

**[Exploring the effect of spatial heterogeneity in dengue fever transmission on the inferences from vector control]**

Master of Epidemiology

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**Abstract**

Dengue fever transmission dynamics are known to be heterogenous across space, at different spatial scales. Given that there are currently no licenced vaccines in the general population, control strategies are focused on vector control. Model simulations are often carried out to inform on the optimal control strategy but many models assume homogeneity in transmission across space. This analysis uses a patch- based system to create two levels of transmission heterogeneity and explore the implications of this on the outcome of vector control. The patch-based system allows for the disaggregation of the host population and having a second level is interpreted as further disaggregating a sub-population leading to more resolution. The sub-populations are seen as resident in areas with varying transmission intensity as a result of varying number of vectors. Hosts’ movement, implemented in the model using a coupling parameter, joins these areas. Similar to other analyses of heterogeneity in transmission intensity, the current analyses found that the optimal control strategy would be to target high transmission settings. Using patch-based models is a simple way to factor in a more realistic dynamic in the distribution of transmission intensity. Despite there being more detailed micro-simulation models of heterogeneities, patch based models could be sufficient depending on the aim of the analysis.

**Introduction**

Dengue fever is a vector borne viral infection transmitted from human to human through the mosquito vector *Aedes aegpti*. There are four major serotypes of the virus in circulation. The mechanisms of interaction of these serotypes at host immunity level are complex, but it is generally believed that infection with one serotype confers life long immunity to that particular serotype. The spectrum of disease severity ranges from asymptomatic to severe cases of dengue haemorrhagic fever resulting in death in 1 out of 1000 cases (1).

Dengue fever has experienced an increase in global prevalence over the years. This global rise can be attributed to several factors such as urbanisation or human movement (2). The rise in numbers is a challenge for global health initiatives. As with many infectious diseases, dengue fever is characterized by spatially heterogeneous transmission intensity, an additional challenge for control efforts (3) (4). The structuring of human populations into sub (meta)-populations and the movement of people across these populations can greatly impact the spread of an infectious disease. It is due to this that movement restrictions are sometimes implemented for the emergence of novel disease outbreaks. Movement restrictions on the human population would however not be a viable control measure for dengue.

Mathematical models have played an important role in understanding the dynamics of infection and making predictions that guide in control policies. Increasingly, mathematical models have been employed in order to understand the role played by host and/or vector movement, and identify possible targets for control. Many models of dengue had previously assumed homogeneous transmission across space (5)(6). With the increase in availability of more detailed data on disease incidence and human demographics, there has been an increase in the use of models that factor in spatial heterogeneity in dengue transmission. These models have explored different scales across space, ranging from micro-simulations that track and individual host and/or vector’s movement across space to macro-simulations (7)(8)(9). Macro-simulation models are also known as patch-based models as they cluster host and vector populations into sub-populations (patches) and simulate movements of hosts and vectors between patches. The size of a “patch” can range from a household with a few hosts to a neighbourhood of local area with thousands of people. The choice of size is dependent on the dynamics of the disease, the purpose of the analysis and the data available to inform the model. Generally, micro-simulations are complex and require highly detailed data while, depending on the scale, macro-simulations are simpler to implement and analyse.

There is currently no licenced vaccine in use against dengue fever and most control efforts are focused on vector control strategies. The strategies include chemical treatment of immature forms of the vector (larvicide) and treatment of the adult vector (adulticide). There are also environmental strategies that aim at source reduction through elimination of breeding sites and other efforts. Models have been used to predict the impact of one or more of these vector control interventions, with other hypothesizing the effect of a vaccine as well. The simulations have shown that no single intervention is capable of eliminating infection in a population, and the most effective plan is to combine the different control strategies (5,10,11). Despite the beneficial predicted impact of different control strategies, most simulations have been conducted under the assumption of a homogeneous transmission setting, which is not the case for dengue. A recent publication looked into the role of residence times (host movement) in a two-patch meta-population model on transmission dynamics and optimal control (12) . The approach taken in this analysis was relatively simple with no reference to any control intervention in particular just a reduction in transmission, the point of the analysis being to estimate the optimal control function. Given this more realistic approach of a two heterogeneous sub-populations, it would be of interest to look at vector control under this assumption. As such, the objective of the analysis presented here is to look at the effect of vector control on a population disaggregated into two heterogeneous sub-populations linked through human movement across the patches. Given that there are different scales of heterogeneity, this analysis will go a step further and subdivide each sub-population into two patches resulting in a four-patch system that represents two levels of spatial structure. A comparison of the effect global versus patch specific control interventions will then be made.

