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## A MATHEMATICAL STUDY OF TUBERCULOSIS INFECTIONS USING A DETERMINISTIC MODEL IN COMPARISON WITH CONTINUOUS MARKOV CHAIN MODEL

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**Abstract:** Mathematical model of the transmission of tuberculosis infection was widely studied to capture the transient behavior of the disease transmission. In this study we model the dynamic of the disease by considering an epidemiological model called SEIIR model to capture the deterministic behavior of the disease. We also applied a continuous-time Markov chain model to take into consideration the randomness of the system. In the deterministic model, a disease-free equilibrium point and a basic reproduction number of the model are found which are mainly influenced by the contact rate of susceptible individuals with infective individuals. Other parameters such as progression rate of the latent individuals to be infectious individuals and the treatment rate of latent individuals also influence not only the deterministic model but also the stochastic sample paths. For a certain critical value of the treatment rate of latent class, deterministic and stochastic solutions show different behavior at the final time of observation. A high degree of randomness is observed in the latent and infected class (hospitalize or not-hospitalized). While in the susceptible class, effect of randomness is almost not observed. This suggests the robustness of deterministic model of susceptible class to the stochastic perturbations.

**Keywords:** tuberculosis; SEIIR epidemic model; basic reproduction number; continuous-time Markov chain;

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## 1. INTRODUCTION

Tuberculosis is a contagious disease caused by infection with the bacteria *Mycobacterium tuberculosis* (Mtb). Some of the factors that trigger infection are an unhealthy lifestyle and low human immunity since the bacteria can spread from one person to another through tiny droplets released into the air through coughing and sneezing of people with acute infection. When the human body contains bacteria, the immune system can usually prevent it from getting sick. People with this condition are called latent TB where the bacteria in their bodies are inactive and cause no symptoms. However, without treatment, latent TB can turn into active TB. If not handled immediately, active tuberculosis can be dangerous. Therefore, treatment is needed for people with latent TB and to help control the spread of TB [1], [2]. Furthermore, in order to clear the infection and prevent the development of antibiotic resistance, people with active TB have to take several types of drugs for months. Without drug treatment, Infectious tuberculosis has the potential to become a serious disease because it attacks the lungs and also affects other parts of human body, including kidneys, spine or brain. According to the WHO data, the deadliest infectious killer in the world is still caused by this TB disease. More than 4,000 people lose their lives every day due to the infection of TB. Nearly 30,000 people fall ill from this preventable and curable disease. However, global efforts to fight the TB infection have saved an estimated 58 million lives since 2000 [2].

Due to the population growth, tuberculosis remains a major global health problem in the world [1], [3]. Some diagnostics and novel therapies have been developed to bring great potential to reduce TB burden and mortality. However, limitations on the resources of TB endemic settings remain exist. A theoretical approach is needed to estimate the impact of various interventions on the outcome of interest. An intensive research will also provide an area for developing diagnostic

tests and treatment regimens for TB. One of theoretical approaches that can present a useful insight is mathematical modelling. Mathematical epidemiology modelling provides useful insights by explaining <sup>7</sup> the types of interventions that might maximize impact at the population level and highlighting gaps in the current knowledge that are most important for making such judgments [4-9]. Epidemiological models <sup>50</sup> focus on reviewing the impact of TB control interventions by designing <sup>38</sup> the transmission models to assess or understand the population-level (epidemiological) [9]. Various <sup>38</sup> mathematical models have been developed to model the transmission of TB and to highlight <sup>15</sup> the major contribution of TB transmission models in general such as the slow and fast dynamic of TB transmission [10-12], reinfection and drug-resistant strains [13-18], prevention of TB [19-24]. Most of them used compartmental model which described the transmission of infectious disease using the flow rate between compartments based on the characteristic of the infectious disease [25-27]. Nevertheless, other types of models were also developed to model the specific transmission dynamic of TB such as [28-30]. The use of mathematical approach and simulation gained more attention due to a convenient summary in predicting future outbreak as the infection progresses. It also provided better understanding regarding the transmission of the infection disease and decisions for the control of the underlying disease. In this study, we also develop a compartmental model <sup>15</sup> to improve understanding of the behaviour of TB transmission based on the epidemiological understanding. We formulate the model deterministically using systems of ordinary differential equations and stochastically via continuous-time Markov chains. The deterministic model provides a framework for formulating the stochastic model with taking into consideration the stochastic perturbations. We believe that this study will provide a better understanding regarding the dynamic of TB infection to design an appropriate treatment strategy to reduce the infection probability of the pathogen.

