Disease Modeling with Application to Parasite-borne Diseases

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Abstract

The study of the spread of diseases brings together many different questions, which include biological, epidemiological, clinical, and public health issues. System Dynamics provides a suitable framework for modeling diseases that enables one to bring together these questions in a convenient and manageable way.

In the present paper, which is part of a program of work, we discuss models for the development and transmission of parasite-borne diseases, in particular, diseases which involve a primary host, a vector, and a parasite. We shall here regard humans as the primary (or definitive) host and mosquitoes as the vector; the same method applies to other instances of the vector and the primary host. The models discussed here will be applied to different types of diseases. The data in this paper will refer primarily to the filariae.

We first examine models for the biology of the disease in a single vector and in a single host, and for disease transmission between two humans through a vector.

We then discuss a model for disease transmission in a population of vectors interacting with a population of hosts. Besides disease-free and infective states, the model allows for states of the host and the vector in which the host or vector has been exposed to the disease but is not yet infective. For the host, it also allows for recovered states.

We examine the effect of different control strategies, including preventive measures as well as treatment for the disease. We also examine the possible effects of changes in the environment on the spread of the disease. We point out some of the complexities inherent in the biological processes, and the variability resulting from change in the values of the parameters in the system.

1. Introduction

Mathematical Modeling of Diseases is an important field of research, and has resulted in a large, continually growing body of work. [e.g. see Reference 1 for a partial listing of such work.]

There are several complications in creating satisfactory models for the transmission and spread of diseases. The biology of a disease often involves interactions among different organisms. There are diseases which involve just direct contact between the afflicted host and the pathogen. Even for such diseases, there are features that are not well understood, and mathematical problems to be resolved.

There are several diseases which involve one or more intermediate agents between the definitive host and the pathogen. A well-known category of such diseases is diseases involving parasites, some of which such as malaria continue to affect millions of people globally. A well-defined set of diseases of this type involves parasites carried by a vector (such as a mosquito or a snail). The vector acts both as a carrier and as an organism within which the parasite develops to an infectious stage before it is carried by the vector to the definitive host, and transferred to the host during a bite. Work on modeling the transmission of such infections has been done [(1)] , but there are important questions remaining to be answered satisfactorily.

In this paper, we formulate models for different aspects of diseases involving a definitive host, a vector, and a parasite (which typically develops through multiple stages to a form that causes infection in the host). We are looking at this model in connection with different diseases. In discussing results in the present paper, we shall focus on Lymphatic Filariasis (LF), popularly known as filaria, as a specific example [(2) (3 – 8)].

In modeling the transmission and spread of diseases, we need to look at several different types of factors – biological, clinical, epidemiological , as well as public-health and policy related factors.

System Dynamics [(9)] provides a framework for incorporating these different factors in a manageable way. Disease modeling needs to take into account the essentially nonlinear behavior of most biological systems, and in particular several feedback effects in the systems of interest. System Dynamics is particularly suited for handling these features, and provides a convenient formalism for formulating the details of the problem, which we have found very useful in the present work.

In Section 2, we present and discuss a set of models which address different aspects of the host-vector-parasite system. The models are for

(a) the biology of a single vector with a parasite;
(b) the biology of a single (human) host with a parasite.
(c) The transmission of infection from one human to another, mediated by a vector.

Each model is a compartmental model, and is described by a set of simplified differential equations.

For each of these, results have been obtained by carrying through simulations for different values of the parameters. A selection of these results is presented here in summary.

Control points are identified in the systems, at which intervention strategies can be implemented. Results are shown for the effects of different intervention strategies. *We stress that these results are meant to show the qualitative trends and dependencies, and not numerical values.* We believe that the models show these qualitative trends correctly.

In Section 3, we outline a model for the transmission and spread of infection in a system with interacting vector and host populations. Again, results are obtained by carrying through simulations for different values of

the parameters. Partial results are presented here; this is work in progress, and more results will be reported later.

In Section 4, control points are identified for a system with interacting vector and host populations, which are suitable for implementing intervention strategies. Results are shown for different intervention strategies. *We again stress that these results are meant to show the qualitative trends and dependencies, and not numerical values*.

We believe that the qualitative trends shown here can provide useful input for making decisions on epidemiological and public-health issues.

In Section 5, we summarize the work and our conclusions.

Biological systems have several complexities. The description of the dynamics in a form which allows one to obtain computational results necessarily requires many simplifying assumptions.

Further, the parameters occurring in the systems considered here are subject to a large degree of variation; their values are often at best known to be within a range (which can sometimes be quite wide). We have taken the values of the parameters from available reported data.

Some features of the systems we are considering are essentially stochastic. We have taken this into account in a simplified way by varying the parameters and examining the spread of the results. More work will be done in taking into account the stochastic nature of the system.

The work reported here is part of a program of work in progress; we are addressing the questions mentioned here, and will report other results in the future.

2. The Model(s)

As the details of the models here will refer to filarial infections in humans (Lymphatic Filariasis or LF), we first give a brief, simplified description of the processes involved in the transmission of LF to and among humans.

For human lymphatic filariasis, the human is the definitive host, and the mosquito the vector. The mosquito acts both as the carrier of the parasite and as a host for the development of the LF larvae which infect humans (and cause filaria). Therefore, in describing the transmission cycle, we need to examine the processes in the mosquito as well as the human.

The main parasite which causes LF is *Wuchereria bancrofti*. The mosquito carriers that have been best studied are the Anopheles and the Culex mosquitoes. For a person infected with LF, the adult worms (macrofilariae) reside in the host's lymphatic system, and have a reported lifetime of 5 to 10 years. The female worms, after mating with the males, produce a large number of microfilariae (Mf) every day; these Mf move into the bloodstream and are the measurable indicators of infection. The reported lifetime of the mf span a wide range, e.g. 6 to 24 months. An average number that has been used is about a year.

A mosquito ingests Mf when it takes a blood meal from a filariasis-infected individual. [For instance, in experiments in Pondicherry, the mean Mf intake reported from immediate dissections of Culex mosquitoes was about 20 Mf per mosquito. A part of this was lost either because of the death of the mosquito before the matured larvae were formed, or because of the death of the larvae while they were being formed.]

In the mosquito, the Mf develop (through intermediate stages) into L3 larvae over a period of about 12 to 14 days. [The number of L3 larvae reported for Culex mosquitoes after 12 days in the experiments referred to above was about 6 to 7 per mosquito.]

When the mosquito subsequently bites another human after the L3 larvae have been developed, the larvae make their way into the human and move to the lymph nodes. In the course of this migration, some of them may be lost. The immature larvae mature into adult worms in about 90 to 180 days. The female and male adult worms mate and produce Mf, completing the cycle.

a. <u>The Single Vector + Parasite Model</u>

We first outline the model for the processes within a single vector (mosquito). The mosquito takes in blood from an infected primary host (human) , which leads to development of larvae within the vector, which in turn can be transmitted to another human host in a subsequent bite.

The model diagram is given in Fig. 1.

A mosquito biting a human host takes in a blood meal, which has a certain concentration of the microfilariae (Mf). In the mosquito, the Mf mature into larvae over a period of about 12 to 14 days.

The model solves for the larvae level in the mosquito, and the Mf level. It allows for death rates for the Mf and for the larvae, and for density dependence (i.e. crowding effects) during the development of the larvae within the mosquito.

The state variables in the model are the Mf level in the vector and the larvae level in the vector.

The rate (or flow) variables are the mf intake rate during the mosquito's blood meal, the larvae formation rate, and the corresponding outflow rates.

The relevant delay (or time lag) is that in the conversion of the mf into larvae.

The dynamical equations describing the system are the following:

(1a) d/dt [Mf level] = mf intake rate – [mf death rate + rate of mf-to-larvae conversion after a time lag]

(1b) d/dt [L3 Larvae level] = mf-to-larvae conversion rate – larvae death rate

The larvae death rate is modeled allowing for density-dependence (i.e. crowding effects).

The physical environment can affect the process, primarily through temperature. We allow for the effect of the temperature on both the larvae death rate and the larvae maturing period.

The number of microfilariae taken in during a blood meal is treated as a statistical variable, and the model is run with varying values between 5 and 13.

The mf death rate used in this model is an effective death rate, which includes the removal of parasites either because of the death of the parasites or because of the death of the infected mosquito. It is here given a value of 0.02 per day, which is consistent with the results reported by the Pondicherry group [(5)] (i.e. a reduction of 25% to 33% during the development from Mf to larvae).

The fraction of Mf which successfully convert to larvae is treated as a variable; this will depend on the processes within the mosquito. We do the model calculation for an assumed average value of 80% for this ratio.

For the larval death rate, reliable measurements are not available. We vary the larval lifetime between values that are 2 and 4 times the Mf-to-larva maturing period; the results are not sensitive to this variation.

So we do the model calculations for a larval lifetime equal to twice the Mf-to-larva maturing period.

All the calculations are done for a value of the Mf-to-larva maturing period equal to 14. The qualitative nature of the results are not sensitive to a variation of this between 12 and 14.

In Fig. 1a, we show the results obtained for the following two quantities:

-- the ratio of the Mf level in the vector (as a function of time) to the Mf intake rate from the human, and

-- the ratio of the larvae level in the vector (as a function of time) to the Mf intake rate from the human.

The Mf intake rate is the number of Mf taken in by the mosquito during the blood meal, treated as a stochastic variable, and has been varied in the range between 5 and 13. From the available data, the upper limit of 13 of this range appears to be close to the maximum number of larvae, which we also interpret as the carrying capacity of the vector for these larvae.

Note that the first ratio (Mf level in the vector / Mf Intake value) remains the same over the range of Mf Intake values.

However, the second ratio (larval level in the vector / Mf Intake value) depends on the Mf Intake value. The ratio is smaller for larger values of the Mf Intake rate. This is because of the larval crowding effect. When the larval crowding effect is removed from the model, this ratio also remains the same for different values of the Mf Intake rate.

The Pondicherry data [(5)] do show a dependence of the larval level in the vector which is consistent with the larval crowding effect in this model.

Effect of Climatic Conditions: The most important climatic factor affecting the processes in the mosquito seems to be the environmental temperature.

When the environmental temperature is significantly higher or lower than the favored range, which has been estimated to be about 24 deg C to 29 deg C for Anopheline mosquitoes,we expect the process of converting the ingested Mf to larvae to be affected.

This can affect the length of the larval developmental cycle, and in turn the mosquito feeding frequency. An indirect effect would be that if the environmental effects reduce the average mosquito lifetime to a value below the mf-to-larvae maturing period, this will also reduce the larval production.

In this model, we assume that the effect on the biological process for a single mosquito will be through the influence of the environmental temperature on the mf-to-larvae maturing time and on the larval death rate (either direct larval death or because of the death of the mosquito hosting the larvae).