**Methodology**

Model of natural history

The model used is a deterministic compartmental model that has host and vector populations. The dynamics within the host are similar to those implemented by *Burattini et al* (11) with an SIR structure. There are three possible disease states for an individual host, susceptible (Sh), infected (Ih) and recovered (Rh). All hosts are born susceptible, acquire infection at a rate λh and move into the infected (and infectious class). λh is the force of infection acting on the hosts and is given by the expression . The average duration of infection is 7 days with a fraction 0.001 of infected individuals dying as a result of the disease. Hosts who survive infection progress into the recovered and immune class where they retain their immunity for the rest of their lives. The host population is made to stay constant in size over time by ensuring the total number of births equals total number of deaths. The incubation period within the host and possible subsequent infections with different viral serotypes have been left out of the analysis, as the main aim is to look at the effect of vector control on infection in general.

The mosquito population is modelled as in *Knerer et al* (10) with an ASEI structure. The mosquitos are either in aquatic (immature) stage (Am) or as adults. It is assumed that the immature forms do not experience infection through vertical transmission. The aquatic stage mosquitos progress in to adulthood at a rate Ps (maturation rate) and enter the susceptible mosquito compartment (Sm). The rate Ps is subjected to seasonal forcing through a cosine function to reflect seasonal variation in mosquito populations due to weather changes. Unlike in *Knerer et al* (10), the Cs(t) function implemented here is simple and non specific to any particular climate. The susceptible mosquitos get infected at a rate and move into the exposed compartment (Em) where they are infected but not yet infectious. To reflect a more realistic distribution for the duration on the extrinsic incubation period the Em compartment was split into three, Em1, Em2, Em3, changing the distribution from exponential to gamma. The rate of progression out of each of the exposed classes is 3\*(1/ duration of incubation). Alternatively a delay function could have been used as was the case in *Knerer et al*. From the exposed stage the mosquitos move into the infectious compartment and are assumed not to recover from infection. Infection induced mortality within the mosquitos is assumed to be negligible. Figure 1 shows the described flow of the mosquitos and hosts.

Implementation of spatial structure

On relaxing the assumption on homogeneity in transmission across the whole population, the general host and mosquito population was split into two sub-populations each of which was then split into two further sub-populations. The populations are defined as resident in neighbouring areas (patches) A1, A2, A3, A4. The number of hosts is assumed to be equal in the four areas but the number of vectors is variable. Variability in vector numbers across space is interpreted as variability in transmission across space. The method of modelling the populations and their interactions is as implemented in *Lee et al* (12). The two level structure is such that area A1 and A2 are in the same “global” patch, P1, and are thus more closely linked to each other than to either patch A3 or A4. In the same way, areas A3 and A4 are in the same “global” patch, P2. The areas are linked through coupling parameter pij , where pij is the proportion of time that a person living in area i spends in area j. Areas in the same patch are strongly symmetrically coupled with pij = pji = 0.39 and pii = 0.59. Areas in different patches are weakly symmetrically coupled with pij=pji=0.01. The summation of the time proportion of time spent by an individual in the four patches is 1. For more details on the coupling parameter see (9,12). To reflect spatial heterogeneity patch P1 and P2 were assumed to have low and high transmission respectively, as reflected by the number of vectors. Within the patches it was further assumed that the areas have heterogeneous transmission with A1 being a low transmission area in a low transmission patch and A4 being a high transmission area in a high transmission patch. Figure 2 shows the patches.

