_1)R_1^T,
\end{aligned}
\tag{5.2}
$$

for the cattle host population, where $\lambda_1^Y(t) = \frac{a_1^Y \beta_1 I_V(t)}{N_1^Y(t)}$, $\lambda_1^A(t) = \frac{a_1^A \beta_1 I_V(t)}{N_1^A(t)}$,

$$\begin{aligned}
\frac{d}{dt}S_i &= \Lambda_i + \nu_i R_i - \mu_i S_i - \lambda_i(t-T_i)S_i(t-T_i),\\
\frac{d}{dt}I_i &= \lambda_i(t-T_i)S_i(t-T_i) - (g_i+\sigma_i)I_i,\\
\frac{d}{dt}R_i &= g_i I_i - (\mu_i+\nu_i)R_i,
\end{aligned} \tag{5.3}$$

for the human and wildlife populations, where $\lambda_i(t) = \frac{a_i \beta_i I_V(t)}{N_i(t)}$, $i = 2, 3$, and

$$\begin{aligned}
\frac{d}{dt}S_V &= \Lambda_V - e^{-m_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - m_V S_V,\\
\frac{d}{dt}I_V &= e^{-m_V T_V}\lambda_V(t-T_V)S_V(t-T_V) - m_V I_V,
\end{aligned} \tag{5.4}$$

for the tsetse vector population, where $\lambda_V = \frac{\alpha_1[a_1^Y I_1^Y(t) + a_1^A(I_1^A(t)+I_1^T(t))]}{N_1(t)} + \sum_{i=2}^{3}\frac{\alpha_i a_i I_i(t)}{N_i(t)}$. All variables and parameters in the model (5.2-5.4) are considered to be positive and the model lies in the region

$$\Gamma_A = \left\{(S_1^Y, I_1^Y, R_1^Y, S_1^A, I_1^A, R_1^A, S_1^T, I_1^T, R_1^T, S_i, I_i, R_i, S_V, I_V) \in \mathbb{R}_+^{17} : N_1 \le \frac{\Lambda_1}{\mu_1}, N_i \le \frac{\Lambda_i}{\mu_i}, N_V \le \frac{\Lambda_V}{m_V}\right\},$$

where $i = 2, 3$.

5.2.1 Basic reproduction number

We use the next generation method to obtain the basic reproduction number. The disease-free equilibrium is given by

$$E_0 = (\frac{\Lambda_1}{\mu_1+\kappa}, 0, 0, \frac{\Lambda_1\kappa(1-\pi_A)}{\mu_1(\mu_1+\kappa)}, 0, 0, \frac{\Lambda_1\kappa\pi_A}{\mu_1(\mu_1+\kappa)}, 0, 0, \frac{\Lambda_2}{\mu_2}, 0, 0, \frac{\Lambda_3}{\mu_3}, 0, 0, \frac{\hat{\Lambda}_V}{\hat{m}_V}, 0),$$

where $\pi_A = \frac{\psi_A}{\psi_A+\mu_1+d}$ and $\hat{m}_V = \mu_V + a_1^A m \pi_A$. The expression for $\hat{\Lambda}_V$ is given by equation (A.12) in the Appendix. Using the notation used in [66], we obtain the matrices F (for the new infections) and V (for the transition terms) as

$$F = \begin{pmatrix}
0 & 0 & 0 & 0 & 0 & a_1^Y\beta_1\\
0 & 0 & 0 & 0 & 0 & a_1^A\beta_1(1-\pi_A)\\
0 & 0 & 0 & 0 & 0 & a_1^A\beta_1\pi_A\\
0 & 0 & 0 & 0 & 0 & a_2\beta_2\\
0 & 0 & 0 & 0 & 0 & a_3\beta_3\\
\frac{\hat{A}\alpha_1 a_1^Y\hat{\Lambda}_V(\mu_1+\kappa)}{\Lambda_1\hat{m}_V} & \frac{\hat{A}\alpha_1 a_1^A\hat{\Lambda}_V\mu_1(\mu_1+\kappa)}{\Lambda_1\kappa\hat{m}_V} & \frac{\hat{A}\alpha_1 a_1^A\hat{\Lambda}_V\mu_1(\mu_1+\kappa)}{\Lambda_1\kappa\hat{m}_V} & \frac{\hat{A}\alpha_2 a_2\mu_2\hat{\Lambda}_V}{\Lambda_2\hat{m}_V} & \frac{\hat{A}\alpha_2 a_2\mu_2\hat{\Lambda}_V}{\Lambda_2\hat{m}_V} & 0
\end{pmatrix}$$

$$\text{and} \quad V = \begin{pmatrix} \kappa+g_1+\sigma_1 & 0 & 0 & 0 & 0 & 0 \\ -\kappa & \psi_A+g_1+\sigma_1 & -d & 0 & 0 & 0 \\ 0 & -\psi_A & g_1+\sigma_1+d & 0 & 0 & 0 \\ 0 & 0 & 0 & g_2+\sigma_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & g_3+\sigma_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & \hat{m}_V \end{pmatrix},$$

respectively, where $\hat{A} = e^{-\hat{m}_V T_V}$. The basic reproduction number which is given by the spectral radius of the next generation matrix, FV^{-1} is

$$R_A^T = \sqrt{\frac{\hat{A}\hat{\Lambda}_V}{\hat{m}_V^2}(R_{A1} + \sum_{i=2}^{3} R_{Ai})}, \tag{5.5}$$

where $R_{A1} = \frac{\alpha_1\beta_1(\kappa+\mu_1)}{\Lambda_1\kappa(g_1+\sigma_1)(\kappa+g_1+\sigma_1)}[(a_1^Y)^2\kappa(g_1+\sigma_1) + (a_1^A)^2\mu_1(\kappa+g_1+\sigma_1) + a_1^{(Y+A)}\kappa\mu_1]$ and $R_{Ai} = \frac{\alpha_i a_i^2 \beta_i \mu_i}{\Lambda_i(g_i+\sigma_i)}$. R_A^T gives the expected number of secondary cases produced in a completely susceptible population of tsetse flies, humans, cattle and wildlife, by a typical infective host or tsetse vector in the presence of insectide-treated adult cattle. If $R_A^T > 1$, then the disease may emerge in one of the populations. However, if $R_A^T < 1$, then the disease-free equilibrium is locally asymptotically stable [66].