We do not have definitive data for the temperature dependence of the parameters. However, this issue is important enough to warrant looking at plausible scenarios. A possible scenario for the qualitative influence of the temperature is shown in Fig. 1b.

It is important to find out more about the temperature dependence of the process in the mosquito, as it can influence the transmission rate of the disease. We shall return to this question when discussing the interaction of mosquito and human populations.

b. The Human Host + Parasite Model

We next describe the model for the parasite in the definitive (human) host. This is shown in Fig. 2.

To begin with, an infective mosquito, carrying the infective larvae, bites a human. The larvae in the mosquito enter the human and get to a lymph node. Over a period which may vary between 90 and 180 days, the larvae mature into adult worms. Some of them may die during this period. At the end of this maturing period, the adult male and female worms mate, and produce microfilariae (Mf) which are released into the blood stream.

The state variables in this model, as shown in Fig.2, are the Immature Worm (Larval) population level in the human host, the Adult Worm population level, and the Mf concentration level in the blood.

The rate (or flow) variables are the larvae intake rate, the adult worm formation rate, the mf formation rate, and the corresponding outflow rates.

The relevant delays (or time lags) are those in the maturing of the larvae into adult worms, and the time lag between adult worm formation and the Mf production by the female adult worms.

The dynamical equations for the system are the following:

(2a) d/dt [Larvae population] =
larvae intake rate – [larvae death rate + rate of larvae-to-adult worm conversion after a time lag]

(2b) d/dt [Adult worm population] = larvae-to-adult worm conversion rate – adult worm death rate,
where the adult worm death rate is modeled with density dependence.

(2c) d/dt [Mf concentration] = Mf production rate by adult worms (after a time lag) – Mf death rate

Values of the relevant biological parameters :

Larvae Intake rate: This intake is from the mosquito bite; we examine a range of 4 to 16.
Larvae-to-Adult worm maturing period: This varies between 90 and 180 days.
Larvae death rate in human host : Reliable measured values not available.
[We shall try values of 100 or larger.]
Adult worm death rate: The adult worm lifetime range is believed to be about 5 to 10 years.
Mf formation delay : About 90 days
Body Blood Volume: about 5 to 6 liters
Mf production rate per (female) adult worm per day: About 20,000

Using these values, we run the model and calculate the Mf concentration in the human as a function of time.

The larvae-to-adult worm maturing period is an important parameter; we treat it as a stochastic variable, and find the values and spread of the results as it is varied between 90 and 180 days.

The results, obtained for three values (4, 10 and 16) of the bite efficiency (= the number of larvae transmitted into the human during a mosquito bite) are shown in Fig. 2a.

The three curves for each bite value are for values of 90, 135 and 180 days for the larvae-to-adult worm maturing period.

Note that the Mf concentration in the human spans the range of values seen in the Pondicherry data. There is an overall correspondence between the results of the model formulated here and the experimental data. This gives at least qualitative validation of the biological assumptions made in our model.

c. Model for Human-to-human Disease Transmission through the Parasite

We next combine the models for the processes within a vector and within a human.

The basic model for human-to-human disease transmission through a parasite carried by a vector is the following:

A human is bitten by an infective mosquito, which transfers larvae to the human. Some of these (immature) larvae mature into adult worms (in 90 to 180 days); these adult worms mate and (after another 90 days) release Mf into the bloodstream of the human.

At a later time, another mosquito has a blood meal on this infected human, and takes in a few Mf, which develop into larvae within the mosquito (in about 14 days). The mosquito is now infective; when it subsequently bites a second human, it transfers larvae into the human, which ultimately lead to Mf production and release into the bloodstream of this second human.

This leads to vector-mediated transmission of the infection from the first infected human to a second one.

The model diagram for this is given in Figure 3, where only the essentials are shown, to avoid making the diagram too crowded.

This model has been run for selected values of the relevant parameters, and results obtained for the number of parasites in the first and second human, as a function of time. Some of these results are shown in Fig. 3b.

The model as shown in Fig. 3 indicates possible "Control Points" in the transmission process, which would be suitable for intervention measures. These are shown in Bold Italics in the diagram.

We shall focus on the vector-human contact factors shown in three places in the diagram, and the Mf Concentration in the Human Host in the first human and the second human, and see how they can be used as a starting point for planning control strategies. .

The contact factors incorporated here are a simplified way of taking into account the probability of contact between the mosquito and the human. When nothing is done to control such contacts, the factors have the value equal to 1. A control strategy depending on these contact factors would, for instance, include the use of mosquito nets (treated and untreated), repellents, reducing the resting places for the mosquitoes, and other such measures.

When such a control strategy is adopted for reducing the frequency and effects of the mosquito-human contact, the contact factor would be assigned a value of between 0 and 1.

Controlling the Mf Concentration in the Human would be done by the use of chemical agents (medications) administered to the human, which destroy part of the Mf in the blood stream.

To see how such measures would affect the transmission of the infection from one human to another, we here obtain results for examples in which

(a) the contact factors are influenced after the first human has been infected, and/or before a contact is made with the second human; and/or
(b) The Mf concentrations in one or both humans are reduced by the use of medications.

[In these examples, the first human may be interpreted as representative of the introduction of infection into a population, and the second human as representative of the rest of the susceptible population.]

As a measure of the transmission, we look at the comparative values of the Mf concentration in the second human and the Mf concentration in the first human, as these are the quantities normally measured. We also show the adult worm level in the second human, as these would be the source of Mf in the future.

We present in Fig. 4 the calculated results for eight strategies.

Fig. 4a shows the Mf concentration in the two humans for the base case of No Intervention.

Fig. 4b shows the Mf concentration in the two humans for the eight selected Intervention strategies:

NOTE: We have deliberately not shown the No-Intervention results in the same figure as the results with Interventions, as the different scales would mask the visibility of the results with intervention.

(a) *Intervention 1:* The first contact factor ("***human-vector contact factor*** " in the model diagram), which occurs immediately after the first human has been infected is reduced by a factor of 10. This may be interpreted as representative of the isolation of known infected humans.

(b) *Intervention 2*: The contact factor ("***infective-vector to human contact factor")*** at the point when the mosquito bites the second human in the model is reduced by a factor of 10. This may be interpreted as representative of using measures for the prevention of susceptible humans from being exposed to (infective) mosquitoes.

(c) *Intervention 12 (-- read as 1 + 2):* -- A combination of Intervention1 and Intervention 2, where the measures in Interventions 1 and 2 are both implemented. This may be interpreted as representative of simultaneously isolating known infected humans and using measures for preventing susceptible humans from being exposed to (infective) mosquitoes.

(d) *Intervention 4:* The Mf concentration in the first human is reduced by administering medication at a level that kills a fraction (5% or 10%) of the Mf per day. We have obtained results for both values of the fraction of Mf destroyed. This may be interpreted as representative of the treatment with medication of known infected humans who have a relatively high level of infection, using different strengths of medication.

(e) *Intervention 5:* A combination of Intervention 1 and Intervention 4, where the measures in Interventions 1 and 4 are both implemented. This may be interpreted as representative of simultaneously isolating known infected humans (who have a relatively high level of infection) and reducing the Mf concentration in their blood by administering medication at a level that kills a fraction (taken as 5%) of the Mf per day.

(f) *Intervention 6:* A combination of Intervention 2 and the analog of Intervention 4 for the second human, where the measures in Intervention 2 and a measure analogous to Intervention 4 for the second human are both implemented. This may be interpreted as representative of simultaneously preventing humans from being exposed to (infective) mosquitoes, and treating all infected ones among them by administering medication at a level that kills a fraction (5%) of the Mf per day.

(g) *Intervention 7:* The Mf concentration in both the first and the second human are reduced by administering medication at a level that kills a fraction (5%) of the Mf per day. . This may be interpreted as representative of the treatment with medication of all infected humans.

(h) *Intervention 8:* A Combination of Intervention 12 and Intervention 4.

This may be interpreted as representative of using measures for the prevention of all humans from being exposed to mosquitoes, and at the same time, treating known infected humans who have a relatively high level of infection. by administering medication at a level that kills a fraction (5%) of the Mf per day. .

Results:

The relative effectiveness of the eight strategies, as shown in Fig. 4b, have been found to be in the following order (the most effective being the first):

Intervention 8
Intervention 7
Intervention 6
Intervention 5
Intervention 12
Intervention 4 with 10% reduction of Mf concentration per day
Intervention 4 with 5% reduction of Mf concentration per day
Intervention 2
Intervention 1

The most effective Intervention strategy among the ones considered here is Intervention 8, in which measures are taken to prevent exposure of the population from mosquitoes and simultaneously treat known infected humans.

The results for the effectiveness of the Intervention strategies 7, 6, 5, and 12 given above are very close to one another, and not much less than the best Intervention strategy 8. Other criteria (including economic and sociological ones) would be needed to select a strategy among them.

Note that the most effective Intervention strategy. found here is in accord with the approach taken in the integrated malaria control programs in many countries, of combining preventive measures with chemical treatment. The cost and social acceptability of the measures are the main factors to be considered.

3. Model for Interacting populations of Humans and Vectors.

In the previous section, we have discussed a model which expresses the biology of the processes within a vector-and-parasite system, a human-and-parasite system, and a human-parasite-vector system.

In the present section, we discuss a model at a different level – a model for a population of vectors interacting with a population of humans. The influence of the infection is taken into account by looking at transitions among states of the human and states of the vector.

We use compartment models for both the vector and the host.
We assume that the vector can be described as being in one of three states – **Susceptible, Exposed or Infected**. Similarly, we assume that the human host can be described as being in one of four states – **Susceptible, Exposed, Infected or Recovered.**

The dynamical equations for the system are the folloing:

a. For the Human Population:

Notation: S -- Susceptible Population; E – Exposed Population (not yet infective)
I – Infected (and Infective) Population R – Recovered Population

(3a) d/dt [S] =
(Population Birth + Immigration) Rate + Conversion rate of Recovered Population to Susceptibles
– Exposure rate of Susceptibles – Death rate of Susceptibles

(3b) d/dt [E] =
Exposure rate of Susceptibles – Conversion Rate of Exposed Population to Infected Population
– Death rate of Exposed Population

(3c) d/dt [I] =
Conversion Rate of Exposed Population to Infected Population – Recovery Rate of Infected Population -
– Death rate of Infected Population

(3d) d/dt [R] =
Recovery Rate of Infected Population – Conversion rate of Recovered Population to Susceptibles
– Death rate of Recovered Population

b. For the Vector Population:

Notation: S_v -- Susceptible Population; E_v – Exposed Population (not yet infecttive)
I_v – Infected (and Infective) Population

(3a) d/dt [S_v] =
Vector Birth Rate – Exposure rate of Susceptible Vectors – Death rate of Susceptible Vectors

(3b) d/dt [E_v] =
Exposure rate of Susceptible Vectors – Conversion Rate of Exposed Vectors to Infected Vectors
– Death rate of Exposed Vectors

(3c) d/dt [I_v] =
Conversion Rate of Exposed Vectors to Infected Vectors – Death rate of Infected Vectors

In obtaining the set of results given in this paper, we omit the birth and death rates, for simplicity, as we shall focus on other features of the phenomena we are looking at.

