Infectious Disease Transmission as a Complex System Process

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Abstract

The development and transmission of infectious diseases involve complex systems at different levels, and bring together biological, epidemiological, clinical, and public health issues.

We here discuss vector-borne parasitic diseases, in particular, diseases which involve a primary host, a vector, and a parasite. Here the humans are the primary (or definitive) host and the mosquitoes are the vector; the same method applies to other instances of the vector and host. The results shown here are for Lymphatic Filariasis (LF).

We separate out the two primary subsystems – one involving the biology of the pathogen in a single vector, and the other involving the biology of the pathogen in a single (human) host. We first model each separate subsystem, and then the system made up of the two subsystems in interaction, which describes the transmission of infection between two humans through a vector.

We then discuss a model at a different level -- for the transmission of infection in a population of vectors interacting with a population of hosts. Besides disease-free and infective states, the model allows for exposed but non-infective states of the host and vector, and for recovered states for the host.

We further discuss the effect of different control strategies and the effects of environmental factors, and point out the complexities inherent in the biological processes. In ongoing work we examine additional questions such as the role of the immune system and the use of individual agent-based methods.

Section 1 Introduction

Disease modeling involves biological systems, which are prototypical complex systems. They typically have several interacting systems and subsystems, with intricate feedback processes, and time lag effects which complicate the phenomena occurring in them..

There are several diseases which involve one or more intermediate agents between the definitive host and the pathogen. A well-known category consists of 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). This model applies to different diseases. 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. In Section 2, we summarize the key features of Lymphatic Filariasis . In Section 3, 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. The calculations in this paper are simulations using VENSIM, a System Dynamics toolkit. [9]

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 4, 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 5, control points are identified for the system with interacting vector and host populations, which are suitable for implementing intervention strategies. Results are shown for different intervention strategies. We believe that the qualitative trends shown here can provide useful input for making. In Section 6, we summarize our conclusions.

The model diagrams and figures with selected results are shown in the Appendix .

Section 2 Lymphatic Filariasis (LF) in Humans -- a Simplified Description

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.

3. The Model(s)

3.1. The Single Vector + Parasite Model

We first outline the model for the processes within a single vector (mosquito).

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 adult larvae mate and produce Mf, which in turn can be transmitted to another human host in a subsequent bite.

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 variables in the model are the Mf level and the larvae level in the vector, the mf intake rate during the mosquito's blood meal, the larvae formation rate, and the corresponding outflow rates. There is a time lag in the conversion of the mf into larvae.

The dynamical equations are the following:

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

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

The larvae death rate is modeled allowing for density-dependence (because of 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.

Results have been obtained for the ratio of the Mf level in the vector to the Mf intake rate from the human, and for the ratio of the larvae level in the vector to the Mf intake rate from the human.

The Mf intake rate 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.

Because of space limitations, we give just a verbal description of the results.

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; so we have looked at plausible scenarios. 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.

3.2. The Human Host + Parasite Model

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

To begin with, an infective mosquito bites a human. The larvae in the mosquito enter the human and get to a lymph node. Over a period varying between 90 and 180 days, the larvae mature into adult worms, some of whom 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 variables in this model are the Immature Worm (Larval) population level in the human host, the Adult Worm population level, the Mf concentration level in the blood, the larvae intake rate, the adult worm formation rate, the mf formation rate, and the corresponding outflow rates. The relevant delays are the time for the larvae to mature into adult worms, and the time lag between adult worm formation and the Mf production.

The dynamical equations are the following:

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

(2b) d/dt [Adult worm popul] = 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] = delayed Mf production rate by adult worms – 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 : We try values of 100 or larger; reliable measured values are not available.
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

The blood Mf concentration in the human is calculated as a function of time. We treat the larvae-to-adult worm maturing period as a stochastic variable, and find the spread of the results as this period 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 assumptions made in our model.

3.3. 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 to give the model for human-to-human disease transmission through a vector-borne parasite.

