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Mathematical Modeling of Infectious Disease Transmission Dynamics in a Metapopulation

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Abstract: *Epidemic modeling is an important theoretical approach for investigating the transmission dynamics of infectious diseases. It formulates mathematical models to describe the mechanisms of disease transmissions and dynamics of infectious agents and then informs the health control practitioners the likely impact of the control methods. In this paper we investigate the spread of an infectious disease in a human population structured into n-patches. The population is initially fully susceptible until an infectious individual is introduced in one of the patches. The interaction between patches is dominated by movement of individuals between patches and also the migration of individuals and therefore any infection occurring in one patch will have a force of infection on the susceptible individuals on the other patches. We build a mathematical model for a metapopulation consisting of n patches. The patches are connected by movement of individuals. For $n = 2$, we obtained the basic reproduction number and obtained the condition under which the disease free equilibrium will be asymptotically stable. We further described in terms of the model parameters how control methods could be applied to ensure that the epidemic does not occur and validated the results by the use of the numerical simulation. We showed that the global basic reproduction number cannot exceed one unless the local basic reproduction number is greater than one in at least one of the sub-populations. We further showed that the control of the epidemic in this case can be achieved by applying a control method that decreases the transmission parameters in patches where the local basic reproduction number is greater than one.*

Keywords: *Metapopulation, Basic reproduction number, Epidemic Control, Target reproduction number, migration, Lipchitz continuity.*
Mathematics Subject Classification: 97M60, 00A71, 92A07, 92D30.

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List of Symbols and Notations.

r	Birth rate
R_0	Global Basic Reproduction Number
$\mathcal{R}_i$	Local reproduction number for patch i.
K	Next generation matrix.
$\widehat{K}$	Alternative next generation matrix.
$\widetilde{K}$	Target matrix
$\widehat{\widetilde{K}}$	Target matrix for alternative next generation matrix.
K^c	Controlled next generation matrix
$\mathcal{T}$	Target reproduction number
ω	Target set for disease control
$\mathbb{T}$	Type reproduction number
μ	per-capita death rate
β	Transmission probability
γ	Recovery rate
ψ	Rateof migration of susceptible individuals
ϕ	Rateof migration of infectious individuals
ξ	Rateof migration of recovered individuals

I. Introduction

Epidemic modeling is a tool used to study the mechanism through which communicable diseases spreads, predict the future course of the epidemic and identify possible strategies that can be employed to prevent the disease from spreading further. The threshold for many epidemic models is the basic reproduction number which is defined as the average number of secondary infections resulting from an index case in an otherwise susceptible population [2]. For many infectious diseases, an infectious agent will invade the population if and only if the basic reproduction number (R_0) is greater than one and therefore in many occasions, the basic reproduction number is usually considered as the threshold quantity that determines whether an infectious disease will invade the population or not. Despite the extensive vaccination programs, improved sanitation and use of antibiotics, infectious diseases continue to be a major cause of morbidity and mortality throughout the world. In addition, pathogens adapt and evolve so that new infectious diseases continue to emerge [7]. Drug and antibiotic resistance has also become a serious issue in the control of several communicable diseases such as Malaria, Tuberculosis, Dengue and Gonorrhea. In recent years, the emergence of new infectious agents known as prions has caused major problem in public health. The invasion of humans and animals to new ecosystems, global warming and increased international travel continue to provide opportunities for infectious diseases to spread to new regions [9]. In future therefore, there will be need to have sound quantitative methods to guide disease control measures.

In this paper, we consider the transmission of an infectious disease in a metapopulation structured into n - patches. Many infectious disease models assume that there is homogeneous mixing of individuals in the population which means that each individual in the population has the same probability of contacting any other individual in the population. However, in real populations, individuals occupy spatially structured population patches that are connected by human travel. We therefore sub-divide the population into spatially separated patches. Each of these patch will have its own dynamics which will be affected by migration of individuals. Such a distinct group of population in a given patch is known as a metapopulation. In a metapopulation setup, a patch will be termed infected if there exist at least one infected individual in that patch otherwise the patch is uninfected.

The study conducted by [1] was designed to study the influence of the travel rates with respect to the transmission of Influenza in a metapopulation setup. The results of the model analysis indicated that in the case of isolated patches, the disease approached disease free equilibrium in one patch and an endemic equilibrium in the other. On introducing the movement of individuals at a low rate, the disease status approached endemic equilibrium in both patches however, when the travel rates were increased further, the disease status approached disease free equilibrium in both patches. The study carried out by [5] to investigate the impact of human mobility on HIV transmission in Kenya using mobile phone data to track movement of individuals showed that movement of individual had little effect on HIV transmission in Kenya. However, the important consequence of movement of individuals on the transmission of HIV was the transmission of HIV from high prevalence to low prevalence areas. The authors also showed that mobility of individuals slightly increased HIV incidences in areas with initially low prevalence and decreased HIV incidences in areas with initially high prevalence. [6] investigated the effect of migration on the persistence of the infectious agent in a metapopulation setup. Their study revealed that a higher migration rate would lead to the increase in the probability of persistence of infectious agent in the population. [3] on the other hand used an SIRS metapopulation model with vital dynamics and described a novel approach of investigating the effect of various control methods. The methods described by the author made use of various alternative next generation matrices to investigate the effect of various control measures. Each next generation matrix was designed for a particular control method. Using this technique, the author showed the dependence of the transmission dynamics on the targeted parameters.

In this paper, we use an SIR model with demographic factors to investigate the transmission dynamics of a communicable disease in a metapopulation structured into n - patches and connected by migration of individuals. Interaction between individuals will involve both intra-patch interactions and inter-patch interactions. We assume that there is homogeneous mixing of individuals within each patch. However inter-patch interactions will be modeled by two methods depending on the frequency of movement of individuals between these patches. When the interaction between the two patches is dominated by frequent movement of individuals such as people traveling to and from work, then the patches will be assumed to be interacting in a random manner. In this case each infection occurring in one patch will have a force of infection on the other connected patch. We define the *force of infection* as per capita rate at which the disease is transmitted from the infected individuals to the susceptible individuals. If on the other hand the interaction between the two patches take the form of migration, then an individual will move to the host patch with the disease status acquired in the home patch and then participate in the disease transmission in the host patch[8]. Previously these two cases have been studied separately but are likely to occur concurrently in real world. We therefore build a metapopulation model that incorporate both patch coupling and migration of individuals. We model a non-fatal disease with per-capita transmission rate β, recovery rate γ in a population with constant birth rate r and per capita death rate μ

thus the basic framework is the SIR model with demography and is of the form;

$$\begin{aligned}\frac{dS}{dt} &= r - \beta SI - \mu S \\ \frac{dI}{dt} &= \beta SI - (\gamma + \mu)I \qquad (1) \\ \frac{dR}{dt} &= \gamma I - \mu R\end{aligned}$$

The model is a normalised system in which all the variables are proportions of the total population thus

$$S + I + R = 1 \qquad (2)$$

The force of infection for the above SIR model is given by βSI. For a metapopulation having *n*-patches, the force of infection on patch *i* will be affected by the sum of the infection situations on the patches that are connected to patch *i*. Thus the force of infection on patch *i* is given by $\sum_{j=1}^{n} \beta_{ij} S_i I_j$ where β_{ij} is the per capita rate of transmission of the disease for a contact in patch *j* between a susceptible individual from patch *i* and an infectious individual in patch *j*. The per capita migration rates of susceptible, infectious and the recovered individuals will be denoted by ψ, ϕ and ξ respectively. The rate of immigration from patch *j* to patch *i* is denoted by ψ_{ji} while the emigration rate from patch *i* to patch *j* will be denoted by ψ_{ij}. In general the subscript *ij* will denote migration from patch *i* to patch *j* while *ji* will denote migration to patch *i* from patch *j*. The SIR model for the system becomes;

$$\begin{aligned}\frac{dS_i}{dt} &= r - \mu S_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j + \sum_{j=1, j\neq i}^{n} \psi_{ji} S_j - \sum_{j=1, j\neq i}^{n} \psi_{ij} S_i \\ \frac{dI_i}{dt} &= \sum_{j=1}^{n} \beta_{ji} S_j I_i - (\mu + \gamma_i) I_i + \sum_{j=1, j\neq i}^{n} \phi_{ji} I_j - \sum_{j=1, j\neq i}^{n} \phi_{ij} I_i \qquad (3) \\ \frac{dR_i}{dt} &= \gamma_i I_i - \mu R_i + \sum_{j=1, j\neq i}^{n} \xi_{ji} R_j - \sum_{j=1, j\neq i}^{n} \xi_{ij} R_i\end{aligned}$$

For $n = 2$, the disease transmission dynamics in a metapopulation may be represented by Figure 1 below.

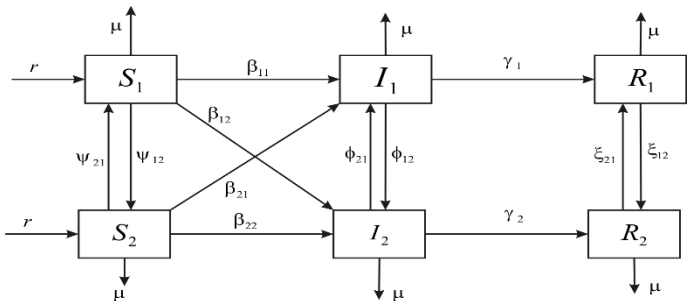


Figure1: Infectious Disease Transmission Dynamics in a Two Patch Metapopulation Model with Demographic Factors and Migration

The mathematical model for the system becomes;

$$\begin{aligned}\frac{dS_1}{dt} &= -\beta_{11} S_1 I_1 - \beta_{12} S_1 I_2 - \psi_{12} S_1 + \psi_{21} S_2 + r - \mu S_1 \\ \frac{dS_2}{dt} &= -\beta_{21} S_2 I_1 - \beta_{22} S_2 I_2 + \psi_{12} S_1 - \psi_{21} S_2 + r - \mu S_2 \\ \frac{dI_1}{dt} &= \beta_{11} S_1 I_1 + \beta_{21} S_2 I_1 - \mu I_1 - \gamma_1 I_1 - \phi_{12} I_1 + \phi_{21} I_2 \\ \frac{dI_2}{dt} &= \beta_{12} S_1 I_2 + \beta_{22} S_2 I_2 - \mu I_2 - \gamma_2 I_2 + \phi_{12} I_1 - \phi_{21} I_2 \qquad (4) \\ \frac{dR_1}{dt} &= \gamma_1 I_1 - \mu R_1 - \xi_{12} R_1 + \xi_{21} R_2 \\ \frac{dR_2}{dt} &= \gamma_2 I_2 - \mu R_2 + \xi_{12} R_1 - \xi_{21} R_2\end{aligned}$$

II. Basic Reproduction Number

The basic reproduction number (R_0) is defined as the average number of secondary infections resulting from the index case in a wholly susceptible population. In emerging epidemics, this number is usually useful as a measure of the strength of the control measure needed to break the epidemic. [4] identified the basic reproduction number as the spectral radius of the next generation matrix. To compute the next generation matrix, one first identifies the infected subsystem of the model. These are the set of equations that describe the new infections and the changes of state of the system. The infected sub system is then linearlised about the disease free equilibrium forming the Jacobian matrix (*J*). The Jacobian matrix is then decomposed as $J = T - V$. Where *T* describes the production of new infections while *V* describes the changes in state and is a non-singular M-matrix. The next generation matrix (*K*) is then defined as $K = TV^{-1}$. However [3] showed that there exist

different splitting of J that would satisfy the same properties of T and V thus there exist an alternative next generation matrix (K_1).