Fig. 5 shows the model diagram for the processes occurring in the interacting vector and host populations.

Because of the computational complexities caused by large time lags within such a system, we are evaluating the results in two stages.

In this first paper, we shall give the results for the interacting system with small time lags. This will take into account the time lags in the (vector + parasite) system and allow for small time lags in the (human + parasite) system.

In work in progress, we are obtaining results for the interacting system allowing for large time lags. This will take into account the processes occurring in Filaria, where the worm maturing gives rise to a time lag of 90 to 180 days.

The results for the first part are given in the graphs in Figures 5a, 5b and 5c. These give the variation in time of the number of humans or the number of hosts in each state. For us, the results of most interest are the ones which show the number of humans or hosts in the infected state. The results shown here are for a total human (host) population of 1000, and a total starting vector population of 100.

We group the results according to the values of the infection transmission parameter (arising from the vector biting the host) and the recovery parameter (expressing the transition from an infected state of the human to a state free of infection), which can represent, for instance, the recovery induced by treatment with medication..

Fig. 5a gives sample results for a zero value of the recovery parameter. It shows how the number of hosts in the susceptible or exposed or infected state varies with time, for six progressively increasing values of the infection transmission parameter (in proportion to 1, 2, 4, 8, 16 and the saturation value). We point out below the the qualitative trend of the results.

We find that for a range of values of the infection transmission parameter, the number of humans in the infected state first rises and then levels off to an “endemic” steady-state value, less than the total population. As we keep increasing the infection transmission parameter, it reaches a saturation value where the whole population is infected; we can interpret this as an epidemicc.

Fig. 5b gives the results for the number of vectors in the susceptible, exposed or infected states as a function of time. These are of interest in connection with possible control strategies directed on the vector population.

Fig. 5c gives sample results where the recovery rate is varied as a parameter.

The results are shown for the variation with time of the number of hosts in the infected and recovered states, for a fixed value of the infection transmission parameter, here selected as the saturation value (for zero recovery rate), and values of the recovery rate in proportion to 0, 2, 4, 8 and 16.

In work in progress for interacting populations in a system with large time lags, which are relevant to filaria, we find threshold effects, which indicate bifurcation points as a function of the variables in the system. For instance, as the recovery rate is varied, there is a fairly sharp transition from an endemic behavior to one in which the infection dies down. The transition point depends on the population size and the values of the time delays in the system.

4. Effect of Control Strategies. Epidemiological and Public-health Questions

The model discussed in the last section for interacting human and vector populations offers a number of Control Points, which are suitable for trying out strategies for control.

In this Section, we examine the results of trying different Control Strategies.
The Control points are divided into three categories:

1) **Vector Human Contact Factors** (VHCF) – we show two of these – VHCF1 and VHCF2, which control the vector-human contact by multiplicative factors.

2) **Vector Control Measures** (VCM) -- we show three of these – VCM-1, VCM-2, and VCM-3 – these represent control of the vector population by controlling their overall level and/or their births and deaths.

3) **Drug Treatment Measures** (DTM) – we show three of these – DTM-1, DTM-2, DTM-3 – these represent control of the parasite level in the human host by reducing the parasite level. DTM-1 and DTM-2 can be interpreted as influencing the Mf level, and DTM-3 as influencing the adult worm level.

In Figure 6, we show the qualitative effects of the different Control Strategies. As the numbers shown here are not "calibrated", they should be interpreted as qualitative and showing trends rather than giving numerical results.

The baseline curve corresponds to no Control Measure; it has beeen selected to represent a high level of infection in the population , where there is an endemic level of about 92% infection in a population of 1000 humans.

We also show in Fig. 6 the results for the population of infected vectors.

The results shown in Figure 6 for the Infection level in the host indicate the following qualitative trends:

a) The Vector-Human Contact control and the Vector Control measures overall have the effect of reducing the endemic level of the infection, rather than bringing the infection down to zero.
Reducing the biting of suscepitble humans by infected mosquitoes is very effective in reducing the endemic level of infection in a population.

b) Given any substantial level of infection, drug treatment measures seem to be required for reducing the infection level to zero (i.e. very low values).
c) A combination of the two types of measures can be very effective.
In an example run here, the combination of VHCF2 (reducing the biting of susceptible humans by infected mosquitos) and DTM2 (interpreted as using drug treatment to reduce the Mf level) seems to have the ability to bring down the infection level in the way required by an eradication program. As observed earlier, this is in accord with the approach taken in eradication programs for such diseases in some countries.

We stress that these results should be interpreted as indicating the qualitative trends to be expected, and not as actual numeric values. We suggest that these qualitative results will be useful for decision-making at an epidemiologocal and public-health level.

In regions in which infection control programs are being planned, it should be possible to attempt a qualitative verification of such results for the expected trends.

5. Summary and Conclusions

In this paper (which presents part of work in progress) , we have outlined a model (as a set of sub-models) for the transmission and spread of infectious diseases in a host, mediated by a vector and a parasite. This model is applicable to a variety of diseases, which we are looking at; in the present paper, we are discussing it with special reference to Lymphatic Filariasis (popularly known as filaria), where the host is a human and the vector is a mosquito.

We have discussed the models for
(a) the biology of a single vector with a parasite;
(b) the biology of a single (human) host with a parasite.
(c) The biology of the transmission of infection from one host to another through an intermediate vector;
(d) The transmission and spread of infection in a system with interacting vector and host populations.

Each model has been described by a set of simplified differential equations. The methods of System Dynamics provide a convenient framework for formulating these equations and finding solutions.

Biological systems have many inherent complexities, which have to be dealt with in obtaining results for disease modeling, such as in the present work. Firstly, most of the parameters for describing the infection can at best be measured only approximately; generally they are known only as being within a range of values. Secondly, there can be a substantial variation in the quantities describing the infection or disease – depending on geographical region, population segment, and several other factors. Also, some of the parameters are essentially stochastic.

Although the model given here starts with deterministic equations, we take into account the statistical spread of the parameters in the calculational scheme. This is shown in some of the results presented here.

Another complication in the biological systems we are dealing with is the occurrence of large time lags, which can considerably complicate the solution process. We are looking into better ways of handling this in the work in progress.

Modeling of diseases brings together different questions – in particular, the biological, clinical, epidemiological, and public-health issues. The framework we are using here allows us to do this in a manageable way, as we have demonstrated.

The results we have presented here may be summarized as follows:

1) The results of the models for the biology of a (vector + parasite) have magnitudes and trends of variation In accord with what is known from available measured data.

2) Similarly for the results of the models for the biology of a (human + parasite), and for the model for the human-to-human infection transmission by an intermediate vector.

3) For each model we have looked at, we have identified some control points, at which an intervention can be made. For the human-to-human infection transmission model, and for a system with interacting vector and human populations, we have examined how the prevalence of the infection can be influenced by particular control strategies, and presented the results graphically.

We stress that these are meant to show qualitative trends, and not numerical values.

We believe that the qualitative trends shown here are correct, and that such results are useful inputs for decision-making in epidemiological and public-health issues.

We have also indicated how we can take into account the effects of environmental factors, especially climate-related ones, and are looking into this in more detail. This is an important question, esp. in the context of possible global climatic changes. Availability of relevant data on climatic dependence of the parameters will enable one to do this semi-quantitatively.

As we have mentioned, this paper is part of a program of work in progress, which includes comparing the results for different diseases, and other extensions of what has been reported here.

REFERENCES

The available references to the topics discussed or referred to in this paper are numerous. Here, we give a few selected references to papers in journals and to books; these in turn give a large number of references to relevant work.

1. R.M. Anderson and R.M. May (1991): *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press.

2. For an overview of filaria, one may refer to : T.R. Klei and T.V. Rajan (ed.)(2002) : *The Filaria,* Kluwer Academic Publishers.

3. M.S. Chan et al : *Am.J. Trop. Med. Hyg.* (1998) **59**, 606

4. A.P. Plaisier et al: *Methods Inf Med* (1998) **37**, 97.

5.. S. Subramanian et al : (1998) *Parasitology* **116**, 243.

6. P.K.Das and S. Subramanian: *Ann. Trop. Med. Parasitol*. (2002) **96**, S 153.

7. W.A. Stolk et al: *Parasitology* (2004) **128**, 467.

8. E. Michael et al : *Trends Parasitol.* (2006) **20**, 537.

9. For an introduction to System Dynamics methods, a useful reference is John Sterman's book –
John Sterman (1996): *Business Dynamics* .
This contains several relevant references to other work.