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 about 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, now infective, subsequently bites a second human, and transfers larvae into the human, which ultimately lead to Mf production and release into the bloodstream of this second human.

The essentials of the model diagram for this is given in Figure 3. This model has been simulated 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.

The model suggests possible “Control Points” in the transmission process, which would be suitable for intervention measures. We shall focus on the vector-human contact factors shown in the diagram, and the Mf Concentrations in the Human Host in the first and the second human, and see how they can be used as a starting point for planning control strategies. .

The vector-human contact factors incorporated here are a simplified way of taking into account the probability of contact between the mosquito and the human. A control strategy depending on these contact factors would, for instance, include the use of (treated and untreated) mosquito nets, use of repellents, reducing the resting places for the mosquitoes, and similar measures.

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.

We obtain results for different ways of influencing the contact factors and the Mf concentrations. Note that 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.

We have calculated the results for eight selected Intervention strategies:

(a) *Intervention 1:* The first contact factor is reduced, which may be interpreted as the isolation of known infected humans.

(b) *Intervention 2*: The second contact factor is reduced, which may be interpreted as the use of 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, which may be interpreted as simultaneously isolating known infected humans and preventing susceptible humans from being exposed to (infective) mosquitoes.

(d) *Intervention 4:* The Mf concentration in the first human is reduced by administering medicationd. This may be interpreted as the treatment with medication of known infected humans who have a relatively high level of infection.

(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 simultaneously isolating known infected humans and reducing the blood Mf concentration by using medication.

(f) *Intervention 6:* A combination of Intervention 2 and the analog of Intervention 4 for the second human. This may be interpreted as simultaneously preventing humans from being exposed to (infective) mosquitoes, and treating infected ones among them with medication.
(g) *Intervention 7:* The Mf concentration in both the first and the second human are reduced by administering medication, which may be interpreted as the treatment with medication of all infected humans.
(h) *Intervention 8:* A Combination of Intervention 12 and Intervention 4.

Results:

The relative effectiveness of the eight strategies have been found to be in the following order (the most effective being the first):

Intervention 8, Intervention 7, Intervention 6, Intervention 5,
Intervention 1-2, Intervention 4, 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. This is in accord with the approach taken in the integrated malaria control programs in many countries, of combining preventive measures with chemical treatment

The results for the effectiveness of the Intervention strategies 7, 6, 5, and 1-2 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.
The cost and social acceptability of the measures are the main factors to be considered.

4. Model for Interacting populations of Humans and Vectors.

In this 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 following:

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 infective) 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 results shown here, we omit the birth and death rates, for simplicity, as our focus is on other features of the phenomena. Fig. 6 shows the model diagram for the processes occurring in the interacting populations. This suggests a number of control points and intervention strategies.

In this paper, we shall just show the effects of different intervention strategies; these will be summarized in the next section.

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

The model outlined in the last section for interacting human and vector populations suggests a number of Control Points, which are suitable for trying out strategies for controlling the spread of the infection. In this Section, we summarize the results of trying different strategies.

The Control strategies are divided into three categories: **Vector Human Contact Factors** (VHCF), which control the vector-human contact; **Vector Control Measures** (VCM), which control the vector population; and **Drug Treatment Measures** (DTM), which reduce the parasite level.

The results, shown in Fig. 5, show the qualitative effects of the different Control or Intervention Strategies, and . 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 is needed for an effective eradication program.

6. 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 ; in the present paper, we are discussing it with reference to Lymphatic Filariasis.

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 a vector-carrier;
(d) The transmission and spread of infection in a system with interacting vector and host populations.

The biological systems involved in disease modeling have many inherent complexities. Firstly, most of the parameters can at best be measured only approximately. Secondly, there can be a substantial variation in these parameters – depending on geographical region, population segment, and several other factors. Also, some of the parameters are essentially stochastic. We take into account the statistical spread of the parameters in the calculational scheme.

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.
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.

2) We have identified 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.

3) We have 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.