For the metapopulation system 4, the infected subsystem is given by;

$$\begin{aligned} X_1 &= \beta_{11}S_1I_1 + \beta_{21}S_2I_1 - \mu I_1 - \gamma_1 I_1 - \phi_{12}I_1 + \phi_{21}I_2 \\ X_2 &= \beta_{12}S_1I_2 + \beta_{22}S_2I_2 - \mu I_2 - \gamma_2 I_2 + \phi_{12}I_1 - \phi_{21}I_2 \end{aligned} \quad (5)$$

Linearising about the DFE we get the Jacobian matrix J as follows;

$$J = \begin{pmatrix} \beta_{11} + \beta_{21} - (\mu + \gamma_1 + \phi_{12}) & \phi_{21} \\ \phi_{12} & \beta_{12} + \beta_{22} - (\mu + \gamma_2 + \phi_{21}) \end{pmatrix} \quad (6)$$

To compute the NGM, we decompose the matrix J into $T - V$

where $T = \begin{pmatrix} \beta_{11} + \beta_{21} & \phi_{21} \\ \phi_{12} & \beta_{12} + \beta_{22} \end{pmatrix}$ and

$V = \begin{pmatrix} \mu + \gamma_1 + \phi_{12} & 0 \\ 0 & \mu + \gamma_2 + \phi_{21} \end{pmatrix}$

we note that V is a non-singular M-matrix and its inverse is given by

$$V^{-1} = \begin{pmatrix} \dfrac{1}{\mu + \gamma_1 + \phi_{12}} & 0 \\ 0 & \dfrac{1}{\mu + \gamma_2 + \phi_{21}} \end{pmatrix}$$

The NGM $K = TV^{-1}$ becomes

$$K = TV^{-1} = \begin{pmatrix} \frac{\beta_{11}+\beta_{21}}{\mu+\gamma_1+\phi_{12}} & \frac{\phi_{21}}{\mu+\gamma_2+\phi_{21}} \\ \frac{\phi_{12}}{\mu+\gamma_1+\phi_{12}} & \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2+\phi_{21}} \end{pmatrix} \quad (7)$$

Computing the spectral radius of this matrix, we get the basic reproduction number R_0. Thus

$$R_0 = \rho(TV^{-1})$$

$$R_0 = \frac{1}{2}\left(\frac{\beta_{11}+\beta_{21}}{\mu+\gamma_1+\phi_{12}} + \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2+\phi_{21}}\right) + \frac{1}{2}\sqrt{\left(\frac{\beta_{11}+\beta_{21}}{\mu+\gamma_1+\phi_{12}} - \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2+\phi_{21}}\right)^2 + \left(\frac{4\phi_{12}\phi_{21}}{(\mu+\gamma_1+\phi_{12})(\mu+\gamma_2+\phi_{21})}\right)} \quad (8)$$

If $R_0 < 1$ then each infectious individual will on average infect less than one other individual during the entire period that he/she remains infectious and the epidemic will die out. In this case no control measures are necessary to contain the epidemic. However if $R_0 > 1$ then each infectious individual will on average infect more than one other individual during the period that he/she remains infectious thus the disease will invade the population. In this case control measures need to be applied to contain the epidemic. Since the control measures must target to reduce the basic reproduction number to less than unity, then the strategies should target the transmission rates ($\beta_{11}, \beta_{12}, \beta_{21}, \beta_{22}$), the migration rates ($\phi_{12}, \phi_{21}$) of the infectious individuals or the combination of the two. From equation 8 we note that changing the values of $\beta_{11}, \beta_{12}, \beta_{21}, \beta_{22}, \phi_{12}$ and ϕ_{21} will change the value of the basic reproduction number R_0 thus various control strategies are available for the health control practitioners. These strategies include but not limited to;

1. Control strategy that targets transmission rates in one or both patches.
2. Control strategy that targets the migration rates.
3. Combination of the above two strategies.

2.1 Target Reproduction Number

In homogeneous populations, the basic reproduction number measures the strength of the control measures necessary to break the epidemic. A large value of R_0will therefore indicate a disease which is difficult to control. However, in heterogeneous populations where individuals are divided into different host types, the growth or the decay of the epidemic is given in terms of the generation process. The next generation matrix gives the transmission of the infection from one generation to the next [11]. The entry k_{ij} of the next generation matrix usually gives the number of expected cases that an infectious individual of type *j* causes among the susceptible individuals of type *i*. If the applied control strategy targets all individuals in the population regardless of their epidemiological type, then the basic reproduction number will measure the strength of the control measure required to eliminate the infection from the specified population provided that it is possible to change all the entries of the next generation matrix. However, limitations may arise when employing the control

measure because some of the entries of the next generation matrix may not accommodate change. In such a case, a control strategy may be applied that targets only a specified host type. Such a control measure would imply changing only the elements of a given row or column of the next generation matrix [10]. A different strategy may be applied that only affects the interaction between hosts without affecting the disease status of the host but only the contacts between them [11]. The reproduction numbers associated with these strategies are known as the type reproduction ($\mathbb{T}$) and target reproduction ($\mathcal{T}$) numbers respectively and gives the measure of the strength of the control measure necessary to break the epidemic when the specified method is applied. We now give a brief overview of the design of a control method as outlined by [3]. Given the next generation matrix K, one begins by identifying the entries containing the targeted parameters forming a set ω. This is the set of entries in the next generation matrix that are subject to change when applying the specified control method. The target matrix $\widetilde{K}$ is then defined as;

$$\widetilde{K} = \begin{cases} k_{ij} & (i,j) \in \omega \\ 0 & otherwise \end{cases}$$

The control of the epidemic by targeting the identified parameters is possible if and only if $\rho(K - \widetilde{K}) < 1$. This condition is termed the controllability condition. Provided that the controllability condition holds, then the target reproduction number ($\mathcal{T}_\omega$) is defined by $\mathcal{T}_\omega = \rho(\widetilde{K} \cdot (I - K + \widetilde{K})^{-1})$ where I is a unit matrix. If the basic reproduction number $R_0 > 1$ and the controllability condition holds then $\mathcal{T}_\omega > 1$ and the entry k_{ij}, $(i,j) \in \omega$ of the next generation matrix can be replaced by $\frac{k_{ij}}{\mathcal{T}_\omega}$ to form a new next generation matrix with spectral radius less than unity. If on the other hand $\rho(K - \widetilde{K}) > 1$ then the control of the epidemic by targeting the set ω is not possible and the control measure must be extended to other parameters.

III. Design of the Control Methods for a Two-Patch Metapopulation

In this section we discuss the design of the control methods targeting various parameters and demonstrate how these control strategies could be implemented to bring the epidemic to an end.

3.1 Strategy I: Control strategy that targets transmission rates in both patches.

We consider in this case a control method that target the transmission parameters in both patches i.e. $\beta_{11}, \beta_{12}, \beta_{21}$ and β_{22}. We note that these parameters appear in the elements k_{11} and k_{22} of the next generation matrix (7) thus the target set is given by $\omega = \{(1,1), (2,2)\}$ and the target matrix becomes

$$\widetilde{K} = \begin{pmatrix} \dfrac{\beta_{11} + \beta_{21}}{\mu + \gamma_1 + \phi_{12}} & 0 \\ 0 & \dfrac{\beta_{12} + \beta_{22}}{\mu + \gamma_2 + \phi_{21}} \end{pmatrix}$$

the controlability condition $\rho(K - \widetilde{K}) < 1$ may therefore be stated as

$$\rho(K - \widetilde{K}) = \max_{\lambda} \begin{vmatrix} -\lambda & \dfrac{\phi_{21}}{\mu + \gamma_2 + \phi_{21}} \\ \dfrac{\phi_{12}}{\mu + \gamma_1 + \phi_{12}} & -\lambda \end{vmatrix} < 1$$

or

$$\frac{\phi_{12}\phi_{21}}{(\mu + \gamma_1 + \phi_{12})(\mu + \gamma_2 + \phi_{21})} < 1$$

Since $(\mu + \gamma_1 + \phi_{12})(\mu + \gamma_2 + \phi_{21}) > \phi_{12}\phi_{21}$ then the controlability condition is satisfied and the target reproduction number ($\mathcal{T}_\omega$) is given by;

$$\mathcal{T}_\omega = \rho\left(\widetilde{K}\left(\left(I - K + \widetilde{K}\right)^{-1}\right)\right) = \frac{1}{2}\left(A + \sqrt{B + 4C}\right)$$

where

$$A = \frac{(\beta_{11} + \beta_{21})(\mu + \gamma_2 + \phi_{21}) + (\beta_{12} + \beta_{22})(\mu + \gamma_1 + \phi_{12})}{(\mu + \gamma_1 + \phi_{12})(\mu + \gamma_2 + \phi_{21}) - \phi_{12}\phi_{21}}$$

$$B = \left(\frac{(\beta_{11} + \beta_{21})(\mu + \gamma_2 + \phi_{21}) - (\beta_{12} + \beta_{22})(\mu + \gamma_1 + \phi_{12})}{(\mu + \gamma_1 + \phi_{12})(\mu + \gamma_2 + \phi_{21}) - \phi_{12}\phi_{21}}\right)^2$$

and

$$C = \frac{(\beta_{11} + \beta_{21})(\beta_{12} + \beta_{22})\phi_{12}\phi_{21}}{[(\mu + \gamma_1 + \phi_{12})(\mu + \gamma_2 + \phi_{21}) - \phi_{12}\phi_{21}]^2}$$

since $R_0 > 1$ then by [11, Theorem 2.1], $\mathcal{T}_\omega > 1$ and the disease will be eliminated if the transmission rate β_m is

reduced to less than $\frac{\beta_m}{\mathcal{T}_\omega}$ where $\beta_m = \{\beta_{11}, \beta_{12}, \beta_{21}, \beta_{22}\}$.