APPENDIX A – Model Diagrams and Figures showing Typical Results

Figure 1 Model for Single Vector + Parasite

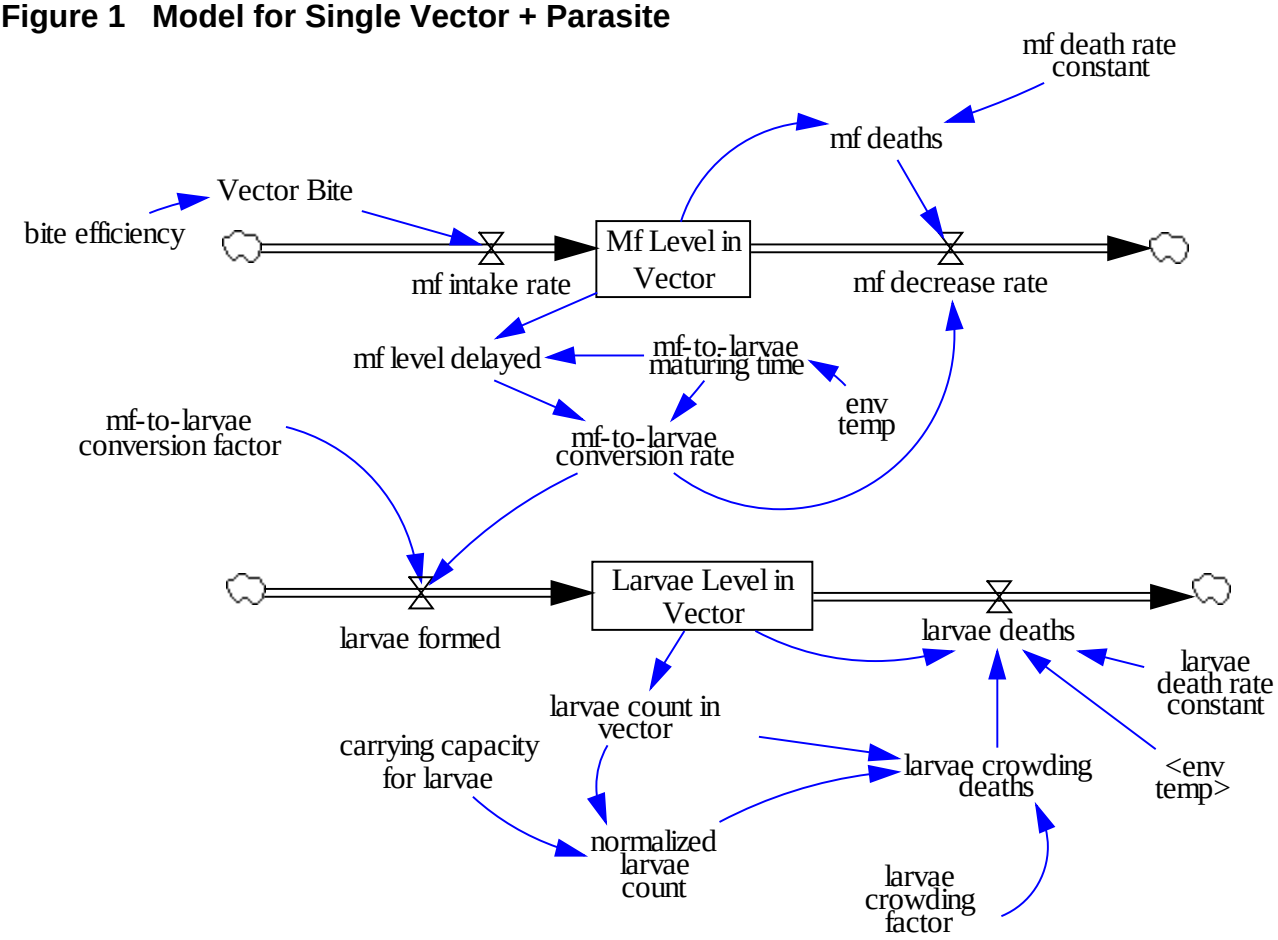

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Figure 1b. Example of Evaluation of Enviromental Effects on the Larvae Level

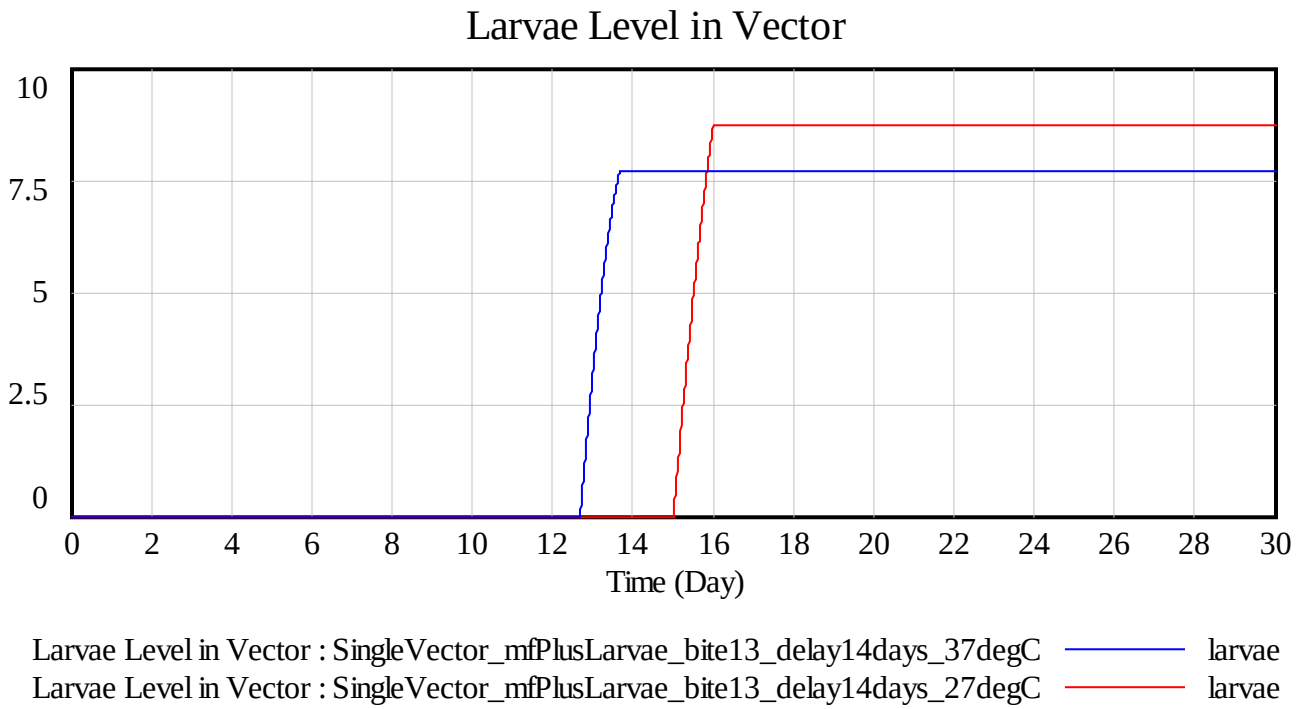
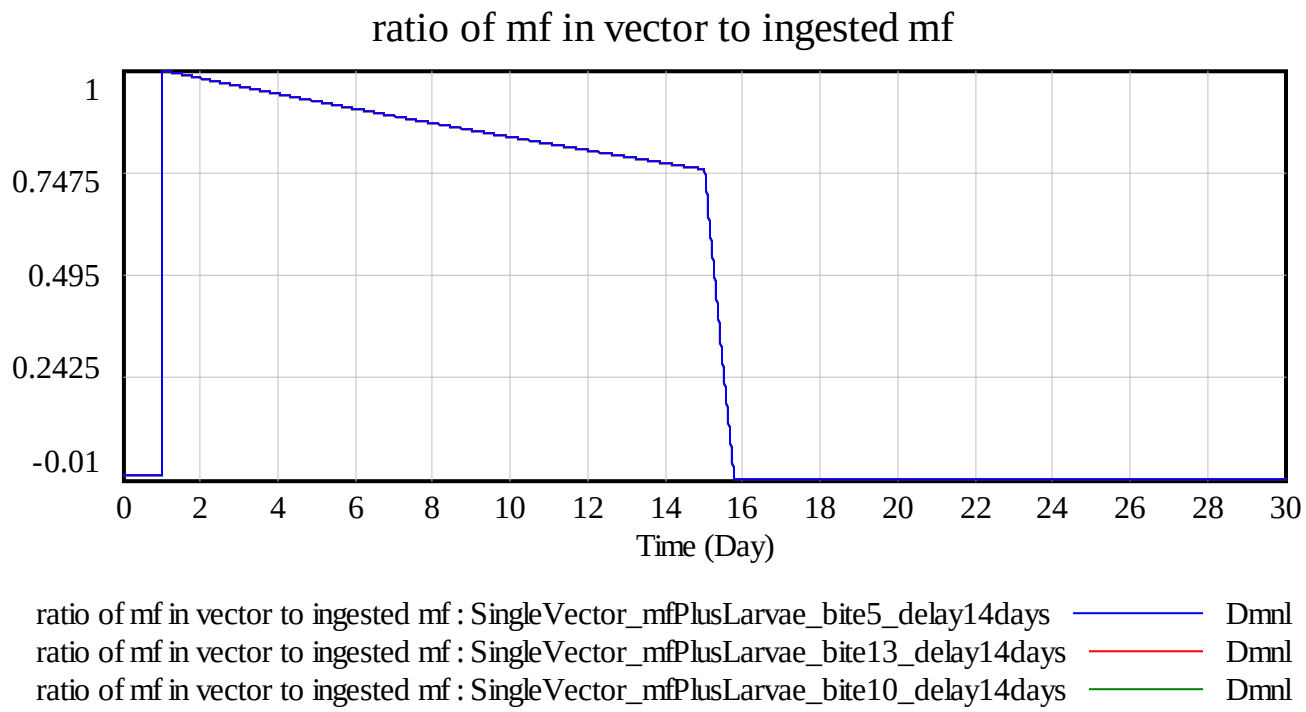


Figure 1a . Ratio of Mf level and Larval level in the Vector to the ingested Mf level



