Modeling the Dynamics of Tuberculosis in a Coupled Metapopulation

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Abstract

Tuberculosis (TB) is currently one of the key health tests in many developing countries, Kenya included. TB is a curable transmissible ailment caused by Mycobacterium tuberculosis. The formation of the tubercles in tissues of the body like in the lung tissues describes the disease. Interaction with transmissible individuals can make one acquire TB. The behavior of transmissible diseases, its impacts and possible future prediction about its spread has been best understood with the knowledge of mathematical epidemiology. In this study, delay differential equations were formulated for purposes of determining stability of Disease Free Equilibrium (DFE). The delay component was incorporated into Susceptible-Exposed-Infectious-Recovered (SEIR) model. A parameter called the basic reproduction number was computed and numerical simulations were done using MATLAB for validation of the analytical results. Parameter values were obtained from secondary data.

Keywords: TB; Reproduction number; Delay differential equations; Stability; Disease free equilibrium

Introduction

Tuberculosis (TB) is a bacterial infections ailment of humans and animals initiated by the Mycobacterium Tuberculosis Complex (MTBC) which include four TB causing Mycobacteria: M. bovis, M. africanum, M. canetti and M. microti. The formation of tubercles on the lungs and other tissues of the body characterize the ailment, frequently developing extensively after the primary infection. It is an airborne disease which is transmitted when individuals with active TB cough, sneeze, speak, sing or spit. Mycobacterium tuberculosis is among the causes of mortality [1-17]. In the case of incomplete treatment, the remains of mycobacterium tuberculosis in the human system often results in the bacterium developing resistance to antibiotics. This leads to Multi-Drug Resistance-TB (MDR-TB) [9,18].

Mathematical epidemiology has contributed to a more in-depth appreciative of the activities of tuberculosis as a transmissible ailment, its effects and possible future forecast about its spread and the mechanisms of its control. The planning, evaluation, prevention and control of TB in a population will be facilitated by model analysis [11]. Many populations are structured in space but interconnected by human travelling. A population may be subdivided into separated patches also called subpopulations, each with its dynamics. A group of such a distinctive subpopulation is known as a metapopulation [12]. Subpopulation interconnections may be; random, all-to-all, one-to-many or nearest neighbor connection [2].

Coupling configurations

Coupling is the arrangement of subpopulations in a way that can affect each other. There are different forms of nearest neighbor coupling. Nearest neighbor coupling is where a subpopulation is connected to their immediate neighbor [3]. The following are the coupling configurations: Coupling on a line, Coupling on a ring, Coupling on a two-dimensional Bravais lattice, One-to-all coupling, All-to-all coupling and Coupling on three-dimension.

Review of Related Literature

The increasing rate of Tuberculosis (TB) cases in many countries of Sub-Saharan Africa over the past decade is largely attributed to the Human Immunodeficiency Virus (HIV) and other emerging infections. Mathematical models developed for tuberculosis transmission are numerous; some of...
them have been reviewed as follows: According to [14] they studied the spread of TB through a two patch epidemiological model. They made an assumption that susceptible individuals can migrate between two patches but not infective individuals. They formulated the model by considering a two patch SEI TB. They then analyzed the model by computing the DFE and $R_0$. They went further and determined the global stability of DFE by showing that DFE has global asymptotic stability when $R_0<1$. In [5] they formulated a model on pulmonary and MDR TB with vaccination. Here, they considered a quarantine class in their epidemic model for MDR TB patients. They observed that quarantine plays an important part in the control of the infection. They formulated Susceptible-Exposed-Infectious-Quarantine-Recovered-Susceptible having a Vaccinated class (SEI-QRS-V). The model was used in describing changing aspects of TB spread in relation to time in human being populace. The results showed that the disease $R_0$, DFE and their stability were determined. They showed that if $R_0<1$, DFE stability is global in the feasible zone and the disease is wiped out. If $R_0>1$, an exceptional endemic balance occurs and has a nearby (local) asymptotic stability. According to [4] they studied a non-linear mathematical model of TB with a case detection and treatment. In the paper, the whole population under consideration was in four compartments; Susceptible Exposed Infectious and Recovered (SEIR) model which they used to study transmission dynamics of TB. They computed $R_0$ and determined the equilibria of the model. Their results showed that an increase in the rate of case detection lead to an increase in the threshold value of $R_0$. Also, the treatment reduced the equilibrium level of the infective class.