The results for this control strategy are illustrated using figure below, we use the initial conditions $S_1(0) = 0.83$, $S_2(0) = 0.90$, $I_1(0) = 0.17$, $I_2(0) = 0.10$ and $R_1(0) = R_2(0) = 0$ and choose the parameter values $\beta_{11} = 0.13, \beta_{12} = 0.10, \beta_{21} = 0.06, \beta_{22} = 0.14, \gamma_1 = 0.05, \gamma_2 = 0.04, \phi_{12} = \psi_{12} = \xi_{12} = \xi_{21} = 0.02, \phi_{21} = 0.03, \psi_{21} = 0.01$, $\mu = 0.01429$ per year and $r = 0.0384$ per year. By using these values, the value of the basic reproduction number becomes $R_0 = 3.5694$ while the controlability condition $\rho(K - \overline{K}) = 0.3497$ which is less than unity and therefore the control of the transmission is possible using the specified control method. We compute the value of the target reproduction number and its value is $\mathcal{T}_\omega = 4.7786$. The disease is therefore controlled by reducing the transmission parameter β_m to less than $\frac{\beta_m}{\mathcal{T}_\omega}$ where $m \in \{11,12,21,22\}$. Figure 2 show the solution curves before the intervention strategies are applied.From this figure, we note that when the infectives are introduced into the population, an outbreak occurs in both patches. When the intervention strategies are introduced, the value of R_0 reduces to 0.9971 and the epidemic does not occur. This is demonstrated by figure 3. From this figure we observe that the number of infectives decays as a function of time (red and black continuous curves) in both patches hence the epidemic is prevented.

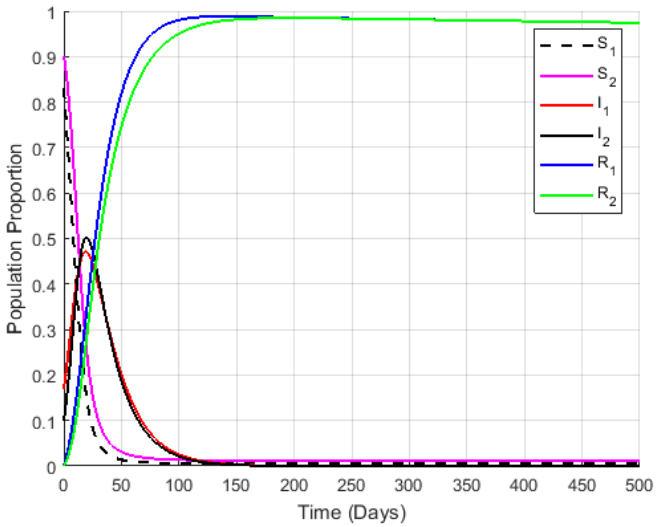


Figure 2: Solution curves for $R_0 = 3.5694$ without control. The basic reproduction number is greater than one and there is an outbreak of the disease in both patches.

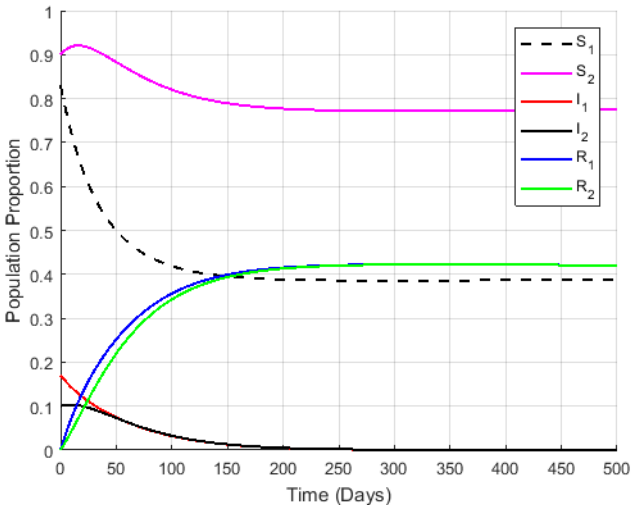
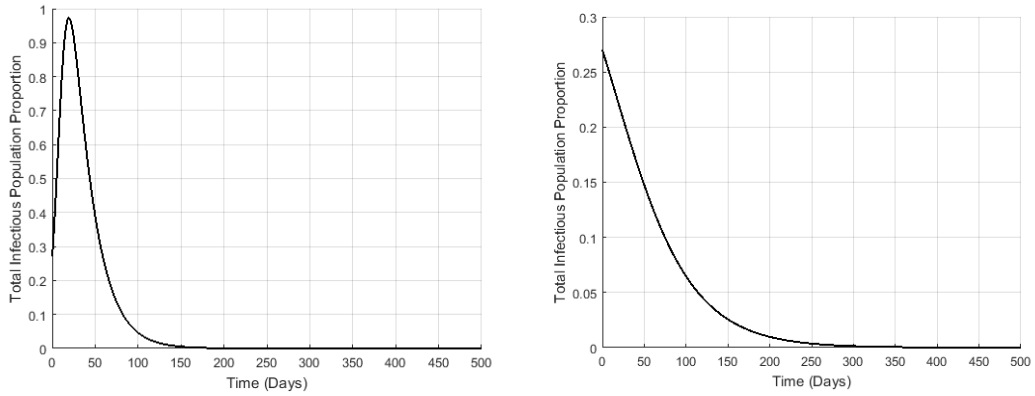


Figure 3: Morbidity curves for $R_0 = 3.5694$. After applying the control strategy the basic reproduction number reduces to 0.9971 which is less than one and the outbreak of the disease is prevented.

Figure 4 (a) show the propagation of the infectious population before the introduction of the intervention strategies. When the infectious individuals are introduced into the population with $R_0 > 1$, the infectious population grows rapidly which indicates an outbreak of the disease in both patches affecting close to half of the entire population. Figure 4 (b) on the other hand show the transmission dynamics of the infectious disease after the introduction of intervention methods. We note that after the infectious individuals are introduced into the population, their population will decay as function of time for all time and the epidemic does not occur. This indicates that the intervention strategies introduced are adequate for the control of the epidemic in both patches.



(a) (b)

Figure 4: Transmission dynamics of the total infectious population proportion (a) before intervention strategies are applied and (b) after intervention strategies are applied

3.2 Strategy II: Control Targets the Transmission and Migration Rates in One Patch

Without losing the generality of the control strategy being applied, we assume that the control strategy targets the transmission and migration rates in the first patch. The target set is therefore given by $\omega = \{(1,1),(2,1)\}$ while the target matrix is given by;

$$\widetilde{K} = \begin{pmatrix} \dfrac{\beta_{11}+\beta_{21}}{\mu+\gamma_1+\phi_{12}} & 0 \\ \dfrac{\phi_{12}}{\mu+\gamma_1+\phi_{12}} & 0 \end{pmatrix}$$

and the controllability condition $\rho\left(K-\widetilde{K}\right) < 1$ is given by;

$$\frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2+\phi_{21}} < 1$$

If the controllability condition is valid then the target reproduction number $\mathcal{T}_\omega$ is given by

$$\mathcal{T}_\omega = \rho\left(\widetilde{K}\left(I-K+\widetilde{K}\right)^{-1}\right)$$

where

$$I-K+\widetilde{K} = \begin{pmatrix} 1 & -\dfrac{\phi_{21}}{(\mu+\gamma_2+\phi_{21})} \\ 0 & \dfrac{(\mu+\gamma_2+\phi_{21})-(\beta_{12}+\beta_{22})}{\mu+\gamma_2+\phi_{21}} \end{pmatrix}$$

and

$$\widetilde{K}\left(I-K+\widetilde{K}\right)^{-1} = \begin{pmatrix} \dfrac{\beta_{11}+\beta_{21}}{\mu+\gamma_1+\phi_{12}} & \dfrac{\phi_{21}(\beta_{11}+\beta_{21})}{(\mu+\gamma_1+\phi_{12})(\mu+\gamma_2+\phi_{21}-\beta_{12}-\beta_{22})} \\ \dfrac{\phi_{12}}{\mu+\gamma_1+\phi_{12}} & \dfrac{\phi_{12}\phi_{21}}{(\mu+\gamma_1+\phi_{12})(\mu+\gamma_2+\phi_{21}-\beta_{12}-\beta_{22})} \end{pmatrix}$$

which is a singular matrix thus

$$\mathcal{T}_\omega = \frac{\beta_{11}+\beta_{21}}{\mu+\gamma_1+\phi_{12}} + \frac{\phi_{12}\phi_{21}}{(\mu+\gamma_1+\phi_{12})(\mu+\gamma_2+\phi_{21}-\beta_{12}-\beta_{22})}$$
$$= \frac{(\beta_{11}+\beta_{21})(\mu+\gamma_2+\phi_{21}-\beta_{12}-\beta_{21})+\phi_{12}\phi_{21}}{(\mu+\gamma_2+\phi_{21}-\beta_{12}-\beta_{21})(\mu+\gamma_1+\phi_{12})}$$

Since $R_0 > 1$ then theorem 2.1 [11] implies that $\mathcal{T}_\omega > 1$ thus the disease can be controlled by reducing the targeted entries of the next generation matrix. The next generation matrix K^c of the controlled system is constructed such that $k_{11}^c = \frac{k_{11}}{\mathcal{T}_\omega}$, $k_{21}^c = \frac{k_{21}}{\mathcal{T}_\omega}$, $k_{12}^c = k_{12}$ and $k_{22}^c = k_{22}$. We therefore determine the new parameters β_{11}^c, β_{21}^c and ϕ_{12}^c such that

$$\frac{\beta_{11}+\beta_{21}}{(\mu+\gamma_1+\phi_{12})\mathcal{T}_\omega} = \frac{\beta_{11}^c+\beta_{21}^c}{\mu+\gamma_1+\phi_{12}^c} \qquad (9)$$

and

$$\frac{\phi_{12}}{(\mu+\gamma_1+\phi_{12})\mathcal{T}_\omega} = \frac{\phi_{12}^c}{\mu+\gamma_1+\phi_{12}^c} \qquad (10)$$

From 10 we have

$$\mu + \gamma_1 + \phi_{12}^c = \frac{\phi_{12}^c \mathcal{T}_\omega (\mu+\gamma_1+\phi_{12})}{\phi_{12}} \qquad (11)$$

substituting equation 11 into 9 and simplifying, we get

$$\beta_{11}^c + \beta_{21}^c = (\beta_{11} + \beta_{21})\frac{\phi_{12}^c}{\phi_{12}}$$

From which

$$\beta_{11}^c = \frac{\beta_{11}\phi_{12}^c}{\phi_{12}}$$

$$\beta_{21}^c = \frac{\beta_{21}\phi_{12}^c}{\phi_{12}}$$

on transposing equation 10, we get

$$\phi_{12}^c = \frac{(\mu+\gamma_1)\phi_{12}}{(\mu+\gamma_1+\phi_{12})\mathcal{T}_\omega - \phi_{12}}$$

We note that $\frac{\phi_{12}^c}{\phi_{12}} = \frac{\mu+\gamma_1}{(\mu+\gamma_1)\mathcal{T}_\omega+\phi_{12}(\mathcal{T}_\omega-1)} < 1$ hence the epidemic control is achieved by decreasing the transmission rates in patch one and the travel outflow from patch one to patch two.