Ongoing work will deal with additional questions such as the role of the immune system , the use of individual agent based methods, comparing the results for different diseases, and other extensions of what has been reported here

We stress that the results shown here should be interpreted as indicating the qualitative trends to be expected, and not as actual numeric values. Such qualitative results should be useful for decision-making in epidemiologocal and public-health issues.

REFERENCES

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

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APPENDIX – Model Diagrams and Selected Results

Figure 1 Model for Single Vector + Parasite

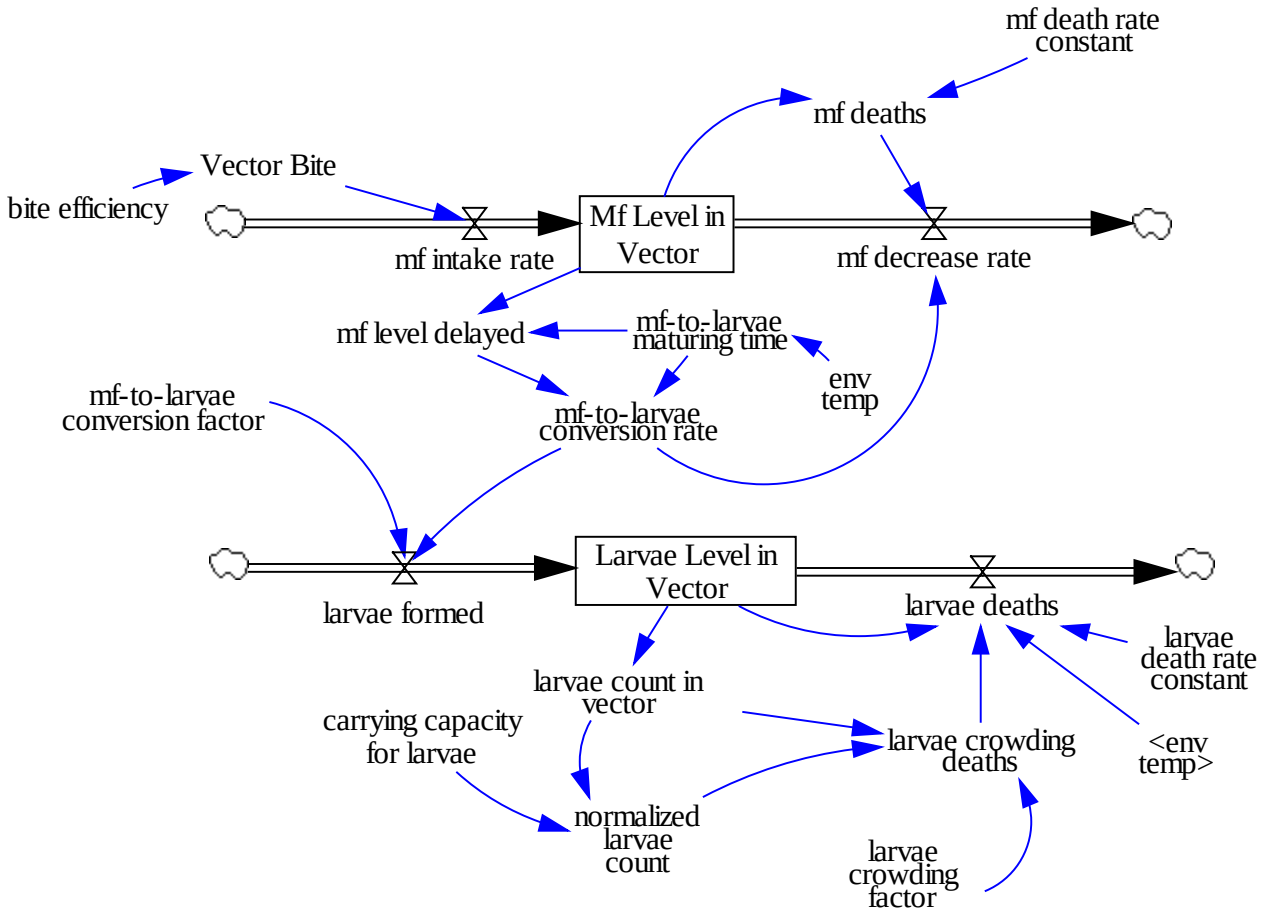
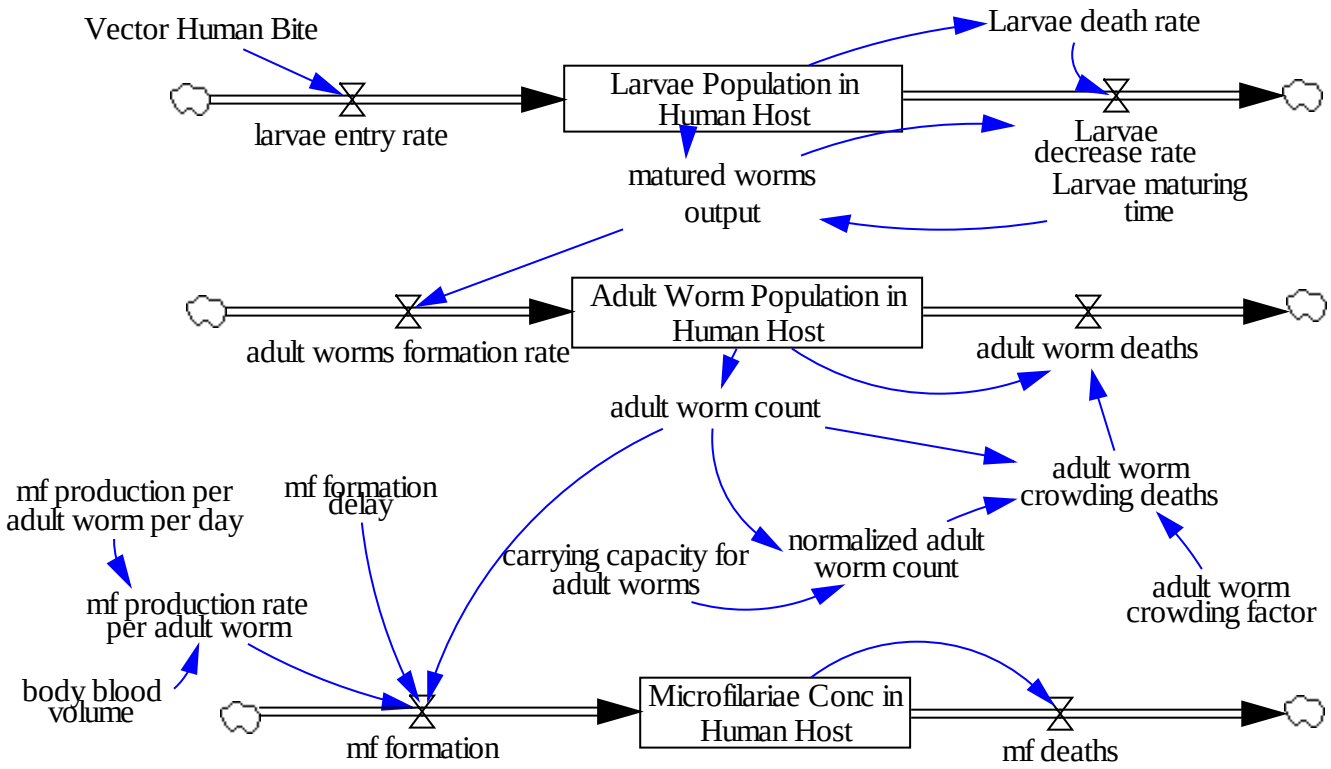