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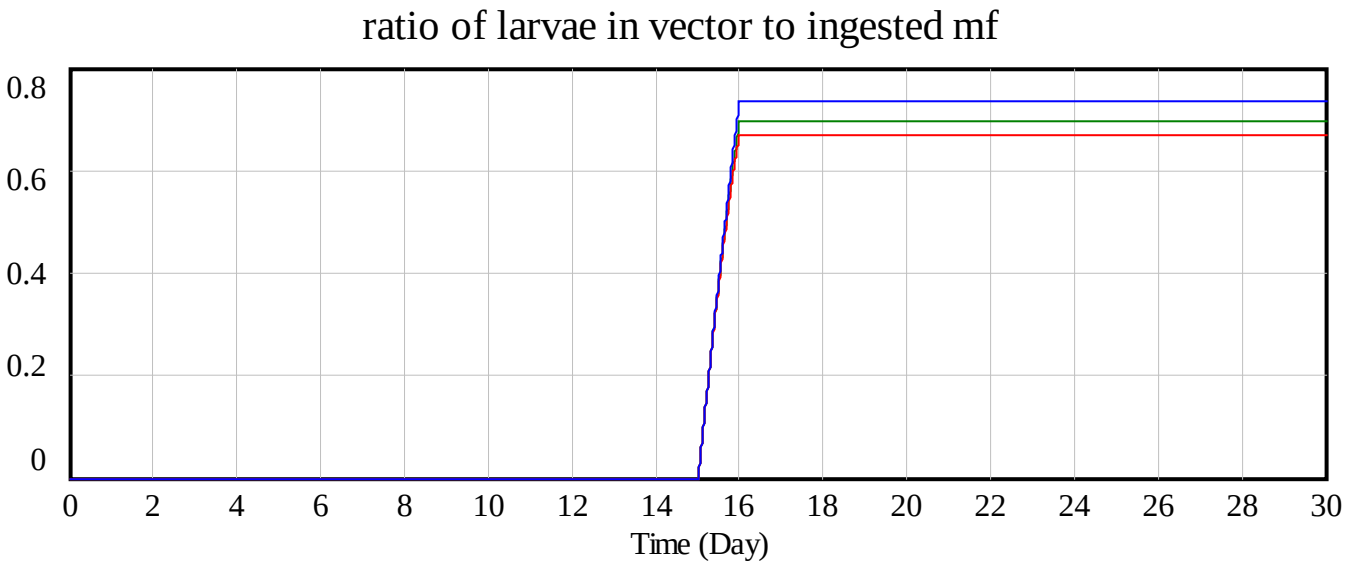
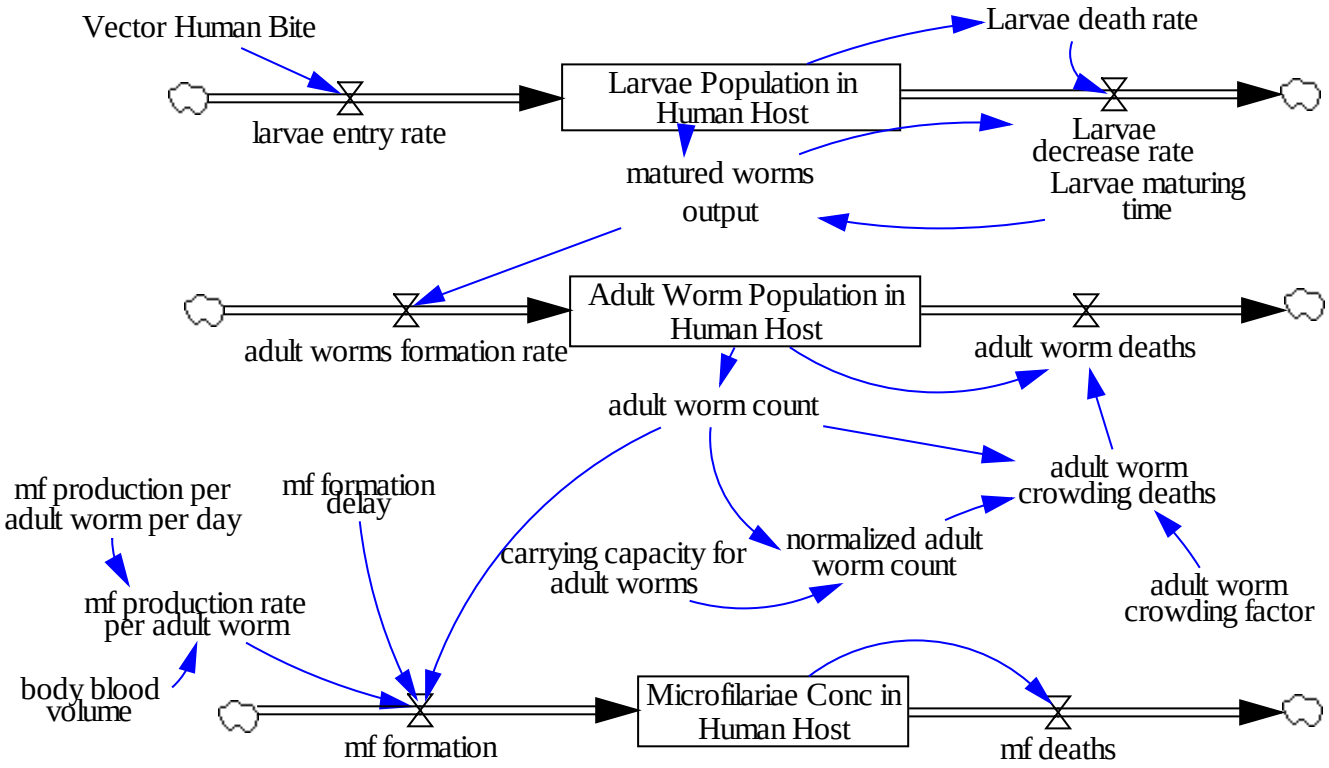


Figure 2. Model for Parasite process in the Host



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Fig, 2a Effect of Variations in the Larvae Entry Rate and the Larvae maturing period on the Mf Concentration in the Human.

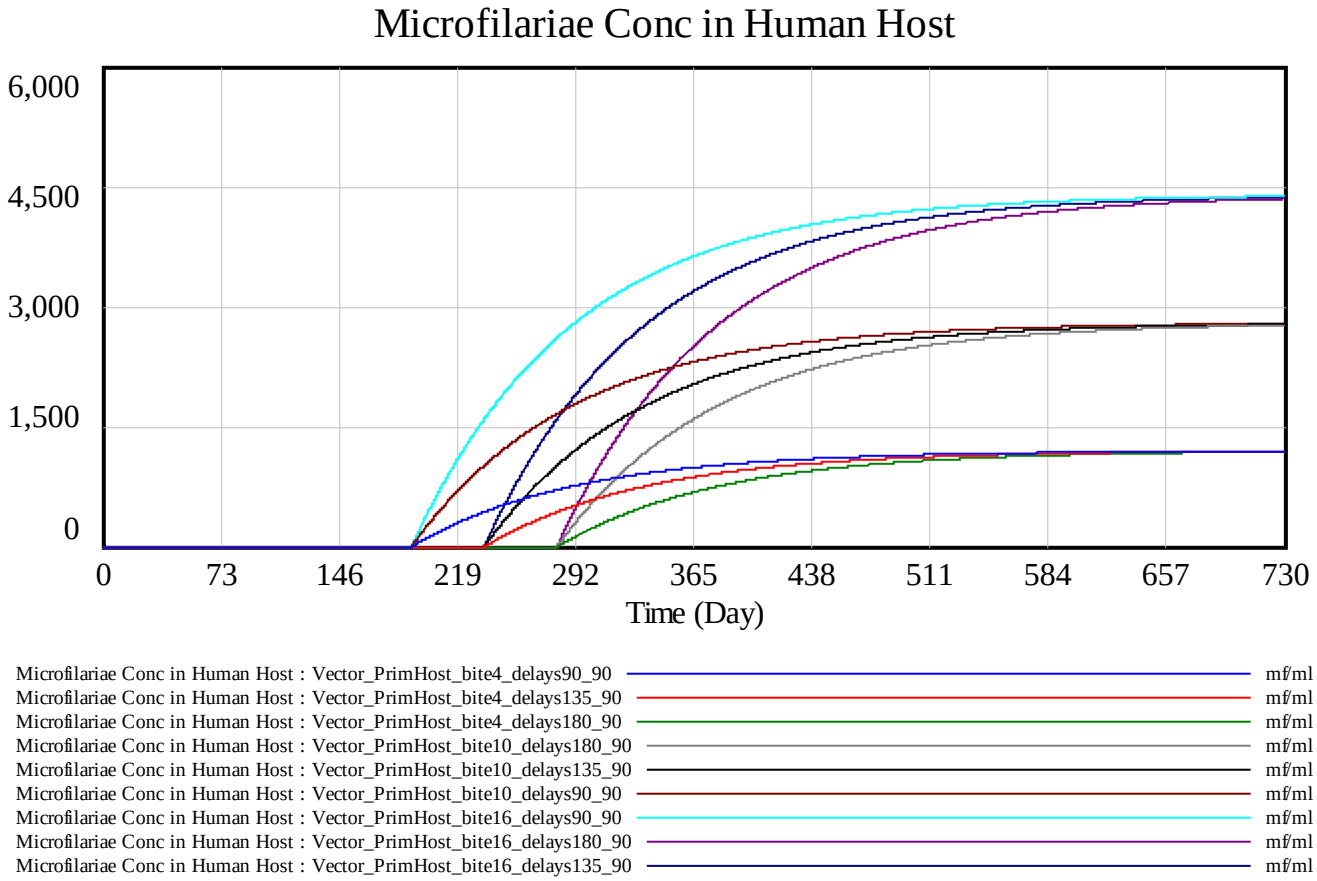


Figure 3. Model Diagram for Human-to-Human Infection Transmission through a vector and parasite

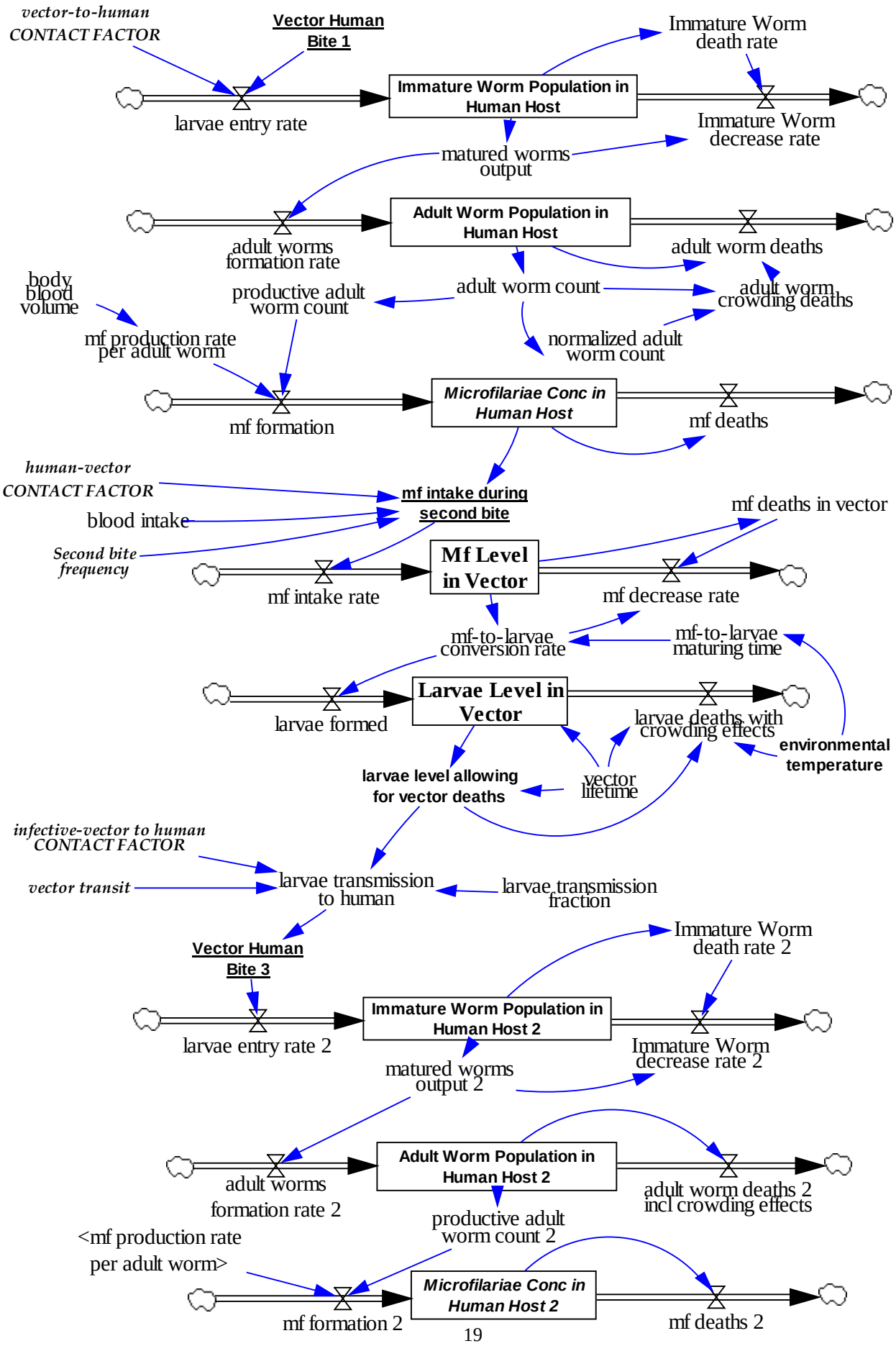
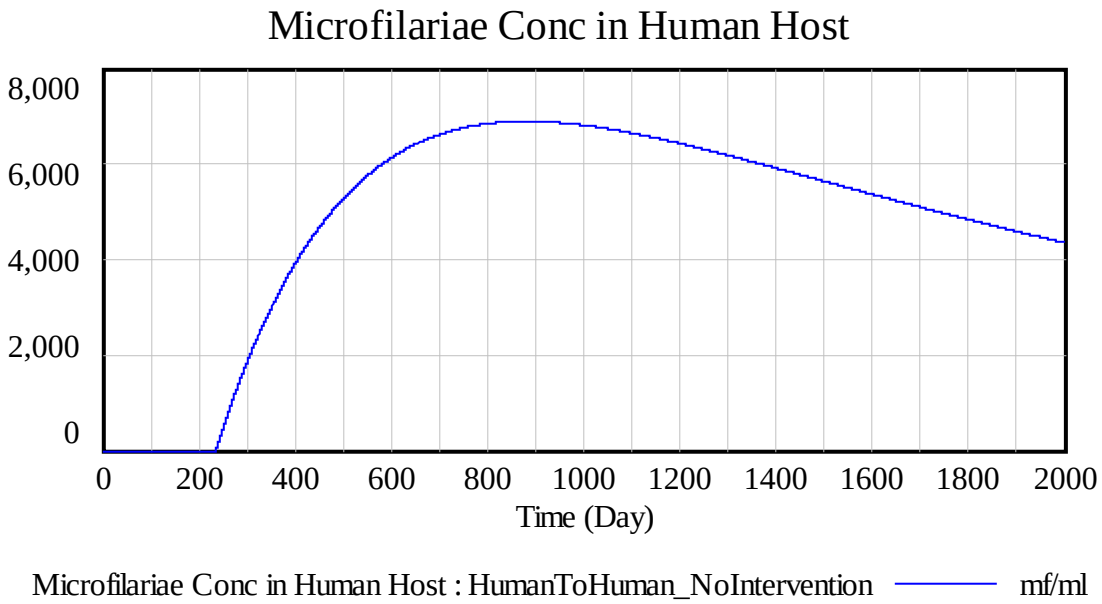