We illustrate this control method by using the initial conditions $S_1(0) = 0.83$, $S_2(0) = 0.90$, $I_1(0) = 0.17$, $I_2(0) = 0.10$ and $R_1(0) = R_2(0) = 0$ and choose the parameter values $\beta_{11} = 0.29, \beta_{12} = 0.15, \beta_{21} = 0.19, \beta_{22} = 0.15, \gamma_1 = 0.20, \gamma_2 = 0.22, \phi_{12} = 0.08, \phi_{21} = 0.09 \psi_{12} = \xi_{12} = \xi_{21} = 0.02, \psi_{21} = 0.01,$ $\mu = 0.01429$ per year and $r = 0.0384$ per year. By using these values, we get $R_0 = 1.8122$ while the controllability criteria $\rho(K - \tilde{K}) = 0.9568 < 1$ hence the disease is controllable. The type reproduction number becomes $\mathcal{T}_\omega = 3.4809$. Thus the critical migration and transmission parameters are given by $\phi_{12}^c = 0.0179$, $\beta_{11}^c = 0.0648$ and $\beta_{21}^c = 0.0425$. Figure 5 show the solution curves for the transmission of the communicable disease before intervention strategies are applied. After applying the control strategy, the basic reproduction number is reduced to less than one and the epidemic is prevented as can be seen in figure 6.

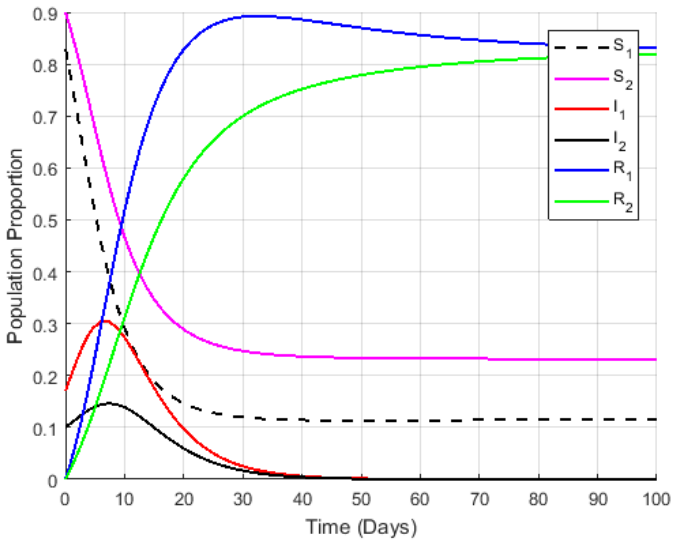


Figure 5: Morbidity curves for $R_0 = 1.8122$ before the control method is applied.

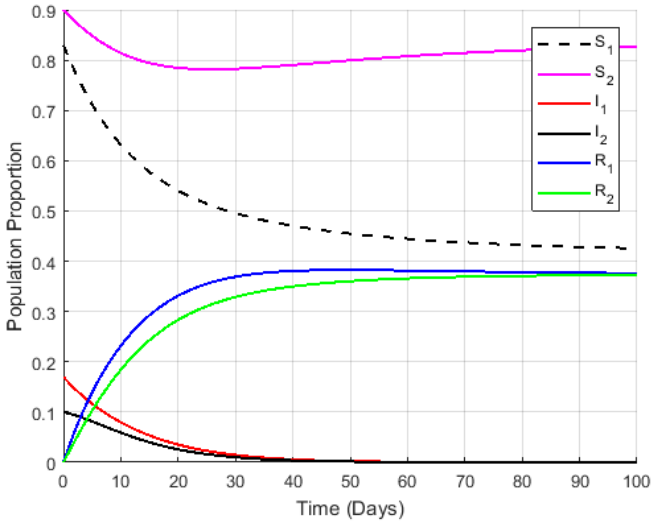
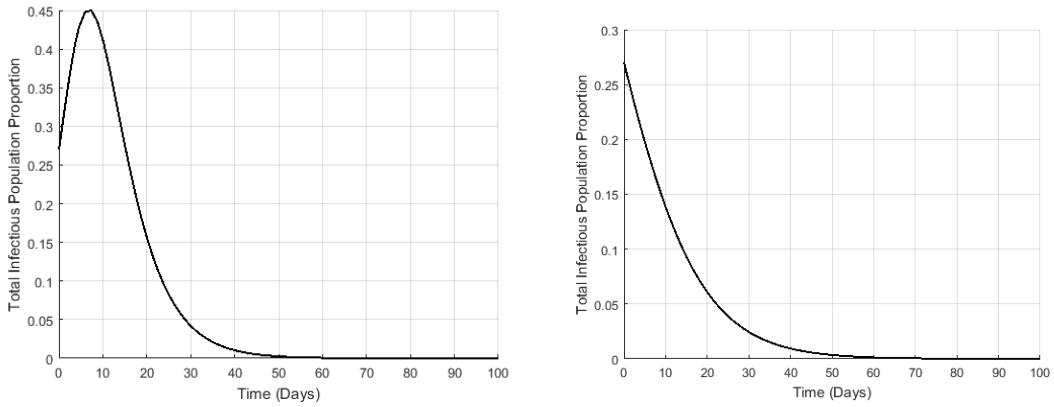


Figure 6: Morbidity curves for $R_0 = 1.8122$. After applying the control strategy the basic reproduction number reduces to less than one and the outbreak of the disease is prevented

Figure 7 (a) show the propagation of the infectious population before the introduction of the intervention strategies. We observe that when the infectious individuals are introduced into the population with $R_0 > 1$, there will be a sharp growth of the infectious population which indicates the outbreak of the disease in both populations. Figure 7 (b) show the transmission dynamics of the infectious population after the introduction of intervention methods. We note that after the infectious individuals are introduced into the population, their population will decay as function of time for all time and the epidemic does not occur. This indicates that the intervention strategies are adequate for the control of the epidemic in both the sub populations.



(a) (b)

Figure 7: Transmission dynamics of the total infectious population proportion (a) before intervention strategies are applied and (b) after intervention strategies are applied.

3.3 Strategy III: Control Targets the Migration Rates

We now investigate a control method that seeks to control the epidemic by changing the travel rates. Let C_1 and C_2 denote the sums of the first and second columns of the next generation matrix 7 and let $\mathcal{R}_1$ and $\mathcal{R}_2$ denote the local reproduction numbers in patch 1 and patch 2 respectively, then

$$C_1 = \frac{\beta_{11} + \beta_{21} + \phi_{12}}{\mu + \gamma_1 + \phi_{12}}, \qquad C_2 = \frac{\beta_{12} + \beta_{22} + \phi_{21}}{\mu + \gamma_2 + \phi_{21}}$$

and

$$\mathcal{R}_1 = \frac{\beta_{11} + \beta_{21}}{\mu + \gamma_1}, \qquad \mathcal{R}_2 = \frac{\beta_{12} + \beta_{22}}{\mu + \gamma_2}$$

A standard result from the theory of matrices is that the spectral radius of a non-negative square matrix is bounded below and above by the minimum and the maximum of the column sums respectively [12].

If $\beta_{11}+\beta_{21}<\mu+\gamma_1$ then $\frac{\beta_{11}+\beta_{21}}{\mu+\gamma_1}<1$ and

$\lim_{\phi_{12}\to\infty}\left(\frac{\beta_{11}+\beta_{21}+\phi_{12}}{\mu+\gamma_1+\phi_{12}}\right)=1.$

Thus $C_1=\frac{\beta_{11}+\beta_{21}+\phi_{12}}{\mu+\gamma_1+\phi_{12}}$ is an increasing function of ϕ_{12} and

$\mathcal{R}_1=\frac{\beta_{11}+\beta_{21}}{\mu+\gamma_1}<\frac{\beta_{11}+\beta_{21}+\phi_{12}}{\mu+\gamma_1+\phi_{12}}<1$

If on the other hand $\beta_{11}+\beta_{21}>\mu+\gamma_1$ then $\frac{\beta_{11}+\beta_{21}}{\mu+\gamma_1}>1$ and

$\lim_{\phi_{12}\to\infty}\left(\frac{\beta_{11}+\beta_{21}+\phi_{12}}{\mu+\gamma_1+\phi_{12}}\right)=1$

Thus $C_1=\frac{\beta_{11}+\beta_{21}+\phi_{12}}{\mu+\gamma_1+\phi_{12}}$ is a decreasing function of ϕ_{12} and

$1<\frac{\beta_{11}+\beta_{21}+\phi_{12}}{\mu+\gamma_1+\phi_{12}}<\frac{\beta_{11}+\beta_{21}}{\mu+\gamma_1}=\mathcal{R}_1$

Similarly if $\beta_{12}+\beta_{22}>\mu+\gamma_2$ then $\frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2}>1$ and

$\mathcal{R}_2=\frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2}<\frac{\beta_{12}+\beta_{22}+\phi_{21}}{\mu+\gamma_2+\phi_{21}}<1$

and when $\beta_{12}+\beta_{22}<\mu+\gamma_2$ then $\frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2}>1$ and

$1<\frac{\beta_{12}+\beta_{22}+\phi_{21}}{\mu+\gamma_2+\phi_{21}}<\frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2}=\mathcal{R}_2$

From the results above we note that the spectral radius of the next generation matrix and therefore the basic reproduction number is bounded below and above by the minimum and the maximum of the local reproduction numbers respectively.