Figure 2. Model for Parasite process in the Host



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

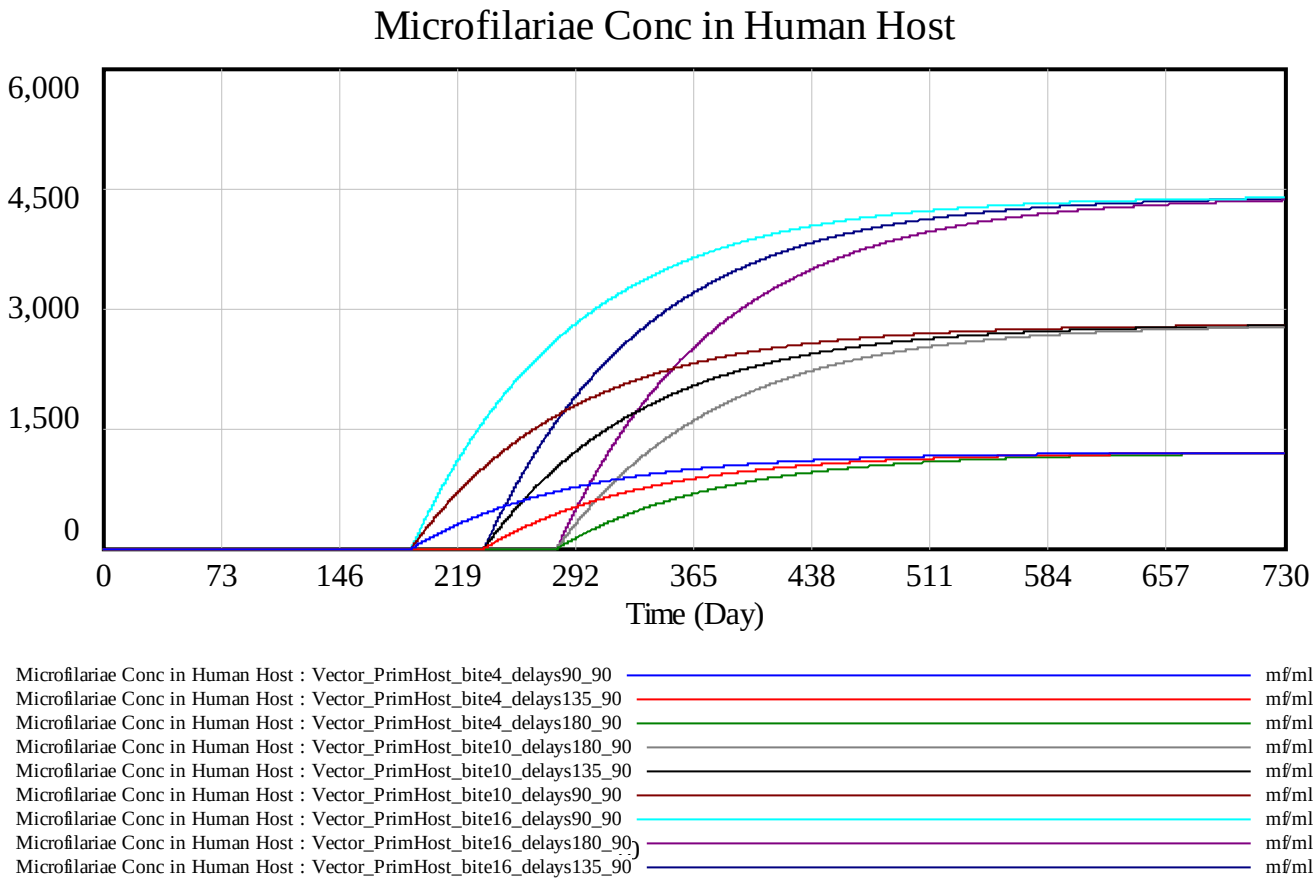


Figure 3. Model Diagram for Human-to-Human Infection Transmission through a vector and parasite