5.2.2 Benefit-cost analysis

In Chapter 4 we analysed the benefits of ITC control programmes by looking at the DALYs averted in the human population. In this Subsection, we concentrate on the benefits of ITC to the farmer by keeping cattle free from *T. b. rhodesiense* infection. We take the benefits to be equivalent to the monetary price of a healthy cow. If C_Y and C_A are the price of a young and an adult cow, respectively, then the total benefits after running the ITC control programme for a period of T years are given by

$$B(T) = (U^T - U^*)e^{-rT}, \tag{5.6}$$

where

$$\begin{aligned} U^* &= C_Y[S_1^Y(0) + R_1^Y(0)] + C_A[S_1^A(0) + R_1^A(0) + S_1^T(0) + R_1^T(0)] \quad \text{and} \\ U^T &= C_Y[S_1^Y(T) + R_1^Y(T)] + C_A[S_1^A(T) + R_1^A(T) + S_1^T(T) + R_1^T(T)] \end{aligned}$$

are the total cost price of healthy/un-infected cattle at the beginning of the ITC programme and after T years of the control programme, respectively, and r is the discount rate. It is assumed that the control programme starts at the endemic equilibrium point. Taking the cost of treating one cow with insecticides to be C_T as in Chapter 4, we obtain the total cost of maintaining the ITC control programme for a period of T years as

$$TC(T) = \int_0^T C_T \psi_A (S_1^A(t) + I_1^A(t) + R_1^A(t)) e^{-rt} dt, \tag{5.7}$$

where $\psi_A(S_1^A(t) + I_1^A(t) + R_1^A(t))$ is the number of adult cattle treated with insecticides per day and r is the discount rate. The benefit-cost ratio is thus obtained as

$$BCR = \frac{B(T)}{TC(T)}. \tag{5.8}$$

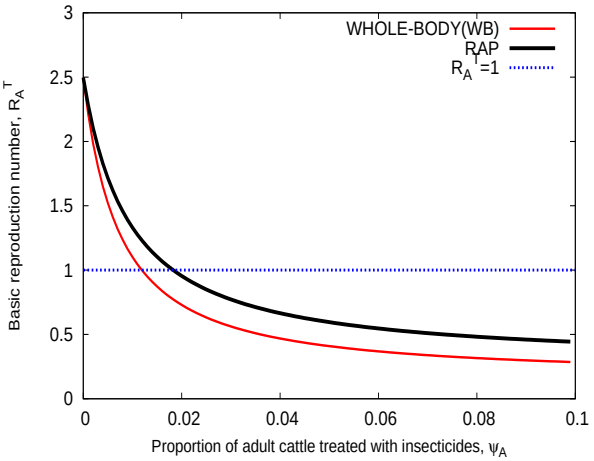
The ITC control programme is deemed acceptable if the benefits are higher than the cost, that is $BCR > 1$. The results of this analysis are shown in Section 5.3.3.

5.3 Numerical Results

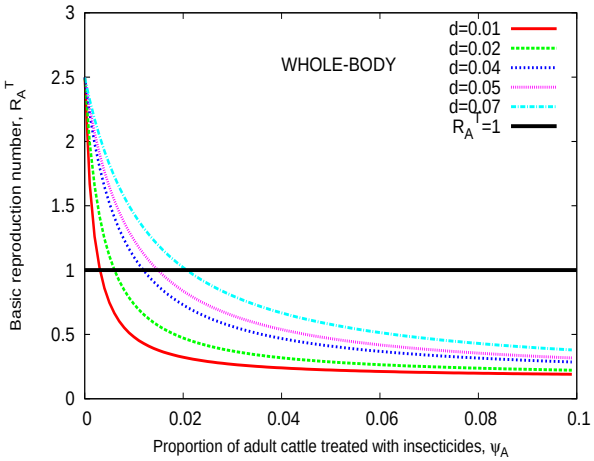
In this Section, we look at the numerical results of model (5.2-5.4). We use the same parameters estimated in Chapter 4 and given in Table 4.3. We assume that the proportion of young cattle that progress to adult cattle every day is $\kappa = 5\%$. We also assume that 90% of all tsetse blood meals obtained from cattle come from the adult cattle and the remaining 10% comes from the young cattle. With this choice of parameter values, we obtain $R_A^T = 2.5$ in the absence of ITC, which is the same as the value obtained in Chapter 4.

5.3.1 Prevention of the epidemic by treating adult cattle only with insecticides

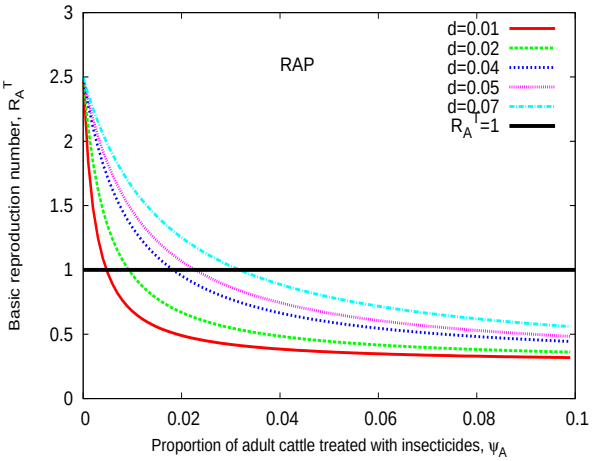
In this subsection, we investigate the impact of treating adult cattle only on the control of tsetse and *T. b. rhodesiense*. Since tsetse prefer to feed off the adult or largest animals, only these members of any herd need to be treated, and it is necessary to determine the required coverage for this particular case.



(a)



(b)



(c)

FIG. 5.2. The effect of treating adult cattle only with insecticides on the basic reproduction number, R_A^T. (a) shows the plot of the basic reproduction number, R_A^T with respect to the proportion of adult cattle treated with insecticides, ψ_A for $d = 0.04$. (b) and (c) shows the critical proportions of adult cattle needed to be treated with insecticides for different values of d for whole body and restricted application, respectively.

Figure 5.2 shows the critical proportion of adult cattle that need to be treated with insecticides for R_A^T to be less than one. The results show that treating 1.3% or 2.0% of the adult cattle population with insecticides through whole body or restricted application, respectively, can reduce R_A^T to less than one and lead to *T. b. rhodesiense* control in both humans and cattle. The insecticide treatment coverage decreases with the increase in the duration, $\frac{1}{d}$, of the killing effect provided by insecticides, and vice versa for both strategies. If the

duration, $\frac{1}{d}$, of the insecticidal killing effect is reduced from 4 weeks to 3 weeks, the critical proportion of adult cattle required to be treated with insecticides through whole-body or restricted application increases to 1.6% or 2.4%, respectively. On the other hand, if $\frac{1}{d}$ is increased to 7 weeks, the critical value of ψ_A decreases to 0.7% or 1.0% for whole-body or restricted application of insecticides, respectively. The results for the coverage for different values of d are shown in figure 5.4 (b) and (c) for whole-body and restricted application of insecticides, respectively, and are close to the ones obtained in Chapter 4.