SH

IH

RH

AM

SM

EM,2

IM

EM,1

EM,3

NHμH

λH

μH

μH

μH

μM

μM

μM

μM

μM

μE

λM

γH

αH

L

H

3τ

3τ

3τ

Humans

Mosquitos

*Figure 1: The flow diagram of hosts and vectors through the different stages of infection*

Key

SH: Susceptible humans

IH: Infectious humans

RH: Recovered humans

AM: Aquatic stage mosquitos

SM: Susceptible mosquitos

EM,i: Incubating mosquitos, i=1…3

IM: Infectious mosquitos

P1

P2

*Figure 2: The two levels of space*

*Ordinary Differential Equations*

The basic reproductive number, Ro, is the number of secondary cases from a single infected individual in a completely susceptible population. Ro was calculated separately for each area without the use of the next generation operator method as this was simpler. However for more accurate descriptions, the next generation method should be used. The area specific Ro is given as:

The area specific forces of infection on the hosts and mosquitos are respectively:

Implementing vector control

Vector control is implemented through an increase in the mortality rates of the adult and aquatic stage mosquito. An increase in mortality rate is equal to a reduction in life span. This reflects adulticide and larvicide treatment, respectively. Control is implemented at equilibrium and is discrete. The choice of a discrete rather than continuous simulation of vector control is so as to more accurately represent how control would be carried our in real life. Control is carried out for two months out of twelve months in a year. The first month of control is at the beginning of the year (and dengue season) the second is after six months. This is done for 5 years.

The parameter values and initial conditions used in the simulation are given in table 1. The parameters are from (10–12)

*Table 1: parameters and initial conditions used in the simulations*

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Description** | **Value** (all rates are per day) |
| μh | Human death/birth rate | 3.5 x 10-5 |
| αh | Dengue mortality rate in humans | 10-3 |
| a | Average daily biting rate | 0.7-1.9 |
| b | Fraction of infective bites on humans | 0.6 |
| γh | Human recovery rate | 0.143 |
| O | Oviposition rate | 50 |
| PS | Maturation rate | 0.15 |
| c | Mosquito susceptibility to infection | 0.375 |
| τ | Extrinsic incubation period | 9 days |
| μA,i  for i=1..4 | Aquatic stage mortality rate (area specific under vector control) | 0.1 |
| μm,i  for i=1..4 | Mosquito mortality rate (area specific under vector control) | 0.083 |
| g | Proportion of infected eggs/ larvae |  |
| f | Frequency of seasonal cycle | 2.8 x 10^-3 |
| θi,σi | Seasonal forcing parameters | varied |
| Pi,j | Coupling parameter connecting the different areas. Pij= the proportion of time that a person living in area i spends in area j | p11=0.59, p12=0.39, p13=0.01, p14=0.01, p21=0.39, p22=0.59, p23=0.01, p24=0.01, p31=0.01, p32=0.01, p33=0.59, p34=0.39, p41=0.01, p42=0.01, p43=0.39, p44=0.59 |
| KEi | Area specific carrying capacity | Varied to support different transmission intensities |
| **Initial conditions** | **Description**  (for each area i=1..4) | **Value** |
| Nhi  Ihi  Rhi  Avi  Svi  Evi1  Evi2,3  Ivi | Total number of hosts  Initial number of hosts infected  Initial number of hosts recovered  Initial number of aquatic stage mosquitos  Initial number of susceptible mosquitos  Initial number of exposed mosquitos in 1st E compartment  Initial number of exposed mosquitos in 2nd and 3rd E compartments  Initial number of infected mosquitos | 250,000  100 for i=1  0  0  107  1000 for i=1  0  0 |

All the simulations were done in Berkley Madonna, beta version 9.0.120 and the code is provided in the appendix section.

**Results**

The model simulations were carried out under different assumption and implementations of the vector control strategies. For all simulations, infection was introduced in area 1 and the system allowed to run to equilibrium. Equilibrium is reached quickly and so the entire simulation period is at most ten years. There were no differences in equilibrium dynamics with change in area of infection introduction (results not shown). The rest of the simulations are as described and results are summarized in table 2 using the cumulative number infected at the end of the simulation period as the comparison output. It is noted that the reduction in absolute difference in numbers when comparing baseline (no intervention) and intervention is very small. The point of this analysis is not to evaluate the effectiveness of the intervention, but to compare the results a homogeneous transmission setting and a heterogeneous transmission setting. Initial simulation was done assuming a homogeneous population i.e. no sub-populations. Control was implemented after five years of initial introduction and continued in pulses as previously described, for five years. The vector and aquatic stage mortality rates were increased by 50%(0.5) and 100%(1) under the control strategies and the output for these compared against no control. Figure 3 shows the results of this simulation in terms of the epidemics and Ro curves post intervention. The epidemic curves have higher peaks but shorter durations while Ro has periods of reduced value during control implementation.