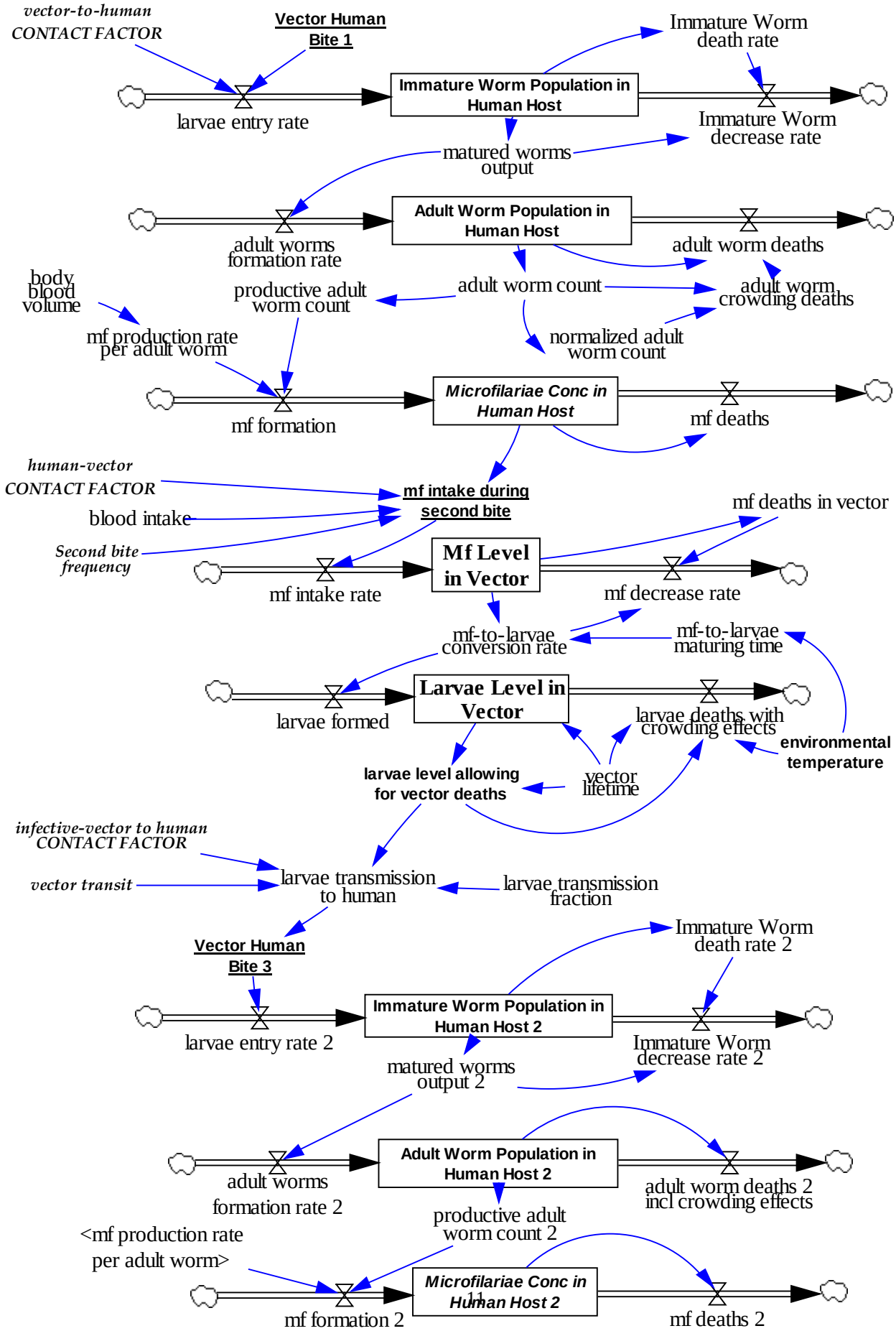


Fig. 4 Parasite Concentrations in Second Host after different Intervention Strategies