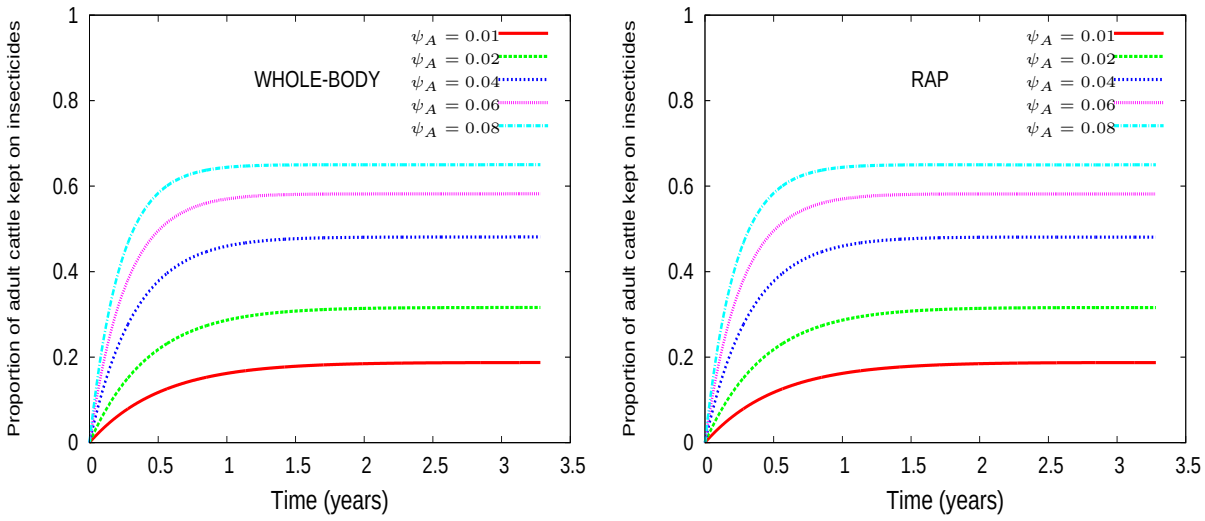
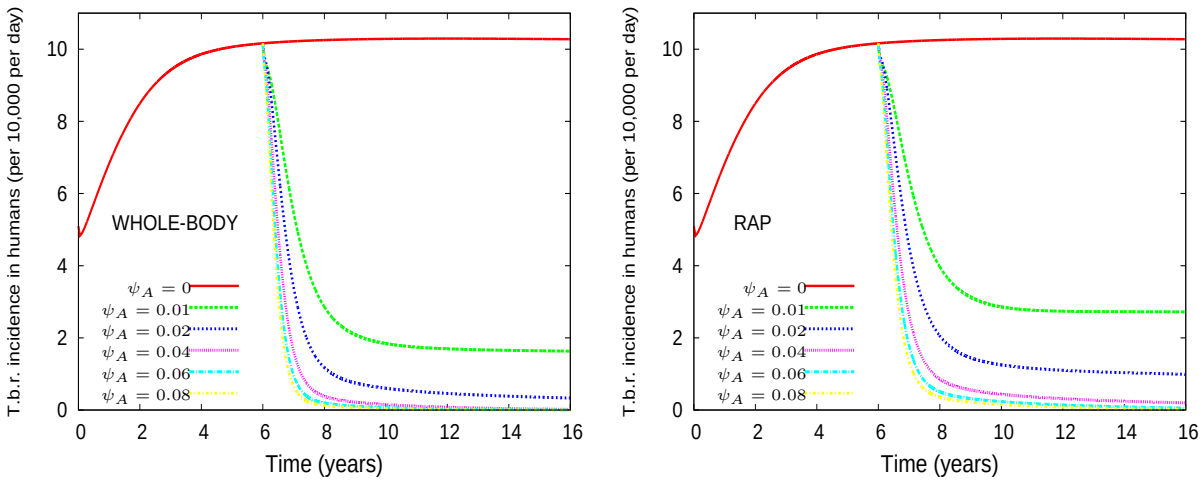


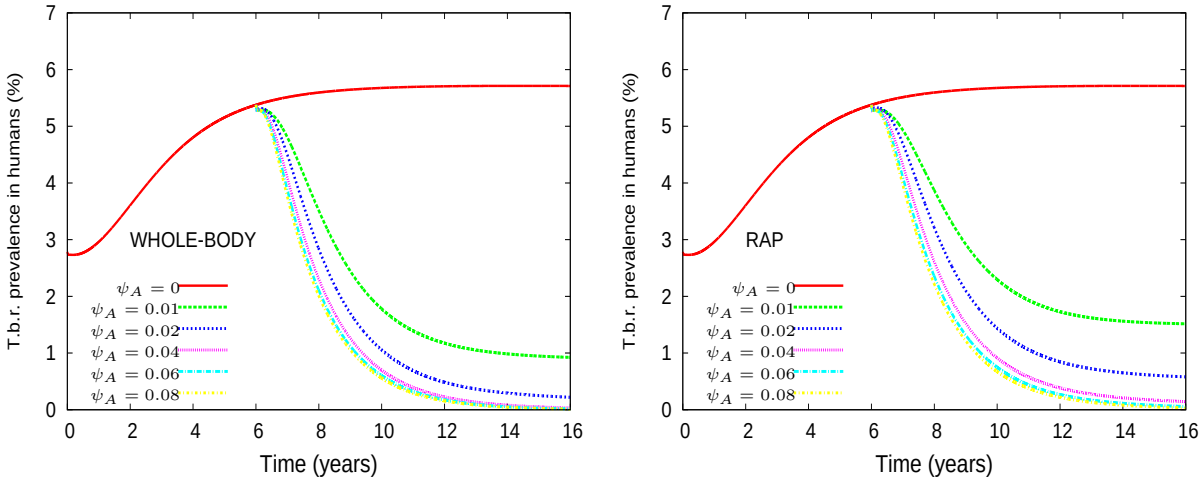
FIG. 5.3. Proportion of adult cattle kept on insecticides

The results for the proportions of adult cattle kept on insectcides were obtained by running model (5.2-5.4) up to a steady state and are shown in figure 5.3. The results show that the critical proportions of 1.3% or 2.0% required to be treated with insecticides per day through whole-body or restricted application for R_A^T to be less than one are equivalent to keeping 24.0% or 33.0% of the adult cattle population on insecticides, respectively. Figures 5.4 and 5.5 show the impact of treating adult cattle only with insecticides on the incidence and prevalence of *T. b. rhodesiense* in humans for both ITC treatment application strategies. The results are shown for the proportion of adult cattle treated with insecticides per day, ψ_A, taken to be $0, 0.01, 0.02, 0.04, 0.06$ and 0.08 for both strategies. In both strategies, there is a significant decrease in the incidence and prevalence of *T. b. rhodesiense* in humans. As in the previous Chapter, the ITC control measure is considered in the presence of wildhosts, without taking monitor lizards to be part of the wildhost population.



(a) (b)

FIG. 5.4. Increased tsetse mortality through treatment of adult cattle only with insecticides. *T. b. rhodesiense* incidence in humans for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b).



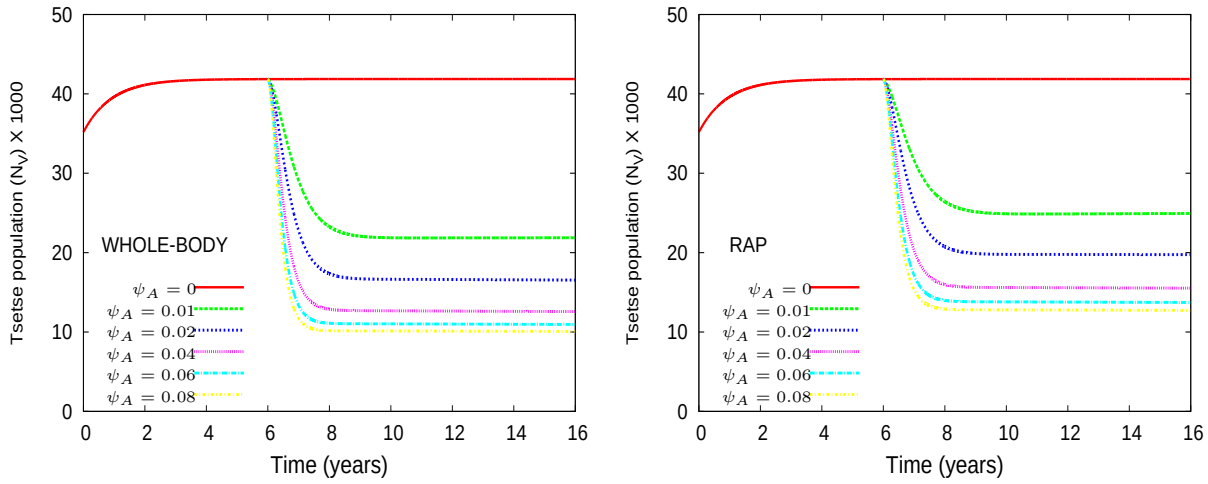
(a) (b)

FIG. 5.5. Increased tsetse mortality through treatment of adult cattle only with insecticides. *T. b. rhodesiense* prevalence in humans for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b).