The next set of simulations were carried out assuming spatial heterogeneity in transmission as reflected by different sizes of vector populations and matching carrying capacities per local area. The increase in mortality rates was as in the homogeneous population assumption. The timing and frequency of vector control could be varied for the different local areas.



*Figure 3: Homogeneous population simulation output of Ro and the epidemic curve post intervention*

Under the heterogeneous transmission assumption, the control strategies explored were:

1. Homogeneous: same timing and frequency for all areas
2. Heterogeneous: delaying timing of intervention in area 1 and 2 by 25 days
3. Heterogeneous: Doubling frequency of intervention in high transmission areas A2 and A3
4. Heterogeneous: Doubling frequency of intervention in high transmission areas A3 and A4

Strategy (a) and (b) produced the same results which can be seen in figure 4(a). Doubling frequency in area 2 and 4 was more beneficial and the output can be seen in figure 4(b).

*Table 2: Summary of the simulation output using cumulative number infected as outcome*

*The figures in brackets are the percentage decreases relative to baseline.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Proportion increase in mortality rate | Homogeneous population | Heterogeneous population | | | |
| Homogeneous control | Heterogeneous control | | |
| Delay in timing | Doubling frequency | |
| A2 and A4 | A3 and A4 |
| 0  (Baseline) | 1133953  (0) | 1002759  (0) | 1002759  (0) | 1002759  (0) | 1002759  (0) |
| 0.5 | 1133926  (0.002) | 1002749  (0.001) | 1002749  (0.001) | 1002671  (0.009) | **1002508**  **(0.025)** |
| 1 | 1133913  (0.004) | 1002740  (0.002) | 1002740  (0.002) | **1002682**  **(0.008)** | 1002778  (0.002 inc) |



4(b)

4(a)

*Figure 4: Output for heterogeneous implementation of vector control*

**Discussion**

Dengue fever is a vector-borne disease whose prevalence has been increasing globally over the years. Transmission has been shown to be heterogeneous across space and human movements have been associated with the spread of infection (9). In planning for control, it is important to factor in spatial heterogeneity and human movement in order to make accurate predictions of the impact of different control strategies.

Mathematical models are increasingly being used in order to understand transmission dynamics and predict the impact of single or combined control strategies. Many models have assumed homogeneity in transmission across space, which has the potential to give misleading predictions on the impact of control. There are different spatial scales at which heterogeneity exists and thus can be modelled, the choice depending on the purpose of the analysis and the data available (13). In this current analysis, the aim was to compare the impact of vector control under a homogeneous transmission assumption to vector control under a spatially heterogeneous transmission assumption. The approach taken is that of a patch based system as used by *Lee et al* (12), with the addition of an extra level of space to explore the idea of “hot-spots within hot-spots” and how this reflects on the optimal control strategy.

The results of this analysis suggest that given heterogeneity in transmission, the optimal control intervention would also be heterogeneous. Vector control was simulated as a discontinuous process to reflect the more realistic scenario where it is more likely to be implemented in pulses through out a year or season. If the control resulted in a 50% increase in adult and immature vector mortality rate, the optimal strategy would be to target the areas within a high transmission setting. That is, target the “parent hot-spot”. Where the intervention results in a 100% increase in mortality rate, it would be more optimal to target the lower level hot-spots of transmission.

The recommendation that high transmission settings should be targeted for control is not a new finding (3,12). The interest point of this analysis is that the scale at which to target might also be influenced by the impact of the vector control intervention, in this case the percentage increase in vector mortality rate. However, given the many simplifying assumptions that went into this analysis, this result needs to be further investigated before any claims can be made. A staring point would be a sensitivity analysis on the parameters that went into the model, of particular interest is the average daily vector-biting rate. The value of this parameter has been shown to range from 0.7 to 1.9 per day (14) and this might greatly influence model outcomes.