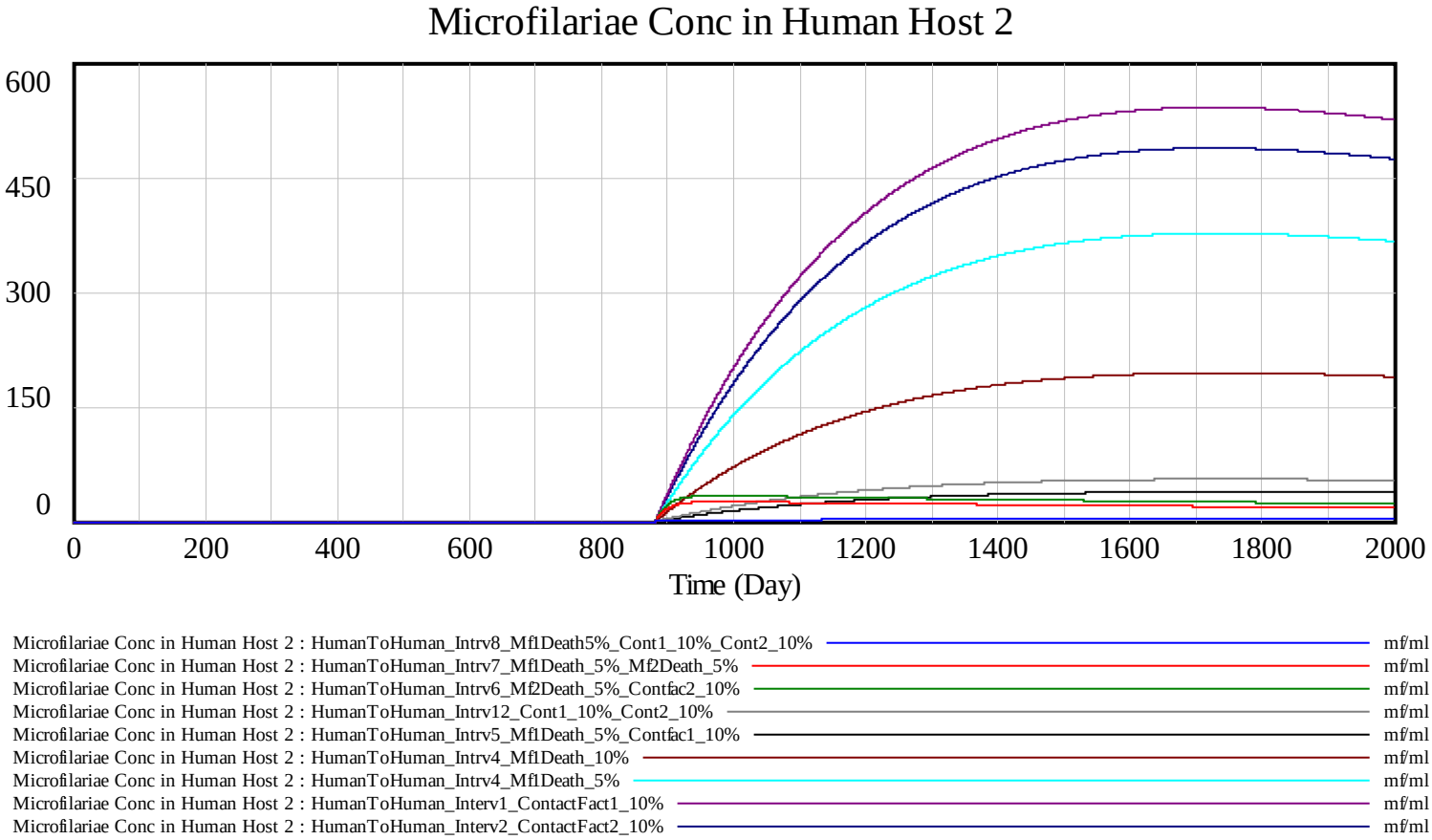


Fig. 5 Qualitative Effects of Control Strategies for Reducing Infection in Populations