Fig. 4a Mf Concentration with No Intervention



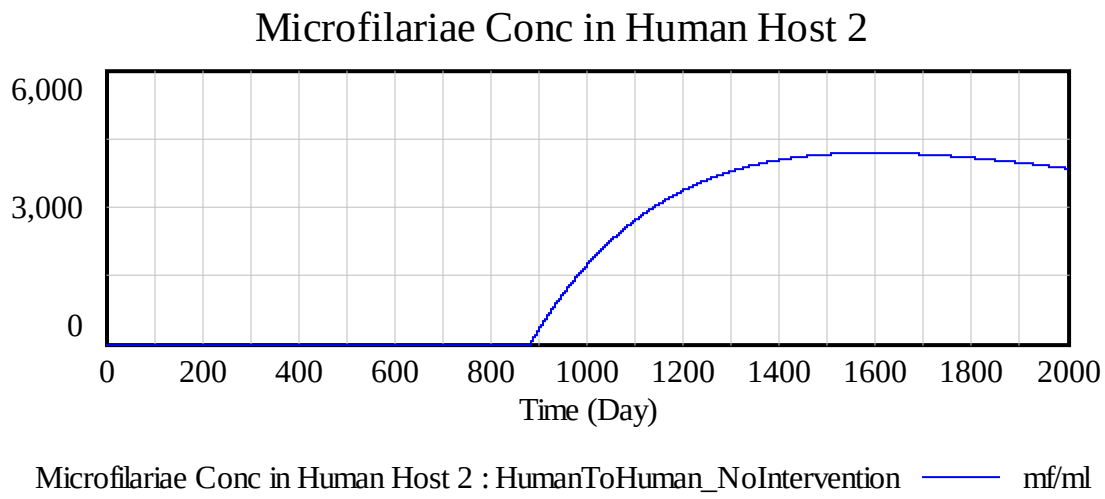
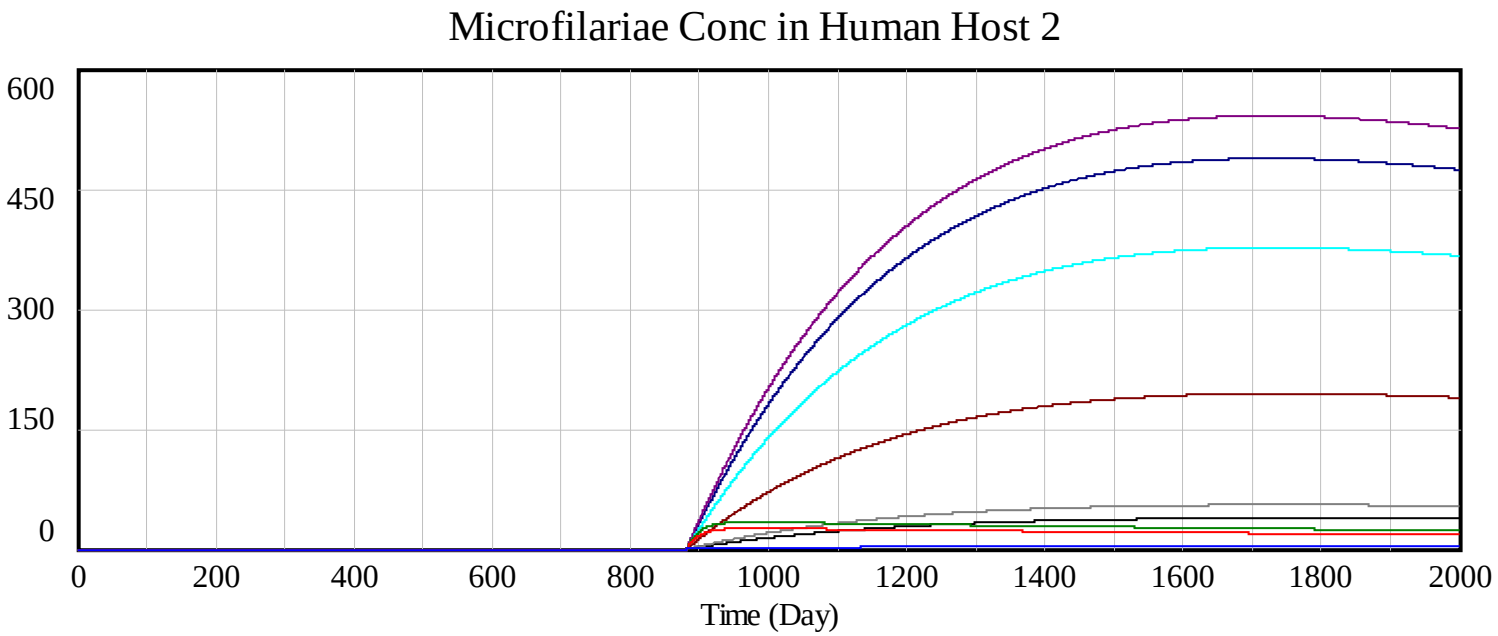
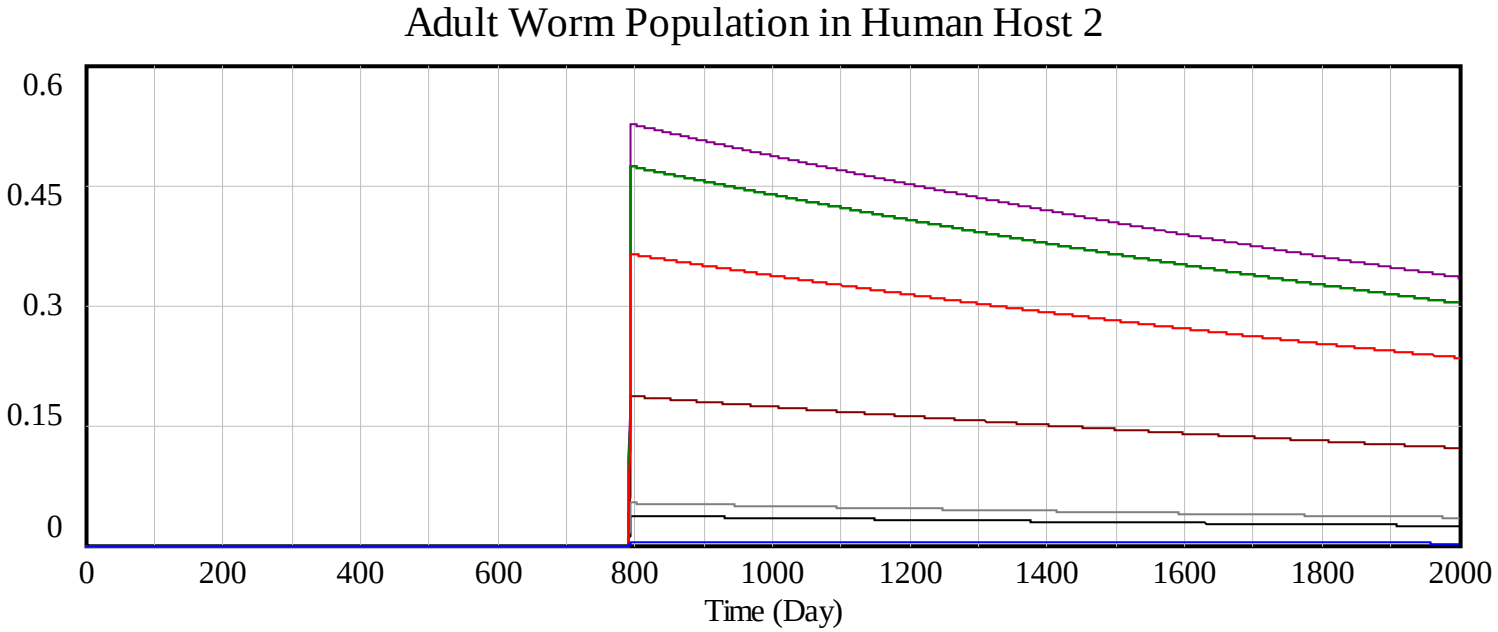


Fig. 4b Parasite Concentrations in Second Host after different Intervention Strategies



Microfilariae Conc in Human Host 2 : HumanToHuman_Intrv8_Mf1Death5%_Cont1_10%_Cont2_10% mf/ml
Microfilariae Conc in Human Host 2 : HumanToHuman_Intrv7_Mf1Death_5%_Mf2Death_5% mf/ml
Microfilariae Conc in Human Host 2 : HumanToHuman_Intrv6_Mf2Death_5%_Contfac2_10% mf/ml
Microfilariae Conc in Human Host 2 : HumanToHuman_Intrv12_Cont1_10%_Cont2_10% mf/ml
Microfilariae Conc in Human Host 2 : HumanToHuman_Intrv5_Mf1Death_5%_Contfac1_10% mf/ml
Microfilariae Conc in Human Host 2 : HumanToHuman_Intrv4_Mf1Death_10% mf/ml
Microfilariae Conc in Human Host 2 : HumanToHuman_Intrv4_Mf1Death_5% mf/ml
Microfilariae Conc in Human Host 2 : HumanToHuman_Interv1_ContactFact1_10% mf/ml
Microfilariae Conc in Human Host 2 : HumanToHuman_Interv2_ContactFact2_10% mf/ml