If $\mathcal{R}_1<1$ and $\mathcal{R}_2<1$ then $R_0=\rho(K)<1$ hence the disease free equilibrium is asymptotically stable and no amount of travel rates can destabilize this state.

If on the other hand $\mathcal{R}_1>1$ and $\mathcal{R}_2>1$ then $R_0=\rho(K)>1$ and no amount of travel rate can reduce it to less than one. In this case a control measure targeting to change the travel rates cannot prevent the epidemic. That is the control of the epidemic cannot be achieved by increasing or decreasing the travel rates alone but the control strategy must be extended to the transmission rates.If however one of the local reproduction number is less than one while the other is greater than one, then the control measure targeting the travel rates may be applied to control the epidemic.

Without losing the of generality of the control strategy, we assume that $\mathcal{R}_1>1$ and $\mathcal{R}_2<1$.

Thus $\beta_{11}+\beta_{21}>\mu+\gamma_1$ and $\beta_{12}+\beta_{22}<\mu+\gamma_2$

We consider a different splitting of the Jacobian matrix (J) 6 such that $J=T-V$ to form an alternative Next Generation Matrix $(\widehat{K})$.

where T is a non-negative matrix and V is a non-singular M- Matrix. Thus

$$J=\begin{pmatrix}\beta_{11}+\beta_{21}-(\mu+\gamma_1) & 0\\ 0 & \beta_{12}+\beta_{22}\end{pmatrix}-\begin{pmatrix}\phi_{12} & -\phi_{21}\\ -\phi_{12} & \mu+\gamma_2+\phi_{21}\end{pmatrix}=T-V$$

where

$$T=\begin{pmatrix}\beta_{11}+\beta_{21}-(\mu+\gamma_1) & 0\\ 0 & \beta_{12}+\beta_{22}\end{pmatrix}$$

and

$$V=\begin{pmatrix}\phi_{12} & -\phi_{21}\\ -\phi_{12} & \mu+\gamma_2+\phi_{21}\end{pmatrix}$$

$|V|=(\mu+\gamma_2+\phi_{21})\phi_{12}-\phi_{12}\phi_{21}=(\mu+\gamma_2)\phi_{12}$

Hence

$$V^{-1}=\frac{1}{(\mu+\gamma_2)\phi_{12}}\begin{pmatrix}\mu+\gamma_2+\phi_{21} & \phi_{21}\\ \phi_{12} & \phi_{12}\end{pmatrix}$$

we note that T is non-negative and V is a non-singular $M-$ matrix thus the alternative Next Generation Matrix $(\widehat{K})$ is given by;

$$\widehat{K} = TV^{-1} = \begin{pmatrix} \frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)(\mu+\gamma_2+\phi_{21})}{(\mu+\gamma_2)\phi_{12}} & \frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)\phi_{21}}{(\mu+\gamma_2)\phi_{12}} \\ \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2} & \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2} \end{pmatrix} \quad (12)$$

From equation 12, we note that the targeted parameters appears only in the first row of the alternative Next Generation Matrix thus the target set is given by $\omega = \{(1,1),(1,2)\}$. The target Matrix $(\bar{\widehat{K}})$ is given by;

$$\bar{\widehat{K}} = \begin{pmatrix} \frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)(\mu+\gamma_2+\phi_{21})}{(\mu+\gamma_2)\phi_{12}} & \frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)\phi_{21}}{(\mu+\gamma_2)\phi_{12}} \\ 0 & 0 \end{pmatrix}$$

and

$$\widehat{K} - \bar{\widehat{K}} = \begin{pmatrix} 0 & 0 \\ \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2} & \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2} \end{pmatrix}$$

The controlability condition therefore becomes

$$\rho(\widehat{K} - \bar{\widehat{K}}) = \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2} = \mathcal{R}_2 < 1$$

To find the target reproduction number, we re-write the alternative next generation matrix 12 as;

$$\widehat{K} = \begin{pmatrix} k_{11} & k_{12} \\ k_{21} & k_{22} \end{pmatrix}$$

where

$$k_{11} = \frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)(\mu+\gamma_2+\phi_{21})}{(\mu+\gamma_2)\phi_{12}}$$

$$k_{12} = \frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)\phi_{21}}{(\mu+\gamma_2)\phi_{12}}$$

$$k_{21} = k_{22} = \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2}$$

Thus

$$I - \widehat{K} + \bar{\widehat{K}} = \begin{pmatrix} 1 & 0 \\ -k_{21} & 1-k_{22} \end{pmatrix}$$

whose inverse is given by;

$$(I - \widehat{K} + \bar{\widehat{K}})^{-1} = \begin{pmatrix} 1 & 0 \\ \frac{k_{21}}{1-k_{22}} & \frac{1}{1-k_{22}} \end{pmatrix}$$

and

$$\widehat{K}(I - \widehat{K} + \bar{\widehat{K}})^{-1} = \begin{pmatrix} k_{11} + \frac{k_{12}k_{21}}{1-k_{22}} & \frac{k_{12}}{1-k_{22}} \\ 0 & 0 \end{pmatrix}$$

which is a singular matrix hence the target reproduction number is given by;

$$\mathcal{T}_\omega = \rho(\bar{\widehat{K}}(I - (\widehat{K} - \bar{\widehat{K}}))^{-1})$$

$$\mathcal{T}_\omega = k_{11} + \frac{k_{12}k_{21}}{1-k_{22}} = \frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)(\mu+\gamma_2+\phi_{21})}{(\mu+\gamma_2)\phi_{12}} + \frac{\frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)\phi_{21}}{(\mu+\gamma_2)\phi_{12}} \cdot \frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2}}{1-\frac{\beta_{12}+\beta_{22}}{\mu+\gamma_2}}$$

$$= \frac{\beta_{11}+\beta_{21}-\mu-\gamma_1}{(\mu+\gamma_2)\phi_{12}}\left(\mu+\gamma_2+\phi_{21}+\frac{(\beta_{11}+\beta_{22})\phi_{21}}{\mu+\gamma_2-\beta_{12}-\beta_{22}}\right)$$

Since $R_0 > 1$ then $\mathcal{T}_\omega > 1$ thus the controlled matrix $(\bar{\widehat{K}}^c)$ can be constructed by defining its elements k_{ij}^c by; $k_{11}^c = \frac{k_{11}}{\mathcal{T}_\omega}$, $k_{12}^c = \frac{k_{12}}{\mathcal{T}_\omega}$, $k_{21}^c = k_{21}$ and $k_{22}^c = k_{22}$. We therefore need the transformation of the parameters ϕ_{12} and ϕ_{21} such that $k_{11}^c = \frac{k_{11}}{\mathcal{T}_\omega}$ and $k_{12}^c = \frac{k_{12}}{\mathcal{T}_\omega}$. The new travel rates ϕ_{12}^c and ϕ_{21}^c are determined such that

$$\frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)(\mu+\gamma_2+\phi_{21})}{(\mu+\gamma_2)\phi_{12}\mathcal{T}_\omega} = \frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)(\mu+\gamma_2+\phi_{21}^c)}{(\mu+\gamma_2)\phi_{12}^c} \quad (13)$$

and

$$\frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)\phi_{21}}{(\mu+\gamma_2)\phi_{12}\mathcal{T}_\omega} = \frac{(\beta_{11}+\beta_{21}-\mu-\gamma_1)\phi_{21}^c}{(\mu+\gamma_2)\phi_{12}^c}$$

Multiplying both sides of equation 13 by $\frac{\mu+\gamma_2}{\beta_{11}+\beta_{21}-\mu-\gamma_1}$ and simplifying, we get;

$$\frac{1}{\phi_{12}\mathcal{T}_\omega}(\mu+\gamma_2)+\frac{\phi_{21}}{\phi_{12}\mathcal{T}_\omega} = \frac{1}{\phi_{12}^c}(\mu+\gamma_2)+\frac{\phi_{21}^c}{\phi_{12}^c}$$

from which

$\phi_{12}^c = \phi_{12}\mathcal{T}_\omega$

$\phi_{21}^c = \phi_{21}$

The control strategy therefore involves increasing the travel inflow into patch 2 with $\mathcal{R}_2 < 1$ while the travel inflow into patch 1 with $\mathcal{R}_1 > 1$ should remain unchanged.

The results for this control method are illustrated by the figures 12 and 13. In the numerical simulations we use the initial conditions $S_1(0) = 0.83$, $S_2(0) = 0.90$, $I_1(0) = 0.17$, $I_2(0) = 0.10$ and $R_1(0) = R_2(0) = 0$ and choose the parameter values $\beta_{11} = 0.16, \beta_{12} = 0.007, \beta_{21} = 0.10, \beta_{22} = 0.009, \gamma_1 = 0.14, \gamma_2 = 0.20, \phi_{12} = 0.05, \phi_{21} = 0.08, \psi_{12} = \xi_{12} = \xi_{21} = 0.02, \psi_{21} = 0.01,$ $\mu = 0.01429$ per year and $r = 0.0384$ per year. Using these values, $R_0 = 1.4232$ and the controllability criteria $\rho(K-\bar{K}) = 0.08 < 1$ thus the target reproduction number is computed and its value is $\mathcal{T}_\omega = 3.4421$.

Figure 8 show the solution curves for the transmission of the communicable disease before intervention strategies are applied. After applying the control method, the basic reproduction number reduces to $R_0 = 0.9839$ which is less than one and the epidemic is prevented as can be seen in figure 9.