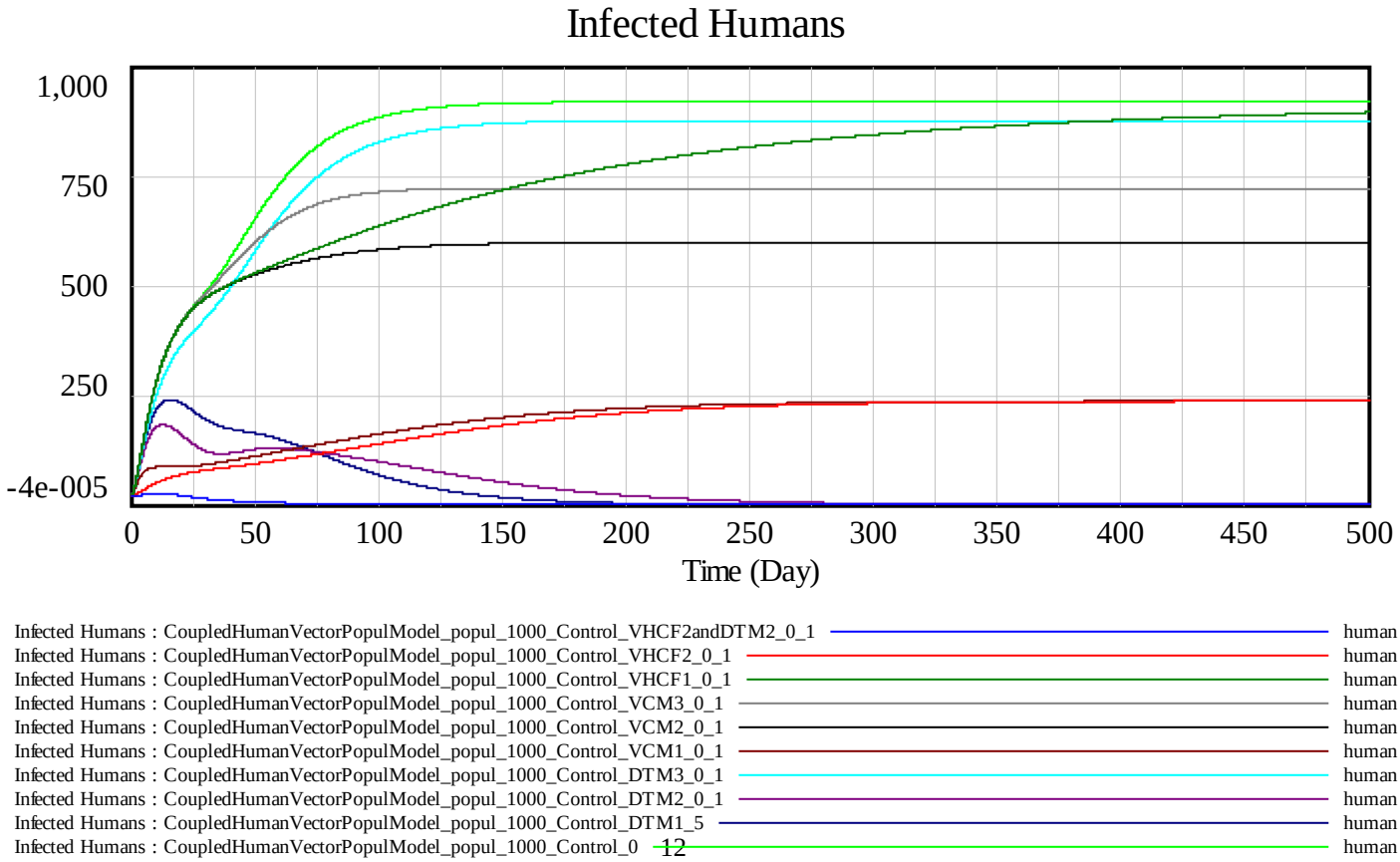


Figure 6. Interacting Human & Vector Populations -- Model Diagram

[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.