Adult Worm Population in Human Host 2 : HumanToHuman_Intrv8_Mf1Death5%_Cont1_10%_Cont2_10% adult Worms
Adult Worm Population in Human Host 2 : HumanToHuman_Intrv7_Mf1Death_5%_Mf2Death_5% adult Worms
Adult Worm Population in Human Host 2 : HumanToHuman_Intrv6_Mf2Death_5%_Contfac2_10% adult Worms
Adult Worm Population in Human Host 2 : HumanToHuman_Intrv12_Cont1_10%_Cont2_10% adult Worms
Adult Worm Population in Human Host 2 : HumanToHuman_Intrv5_Mf1Death_5%_Contfac1_10% adult Worms
Adult Worm Population in Human Host 2 : HumanToHuman_Intrv4_Mf1Death_10% adult Worms
Adult Worm Population in Human Host 2 : HumanToHuman_Intrv4_Mf1Death_5% adult Worms
Adult Worm Population in Human Host 2 : HumanToHuman_Interv1_ContactFact1_10% adult Worms
Adult Worm Population in Human Host 2 : HumanToHuman_Interv2_ContactFact2_10% adult Worms

Figure 5. Interacting Human & Vector Populations -- Model Diagram

[In this diagram, the vector population levels are on the left, and the human population levels on the right.

[Note that the interaction between the two populations occurs twice – first when the infectious vector bites a human (which is shown below explicitly), and second when a vector bites an infected human and takes a blood meal. The first is shown explicitly by the line connecting the "Infectious Vectors" level on the left to the input rate to the "Exposed Humans" level on the right, through the variable "human exposure rate". To avoid confusing criss-crossing lines, the second interaction is shown by using the shadow variable in the left of the diagram for the "infected humans" level (which belongs to the right). This interaction represents a connection from the "Infected Humans" level on the right to the input rate ("formation rate of exposed vectors") to the "Exposed Vectors" level on the left.]

Notation: **VCM-1,2,3** indicate Vector Control Measures, and **DTM – 1,2,3** indicate Drug Treatment Measures.

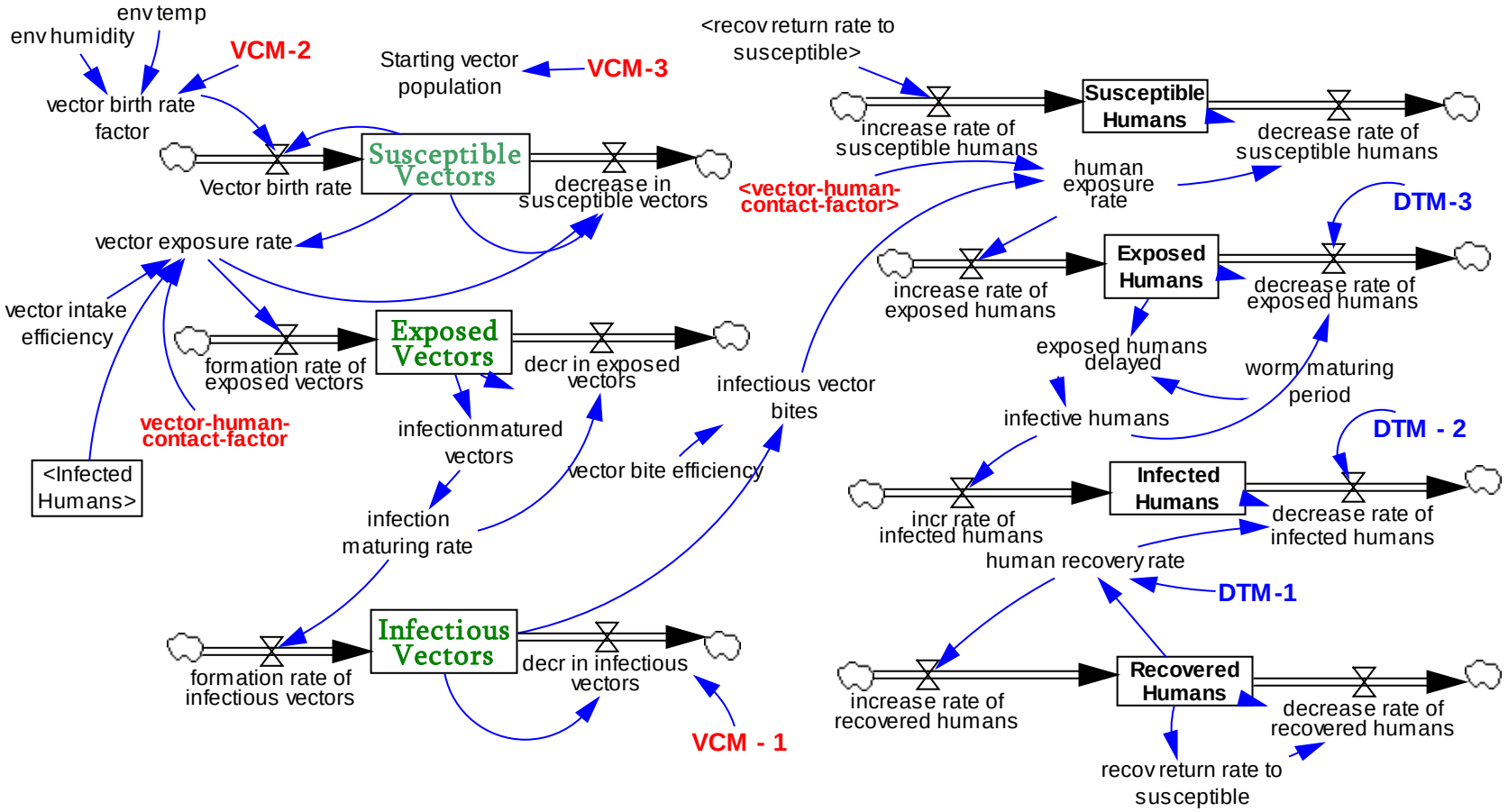
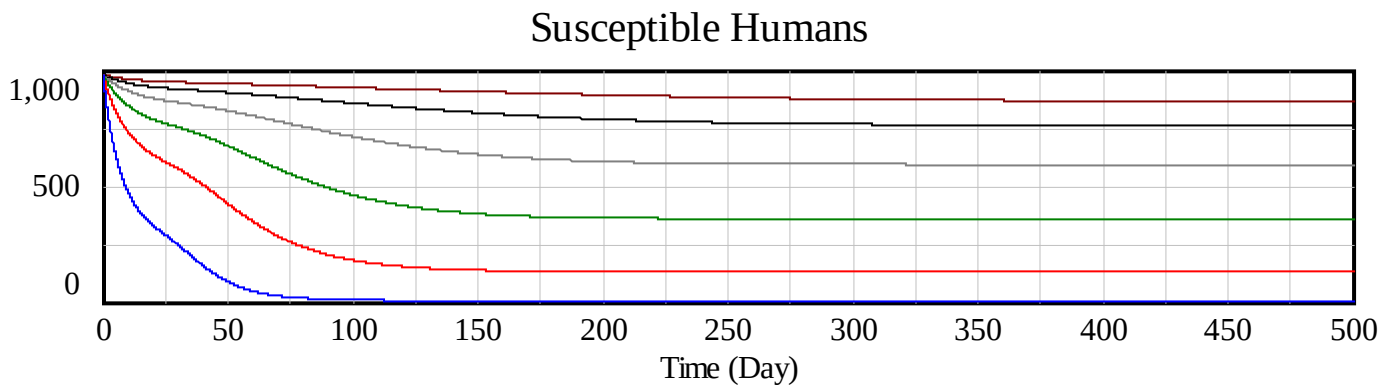
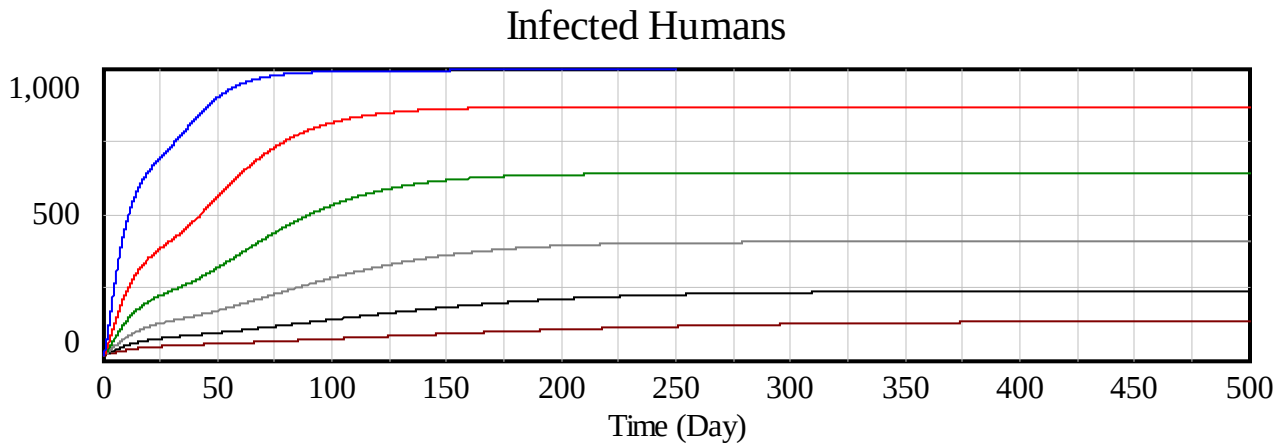


Figure 5a. Interacting Human & Vector Populations: Results for Zero Recovery from Infection



Susceptible Humans : CoupledHumanVectorPopulModel_popul_1000_Transm20 human
Susceptible Humans : CoupledHumanVectorPopulModel_popul_1000_Transm16 human
Susceptible Humans : CoupledHumanVectorPopulModel_popul_1000_Transm8 human
Susceptible Humans : CoupledHumanVectorPopulModel_popul_1000_Transm4 human
Susceptible Humans : CoupledHumanVectorPopulModel_popul_1000_Transm2 human
Susceptible Humans : CoupledHumanVectorPopulModel_popul_1000_Transm1 human