## 2. MATERIAL AND METHODS

### 2.1. SEIR Deterministic Model of Tuberculosis Epidemic

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In order to capture the key relevant complexities in the study of transmission dynamics of Tuberculosis (TB), SEIIR epidemiology model is used to model the dynamic of Susceptible individuals ( $S$ ), Exposed individuals ( $E$ ), Infected individuals but not hospitalized ( $I$ ), Infected individuals and hospitalized ( $I_h$ ), and Recovered individuals ( $R$ ). Our model follows the line of Zhang et al. [11] with some improvements. The connection and interaction between the five classes are depicted in Figure 1.

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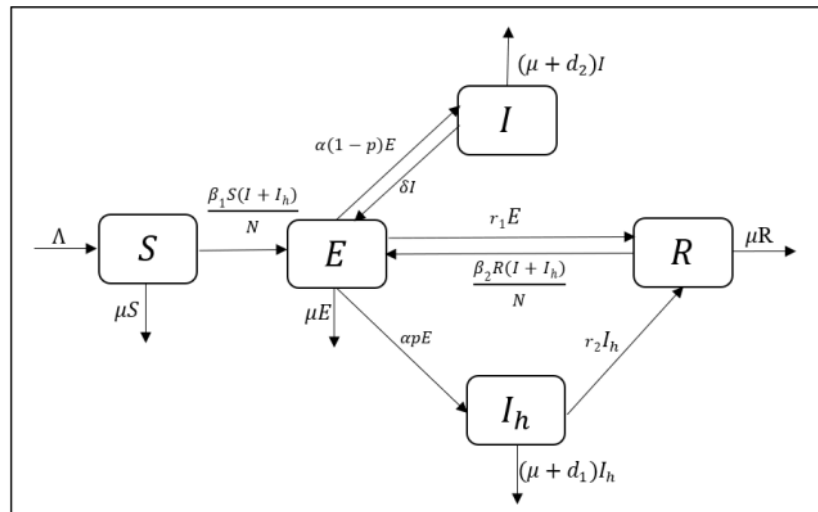


Figure 1. The transfer diagram of SEIIR model.

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In this SEIIR model, individuals are recruited into the susceptible class first with rate constant  $\Lambda$ . The uninfected individuals move into the latent class  $E$  after getting the infection from the active TB with contact rate  $\beta_1$ . The latent individuals are then progressed to active TB with a fractional  $p$  which stands for the proportion of which active TB is hospitalized or not. There is no directly recovery for the non-hospitalized active TB. Self-treatment for active TB produces self-recovered that is not totally eliminate the virus such that it will be moved into the latent class again with self-recovery rate  $\delta$ . After getting some treatments, the latent individuals can move into the recovery class with successfully treatment rate for latent individual  $r_1$ . While the hospitalized active TB

may recover and move to the  $R$  class with successfully treatment rate  $r_2$ . We assume that, after recovering individuals can experience a relapse. Recurrence of tuberculosis infection can occur due to a new infection from the interaction of active TB with contact rate  $\beta_2$ . We assume that  $\beta_1 > \beta_2$  meaning the possibility of recovered individuals for recurrence of tuberculosis infection is lower than the susceptible individuals. Natural mortality is the removal state for all compartments with constant rate  $\mu$ . While mortality due to infection is employed for active TB compartments with mortality rate  $d_1$  for non-hospitalized individuals and  $d_2$  for hospitalized individuals. Using the above assumptions <sup>35</sup> leads to the following non-linear system of equations for the transmission dynamic of TB:

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - \frac{\beta_1 S(I+I_h)}{N} - \mu S, \\ \frac{dE}{dt} &= \frac{\beta_1 S(I+I_h)}{N} - (\mu + \alpha + r_1)E + \delta I + \frac{\beta_2 R(I+I_h)}{N}, \\ \frac{dI}{dt} &= \alpha(1-p)E - (\mu + d_2 + \delta)I, \\ \frac{dI_h}{dt} &= \alpha p E - (\mu + d_1 + r_2)I_h, \\ \frac{dR}{dt} &= r_1 E + r_2 I_h - \mu R - \frac{\beta_2 R(I+I_h)}{N}.\end{aligned}\tag{1}$$

We set total population,  $N = S + E + I + I_h + R$ . <sup>34</sup> By adding the equations of the system (1), we have

$$\Lambda - \mu(S + E + I + I_h + R) - (d_2 I + d_1 I_h) \leq \Lambda - \mu N.$$

Hence,

$$\limsup_{t \rightarrow \infty} (S + E + I + I_h + R) \leq \frac{\Lambda}{\mu}.$$

Therefore, the considered region for the system (1) is

$$\Gamma = \left\{ (S, E, I, I_h, R) : (S + E + I + I_h + R) \leq \frac{\Lambda}{\mu}, S > 0, E \geq 0, I \geq 0, I_h \geq 0, R \geq 0 \right\},$$

with positively invariant  $\Gamma$  meaning that <sup>13</sup> the vector field points into the interior of  $\Gamma$  on the part of the boundary when  $(S + E + I + I_h + R) = \frac{\Lambda}{\mu}$  such that

$$(S + E + I + I_h + R) < \frac{\Lambda}{\mu}, \text{ for } t > 0.$$

## 2.2. SEIR Stochastic Model of Tuberculosis Epidemic

Let  $S(t)$ ,  $E(t)$ ,  $I(t)$ ,  $I_h(t)$ , and  $R(t)$  are random variables which refer to the susceptible class, latent or exposed class, infectious not-hospitalized class, infectious hospitalized class, and recovered class, respectively. Let  $\Delta t$  refers to the small-time interval such that at the time interval  $(t, t + \Delta t)$ , there exists at most one event occurs. Based on the assumptions applied in the deterministic model, the events that may occur at the time interval  $\Delta t$  are described as follows:

1. Event for one susceptible gets infection at the time interval  $(t, t + \Delta t)$  has the transition probability

$$\frac{\beta_1 S(I + I_h)}{N} \Delta t + o(\Delta t),$$

with transition  $S \rightarrow S - 1$  and  $E \rightarrow E + 1$ .

2. Event for one latent is moving into the infection stage and not-hospitalized at the time interval  $(t, t + \Delta t)$  has the transition probability

$$\alpha(1 - p)E\Delta t + o(\Delta t),$$

with transition  $E \rightarrow E - 1$  and  $I \rightarrow I + 1$ .

3. Event for one latent is naturally die at the time interval  $(t, t + \Delta t)$  has the transition probability

$$\mu E\Delta t + o(\Delta t),$$

with transition  $E \rightarrow E - 1$ .

4. Event for one latent becomes infectious and hospitalized at the time interval  $(t, t + \Delta t)$  has the transition probability

$$\alpha p E\Delta t + o(\Delta t),$$

with transition  $E \rightarrow E - 1$  and  $I_h \rightarrow I_h + 1$ .

5. Event for one infected not-hospitalized becomes latent again at the time interval  $(t, t + \Delta t)$  has the transition probability

$$\delta I\Delta t + o(\Delta t),$$

with transition  $I \rightarrow I - 1$  and  $E \rightarrow E + 1$ .

6. Event for one infected not-hospitalized is naturally die or due to the disease at the time interval  $(t, t + \Delta t)$  has the transition probability

$$(\mu + d_2)I\Delta t + o(\Delta t),$$

with transition  $I \rightarrow I - 1$ .

7. Event for one infected hospitalized and not-hospitalized is naturally die or due to the disease at the time interval  $(t, t + \Delta t)$ , respectively, have the transition probability

$$(\mu + d_2)I\Delta t + o(\Delta t),$$

$$(\mu + d_1)I_h\Delta t + o(\Delta t),$$

with transition  $I \rightarrow I - 1$ ,  $I_h \rightarrow I_h - 1$ .