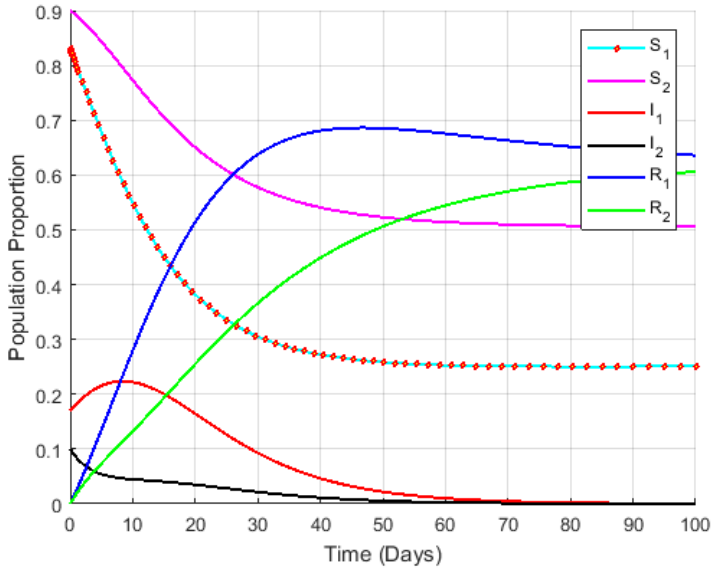


Figure 8: Morbidity curves for $R_0 = 1.4232$. The local reproduction numbers $\mathcal{R}_1 = 1.8566, \mathcal{R}_2 = 0.0800$ thus the epidemic occurs in patch one.

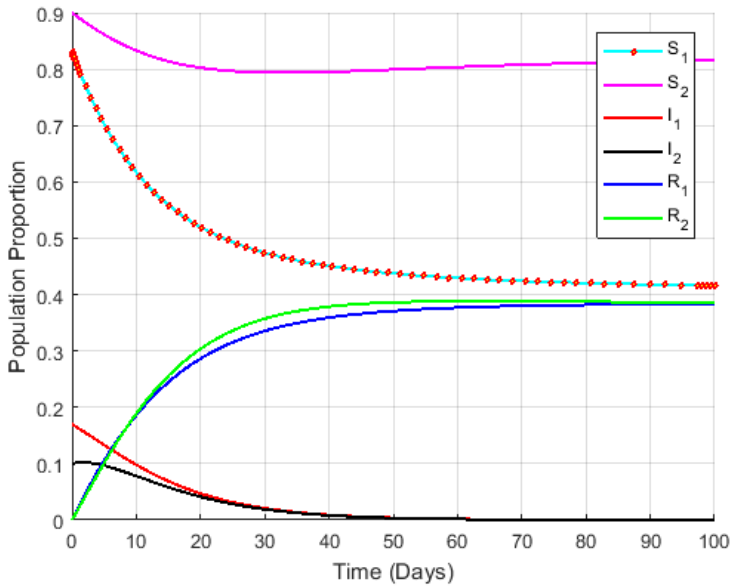


Figure 9: Morbidity curves for $R_0 = 1.4232$. After applying the control strategy the basic reproduction number reduces to less than one and the outbreak of the disease is prevented.

IV. Equilibrium Analysis

At equilibrium $\frac{dS_i}{dt} = \frac{dI_i}{dt} = \frac{dR_i}{dt} = 0, \quad i = 1,2$ thus we get the equations;

$$-\beta_{11}S_1I_1 - \beta_{12}S_1I_2 - \psi_{12}S_1 + \psi_{21}S_2 + r - \mu S_1 = 0$$
$$-\beta_{21}S_2I_1 - \beta_{22}S_2I_2 + \psi_{12}S_1 - \psi_{21}S_2 + r - \mu S_2 = 0$$
$$\beta_{11}S_1I_1 + \beta_{21}S_2I_1 - \mu I_1 - \gamma_1 I_1 - \phi_{12}I_1 + \phi_{21}I_2 = 0 \quad (14)$$
$$\beta_{12}S_1I_2 + \beta_{22}S_2I_2 - \mu I_2 - \gamma_2 I_2 + \phi_{12}I_1 - \phi_{21}I_2 = 0 \quad (15)$$
$$\gamma_1 I_1 - \mu R_1 - \xi_{12}R_1 + \xi_{21}R_2 = 0$$
$$\gamma_2 I_2 - \mu R_2 + \xi_{12}R_1 - \xi_{21}R_2 = 0$$

From equation 14,

$$I_1 = \frac{-\phi_{21}I_2}{\beta_{11}S_1 + \beta_{21}S_2 - \mu - \gamma_1 - \phi_{12}} \quad (16)$$

Substituting this into equation 15, we get;

$$\beta_{12}S_1I_2 + \beta_{22}S_2I_2 - \mu I_2 - \gamma_2 I_2 + \frac{-\phi_{12}\phi_{21}I_2}{\beta_{11}S_1 + \beta_{21}S_2 - \mu - \gamma_1 - \phi_{12}} - \phi_{21}I_2 = 0$$

or

$$\left(\beta_{12}S_1 + \beta_{22}S_2 - \mu - \gamma_2 + \frac{-\phi_{12}\phi_{21}}{\beta_{11}S_1 + \beta_{21}S_2 - \mu - \gamma_1 - \phi_{12}} - \phi_{21}\right) I_2 = 0 \quad (17)$$

4.1 Disease Free Equilibrium (DFE)

At disease free equilibrium state there are no infectious individuals thus we substitute $I_2 = 0$ in equation 16, this yields $I_1 = 0$ thus the entire population comprise of the susceptible individuals only. The disease free equilibrium is therefore given by;

$$(S_1, S_2, I_1, I_2, R_1, R_2) = (1,1,0,0,0,0) \quad (18)$$

4.2 Stability Analysis of the Disease Free Equilibrium

To determine the stability of the disease free equilibrium, we first evaluate the Jacobian matrix J at the equilibrium point. The Jacobian matrix of the system 6 is given by;

$$J = \begin{pmatrix} \Omega_1 & \psi_{21} & -\beta_{11}S_1 & -\beta_{12}S_1 & 0 & 0 \\ \psi_{12} & \Omega_2 & -\beta_{21}S_2 & -\beta_{22}S_2 & 0 & 0 \\ \beta_{11}I_1 & \beta_{21}I_1 & \Omega_3 & \phi_{21} & 0 & 0 \\ \beta_{12}I_2 & \beta_{22}I_2 & \phi_{12} & \Omega_4 & 0 & 0 \\ 0 & 0 & \gamma_1 & 0 & -\mu - \xi_{12} & \xi_{21} \\ 0 & 0 & 0 & \gamma_2 & \xi_{12} & -\mu - \xi_{21} \end{pmatrix} \quad (19)$$

where

$$\Omega_1 = -\beta_{11}I_1 - \beta_{12}I_2 - \psi_{12} - \mu$$
$$\Omega_2 = -\beta_{21}I_1 - \beta_{22}I_2 - \psi_{21} - \mu$$
$$\Omega_3 = \beta_{11}S_1 + \beta_{21}S_2 - \mu - \gamma_1 - \phi_{12}$$
$$\Omega_4 = \beta_{12}S_1 + \beta_{22}S_2 - \mu - \gamma_2 - \phi_{21}$$

substituting the values of $S_1, S_2, I_1, I_2, R_1 \quad and \quad R_2$ at DFE we get;

$$J_{DFE} = \begin{pmatrix} -\psi_{12} - \mu & \psi_{21} & -\beta_{11} & -\beta_{12} & 0 & 0 \\ \psi_{12} & -\psi_{21} - \mu & -\beta_{21} & -\beta_{22} & 0 & 0 \\ 0 & 0 & \Theta_1 & \phi_{21} & 0 & 0 \\ 0 & 0 & \phi_{12} & \Theta_2 & 0 & 0 \\ 0 & 0 & \gamma_1 & 0 & -\mu - \xi_{12} & \xi_{21} \\ 0 & 0 & 0 & \gamma_2 & \xi_{12} & -\mu - \xi_{21} \end{pmatrix} \qquad (20)$$

where

$$\Theta_1 = \beta_{11} + \beta_{21} - \mu - \gamma_1 - \phi_{12}$$
$$\Theta_2 = \beta_{12} + \beta_{22} - \mu - \gamma_2 - \phi_{21}$$

The Eigen values of the Jacobian matrix are given by the equations;

$$\begin{vmatrix} -\psi_{12} - \mu - \lambda & \psi_{21} \\ \psi_{12} & -\psi_{21} - \mu - \lambda \end{vmatrix} = 0 \qquad (21)$$

$$\begin{vmatrix} -\mu - \xi_{12} - \lambda & \xi_{21} \\ \xi_{12} & -\mu - \xi_{21} - \lambda \end{vmatrix} = 0 \qquad (22)$$

$$\begin{vmatrix} \Theta_1 - \lambda & \phi_{21} \\ \phi_{12} & \Theta_2 - \lambda \end{vmatrix} = 0 \qquad (23)$$

From equation 21

$$\lambda_{1,2} = \frac{-(2\mu + \psi_{12} + \psi_{21}) \pm \sqrt{(2\mu + \psi_{12} + \psi_{21})^2 - 4(\mu^2 + \mu(\psi_{12} + \psi_{21}))}}{2}$$

Thus $Re\{\lambda_{1,2}\} < 0$

From equation 22 we get;

$$\lambda_{3,4} = \frac{-(2\mu + \xi_{12} + \xi_{21}) \pm \sqrt{(2\mu + \xi_{12} + \xi_{21})^2 - 4(\mu^2 + \mu(\xi_{12} + \xi_{21}))}}{2}$$

Thus $Re\{\lambda_{3,4}\} < 0$

and from equation 23 we have

$$\lambda_{5,6} = \frac{\Theta_1 + \Theta_2 \pm \sqrt{(\Theta_1 - \Theta_2)^2 + 4\phi_{12}\phi_{21}}}{2}$$

Thus the disease free equilibrium is asymptotically stable if

$$\Theta_1 + \Theta_2 + \sqrt{(\Theta_1 - \Theta_2)^2 + 4\phi_{12}\phi_{21}} < 0$$

From which

$$\frac{\phi_{12}\phi_{21}}{\Theta_1\Theta_2} < 1 \text{ or}$$

$$\frac{(\beta_{11}+\beta_{21})(\mu+\gamma_2+\phi_{21})+(\beta_{12}+\beta_{22})(\mu+\gamma_1+\phi_{12})}{(\beta_{11}+\beta_{21})(\beta_{12}+\beta_{22})+\phi_{21}(\mu+\gamma_1)+\phi_{12}(\mu+\gamma_2)+(\mu+\gamma_1)(\mu+\gamma_2)} < 1 \qquad (24)$$

V. Well posedness

A time invariant system is said to be well posed if it has a unique solution which continuously depends on the data. For a system that describes the population, there is an additional condition that the solution must remain positive at all times [14].