Infected Humans : CoupledHumanVectorPopulModel_popul_1000_Transm20 human
Infected Humans : CoupledHumanVectorPopulModel_popul_1000_Transm16 human
Infected Humans : CoupledHumanVectorPopulModel_popul_1000_Transm8 human
Infected Humans : CoupledHumanVectorPopulModel_popul_1000_Transm4 human
Infected Humans : CoupledHumanVectorPopulModel_popul_1000_Transm2 human
Infected Humans : CoupledHumanVectorPopulModel_popul_1000_Transm1 human

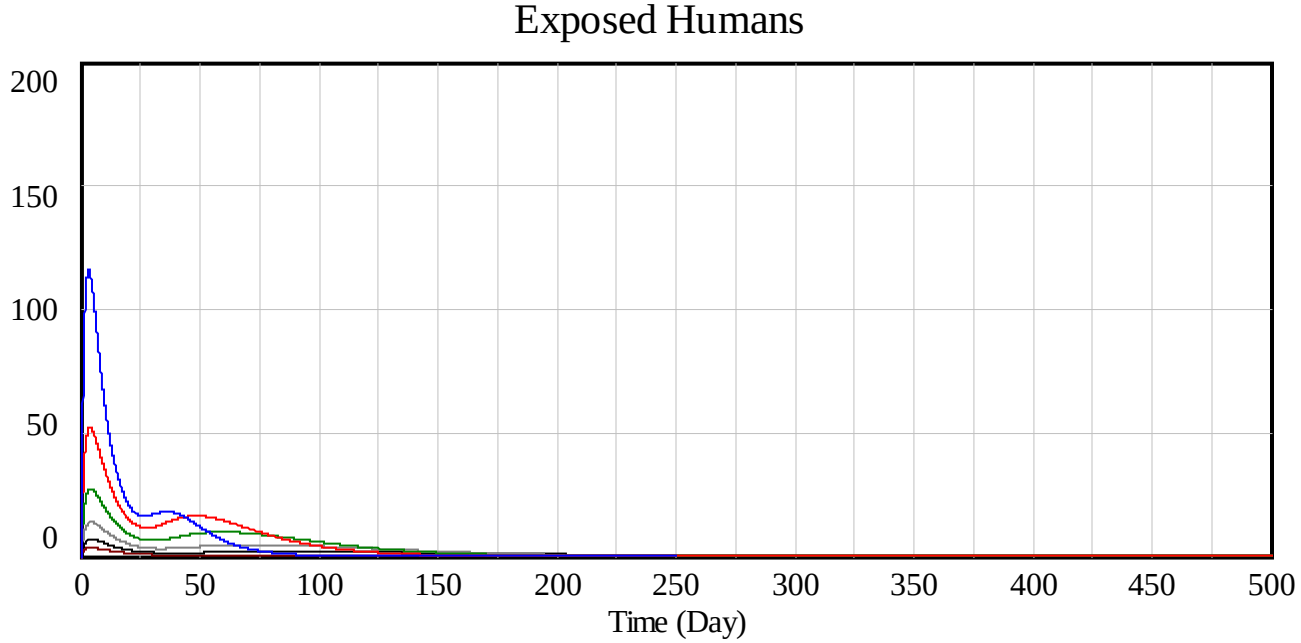


Figure 5b. **Interacting Human & Vector Populations: Results for the Vector – for Zero Recovery**

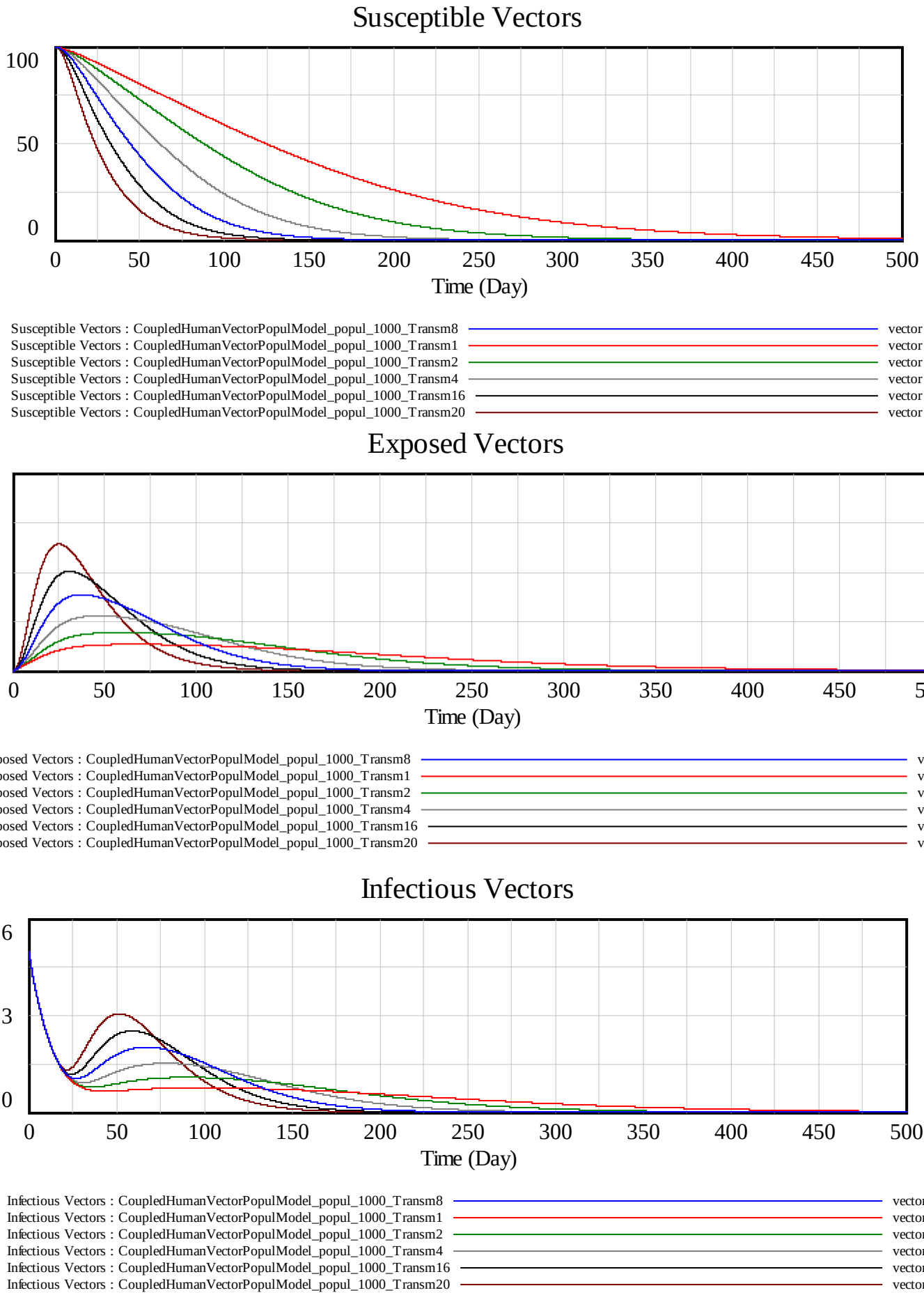


Figure 5c. Interacting Human & Vector Populations: Results including Recovery from Infection

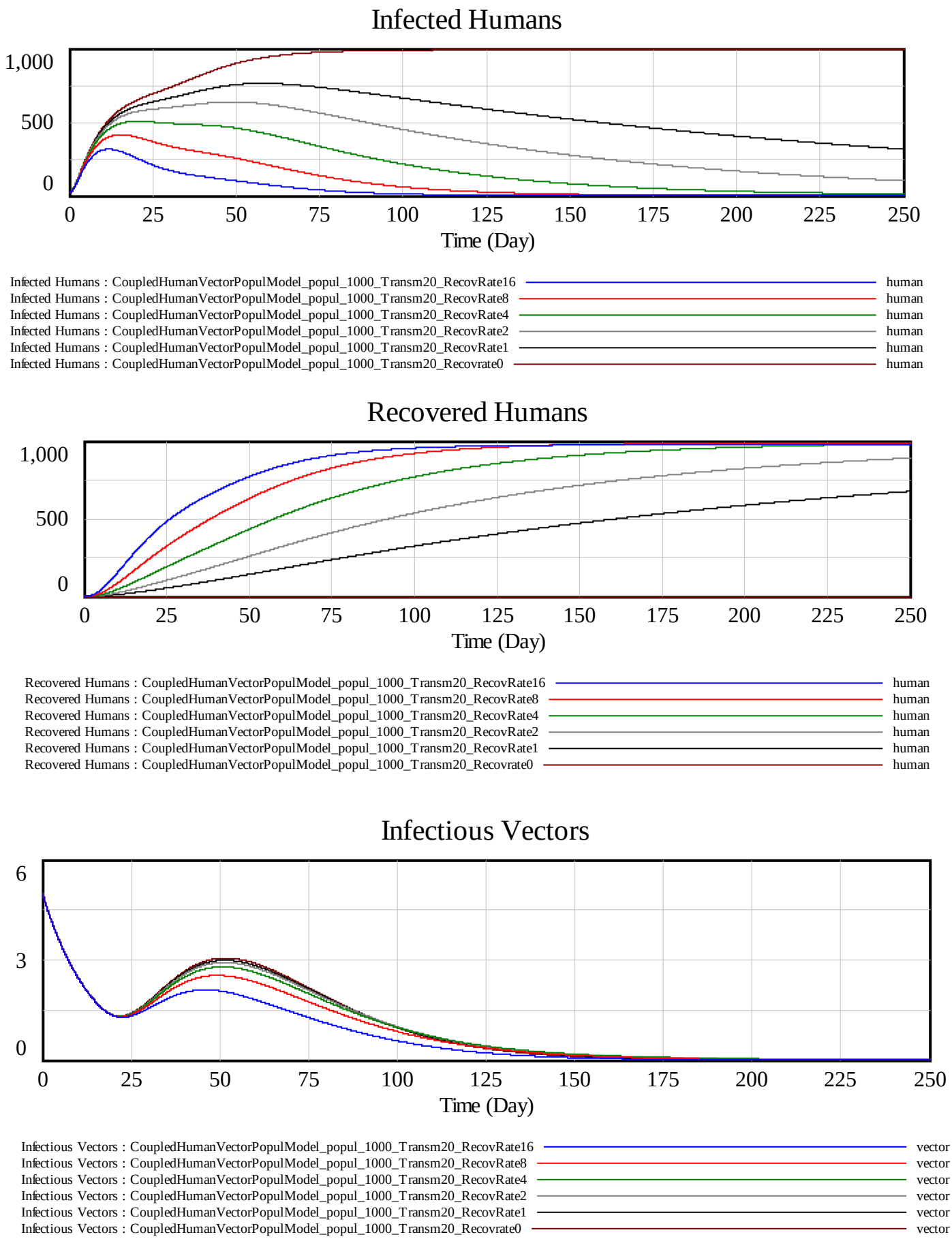


Figure 6. Qualitative Effects of Control Strategies for Reducing Infection in Populations