5.3.2 Effect of treating adult cattle only with insecticides on the tsetse population

Figure 5.6 shows the impact of treating adult cattle only on the tsetse population. The results show a decrease in the tsetse population. These results are similar to the ones

obtained in Chapter 4, Section 4.4. Since tsetse flies like to feed off adult or larger cattle, the same effect can always be achieved by treating adult cattle only with insecticides.



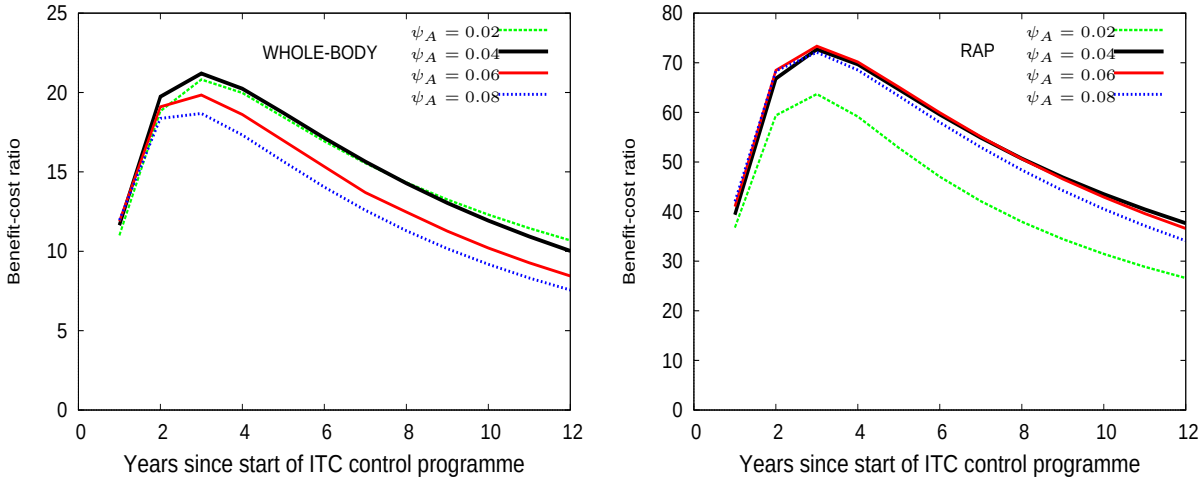
(a) (b)

FIG. 5.6. Effect of increased tsetse mortality through treatment of adult cattle with insecticides on the tsetse population for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b).

5.3.3 Benefit-cost analysis of the ITC control programme

In this subsection, we look at the benefit-cost analysis of controlling trypanosomiasis by treating adult cattle only with insecticides. We give an analysis of the benefits of the ITC control programme to the society. Trypanosomiasis has been shown to lead to diverse economic losses which include losses in animal production, human health and agricultural livelihoods in Africa. The estimated losses due to animal trypanosomiasis in the tsetse infested regions is over US$1 billion annually [10]. Applying appropriate control strategies would to lead to an improved productivity in animal production. In this thesis, we evaluate the benefits of treating adult cattle only with insecticides by looking at the monetary value of healthy cattle. It is assumed that treatment of adult cattle with insecticides starts at the endemic equilibrium. It is assumed that the monetary price of a young and an adult cow is $C_Y = \$200$ and $C_A = \$500$, respectively.

The monetary benefits of the ITC control programme are shown in figure 5.7 for both strategies, that is whole-body and restricted application of insecticides on cattle (RAP).



(a) (b)

FIG. 5.7. The benefit-cost ratio of the ITC control programme through treatment of adult cattle only with insecticides for both strategies; whole-body treatment (a) and restricted application of insecticides to cattle (b).

The results show that RAP has more monetary benefits compared to whole-body treatment of cattle with insecticides. The monetary benefits through RAP are about three times the ones obtained through whole-body treatment strategy. Maximum benefits can be achieved if the ITC programme is aimed at controlling the disease within 3 years. The results do not include monetary benefits obtained from human death avoided.

5.4 Summary

In this Chapter, we developed a mathematical model that describes the transmission of *T. b. rhodesiense* by tsetse vectors in humans, cattle and wildlife. The cattle population is taken to be composed of young and adult cattle, which are assumed to be in ages $0-3$ and $4-10$ years, respectively. The analytical expression of the basic reproduction number, R_A^T, of the model was obtained. The critical proportion of adult cattle required to be treated with insecticides through either whole-body or restricted application for $R_A^T < 1$ is obtained. The critical proportion was shown to increase with an increase in the duration of the killing effect provided by insecticides and vice versa.

We studied the impact of treating only adult cattle with insecticides on the tsetse pop-

ulation, incidence and prevalence of *T. b. rhodesiense* in humans. Our results showed a significant reduction in the vector population, incidence and prevalence of *T. b. rhodesiense* in humans.

We also used the model to evaluate the benefit-cost analysis of controlling *T. b. rhodesiense* in livestock. Both strategies of ITC control give a benefit-cost ratio which is greater than one, with RAP having a higher benefit-cost ratio compared to whole-body treatment.

Chapter 6

Conclusions and recommendations

In this thesis we developed mathematical models for the dynamics of *T. b. rhodesiense* infection with a view to gaining a better understanding of the transmission and control of the disease in Southeastern Uganda. The models were developed and analysed in accordance with the situation in Tororo district, Southeastern Uganda. This is the first attempt to use a mathematical model to do such an evaluation. Chapter 3 of the thesis introduced a model for the transmission of *T. b. rhodesiense* by tsetse vectors in human and cattle populations. The model was used to study the control of *T. b. rhodesiense* through mass chemoprophylaxis and/or insecticide-treated cattle. The basic reproduction number R_0 of the model was derived and critical proportions of cattle required to be treated with either trypanocides and/or insecticides obtained. Sensitivity analysis of the basic reproduction number and the endemic equilibrium with respect to the model was performed. Sensitivity results show that both R_0 and the endemic equilibrium are more sensitive to the tsetse control parameter, which is the proportion of cattle kept on insecticides. The model was used to study the impact of mass chemoprophylaxis and/or insecticide-treated cattle on *T. b. rhodesiense*, and both control measures are shown to have a clear impact. An optimal control analysis was also done and the results show that the control *T. b. rhodesiense* through ITC alone is cheaper than chemoprophylaxis alone or a combination of ITC and chemoprophylaxis.