8. Event for one latent is recover from infection at the time interval  $(t, t + \Delta t)$  has the transition probability

$$r_1E\Delta t + o(\Delta t),$$

with transition  $E \rightarrow E - 1$  and  $R \rightarrow R + 1$ .

9. Event for one infected hospitalized is recover from infection at the time interval  $(t, t + \Delta t)$  has the transition probability

$$r_2I_h\Delta t + o(\Delta t),$$

with transition  $I_h \rightarrow I_h - 1$  and  $R \rightarrow R + 1$ .

10. Event for one recovered becomes latent again at the time interval  $(t, t + \Delta t)$  has the transition probability

$$\frac{\beta_2 R(I + I_h)}{N} \Delta t + o(\Delta t),$$

with transition  $R \rightarrow R - 1$  and  $E \rightarrow E + 1$ .

11. Event for one recovered is naturally die at the time interval  $(t, t + \Delta t)$  has the transition probability

$$\mu R\Delta t + o(\Delta t),$$

with transition  $R \rightarrow R - 1$ .

12. Event for no changes occur in the system at the time interval  $(t, t + \Delta t)$  has the transition probability

$$1 - \left[ \frac{\beta_1 S(I + I_h)}{N} + \alpha(1 - p) + \mu E + \alpha p E + \delta I + (\mu + d_2)I + (\mu + d_1)I_h + r_1 E + r_2 I_h + \frac{\beta_2 R(I + I_h)}{N} + \mu T \right] \Delta t + o(\Delta t),$$

with transition  $S \rightarrow S$ ,  $E \rightarrow E$ ,  $I \rightarrow I$ ,  $I_h \rightarrow I_h$ , and  $R \rightarrow R$ .

Let the changes in the random variables  $S, E, I, I_h, R$  at the time interval  $(t, t + \Delta t)$  are respectively defined as  $\Delta S, \Delta E, \Delta I, \Delta J$ , and  $\Delta R$ , with  $\Delta S = S(t + \Delta t) - S(t)$ ,  $\Delta E = E(t + \Delta t) - E(t)$ ,  $\Delta I = I(t + \Delta t) - I(t)$ ,  $\Delta I_h = I_h(t + \Delta t) - I_h(t)$ , and  $\Delta R = R(t + \Delta t) - R(t)$ . If we set  $S(t) = N(t) - E(t) - I(t) - I_h(t) - R(t)$  then we have the probability of an infinitesimal transition explaining the multivariate Markov chain as follows:

$$\begin{aligned} \text{prob}\{(\Delta E, \Delta I, \Delta I_h, \Delta R) = (i, j, k, l) | (E, I, I_h, R)\} \\ = \begin{cases} \frac{\beta_1 S(I + I_h)}{N} \Delta t + o(\Delta t) & (i, j, k, l) & (1, 0, 0, 0) \\ \alpha(1 - p)E \Delta t + o(\Delta t) & (i, j, k, l) & (-1, 0, 0, 0) \\ \mu E \Delta t + o(\Delta t) & (i, j, k, l) & (-1, 0, 0, 0) \\ \alpha p E \Delta t + o(\Delta t) & (i, j, k, l) & (-1, 0, 1, 0) \\ \delta I \Delta t + o(\Delta t) & (i, k, l) & (1, -1, 0, 0) \\ (\mu + d_2)I \Delta t + o(\Delta t) & (i, k, l) & (0, -1, 0, 0) \\ (\mu + d_1)I_h \Delta t + o(\Delta t) & (i, k, l) & (0, 0, -1, 0) \\ r_1 E \Delta t + o(\Delta t) & (i, k, l) & (-1, 0, 0, 1) \\ r_2 I_h \Delta t + o(\Delta t) & (i, k, l) & (0, 0, -1, 1) \\ \frac{\beta_2 R(I + I_h)}{N} \Delta t + o(\Delta t) & (i, k, l) & (1, 0, 0, -1) \\ \mu R \Delta t + o(\Delta t) & (i, j, k, l) & (0, 0, 0, -1) \end{cases} \quad (2) \end{aligned}$$

Probability of no changes in a population is given by

$$b\{(\Delta E, \Delta I, \Delta I_h, \Delta R) = (0, 0, 0, 0) | (E, I, I_h, R)\} = 1 - \left[ \frac{\beta_1 S(I + I_h)}{N} + \alpha(1 - p)e + \mu E + \alpha p E + \delta I + (\mu + d_2)I + (\mu + d_1)I_h + r_1 E + r_2 I_h + \frac{\beta_2 R(I + I_h)}{N} + \mu T \right] \Delta t + o(\Delta t).$$

The probability of other events is equal to  $o(\Delta t)$ .