According to [13] they presented a paper titled ‘mathematical model for vaccinated tuberculosis disease with VEIT model’. In this model, there are four compartments; Vaccinated Exposed Infected and Treated (VEIT). The paper discussed about formation and analysis of the VEIT model to TB virus infection by exogenous re-infection. They concluded that the model of vaccinated with exogenous re-infection have two equilibria states; DFE and EEP. They showed that the eigenvalue of DFE is always negative so that the system stability is asymptotically stable at DFE.

In [6] a mathematical model that predicted the threat of TB as a contagious airborne infection under stable state and non-unsable state situations was developed. They did this by monitoring the amount of breath out air by contagious persons in a restricted environment. They demonstrated precisely and diagrammatically, the relationship between TB spread possibility and airborne level of infection, average amount of exhaled air taken into consideration TB occurrence and length of contact to contagious persons in a restricted environment. They chose an age structuring model since infection and illness frequency differ in diverse inhabitants on age dependent and host immune aspects. In their study, they found out that TB spread is prevalent in gatherings for instance; schools, public transportation and correctional facilities especially in developing countries. Similarly [1] in his thesis titled ‘mathematical modeling of population dynamics of TB’ presented and analyzed a SLIT (Susceptible Latent Tuberculosis treatment in controlling the spread of Tuberculosis. The administration of Bacillus Calmette Guerin (BCG) vaccines at birth protects children from early infection of the disease, but the effect of these vaccines expires with time. Their results showed that detection and treatment of latent tuberculosis infections using Isoniazid Preventive Therapy prevents the breakdown of latent infections into infectious cases, thus reducing greatly the rate of spread of the disease since only members of the infectious class can spread the disease to others. The DFE will be stable if effort is intensified in bringing down both the contraction rate and the rate of break down to infectious tuberculosis. According to [7] they developed a mathematical model of the spread of TB disease involving the age classes in a susceptible compartment under SEIR model. The model had two equilibrium points; DFE and EEP. The $R_0$ was constructed using the next generation matrix approach. They found out that TB transmission can be reduced through vaccination and increasing life expectancy. The results from simulation showed also that transmission can also be reduced through vaccine protection period and vaccine efficacy. The above studies did not consider the use of Delay Differential Equations (DDE) in the solution to the various equations arising from the models. This study has formulated DDE’s model for the spread of TB in a coupled metapopulation.

**Methodology**

**Introduction**

In epidemiology, the basic reproductive number (sometimes basic reproduction rate or ratio) of an infection is the number of cases one case generates on the average over the course of its infectious period. This metric is useful because it helps determine whether or not an infectious disease can spread through a population. The basic Reproduction number $R_0$ is the threshold for many epidemiological models. When $R_0<1$, the infection dies out in the long run (i.e. each infected individual produces one average less than one new infected individual). One the other hand, if $R_0>1$ the infection will be able to spread in a population (i.e. each infected individual produces more than one new infected individual).

To obtain $R_0$, the dominant eigenvalue of the next generation matrix is considered such that $R_0=ρ(FV−1)$ where $ρ$ is the spectral radius of next generation matrix, Matrix $F$ represents the rate of new infection entering compartment $i$ and matrix $V_i$ represents the rate of transfer into and out of compartment $i$ by other ways.
Since we are dealing with a large population, a deterministic or compartmental mathematical model is used. In the deterministic model, individuals in the population are assigned to different subgroups or compartments, each representing a specific stage of the epidemic. The Susceptible-Exposed-Infected Removed (SEIR) epidemiological models are utilized to study and analyze the disease, thus the simple SEIR model is used to explain the spread of tuberculosis in a population.

**Methods of solution**

The stability of the model has been approached from Jacobian matrix method for checking stability of Disease Free Equilibrium (DFE) and numerical simulations have been done using MATLAB to validate the analytic results.