Chapter 4 introduced a model for the transmission of *T. b. rhodesiense* by tsetse vectors in a multi-host population. The model was used to study the control of tsetse and *T. b. rhodesiense* through insecticide-treated cattle. The basic reproduction number of the

model was obtained. In the absence of ITC, the local stability of the model was done for the case $n = 1$. Assuming that tsetse flies feed on humans, cattle and wildlife, the basic reproduction number, R_{03}, of the 3-host model was obtained. A sensitivity analysis of R_{03} with respect to all parameters in the absence and presence of ITC show that it is most sensitive to the tsetse natural mortality, μ_V, and the parameter for additional tsetse mortality, m, respectively. The impact of monitor lizards, wild hosts that provide tsetse blood meals but do not get infected with *T. b. rhodesiense*, on the transmission of the disease was shown. If tsetse were feeding on monitor lizards most of the time then the transmission rate of *T. b. rhodesiense* would be lower than the case when they are feeding on other hosts which do get infected with trypanosomes.

We studied the impact of ITC on the control of tsetse and *T. b. rhodesiense* and two strategies of ITC were considered, that is, whole-body and restricted application of insecticides on cattle. The results show that both strategies lead to a significant decrease in the incidence and prevalence of *T. b.rhodesiense* in humans. The same effect is expected to happen in all the host species since ITC was shown to decrease the tsetse population, vectors that are responsible for the transmission of the disease. A cost-effectiveness analysis of the ITC control programme was carried out and restricted application of insecticides was found to be more cost-effective than whole-body treatment.

Chapter 5 introduced a model for the transmission of *T. b. rhodesiense* by tsetse vectors in cattle, human and wildlife populations, with the cattle population categorised as young or adult cattle. The model was used to study the control of tsetse and *T. b. rhodesiense* through treatment of adult cattle only. This model was developed in accordance with research which has shown that tsetse flies feed preferentially on large adult animals. The impact of treating adult cattle only on the control of tsetse and *T. b. rhodesiense* was studied. Two strategies of ITC were also considered as in chapter 4. The results show that treating adult cattle only with insecticides through either whole-body or restricted application of insecticides reduces the incidence and prevalence of *T. b. rhodesiense* in humans, and the tsetse population significantly. A benefit-cost analysis of the ITC control programme was carried out and the results show that restricted application has more monetary benefits than whole-body treatment.

The results show the importance of restricted application of insecticides to cattle in the

control of tsetse and trypanosomiasis. Apart from reducing the costs of tsetse and trypanosomiasis control, RAP has a number of other livestock health and productivity benefits. Some of these benefits include:

- Most farmers in Africa have indigenous breeds of cattle, which are resistant to several tick-borne diseases. The resistance depends on young cattle being bitten by infected ticks. With restricted application of insecticides to cattle (RAP), it means that young cattle will not be treated with insecticides, allowing them to be bitten by ticks, which gives them the ability to build up an immunity to diseases carried by ticks [64].
- Widespread of pyrethroids can have adverse impact on the invertebrate dung fauna, which play an important role in maintaining soil fertility [10, 64, 67]. This effect can be controlled by restricting insecticides on the legs and belly of cattle. Thus, RAP gives an added benefit of preserving the environment.
- Studies have shown that most cattle-feeding Diptera land on the legs [64]. This means that restricted application of insecticides on cattle may be an appropriate method for controlling other vector-born diseases of livestock and humans.

It is important to note that *T. b. rhodesiense* will be more efficiently controlled by treating cattle with insecticides in areas like Uganda with few wild hosts, where cattle provide most of tsetse blood meals [31]. If the ITC control measure is applied in areas with many wild hosts, then the vast majority of tsetse flies may feed on wild hosts and treating cattle with insecticides may not help in killing the tsetse vectors. Vector control has also been shown to be more cost-effective in controlling trypanosomiasis at higher incidences [54].

6.1 Limitations and future work

One of the most important challenges in evaluating the burden of trypanosomiasis is lack of reliable data. Data on HAT incidence, morbidity, and mortality is often incomplete and fragmented. Under-reporting of HAT cases as a consequence of insufficient access to health care by patients is also a significant obstacle. Methods for quantifying levels of under-reporting need to be validated and extended to different countries in sub-Saharan Africa [26].

The models we developed do not make a distinction between male and female tsetse, which are known to differ with respect to longevity, mobility and responses to baits. The models assume a constant mortality and age structure for tsetse population. In the presence of insecticide-treated cattle, where cattle are assumed to provide a substantial proportion of tsetse blood meals, the size of the tsetse population and its mean age are expected to decline [31]. The models also do not take the problem of tsetse invasion from adjacent infected areas into consideration. As a future perspective, it would be important to look at studies that take all or some of these problems into consideration. Models that deal with the spatial-temporal dynamics of the disease may also be useful in designing control strategies.

The models in Chapter 4 and 5 were formulated for an arbitrary number of the host population (n). The analysis was done only for 3 hosts, that is, cattle, humans and wildlife. This analysis represents the situation in Uganda where cattle and wildlife are often affected by trypanosomiasis and are important reservoirs of the disease [19]. As a future perspective, it would be interesting to see how the results vary as a function of n. In Chapter 5, it was sufficient to divide the cattle population into discrete classes that differentiates young cattle from adult cattle and obtain reasonable results. An age-structured model where age enters as a continuous parameter and the model becomes a set of partial differential equations would give interesting results. This type of problem was also left for future work.

Appendix A

Derivation of the tsetse recruitment rate, Λ_V

The recruitment rate for the tsetse flies is based on newly emerged flies that are feeding for the first time [31, 50, 72]. These newly emerged flies have to survive death due to natural mortality and the effects of insecticides, and should not have fed for them to be susceptible to *T. b. rhodesiense* infection. We first consider a constant tsetse mortality where the proportion of cattle, p, on insecticides is constant. Assuming a constant birth rate, B_V, then the number of newly born flies that survive and have not fed in one unit of time (that is, between $t-1$ and 1) is given by

$$\Lambda_V = B_V \int_{t-1}^{t} e^{-(a+\mu_V(p))(t-s)} ds. \tag{A.1}$$

Changing variables by letting $u = t - s$ and simplifying, equation (A.1) becomes

$$\Lambda_V = B_V \int_0^1 e^{-(a+\mu_V(p))u} du = \frac{B_V}{(a+\mu_V(p))}(1 - e^{-(a+\mu_V(p))}). \tag{A.2}$$

For a time dependent tsetse mortality where the proportion of cattle treated with insecticides, p, is non-constant, equation (A.1) becomes

$$\Lambda_V = B_V \int_{t-1}^{t} e^{-\int_s^t (a+m_V(p(\xi)))d\xi} ds. \tag{A.3}$$