The current analysis has several limitations. Seasonality is implemented in the model using a simple cosine function, not specific to any particular climate and thus could lead to unrealistic results for places of know dengue fever seasonality. Another point of concern is the fact that the spatial scale is arbitrary in terms of land size. The size of the area would greatly influence how far hosts would move and how frequently, thus influencing the coupling parameter. Although the population sizes could be used to implicitly size up the area, a more precise definition of spatial boundaries would be preferred for better predictions. For malaria transmission at a rural area of Kenya, *Bejon et al* (15) identified the existence of hot-spots within hot-spots for malaria transmission and were able to use the data to inform on the size of a hotspot in terms of kilometres. Once spatial boundaries of transmission have been better defined one could employ gravity models to explore the effect of human movement across these boundaries.

There are different spatial scales that could be explored with dengue transmission each for different utilities. Individual based models are on the finer end of the spectrum and they have been used to explore both host and vector movement. These models make fewer assumptions, hence are considered to be more realistic and as such are complicated, computer intensive and require detailed data to parameterize. With the increase in the availability of more detail in epidemiological and demographic data, individual based models are probably the way of the future. None the less, simpler patch-based models have not lost their utility in the building of an understanding of the transmission dynamics across relatively course spatial scale. The question of how fine a scale is needed has been explored by *Mills et al* (13), and they found that for low mobility, there exists a clear threshold for spatial resolution. The effect of spatial heterogeneity on transmission is clearly an area of growing interest and a lot is yet to be fully understood.

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**Appendix**

Berkley Madonna code for the model

STARTTIME = 0

STOPTIME=10\*365

DT = 0.02

DTOUT = 1

{\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*THE ODEs\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*}

{HUMANS}

{Susceptible}

d/dt(Sh[1..4]) = (muH\*Nh[i]+alphaH\*Ih[i]) - (muH\*Sh[i]) - a\*b\*Sh[i]\*((Im[1]\*p[i,1]/Nh[1])+(Im[2]\*p[i,2]/Nh[2])+(Im[3]\*p[i,3]/Nh[3])+(Im[4]\*p[i,4]/Nh[4]))

{Infected}

d/dt(Ih[1..4]) = a\*b\*Sh[i]\*((Im[1]\*p[i,1]/Nh[1])+(Im[2]\*p[i,2]/Nh[2])+(Im[3]\*p[i,3]/Nh[3])+(Im[4]\*p[i,4]/Nh[4])) - Ih[i]\*(muH+gammaH+alphaH)

{Recovered}

d/dt(Rh[1..4]) = gammaH\*Ih[i] - muH\*Rh[i]

{Total humans}

Nh[1..4]= Sh[i] + Ih[i] + Rh[i]

{Cummulative number of humans infected}

d/dt(CI[1..4]) = a\*b\*Im[i]\*Sh[i]/Nh[i]

{Infected number for entire region}

I = Ih[1] + Ih[2] + Ih[3] + Ih[4]

{Cummulative number infected for entire region}

CC = CI[1] + CI[2] + CI[3] + CI[4]

{MOSQUITOS}

{Susceptible}

d/dt(Sm[1..4]) = Cs[i]\*Ps\*Am[i] - (a\*c\*Sm[i]\*((Ih[1]/Nh[1]\*p[1,i])+(Ih[2]/Nh[2]\*p[2,i])+(Ih[3]/Nh[3]\*p[3,i])+(Ih[4]/Nh[4]\*p[4,i]))) - (muM[i]\*Sm[i])

{Exposed/latent}

d/dt(Em1[1..4]) = (a\*c\*Sm[i]\*((Ih[1]/Nh[1]\*p[1,i])+(Ih[2]/Nh[2]\*p[2,i])+(Ih[3]/Nh[3]\*p[3,i])+(Ih[4]/Nh[4]\*p[4,i]))) - Em1[i]\*(3\*tauM+muM[i])

d/dt(Em2[1..4]) = Em1[i]\*3\*tauM - Em2[i]\*(3\*tauM+muM[i])

d/dt(Em3[1..4]) = Em2[i]\*3\*tauM - Em3[i]\*(3\*tauM+muM[i])