**Model equations**

The dynamics of TB is modeled by the following system of delay differential equations:

\[
\frac{dS_i}{dt} = A - \mu S_i - \beta_i \sum_{j=1}^{n} S_j I_j (t - \tau) - \beta_i S_i I_i (t - \tau) \]  
\[
\frac{dS_j}{dt} = A - \mu S_j - \beta_j \sum_{i=1}^{n} S_i I_i (t - \tau) - \beta_j S_j I_j (t - \tau) \]  
\[
\frac{dE_i}{dt} = \beta_i \sum_{j=1}^{n} S_j I_j (t - \tau) - (1 - \varepsilon_i) E_i (t - \tau) - E_i (\mu + d_i) \beta_i S_i I_i (t - \tau) \]  
\[
\frac{dE_j}{dt} = \beta_j \sum_{i=1}^{n} S_i I_i (t - \tau) + (1 - \varepsilon_j) E_j (t - \tau) - E_j (\mu + d_j) \beta_j S_j I_j (t - \tau) \]  
\[
\frac{dI_i}{dt} = \varepsilon_i E_i (t - \tau) + (1 - \gamma_i) I_i (t - \tau) - I_i (\mu + d_i) \]  
\[
\frac{dI_j}{dt} = \varepsilon_j E_j (t - \tau) + (1 - \gamma_j) I_j (t - \tau) - I_j (\mu + d_j) \]  
\[
\frac{dR_i}{dt} = \gamma_i I_i (t - \tau) - \mu R_i - \sigma R_i \]  
\[
\frac{dR_j}{dt} = \gamma_j I_j (t - \tau) - \mu R_j - \sigma R_j \]  

**Model preliminary analysis**

**Positivity and boundedness of solutions:** Since the model under consideration represents the population dynamics of living organisms, it is necessary to show that the solutions are always positive and bounded.

We define the compact set

\[\{S_i(0), E_i(0), I_i(0), R_i(0)\} \in \mathbb{R}^4 \geq 0, 0 \leq E_i < S_i, 0 \leq I_i < S_i, 0 \leq R_i < S_i\] where \(S_i > 0, a = 1, 2, 3.\)

**Proposition 1:** The set \(\Omega\) is positively invariant for model (3.2), (3.4), (3.6) and (3.8).

**Proof:**

We have \(\frac{dS_i}{dt} |_{S_{i0}} = \Lambda_i \geq 0\)  
\[
\frac{dE_i}{dt} |_{E_{i0}} = 0 = \beta_i \sum_{j=1}^{n} S_j I_j (t - \tau) - \beta_i S_i I_i (t - \tau) \geq 0\text{ Whenever } S_i, I_i, I_i \geq 0\]  
\[
\frac{dI_i}{dt} |_{I_{i0}} = 0 = \varepsilon_i E_i (t - \tau) \geq 0\text{ whenever } E_i \geq 0\]  
\[
\frac{dR_i}{dt} |_{R_{i0}} = 0 = \gamma_i I_i (t - \tau) \geq 0\]  

This confirms that \(\{S_i(t), E_i(t), I_i(t), R_i(t)\} \in \mathbb{R}^4 \geq 0\) with \(\{S_i(0), E_i(0), I_i(0), R_i(0)\} \in \mathbb{R}^4 \geq 0\)

Thus \(\mathbb{R}^4 \geq 0\) is positively invariant for model (3.2) - (3.8).

For boundedness we define;

\[
\frac{dS_i}{dt} = \gamma_i \varepsilon_i \Lambda_i - u_{i0} S_i\]  
\[
\frac{dS_i}{dt} = \gamma_i \varepsilon_i [E_i (u + d_i)]\]  
\[
\frac{dI_i}{dt} = \gamma_i (1 - \varepsilon_i) |I_i (u + d_i)|\]  
\[
\frac{dR_i}{dt} = -(1 - \gamma_i) |I_i (u - \sigma)|\]
Then

\[ N(t) = S_i(t) + E_i(t) + I_i(t) + R_i(t) \]