Changing variables by letting $u = t - s$, equation (A.3) becomes

$$\Lambda_V = B_V \int_0^1 e^{-\int_{t-u}^t (a+m_V(p(\xi)))d\xi} du. \tag{A.4}$$

Changing variables again by letting $x = \xi - t$, equation (A.4) becomes

$$\Lambda_V = B_V \int_0^1 e^{-\int_{-u}^{0}(a+m_V(p(t+x)))dx} du. \tag{A.5}$$

Equation (A.5) can be solved by using the the trapezium rule which is given by,

$$\int_{x_1}^{x_2} f(x)dx = \frac{(x_2 - x_1)}{2n}[f(x_1) + f(x_2) + 2\sum_{k=1}^{n-1} f(x_1 + k(\frac{x_2 - x_1}{n}))]. \tag{A.6}$$

Using equation (A.6), the exponential part of equation (A.5) becomes

$$\frac{-u}{2n_1}[2a + m_V(p(t-u)) + m_V(p(t)) + 2\sum_{k_1=1}^{n_1-1}(a + m_V(p(t + u(\frac{k_1}{n_1} - 1))))]. \tag{A.7}$$

Substituting equation (A.7) into (A.5), we obtain

$$\Lambda_V = B_V \int_0^1 e^{\frac{-u}{2n_1}[2a+m_V(p(t-u))+m_V(p(t))+2\sum_{k_1=1}^{n_1-1}(a+m_V(p(t+u(\frac{k_1}{n_1}-1))))]} du. \tag{A.8}$$

Again, using equation (A.6), A.8) becomes

$$\begin{aligned}\Lambda_V = \frac{B_V}{2n_2}(1 + e^{\frac{-1}{2n_1}[2a+m_V(p(t-1))+m_V(p(t))+2\sum_{k_1=1}^{n_1-1}(a+m_V(p(t+\frac{k_1}{n_1}-1)))]} \\ + 2\sum_{k_2=1}^{n_2-1} e^{-\frac{1}{2n_1}(\frac{k_2}{n_2})[2a+m_V(p(t-\frac{k_2}{n_2}))+m_V(p(t))+2\sum_{k_1=1}^{n_1-1}(a+m_V(p(t+\frac{k_2}{n_2}(\frac{k_1}{n_1}-1))))]}).\end{aligned} \tag{A.9}$$

Taking $n_1 = n_2 = 2$, equation (A.9) reduces to

$$\Lambda_V = \frac{B_V}{4}[1 + 3e^{-\frac{1}{4}(4a+m_V(p(t-1))+3m_V(p(t))}]. \tag{A.10}$$

Due to the delay terms in equation (A.9), cases where $n_1 = n_2 > 2$ reduce to a Λ_V is complex to be solved with systems (3.4-3.12) and (5.2-5.4), given in Chapter 4 and 5, respectively. Since equation (A.6) is an approximate solution of equation (A.5), the numerical results in Chapter 4 and 5 are considered to be approximate solutions.

At the DFE, the proportion of cattle on insecticides is constant and given by $\pi = \frac{\psi}{\psi+d+\mu_1}$. For the case where adult cattle only is treated with insecticides, the proportion of adult cattle on insecticides is given by $\pi_A = \frac{\psi_A}{\psi_A+d+\mu_1}$. The solution for the tsetse recruitment rate at the DFE can thus be obtained by integrating equation (A.5) and is given by

$$\tilde{\Lambda}_V = \frac{B_V}{(a + \tilde{m}_V(\pi))}(1 - e^{-(a+\tilde{m}_V(\pi))}) \tag{A.11}$$

for the case where insecticides are applied to the cattle population without being restricted to adult cattle and

$$\hat{\Lambda}_V = \frac{B_V}{(a + \hat{m}_V(\pi_A))}(1 - e^{-(a+\hat{m}_V(\pi_A))}) \tag{A.12}$$

for the case where insecticides are applied to adult cattle only.

Bibliography

[1] Anderson N.E., Mubanga J., Fèvre E.M., Piccozi K., Eisler M.C., Thomas R., Welburn S.C. (2011), Characterisation of the Wildlife Reservoir Community for Human and Animal Trypanosomiasis in the Luangwa Valley, Zambia, *PLOS Neglected Tropical Diseases*, **5**, e1211.

[2] Artzrouni M. and Gouteux J. (2003), Estimating tsetse population parameters: Application of a mathematical model with density-dependence, *Medical and Veterinary Entomology*, **17**, 272–279.

[3] Artzrouni M. and Gouteux J. (2001), A model of Gambian sleeping sickness with open vector populations, *IMA Journal of Mathematics Applied in Medicine and Biology*, **18**, 99–117.

[4] Artzrouni M. and Gouteux J., *A compartmental model of sleeping sickness in Central Africa*, Journal of Biological Systems, **4**, 459–477.

[5] Bauer B., Amsler-Delafosse S., Kabore I. and Kamuanga M. (1999) Improvement of cattle productivity through rapid alleviation of African animal trypanosomiasis by integrated disease management practices in the agropastoral zone of Yale, Burkina Faso, *Tropical Animal Health and Production*, **31**, 89-102.

[6] Bauer B., Kabore I., Liebisch A., Meyer F. and Petrich-Bauer J. (1992) Simultaneous control of ticks and tsetse flies in Satiri, Burkina Faso, by the use of flumethrin pour-on for cattle, *Tropical Medicine and Parasitology*, **42**, 41-46.

[7] Bekele J., Asmare K., Abebe G., Ayelet G. and Gelaye E. (2010), Evaluation of Deltamethrin applications in the control of tsetse and trypanosomosis in the southern rift valley areas of Ethiopia, *Veterinary Parasitology*, **168**, 177-184.

[8] Berrang-Ford L., Odiit M., Maiso F., Waltner-Toews D. and McDermott J. (1996), Sleeping sickness in Uganda: revisiting current and historical distributions, *African Health Sciences*, **6**, 223–231.

[9] Berrang-Ford L., Waltner-Toews D., Charron D., Odiit M., McDermott J. and Smit B. (2005), Sleeping Sickness in Southeastern Uganda: A Systems Approach, *EcoHealth*, **2**, 183–194.

[10] Bourn D., Grant I., Shaw A. and Torr S. (2005), Cheap and safe tsetse control for live stock production and mixed farming in Africa, *Aspects of Applied Biology*, **75**.

[11] Brun R., Blum J., Chappuis F. and Burri C. (2010), Human African trypanosomiasis, *Lacent*, **375**, 148–159.

[12] Brun R. and Moloo S.K. (1982), In vitro cultivation of animal-infective forms of a West African Trypanosoma vivax stock, *Acta Tropica*, **39**, 135-141.

[13] Chalvet-Monfray K., Artzrouni M., Gouteux J., Auger P. and Sabatier P. (1998), A two-patch model of Gambian sleeping sickness: Application to vector control strategies in a village and plantations, *Acta Biomathematica*, **46**, 207–222.

[14] Chitnis N., Hyman J.M. and Cushing J.M. (2008), Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model, *Bulletin of Mathematical Biology*, **70**, 1272–1296.

[15] Chizyuka H.G.B. and Liguru S.M.K. (1986), Dipping to control vectors of cattle parasites, *Parasitology*, **2**, 123.

[16] Coleman P.G. and Welburn S.C. (2004), Are fitness costs associated with resistance to human serum in *Trypanosoma brucei rhodesiense*?, *Trends in Parasitology*, **20**, 311–315.

[17] Cook J., Principles and standards for benefit-cost analysis of public health preparedness and pandemic mitigation programes, Evans School of Public Affairs, University of Washington, *http://evans.washington.edu/node/3608*.