Let  $s, e, i, j, r$ , respectively, define the value of random variables  $S, E, I, I_h, R$  and  $P_{eijr}(t)$  is the joint probability mass function (joint p.m.f.), i.e.  $P_{eijr}(t) = \text{Prob}\{E(t) = e, I(t) = i, I_h(t) = j, R(t) = r\}$ . Then we have  $P_{eijr}(t + \Delta t)$  as follows,

$$\begin{aligned}
P_{e,i,j,r}(t + \Delta t) &= P_{e-1,i,j,r}(t) \frac{\beta_1(s+1)(i+j)}{N} \Delta t + P_{e+1,i-1,j,r}(t) \alpha(1-p)(e+1) \Delta t \\
&+ P_{e+1,i,j,r}(t) \mu(e+1) \Delta t + P_{e+1,i,j-1,r}(t) \alpha p(e+1) \Delta t \\
&+ P_{e-1,i+1,j,r}(t) \delta(i+1) \Delta t + P_{e,i+1,j,r}(t) (\mu + d_2)(i+1) \Delta t \\
&+ P_{e,i,j+1,r}(t) (\mu + d_1)(j+1) \Delta t + P_{e+1,i,j,r-1}(t) r_1(e+1) \Delta t \\
&+ P_{e,i,j+1,r-1}(t) r_2(j+1) \Delta t + P_{e-1,i,j,r+1}(t) \frac{\beta_2(r+1)(i+j)}{N} \Delta t \\
&+ P_{e,i,j,r+1}(t) \mu(r+1) \Delta t + P_{e,i,j,r+1}(t) \mu(r+1) \Delta t \\
&- P_{e,i,j,r}(t) \left[ \frac{\beta_1 s(i+j)}{N} + \alpha(1-p) + \mu e + \alpha p e + \delta i + (\mu + d_2)i + (\mu + d_1)j \right. \\
&\left. + r_1 e + r_2 j + \frac{\beta_2 r(i+j)}{N} + \mu r \right] \Delta t + P_{e,i,j,r}(t) + o(\Delta t),
\end{aligned} \tag{3}$$

or

$$\begin{aligned}
&\frac{P_{e,i,j,r}(t + \Delta t) - P_{e,i,j,r}(t)}{\Delta t} \\
&= P_{e-1,i,j,r}(t) \frac{\beta_1(s+1)(i+j)}{N} + P_{e+1,i-1,j,r}(t) \alpha(1-p)(e+1) \\
&+ P_{e+1,i,j,r}(t) \mu(e+1) + P_{e+1,i,j-1,r}(t) \alpha p(e+1) + P_{e-1,i+1,j,r}(t) \delta(i+1) \\
&+ P_{e,i+1,j,r}(t) (\mu + d_2)(i+1) + P_{e,i,j+1,r}(t) (\mu + d_1)(j+1) \\
&+ P_{e+1,i,j,r-1}(t) r_1(e+1) + P_{e,i,j+1,r-1}(t) r_2(j+1) \\
&+ P_{e-1,i,j,r+1}(t) \frac{\beta_2(r+1)(i+j)}{N} + P_{e,i,j,r+1}(t) \mu(r+1) \\
&+ P_{e,i,j,r+1}(t) \mu(r+1) \\
&- P_{e,i,j,r}(t) \left[ \frac{\beta_1 s(i+j)}{N} + \alpha(1-p)e + \mu e + \alpha p e + \delta i + (\mu + d_2)i + (\mu + d_1)j \right. \\
&\left. + r_1 e + r_2 j + \frac{\beta_2 r(i+j)}{N} + \mu r \right] + \frac{o(\Delta t)}{\Delta t}.
\end{aligned} \tag{4}$$