Let \( c_{\text{min}}(u_i, \gamma_i, \varepsilon_i, (u_i + \delta_i), (1 - \varepsilon_i)(u_i + \sigma_i)) \)

Then

\[ \frac{dN(t)}{dt} = \Lambda_i - c_{\text{min}}(s_i(t) + E_i(t) + I_i(t) + R_i(t)) \]

Where \( \omega = \Lambda \gamma_i \varepsilon_i \)

\[ \frac{dN(t)}{dt} + c N_i(t) \leq \omega \]

\[ N(t)e^{\omega t} \leq N_i e^{\omega t} + N_0 \]

\[ N(t) \leq \omega + N_i e^{-\omega t} - e^{\omega t} \]

Where \( \omega \geq 0 \). This shows that the solution is bounded.

To obtain \( R_0 \), the dominant eigenvalue of the next generation matrix is considered such that \( R_0 = \rho(FV^{-1}) \) where \( \rho \) is the spectral radius of next generation matrix. Matrix \( F_i \) represents the rate of new infection entering compartment \( i \) and matrix \( V_i \) represents the rate of transfer into and out of compartment \( i \) by other ways.

From the equations (3.1)-(3.8) the matrices \( F_i \) and \( V_i \) are given by:

\[
F_i = \begin{pmatrix}
(1 - \varepsilon_i)E_i(t - \tau) \\
(1 - \varepsilon_j)E_j(t - \tau) \\
(1 - \gamma_i)I_i(t - \tau) \\
(1 - \gamma_j)I_j(t - \tau)
\end{pmatrix}
\]

\[
V_i = \begin{pmatrix}
E_i(\mu_i + d_i) \\
E_j(\mu_j + d_j) \\
I_i(\mu_i + d_i) \\
I_j(\mu_j + d_j)
\end{pmatrix}
\]

(3.18)

We then differentiate matrix \( F_i \) and \( V_i \) partially with respect to state variables to obtain the below 4 \times 4 matrices as;

\[
F_i = \begin{pmatrix}
(1 - \varepsilon_i)e^{-\lambda \tau} & 0 & 0 & 0 \\
0 & (1 - \varepsilon_j)e^{-\lambda \tau} & 0 & 0 \\
0 & 0 & (1 - \gamma_i)e^{-\lambda \tau} & 0 \\
0 & 0 & 0 & (1 - \gamma_j)e^{-\lambda \tau}
\end{pmatrix}
\]

(3.20)

\[
V_i = \begin{pmatrix}
\mu_i + d_i & 0 & 0 & 0 \\
0 & \mu_j + d_j & 0 & 0 \\
0 & 0 & \mu_i + d_i & 0 \\
0 & 0 & 0 & \mu_j + d_j
\end{pmatrix}
\]

(3.21)

Then, the inverse of \( V \) is given by;

\[
V^{-1} = \begin{pmatrix}
\frac{1}{\mu_i + d_i} & 0 & 0 & 0 \\
0 & \frac{1}{\mu_j + d_j} & 0 & 0 \\
0 & 0 & \frac{1}{\mu_i + d_i} & 0 \\
0 & 0 & 0 & \frac{1}{\mu_j + d_j}
\end{pmatrix}
\]

(3.22)
The next generation matrix $FV^{-1}$ is given by:

$$FV^{-1} = \begin{bmatrix} (1-\varepsilon)e^{-ix} & 0 & 0 & 0 \\ 0 & (1-\varepsilon)e^{ix} & 0 & 0 \\ 0 & 0 & (1-\gamma_i)e^{-ix} & 0 \\ 0 & 0 & 0 & (1-\gamma_j)e^{ix} \end{bmatrix} \begin{bmatrix} 1 \\ \mu_i + d_i \\ 0 \\ \mu_j + d_j \end{bmatrix}$$

Which simplifies to:

$$FV^{-1} = \begin{bmatrix} (1-\varepsilon)e^{-ix} & 0 & 0 & 0 \\ 0 & (1-\varepsilon)e^{ix} & 0 & 0 \\ 0 & 0 & (1-\gamma_i)e^{-ix} & 0 \\ 0 & 0 & 0 & (1-\gamma_j)e^{ix} \end{bmatrix} \begin{bmatrix} 1 \\ \mu_i + d_i \\ 0 \\ \mu_j + d_j \end{bmatrix}$$