[18] Dale C., Welburn S.C., Maudlin I. and Malligan P.J. (1995), The kinetics of maturation of *trypanosoma* infections in tsetse, *Parasitology*, **111**, 187-191.

[19] Davis S., Aksoy S. and Galvani A. (2011), A global sensitivity analysis for African sleeping sickness, *Parasitology*, **138**, 516-526.

[20] Edmunds W.J., Medley G.F. and Nokes D.J. (1999), Evaluating the cost-effectiveness of vaccination programmes: a dynamic perspective, *Statistics in Medicine*, **18**, 3263–3282.

[21] Eisler M.C., Torr S.J., Coleman P.G., Machila N. and Morton J.F. (2003), Integrated control of vector-borne diseases of livestock - pyrethroids: panacea or poison?, *TRENDS in Parasitology*, **19**, 341–345

[22] Eisler M.C., Maruta J., Nqindi J., Connor R.J., Ushewokunze-Obatolu U., Holmes P.H. and Peregrine A.S. (1996), Isometamidium concentrations in the sera of cattle maintained under a chemoprophylactic regime in a tsetse-infested area of Zimbabwe, *Trop Med Int Health.*, **4**, 535–541.

[23] Fairbairn H. and Burtt E. (1946), The infectivity to man of a strain of Trypanosoma rhodesiense transmitted cyclically by Glossina morsitans through sheep and antelope; evidence that man requires a minimum infective dose of metacyclic trypanosomes, *Ann Trop Med Parasitol*, **40**, 270-313.

[24] FAO (2007), Comparable costings for alternatives for dealing with tsetse: estimates for Uganda, *http://www.fao.org/ag/pplpi.html*

[25] Fèvre E.M., Coleman P.G., Odiit M., Magona J.W., Welburn S.C. and Woolhouse M.E.J. (2001), The origins of a new Trypanosoma brucei rhodesiense sleeping sickness outbreak in eastern Uganda, *The Lacent*, **358**, 625–628.

[26] Fèvre E.M., Odiit M., Coleman P.G., Woolhouse M.E.J. and Welburn S.C. (2008), Estimating the burden of rhodesiense sleeping sickness during an outbreak in Serere, eastern Uganda, *BMC Public Health*, **8**, 96.

[27] Fèvre E.M., Wissmann B.V., Welburn S.C. and Lutumba P. (2008), The burden of human African trypanosomiasis, *PLOS Neglected Diseases*, **2**, e333.

[28] Fox R.G.R., Mmbando S.O., Fox M.S. and Wilson A. (1993) Effect on herd health and productivity of controlling tsetse ad trypanosomiasis by applying deltamethrin to cattle, *Tropical Animal Health Production*, **25**, 203-214.

[29] Fox-Rushby J. and Hanson K. (2001), Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis, *Health policy and planning*, **16**, 326-331.

[30] Griffin R.C. (1998), The fundamental principles of cost-benefit analysis, *Water resources research*, **34**, 2063-2071.

[31] Hargrove J.W., Ouifki R., Kajunguri D., Vale G.A. and Torr S.J. (2012), Modeling the control of trypanosomiasis using trypanocides or insecticide-treated livestock, *PLOS Neglected Tropical Diseases*, **6**, e1615.

[32] Hargrove J.W., Torr S.J. and Kindness H.M. (2003) Insecticide-treated cattle against tsetse (Diptera: *Glossinidae*): what governs success? *Bulletin of Entomological Research*, **93**, 203-217.

[33] Hargrove J.W., Omolo S., Msalilwa J.S.I. and Fox B. (2000), Insecticide-treated cattle for tsetse control: the power and the problems, *Medical and Veterinary Entomology*, **14**, 123-130.

[34] Hoare A., Regan D.G. and Wilson D.P. (2008), Sampling and sensitivity analysis tools (SaSAT) for computational modelling, *Theoretical Biology and Medical Modelling*, **5**, 77–109.

[35] Hide G., Tait A., Maudlin I. and Welburn S.C. (1996), The Origins, Dynamics and Generation of Trypanosoma brucei rhodesiense Epidemics in East Africa, *Parasitology Today*, **12**, 50-55.

[36] Hide G. (1999), History of Sleeping Sickness in East Africa, *Clinical Microbiology Reviews*, **12**, 112–115.

[37] Lutumba P., Makieya E., Shaw A., Meheus F., Boelaert M. (2007) Human African trypanosomiasis in a rural community, Democratic Republic of Congo *Emerg Infect Dis* **13**, 248-254.

[38] Matemba L.E., Fevre E.M., Kibona S.N., Picozzi K., Cleaveland S., Shaw A.P., and Welburn S.C. (2010), Quantifying the Burden of Rhodesiense Sleeping Sickness in Urambo District, Tanzania, *PLOS Neglected Tropical Diseases*, **4**, e868.

[39] Magona J.W. and Walubengo J. (2011), Mass-treatment and insecticide-spraying of animal reservoirs for emergency control of Rhodesiense sleeping sickness in Uganda *Journal of Vector Borne Diseases* **48**, 105108.

[40] McDermott J.J. and Coleman P.G. (2001), Comapring apples and oranges- model-based assessment of different tsetse-transmitted trypanosomosis control strategies, *International Journal for Parasitology*, **31**, 603–609.

[41] Mohamed-Ahmed M.M. and Odulaja A. (1997), Diel activity patterns and host preferences of *Glossina fuscipes fuscipes* (Diptera: *Glossinidae*) along the shores of Lake Victoria, Kenya, *Bulletin of Entomological Research*, **87**, 179-186.

[42] Murray C.J.L. (1994) Quantifying the burden of disease: the technical basis for disability-adjusted life years, *Bulletin of the World Health Organisation*, **72**, 429-445.

[43] Odiit M., Bessell P.R., Fèvre E.M., Robinson T., Kinoti J., Coleman P.G., Welburn S.C., McDermott J. and Woolhouse M.E.J. (2006), Using remote sensing and geographic information systems to identify villages at high risk of rhodesiense sleeping sickness in Uganda, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **100**, 354–362.

[44] Odiit M., Coleman P.G., McDermott J.J., Fèvre E.M., Welburn S.C., Woolhouse M.E.J. (2004), Spatial and temporal risk factors for the early detection of Trypanosoma brucei rhodesiense sleeping sickness patients in Tororo and Busia districts, Uganda, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **98**, 569-576

[45] Okello-Onen J., Heinonen R., Ssekitto C.M.B., Mwayi W.T., Kakaire D. and Kabarema M. (1994), Control of tsetse flies in Uganda by dipping cattle in deltamethrin, *Tropical Animal Health and Production*, **26**, 21-27.

[46] Onyango R.J., van Hoeve K. and De Raadt P. (1966) The epidemiology of *trypanosoma rhodesiense* sleeping the sickness in Alego location, Central Nyanza, Kenya, *Transactions of The Royal Society of Tropical Medicine and Hygiene*, **60**, 175–183.

[47] Picozzi K., Fèvre E.M., Odiit M., Carrington M., Eisler M.C., Maudlin I. and Welburn S.C. (2005), Sleeping sickness in Uganda: a thin line between two fatal disease, *British Medical Journal*, **331**, 1238–1241.