5.1 Lipschitz Continuity

A function $f(x, y)$ is said to be locally Lipschitz continuous or simply locally Lipschitz at a point $(x, y_0) \in D$ (where D is an open set) if (x, y_0) has a neighbourhood D_0 such that

$$|f(x, y_1) - f(x, y_2)| < L|y_1 - y_2|, \quad \forall \quad (x, y_1), (x, y_2) \in D_0$$

where L is known as the Lipschitz constant and is fixed over the neighbourhood D_0. A function $f(x, y)$ is said to be locally Lipschitz in a domain if it is locally Lipschitz at each point of the domain. We denote the set of all locally Lipschitz functions by L_l and write symbolically $f \in L_l$ whenever f is a locally Lipschitz function. Moreover, we say that a function $f(x, y)$ is globally Lipschitz in a domain D and write $f \in L_g$ (where L_g is the set of all globally Lipschitz functions) if $f(x, y)$ is locally Lipschitz at all points of the domain with the same Lipschitz constant (L) in the entire domain.

Theorem 5.1 ***(Picard-Lipschitz Theorem)****[13] Let $D \subset \mathbb{R}^n$ be a domain and $J \subset \mathbb{R}$ be an interval containing the point x_0. Let Γ be a closed and bounded sub-interval of J such that $x_0 \in \Gamma$. Let $f: J \times D \to \mathbb{R}^n$ be a continuous function. Let $y_i(x) \quad i \in \{1,2,\dots,n\}$ be a solution of the system*

$$\frac{dy_i}{dx} = f_i(x, y_1, y_2, \dots, y_n), y_i(x_0) = y_0 \quad on \quad \Gamma \qquad (25)$$

If the function $f_i(x, y_1, y_2, \dots, y_n)$ satisfies the Lipschitz condition with respect to the variable $y_k, \quad k \in \{1,2,\dots,n\}$ then the system 25 has a unique solution which continuously depends on the data.

Proposition 5.1 *Let $D \subset \mathbb{R}^n$ and let $(t_0, \eta_0) \in D$*
where $\eta_0 = \{S_i(t_0), S_j(t_0), I_i(t_0), I_j(t_0), R_i(t_0), R_j(t_0)\}$ then the system 3 has a unique solution which depends continuously on the data.

Proof. We re-write system 3 as

$$\frac{dS_i}{dt} = f_1(\eta)$$
$$\frac{dI_i}{dt} = f_2(\eta)$$
$$\frac{dR_i}{dt} = f_3(\eta)$$

where

$$f_1(\eta) = r - \mu S_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j + \sum_{j=1, j\neq i}^{n} \psi_{ji} S_j - \sum_{j=1, j\neq i}^{n} \psi_{ij} S_i$$

$$f_2(\eta) = \sum_{j=1}^{n} \beta_{ji} S_j I_i - (\mu + \gamma_i) I_i + \sum_{j=1, j\neq i}^{n} \phi_{ji} I_j - \sum_{j=1, j\neq i}^{n} \phi_{ij} I_i$$

$$f_3(\eta) = \gamma_i I_i - \mu R_i + \sum_{j=1, j\neq i}^{n} \xi_{ji} R_j - \sum_{j=1, j\neq i}^{n} \xi_{ij} R_i$$

and $\eta = \{S_1, S_2, I_1, I_2, R_1, R_2\}$

Let $D \subset \mathbb{R}^n$ and let $(t_0, \eta_0) \in D$ where $\eta_0 = \{S_i(t_0), S_j(t_0), I_i(t_0), I_j(t_0), R_i(t_0), R_j(t_0)\}$, we show that the functions $f_1(\eta), f_2(\eta)$ and $f_3(\eta)$ are all locally Lipschitz with respect to the variable $x \in \eta$.

For the function $f_1(\eta)$ we have;

$$\left|f_1(\eta \backslash S_i, S_i(t_1)) - f_1(\eta \backslash S_i, S_i(t_2))\right|$$
$$= \left| r - \mu S_i(t_1) - \sum_{j=1}^{n} \beta_{ij} S_i(t_1) I_j + \sum_{j=1, j\neq i}^{n} \psi_{ji} S_j - \sum_{j=1, j\neq i}^{n} \psi_{ij} S_i(t_1) \right.$$
$$\left. - \left(r - \mu S_i(t_2) - \sum_{j=1}^{n} \beta_{ij} S_i(t_2) I_j + \sum_{j=1, j\neq i}^{n} \psi_{ji} S_j - \sum_{j=1, j\neq i}^{n} \psi_{ij} S_i(t_2) \right) \right|$$

$$\left|f_1(\eta \backslash S_i, S_i(t_1)) - f_1(\eta \backslash S_i, S_i(t_2))\right| = \left| -\mu - \sum_{j=1}^{n} \beta_{ij} I_j - \sum_{j=1, j\neq i}^{n} \psi_{ij} \right| |S_i(t_1) - S_i(t_2)|$$

$$\left|f_1(\eta \backslash S_i, S_i(t_1)) - f_1(\eta \backslash S_i, S_i(t_2))\right| \leq M_1 |S_i(t_1) - S_i(t_2)|$$

where

$$M_1 = \max_{I_j \in D} \left| -\mu - \sum_{j=1}^{n} \beta_{ij} I_j - \sum_{j=1, j\neq i}^{n} \psi_{ij} \right|$$

$$\left|f_1\left(\eta \backslash S_j, S_j(t_1)\right) - f_1\left(\eta \backslash S_j, S_j(t_2)\right)\right|$$
$$= \left| r - \mu S_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j + \sum_{j=1, j\neq i}^{n} \psi_{ji} S_j(t_1) - \sum_{j=1, j\neq i}^{n} \psi_{ij} S_i \right.$$
$$\left. - \left(r - \mu S_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j + \sum_{j=1, j\neq i}^{n} \psi_{ji} S_j(t_2) - \sum_{j=1, j\neq i}^{n} \psi_{ij} S_i \right) \right|$$

$$\left|f_1\left(\eta\backslash S_j, S_j(t_1)\right) - f_1\left(\eta\backslash S_j, S_j(t_2)\right)\right| = \left|\sum_{j=1, j\neq i}^{n} \psi_{ji}\right| \left|S_j(t_1) - S_j(t_2)\right|$$

$$\left|f_1\left(\eta\backslash S_j, S_j(t_1)\right) - f_1\left(\eta\backslash S_j, S_j(t_2)\right)\right| \leq M_2 \left|S_j(t_1) - S_j(t_2)\right|$$

where

$$M_2 = \left|\sum_{j=1, j\neq i}^{n} \psi_{ji}\right|$$

$$\left|f_1\left(\eta\backslash I_j, I_j(t_1)\right) - f_1\left(\eta\backslash I_j, I_j(t_2)\right)\right|$$
$$= \left| r - \mu S_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j(t_1) + \sum_{j=1, j\neq i}^{n} \psi_{ji} S_j - \sum_{j=1, j\neq i}^{n} \psi_{ij} S_i \right.$$
$$\left. - \left(r - \mu S_i - \sum_{j=1}^{n} \beta_{ij} S_i I_j(t_2) + \sum_{j=1, j\neq i}^{n} \psi_{ji} S_j - \sum_{j=1, j\neq i}^{n} \psi_{ij} S_i \right) \right|$$

$$\left|f_1\left(\eta\backslash I_j, I_j(t_1)\right) - f_1\left(\eta\backslash I_j, I_j(t_2)\right)\right| = \left|-\sum_{j=1}^{n} \beta_{ij} S_i\right| \left|I_j(t_1) - I_j(t_2)\right|$$

$$\left|f_1\left(\eta\backslash I_j, I_j(t_1)\right) - f_1\left(\eta\backslash I_j, I_j(t_2)\right)\right| \leq M_3 \left|I_j(t_1) - I_j(t_2)\right|$$

where

$$M_3 = \max_{S_i \in D} \left|-\sum_{j=1}^{n} \beta_{ij} S_i\right|$$

For the function $f_2(\eta)$ we have;

$$\left|f_2\left(\eta\backslash I_i, I_i(t_1)\right) - f_2\left(\eta\backslash I_i, I_i(t_2)\right)\right|$$
$$= \left| \left(\sum_{j=1}^{n} \beta_{ij} S_j I_i(t_1) - (\mu + \gamma_i) I_i(t_1) + \sum_{j=1, j\neq i}^{n} \phi_{ji} I_j - \sum_{j=1, j\neq i}^{n} \phi_{ij} I_i(t_1) \right) \right.$$
$$\left. - \left(\sum_{j=1}^{n} \beta_{ij} S_j I_i(t_2) - (\mu + \gamma_i) I_i(t_2) + \sum_{j=1, j\neq i}^{n} \phi_{ji} I_j - \sum_{j=1, j\neq i}^{n} \phi_{ij} I_i(t_2) \right) \right|$$

$$\left|f_2\left(\eta\backslash I_i, I_i(t_1)\right) - f_2\left(\eta\backslash I_i, I_i(t_2)\right)\right| = \left|\sum_{j=1}^{n} \beta_{ij} S_j - (\mu + \gamma_i) - \sum_{j=1, j\neq i}^{n} \phi_{ij}\right| \left|I_i(t_1) - I_i(t_2)\right|$$

$$\left|f_2\left(\eta\backslash I_i, I_i(t_1)\right) - f_2\left(\eta\backslash I_i, I_i(t_2)\right)\right| \leq M_4 \left|I_i(t_1) - I_i(t_2)\right|$$

where

$$M_4 = \max_{S_j \in D} \left|\sum_{j=1}^{n} \beta_{ij} S_j - (\mu + \gamma_i) - \sum_{j=1, j\neq i}^{n} \phi_{ij}\right|$$

$$\left|f_2\left(\eta\backslash I_j, I_j(t_1)\right) - f_2\left(\eta\backslash I_j, I_j(t_2)\right)\right|$$
$$= \left| \left(\sum_{j=1}^{n} \beta_{ij} S_j I_i - (\mu + \gamma_i) I_i + \sum_{j=1, j\neq i}^{n} \phi_{ji} I_j(t_1) - \sum_{j=1, j\neq i}^{n} \phi_{ij} I_i \right) \right.$$
$$\left. - \left(\sum_{j=1}^{n} \beta_{ij} S_j I_i - (\mu + \gamma_i) I_i + \sum_{j=1, j\neq i}^{n} \phi_{ji} I_j(t_2) - \sum_{j=1, j\neq i}^{n} \phi_{ij} I_i \right) \right|$$