(3.23)

The eigenvalues of the matrix (3.24) are computed by $|A-\lambda I|=0$ given where $A$ is the matrix $FV^{-1}$ and $I$ is 4 × 4 identity matrix.

$$\lambda_1 = \frac{(1-\varepsilon)e^{ix}}{\mu_i + d_i}$$

$$\lambda_2 = \frac{(1-\varepsilon)e^{-ix}}{\mu_j + d_j}$$

$$\lambda_{3,4}$$ is obtained from the characteristic equation below;

$$\lambda^2 - \lambda \left( \frac{(1-\gamma_i)e^{-ix}}{\mu_i + d_i} + \frac{(1-\gamma_j)e^{ix}}{\mu_j + d_j} \right) + \left( \frac{(1-\gamma_i)e^{ix}}{\mu_i + d_i} \right) + \left( \frac{(1-\gamma_j)e^{-ix}}{\mu_j + d_j} \right) = 0$$

Algebraically,

$$\lambda_3 = \frac{(1-\gamma_i)e^{ix}}{\mu_i + d_i}$$

$$\lambda_4 = \frac{(1-\gamma_j)e^{-ix}}{\mu_j + d_j}$$

Thus $R_0$, which is given by the dominant eigenvalue is given as;

$$R_0 = \frac{(1-\gamma_i)e^{ix}}{\mu_i + d_i}$$

Equilibrium points and stability analysis

In epidemiology, there are basically two equilibrium points, namely Disease Free Equilibrium (DFE) where $i=0$ and Endemic Equilibrium Point (EEP) where $i \neq 0$. DFE occurs in absence of disease while EEP occurs in presence of a disease. The stability of a system is locally studied near fixed points. A system is stable if all the eigenvalues of the system linearized about a fixed point have negative real parts. This condition for stability yields a reproductive ratio denoted by $R_0$ which will form a stability criterion.

**Disease free equilibrium:** This equilibrium point describes a point when the rate of change is equal to zero. It is evaluated by equating the system of delay differential equation (3.1)-(3.8) to zero. DFE occurs when the infective class is absent and consequently the recoveries.

**Stability of Disease Free Equilibrium:** The disease free equilibrium is the state of variable of the model in the absence of disease. Its stability can be tested by using the eigenvalues of the Jacobian matrix obtained at DFE, where at this point $R_0<1$. To obtain Jacobian matrix we differentiate.
equations (3.1)-(3.8) with respect to state variables at DFE to get.

\[
FV = \begin{bmatrix}
-\mu_i & 0 & 0 & 0 & -\beta_s x e^{-\tau_i} & \beta_s \sum_{j=1}^{i} x_j e^{-\tau_j} & 0 & 0 \\
0 & -\mu_j & 0 & 0 & -\beta_j s e^{-\tau_j} & \beta_j s e^{-\tau_j} & 0 & 0 \\
0 & 0 & (1-\varepsilon e^{-\tau_i})-(\mu_i+d_i) & 0 & \beta_i s e^{-\tau_i} & 0 & 0 & 0 \\
0 & 0 & 0 & (1-\varepsilon e^{-\tau_j})-(\mu_j+d_j) & \beta_j s e^{-\tau_j} & 0 & 0 & 0 \\
0 & 0 & \varepsilon e^{-\tau_i} & 0 & (1-\gamma e^{-\tau_i})-(\mu_i+d_i) & 0 & 0 & 0 \\
0 & 0 & 0 & \varepsilon e^{-\tau_j} & 0 & (1-\gamma e^{-\tau_j})-(\mu_j+d_j) & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & \varepsilon e^{-\tau_i} & 0 & -\mu_i \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu_j
\end{bmatrix} \tag{3.25}
\]