[48] RIU, Waking up to better ways of tackling sleeping sickness, *http://www.researchintouse.com/nrk/RIUinfo/PF/AHP10.htm*

[49] Rogers D.J. (1977), Study of the natural population of *glossina fuscipes fuscipes* newstead and a model of fly movement, *J. Anim. Ecol.*, **46**, 309–330.

[50] Rogers D.J. (1988), A general model for the African trypanosomiases, *Parasitology*, **97**, 193-212.

[51] Rowlands G.J., Leak S.G.A., Woudyalew Mulatu, Nagda S. M., Wilson A. and d'ieteren G.D.M. (2000), Use of deltamethrin 'pour-on' insecticide for the control of cattle trypanosomosis in the presence of high tsetse invasion, *Medical and Veterinary Entomology*, **15**, 87-96.

[52] Sassi F. (2006), Calculating QALYs, comparing QALY and DALY calculations, *Health policy and planning*, **21**, 402-408.

[53] Shaw A.P., Cattand P. (2001) Analytical tools for planning cost-effective surveillance in Gambiense sleeping sickness, *Med. Trop (Mars)*, **61**, 412-421.

[54] Shaw A.P.M. (1989), Comparative analysis of the costs and benefits of alternative disease control strategies: vector control versus human case finding and treatment, *Ann. Soc. Belge. Med. Trop.*, **69**, 237-2533.

[55] Simarro P.P., Cecchi G., Poane M., Franco J.R., Diarra A., Ruiz J.A., Fèvre E.M., Courtin F., Mattioli R.C. and Jannin J.G. (2010), The Atlas of human African trypanosomiasis: a contribution to global mapping of neglected tropical diseases, *International Journal of Health Geographics*, **9**:57.

[56] Simarro P.P., Diarra A., Postigo J.A.R., Franco J.R. and Jannin J.G. (2011) The Human African Trypanosomiasis Control and Surveillance Programme of the World Health Organization 2000-2009: The Way Forward, *Plos Neglected Tropical Diseases* **5** 7.

[57] Simarro P.P., Franco J.R., Ndongo P., Nguema E., Louis F.J. and Jannin J. (2006), The elimination of Trypanosoma brucei gambiense sleeping sickness in the focus of Luba, Bioko Island, Equatorial Guinea, *Tropical Medicine and International Health*, **2**, 636–646.

[58] Stamp out sleeping sickness in Uganda *http://www.stampoutsleepingsickness.com/about-sos-.aspx*

[59] Steverding D. (2008), The history of African trypanosomiasis, *Parasites and Vectors*, **1**:3.

[60] Stick A., Abel M.P., and Krishna S. (2002), Human African Trypanosomiasis, *British Medical Journal*, **54**, 341–355.

[61] The Center for Food Security and Public health, (2009), African Animal Trypanosomiasis, *www.cfsph.iastate.edu*

[62] Thomson J.W., Mitchell M., Rees R.B., Shereni W., Schoenfeld A.H. and Wilson A. (1991), Studies on the efficacy of deltamethrin applied to cattle for the control of tsetse flies (*Glossina spp.*) in southern Africa, *Tropical Animal Health and Production*, **23**, 221-226.

[63] Torr S.J., Vale G.A. (2011), Is the Even Distribution of Insecticide-Treated Cattle Essential for Tsetse Control? Modelling the Impact of Baits in Heterogeneous Environments *PLoS Neglected Tropical Diseases*, **5**, e1360

[64] Torr S.J., Maudlin I. and Vale G.A. (2007), Less is more: restricted application of insecticide to cattle to improve the cost and efficacy of tsetse control, *Medical and Veterinary Entomology*, **21**, 53–64.

[65] Uganda Bureau of Statistics (UBOS), National Livestock census 2008, *http://www.ubos.org*

[66] van den Driessche P. and Watmough J. (2002), Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission, *Mathematical Biosciences*, **180** 29-48.

[67] Vale G.A. and Torr S.J. (2005), User-friendly models of the costs and efficacy of tsetse control: application to sterilizing and insecticidal techniques, *Medical and Veterinary Entomology*, **19**, 293–305.

[68] Vale G.A., Mutika G. and Lovemore D.F. (1999), Insecticide-treated cattle for controlling tsetse flies (Diptera: *Glossinidae*): some questions answered, many posed, *Bulletin of Entomological Research*, **89**, 569-578.

[69] Wahab S. and Asuming-Brempong (2007), Benifit-cost analysis and socio-economic considerations of trypanosomiasis control and treatment in Northern Ghana, *AAAE Conference proceedings*, 521-528.

[70] Waiswa C. (2002), *African animal and human trypanosomosis in Southeastrn Uganda: vector competence and characterization of T. brucei isolates*, PhD Thesis, Veterinary Faculty, Makerere University, Kampala, Uganda.

[71] Waiswa C., Picozzi K., Katunguka-Rwakishaya E., Olaho-Mukani W., Musoke R.A. and Welburn S.C. (2006), *Glossina fuscipes fuscipes* in the trypanosomiasis endemic areas of south eastern Uganda: Apparent density, trypanosome infection rates and host feeding preferences, *Acta Tropica*, **99**, 23–29.

[72] Welburn, S.C., Coleman P.G., Maudlin I., Fèvre E.M., Odiit M.O. and Eisler M.C. (2006), Crisis, what crisis? Control of Rhodesian slepping sickness, *Trends in Parasitology*, **22**, 123-128.

[73] Welburn, S.C., Picozzi K., Coleman P.G. and Packer C. (2008), Patterns in age-seroprevalence consistent with acquired immunity against *trypanosoma brucei* in Serengeti Lions , *PLOS Neglected Tropical Diseases*, **2**, e347.

[74] Wellde B.T., Waema D., Chumo D.A., Reardon M.J., Adhiambo A., Olando J., Mabus D. (1989a), The Lambwe Valley and its people, *Ann Trop Med Parasitol.*, **83** 13–20.

[75] Wellde B.T., Waema D., Chumo D.A., Reardon M.J., Oloo F., Njogu A.R., Opiyo E.A. and Mugutu S. (1989b), Review of tsetse control measures taken in the Lambwe Valley in 1980-1984, *Ann Trop Med Parasitol*, **83**, 119–25.

[76] World health Organisation (2006), *Human African trypanosomiasis (sleeping sickness): epidemiological update*, weekly Epidemiological record 2006, **81**, 69–80.

[77] World Health Organisation (2001), *African trypanosomiasis (sleeping sickness)*. Report of the Scientific Working Group meeting on African trypanosomiasis, Geneva, 4-8 June, 2001.

[78] WHO (2008), Uganda: Country health profile *http://www.who.int/countries/uga/en/*

[79] World Health Organisation (1998), *Control and surveillance of African trypanosomiasis*. WHO Technical report series 881, Geneva.

[80] WHO (2011), The Control of Neglected Zoonotic Diseases, *http* : *//www.who.int/neglected_diseases/zoonoses/en/*

[81] Zoller T., Fèvre E.M., Welburn S.C., Odiit M. and Coleman P.G. (2008), Analysis of risk factors for T. brucei rhodesiense sleeping sickness within villages in south-east Uganda, *BMC Infectious Diseases*, **8**, 88.