{Infected}

d/dt(Im[1..4]) =3\*tauM\*Em3[i] - muM[i]\*Im[i]

{Aquatic stage}

d/dt(Am[1..4]) = (O\*(1-(Am[i]/Ke[i]))\*g\*Nm[i]) - Am[i]\*(muA[i]+Cs[i]\*Ps)

{Total vectors}

Nm[1..4] = Sm[i] + Em1[i] + Em2[i] + Em3[i] + Im[i]

{\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*THE BASIC REPRODUCTIVE NUMBER\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*}

Ro[1..4] = a^2 \* b\*c\*(Nm[i]/Nh[i])\*((3\*tauM/(3\*tauM+muM[i]))^3)/(muM[i]\*(muH+gammaH+alphaH))

RoH[1..4] = a\*c\*(Nm[i]/Nh[i])/(muH+gammaH+alphaH)

{\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*INITIAL CONDITIONS\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*}

;;Every area has the same size human population, i.e. homogeneous human population

total = 1000000

init Sh[1..4] = total/4

init Ih[1] = 0 {Infection starts in the first area}

init Ih[2] = 0

init Ih[3] = 0

init Ih[4] = 100

init Rh[1..4] = 0

init CI[1..4] = 0

;; The mosquito poplation per area is heterogenous to reflect heterogeneity in transmission per area

totalV = 10000000

V=totalV/9

init Sm[1] = V

init Sm[2..3] = 2\*V

init Sm[4] = 4\*V

init Em1[1] = 0 {infected vectors also in area 1}

init Em1[2] = 0

init Em1[3] = 0

init Em1[4] = 1000

init Em2[1..4] = 0

init Em3[1..4] = 0

init Im[1..4] = 0

init Am[1..4] = 0

{\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*PARAMETERS\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*}

muH = 3.5 \*(10^ -5) {human natural mortality rate}

a = 0.7 {average biting rate}

b = 0.6 {fraction of actually infective bites}

alphaH = 10^-3 {dengue mortality rate in humans}

gammaH = 0.143 {human recovery rate}

Ps = 0.15 {egg hatching rate}

c = 0.375 {mosquito susceptibility to dengue}

tauM = 1/9 {inverse of extrinsic incubation period}

O = 50 {oviposition rate}

f = 0.0028 {frequency of seasonal cycle}

g = 0.5 {proportion of infected larva/eggs}

{The matrix of human movement probabilities}

p[1..4,1..4] = 0.01

p[1,1]= 0.59

p[2,2]= 0.59

p[3,3]= 0.59

p[4,4]= 0.59

p[1,2]= 0.39

p[2,1]= 0.39

p[3,4]= 0.39

p[4,3]= 0.39

{location specific carrying capacity}

K= (10^8)/9

Ke[1] = K

Ke[2..3] = 2\*K

Ke[4] = 4\*K

{Pulse function in mosquito mortality rate}

rate = 1/12

red = 0

muM[1..4] = IF TIME >= startT[i] THEN IF MOD(TIME,freq[i]) <= 30 THEN rate\*(1+red) ELSE rate ELSE rate

;;The different areas are allowed to start control at differnt points of the year and at different frequencies but control is continuious for one month for all and reduced by the same proportion

startT[1] = 356\*5

freq[1] = 365/2

startT[2] = 365\*5

freq[2] = 356/2

startT[3] = 365\*5

freq[3] = 365/4

startT[4] = 365\*5

freq[4] = 365/4

{Pulse function in aquatic stage mortality rate}

;;Assumption is that larvicide and adulticide are run in parallel, i.e. intiated at the same time and at the same frequency

rate2 = 1/10

muA[1..4] = IF TIME >= startT[i] THEN IF MOD(TIME,freq[i]) <= 30 THEN rate2\*(1+red) ELSE rate2

ELSE rate2

{Seasonal forcing parameters}

Cs[1..4] = 1 + sigma\*cos(f\*2\*pi\*TIME+T[i])

sigma = 0.8

T[1] = 0

T[2] = 0

T[3] = 0

T[4] = 0