The system (3.1)-(3.8) is locally asymptotically stable if all the eigenvalues of linearization matrix (3.25) above are negative. The eigenvalues are:

\[
\lambda_1 = -\mu_i \\
\lambda_2 = -\mu_j \\
\lambda_3 = -\mu_i \\
\lambda_4 = (1-\varepsilon e^{-\tau_i})-(\mu_i+d_i) \\
\lambda_5 = (1-\varepsilon e^{-\tau_j})-(\mu_j+d_j) \\
\lambda_{6,7,8} = -(1-\gamma e^{-\tau_i})-(\mu_i+d_i)(1-\gamma e^{-\tau_j})-(\mu_j+d_j)
\]

Which simplifies to

\[
\gamma \varepsilon e^{-\tau_i} < (\mu_i+d_i)
\]

\[
\gamma \varepsilon e^{-\tau_j} < (\mu_j+d_j)
\]

\[
\gamma \varepsilon e^{-\tau_i} < (\mu_j+d_j)
\]

Thus \( R_0 = \frac{\gamma \varepsilon e^{-\tau_i}}{\mu_j+d_j} < 1 \)

When \( R_0 < 1 \), DFE is attained.

### Numerical Analysis and Results

This chapter comprises of parameter values obtained from secondary data and graphs obtained using Matlab (Table 1).

**Table 1: Parameters, Definition and Value.**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu )</td>
<td>Natural death rate coefficient</td>
<td>0.5</td>
</tr>
<tr>
<td>( d )</td>
<td>Disease-induced death rate</td>
<td>0.2</td>
</tr>
<tr>
<td>( \beta )</td>
<td>Probability that susceptible becomes infected</td>
<td>0.001</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>Treatment rate</td>
<td>( 0 \leq \gamma \leq 1 )</td>
</tr>
<tr>
<td>( \varepsilon )</td>
<td>Rate at which exposed individuals become infectious</td>
<td>0.5</td>
</tr>
<tr>
<td>( \Lambda )</td>
<td>Recruitment rate</td>
<td>0.005</td>
</tr>
<tr>
<td>( S_0 )</td>
<td>Initial susceptible population</td>
<td>1000</td>
</tr>
<tr>
<td>( I_0 )</td>
<td>Initial infected population</td>
<td>50</td>
</tr>
<tr>
<td>( R_0 )</td>
<td>Initial recovered population</td>
<td>15</td>
</tr>
<tr>
<td>( N_0 )</td>
<td>Initial population</td>
<td>1165</td>
</tr>
<tr>
<td>( E_0 )</td>
<td>Initial exposed population</td>
<td>100</td>
</tr>
<tr>
<td>( \tau )</td>
<td>Time delay</td>
<td>To be determined</td>
</tr>
</tbody>
</table>
Figure 1: Population of various compartments against time in days. From the graph, it is evident that, initially the infected were at 80, then it drops drastically to below 20 because treatment, time delay and vaccination played a major role in minimizing infection.

Figure 2: Reproduction number against death rate ($d$). From the graph it is evident that $R_0$ is inversely proportional to $d$.

Figure 3: $R_0$ against progression rate. From the graph it is evident that $R_0$ is inversely proportional to progression rate.

Figure 4: $R_0$ death rate. From the graph it is evident that $R_0$ is inversely proportional to death rate, $\mu$. 
Conclusion

We have formulated a delay differential equation of SEIR TB model in a coupled Meta population. We obtained a basic reproduction number $R_0$ which is less than unity. This ratio plays a vital role in minimizing the spread of tuberculosis (Figures 1–4). The spread of contagious diseases remains a test in developing countries. The government should increase educational awareness on restriction of travel of people in and out of a subpopulation to avoid the infection. This will minimize the spread of the disease across the sub-populations. To lower transmission and spread of the disease in a metapopulation, there is need to use of preventive measures such as isolation of already infected individuals, campaigns on BCG vaccination of all children under 5 years and seeking medical treatment on infected persons.

Suggestions for Further Research

This study has not exhausted all about TB dynamics in coupled Metapopulation. The effect of an individual’s immune response to TB disease is not included. The model can be extended to include co-infection between TB and HIV in a metapopulation. The carrying capacity of the subpopulation, characteristics of the subpopulations like education levels and economic status are also possible insights for further research work on the dynamics of TB disease in Meta-populations.

References