$$\left|f_2\left(\eta\backslash I_j, I_j(t_1)\right) - f_2\left(\eta\backslash I_j, I_j(t_2)\right)\right| = \left|\sum_{j=1, j\neq i}^{n} \phi_{ji}\right| |I_j(t_1) - I_j(t_2)|$$

$$\left|f_2\left(\eta\backslash I_j, I_j(t_1)\right) - f_2\left(\eta\backslash I_j, I_j(t_2)\right)\right| \leq M_5 |I_j(t_1) - I_j(t_2)|$$

where

$$M_5 = \sum_{j=1, j\neq i}^{n} \phi_{ji}$$

$$\left|f_2\left(\eta\backslash S_j, S_j(t_1)\right) - f_2\left(\eta\backslash S_j, S_j(t_2)\right)\right|$$
$$= \left|\left(\sum_{j=1}^{n} \beta_{ij} S_j(t_1) I_i - (\mu + \gamma_i) I_i + \sum_{j=1, j\neq i}^{n} \phi_{ji} I_j - \sum_{j=1, j\neq i}^{n} \phi_{ij} I_i\right)\right.$$
$$\left. - \left(\sum_{j=1}^{n} \beta_{ij} S_j(t_2) I_i - (\mu + \gamma_i) I_i + \sum_{j=1, j\neq i}^{n} \phi_{ji} I_j - \sum_{j=1, j\neq i}^{n} \phi_{ij} I_i\right)\right|$$

$$\left|f_2\left(\eta\backslash S_j, S_j(t_1)\right) - f_2\left(\eta\backslash S_j, S_j(t_2)\right)\right| = \left|\sum_{j=1}^{n} \beta_{ij} I_i\right| |S_j(t_1) - S_j(t_2)|$$

$$\left|f_2\left(\eta\backslash S_j, S_j(t_1)\right) - f_2\left(\eta\backslash S_j, S_j(t_2)\right)\right| \leq M_6 |S_j(t_1) - S_j(t_2)|$$

where

$$M_6 = \max_{I_i \in D} \sum_{j=1}^{n} \beta_{ij} I_i$$

For the function $f_3(\eta)$ we have;

$$\left|f_3\left(\eta\backslash R_i, R_i(t_1)\right) - f_3\left(\eta\backslash R_i, R_i(t_2)\right)\right|$$
$$= \left|\left(\gamma_i I_i - \mu R_i(t_1) + \sum_{j=1, j\neq i}^{n} \xi_{ji} R_j - \sum_{j=1, j\neq i}^{n} \xi_{ij} R_i(t_1)\right) - \left(\gamma_i I_i - \mu R_i(t_2) + \sum_{j=1, j\neq i}^{n} \xi_{ji} R_j\right.\right.$$
$$\left.\left. - \sum_{j=1, j\neq i}^{n} \xi_{ij} R_i(t_2)\right)\right|$$

$$\left|f_3\left(\eta\backslash R_i, R_i(t_1)\right) - f_3\left(\eta\backslash R_i, R_i(t_2)\right)\right| = \left|-\mu - \sum_{j=1, j\neq i}^{n} \xi_{ij}\right| |R_i(t_1) - R_i(t_2)|$$

$$\left|f_3\left(\eta\backslash R_i, R_i(t_1)\right) - f_3\left(\eta\backslash R_i, R_i(t_2)\right)\right| \leq M_7 |R_i(t_1) - R_i(t_2)|$$

where

$$M_7 = \left|-\mu - \sum_{j=1, j\neq i}^{n} \xi_{ij}\right|$$

$$\left|f_3\left(\eta\backslash I_i, I_i(t_1)\right) - f_3\left(\eta\backslash I_i, I_i(t_2)\right)\right|$$
$$= \left|\left(\gamma_i I_i(t_1) - \mu R_i + \sum_{j=1, j\neq i}^{n} \xi_{ji} R_j - \sum_{j=1, j\neq i}^{n} \xi_{ij} R_i\right) - \left(\gamma_i I_i(t_2) - \mu R_i + \sum_{j=1, j\neq i}^{n} \xi_{ji} R_j\right.\right.$$
$$\left.\left. - \sum_{j=1, j\neq i}^{n} \xi_{ij} R_i\right)\right|$$

$$\left|f_3\left(\eta\backslash I_i, I_i(t_1)\right) - f_3\left(\eta\backslash I_i, I_i(t_2)\right)\right| = |\gamma_i| |I_i(t_1) - I_i(t_2)|$$

$$\left|f_3\left(\eta\backslash I_i, I_i(t_1)\right) - f_3\left(\eta\backslash I_i, I_i(t_2)\right)\right| \leq M_8 |I_i(t_1) - I_i(t_2)|$$

where

$$M_8 = \max_{i=1,2,\ldots n} (\gamma_i)$$

$$\left|f_3\left(\eta\backslash R_j, R_j(t_1)\right) - f_3\left(\eta\backslash R_j, R_j(t_2)\right)\right|$$
$$= \left|\left(\gamma_i I_i - \mu R_i + \sum_{j=1, j\neq i}^{n} \xi_{ji} R_j(t_1) - \sum_{j=1, j\neq i}^{n} \xi_{ij} R_i\right) - \left(\gamma_i I_i - \mu R_i + \sum_{j=1, j\neq i}^{n} \xi_{ji} R_j(t_2) - \sum_{j=1, j\neq i}^{n} \xi_{ij} R_i\right)\right|$$

$$\left|f_3\left(\eta\backslash R_j, R_j(t_1)\right) - f_3\left(\eta\backslash R_j, R_j(t_2)\right)\right| = \left|\sum_{j=1, j\neq i}^{n} \xi_{ji}\right| |R_j(t_1) - R_j(t_2)|$$

$$\left|f_3\left(\eta\backslash R_j, R_j(t_1)\right) - f_3\left(\eta\backslash R_j, R_j(t_2)\right)\right| \leq M_9 |R_j(t_1) - R_j(t_2)|$$

where

$$M_9 = \left|\sum_{j=1, j\neq i}^{n} \xi_{ji}\right|$$

We observe that the three functions $f_1(\eta), f_2(\eta)$ and $f_3(\eta)$ are all locally Lipschitz continuous in D and therefore by theorem 5.1 the system 3 has a solution which exist at all times and that this solution is unique and continuously depends on the data and therefore the system is well posed.

VI. Conclusion

In this paper we have done an investigation of the transmission of a infectious disease in a metapopulation setup with both coupling and migration of individuals and developed a mathematical model for the transmission of infectious diseases in a metapopulation with demographic factors and migration of individuals.

We then carried out an investigation of the existence of equilibrium states for the models and observed that the disease free equilibrium was asymptotically stable provided that the basic reproduction number does not exceed one. The analysis of the basic reproduction number showed that its value was affected by the disease reproduction rate in each patch. The analysis also showed that its value could not exceed one unless the local reproduction number of the disease was greater than one in at least one of the sub-populations. We further conducted investigation of various control methods available for the health control practitioners. The object of this investigation was to establish the strength of the control measure required to control the epidemic. The result of this investigation demonstrated that the epidemic control was possible by targeting the transmission rates in the sub-populations where the local reproduction numbers exceeded one. For a two patch model we described how the method could be used to control the outbreak of the disease by applying a method that decreases the transmission probability and travel restrictions and determined the critical effort required for the control of the epidemic. Thus in the case of limited resources, health control practitioners should implement the control methods in the patches where the local reproduction number is greater than one. The control methods may include vaccination of susceptible individuals, contact tracing, social distancing etc. This optimal strategy assumes that the benefit of the recovered individual is the same irrespective of the geographical location of the individual and therefore gives focus to the overall benefit of the entire population when the control strategy is applied rather than specific individuals.

References

[1]. J. Arino, J. R. Davis, D. Hartley, R. Jordan, J. M. Miller, and P. van den Driessche. A multi-species epidemic model with spatial dynamics. *Mathematical Medicine and Biology*, 22(2):129–142, 2005.

[2]. Mutuguta John Wanjau, Rotich Titus and Chepkwony Isaac, Mathematical Modeling of the Transmission Dynamics of Measles under the Effect of Vaccination, *IOSR Journal of Mathematics*, Vol. 15 Issue 4, Ser. II. pp 10-19, ISSN: 2278-5728, 2019.

[3]. Knipl Diana. A new approach for designing disease intervention strategies in metapopulation models. *Journal of Biological Dynamics*, 10(1):71–94, 2016.

[4]. O. Diekmann, J. A. P. Heesterbeek, and M. G. Roberts. The construction of the next generation matrices for compartmental epidemic models. *Journal of Royal Society Interface*, 7:873–885, 2010.

[5]. Augustino Isdory, Eunice W. Mureithi, and David J. T. Sumpter. The impact of human mobility on HIV transmission in Kenya. *PLoS ONE*, 10(11):1–21, 2015.

[6]. M. Jesse and J. A. P. Heesterbeek. Divide and conquer, persistence of infectious agents in spatial metapopulation of hosts. *Journal of Theoretical Biology*, 275:12–20, 2011.

[7]. R. Levins, T. Awerbuch, and U Brinkman. The emergence of new diseases. *American Scientist*, 82:52–60, 1994.

[8]. A. L. Lloyd and V. A. A. Jansen. Spatiotemporal dynamics of epidemics: synchrony in metapopulation models. *Mathematical Biosciences*, 188:1–16, 2004.

[9]. P. Martens. How will climate change affect human health. *American Scientist*, 87:534–541, 1999.

[10]. M.G. Roberts and J.A.P. Heesterbeek. A new method to estimate the effort required to control an infectious disease. *The Royal Society, London*, 270:1359–1364, 2003.
[11]. Zhisheng Shuai, J. A. P. Heesterbeek, and P. van den Driessche. Extending the type reproduction number to infectious disease control targeting contacts between types. *Journal of Mathematical Biology*, 67:1067–1082, 2013.
[12]. Te Wang, Lv Hongbin, and Sang Haifeng. Estimations for spectral radius of non-negative matrices and the smallest eigenvalue of m-matrices. *Journal of Inequalities and Applications*, 477:1–11, 2014.
[13]. Walter Wolfgang,*Ordinary Differential Equations*. Springer-Verlag New York Inc., ISBN: 0-387-98459-3, 1998.
[14]. M. Zhien, Z. Yicang, and W. Jianhong. Modeling and dynamics of infectious diseases. *World Scientific Publishing Co. Pte Ltd*, ISBN: 978-7-04-024757-2, 2009.

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