By taking the limit of (4) as  $\Delta t \rightarrow 0$  leads to the forward Kolmogorov differential equation for the bivariate process,

$$\begin{aligned}
\frac{dP_{e,i,j,r}(t)}{dt} = & P_{e-1,i,j,r}(t) \frac{\beta_1(s+1)(i+j)}{N} + P_{e+1,i-1,j,r}(t) \alpha(1-p)(e+1) \\
& + P_{e+1,i,j,r}(t) \mu(e+1) + P_{e+1,i,j-1,r}(t) \alpha p(e+1) + P_{e-1,i+1,j,r}(t) \delta(i+1) \\
& + P_{e,i+1,j,r}(t) (\mu + d_2)(i+1) + P_{e,i,j+1,r}(t) (\mu + d_1)(j+1) \\
& + P_{e+1,i,j,r-1}(t) r_1(e+1) + P_{e,i,j+1,r-1}(t) r_2(j+1) \\
& + P_{e-1,i,j,r+1}(t) \frac{\beta_2(r+1)(i+j)}{N} + P_{e,i,j,r+1}(t) \mu(r+1) \\
& + P_{e,i,j,r+1}(t) \mu(r+1) \\
& - P_{e,i,j,r}(t) \left[ \frac{\beta_1 s(i+j)}{N} + \alpha(1-p) + \mu e + \alpha p e + \delta i + (\mu + d_2)i + (\mu + d_1)j \right. \\
& \left. + r_1 e + r_2 j + \frac{\beta_2 r(i+j)}{N} + \mu r \right].
\end{aligned} \tag{5}$$

The moment generator technique can be applied to solve the differential equation (5). However, the technique will generate a partial differential equation with five independent variables which is difficult to solve analytically. Therefore, in the next section, numerical technique will be applied to approximate the solution of (5). For the free-disease case,  $E = 0$ ,  $I = 0$ , and  $I_h = 0$ , we get the differential equation for the expectation of  $R$ , i.e.

$$\frac{d\tilde{E}(R(t))}{dt} = -\mu \tilde{E}(R(t)) \tag{6}$$

with  $\tilde{E}(S(t)) = N - \tilde{E}(R(t))$  and  $R(0) = \tilde{E}(R(0))$ .

### 3. RESULTS AND DISCUSSIONS

#### 3.1. Qualitative Analysis of the Deterministic Model

##### 3.1.1. Disease-free equilibrium and local stability

Setting the left-hand side of equations in (1) to zero and solving for the equilibrium values we find a disease-free equilibrium,

$$\hat{E} = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right). \quad (7)$$

Evaluating the Jacobian matrix of system (1) at the disease-free equilibrium (7) gives,

$$\hat{J}(\hat{E}) = \begin{bmatrix} -\mu & 0 & 0 & 0 & 0 \\ 0 & -(\mu + \alpha + r_1) & \delta & 0 & 0 \\ 0 & \alpha(1-p) & -(\mu + d_2 + \delta) & 0 & 0 \\ 0 & \alpha p & 0 & -(\mu + d_1 + r_2) & 0 \\ 0 & r_1 & 0 & r_2 & -\mu \end{bmatrix}.$$

The characteristic polynomial of the Jacobian matrix  $\hat{J}(\hat{E})$  is given by

$$|\lambda I - \hat{J}(\hat{E})| = \begin{vmatrix} \lambda + \mu & 0 & 0 & 0 & 0 \\ 0 & \lambda + (\mu + \alpha + r_1) & -\delta & 0 & 0 \\ 0 & -\alpha(1-p) & \lambda + (\mu + d_2 + \delta) & 0 & 0 \\ 0 & -\alpha p & 0 & \lambda + (\mu + d_1 + r_2) & 0 \\ 0 & -r_1 & 0 & -r_2 & \lambda + \mu \end{vmatrix} = 0.$$

Solving the characteristic polynomial of the Jacobian matrix  $\hat{J}(\hat{E})$  gives the eigenvalues

$$\lambda_{1,2} = -\mu, \quad \lambda_3 = -(\mu + d_1 + r_2),$$

and a quadratic polynomial,

$$\lambda^2 + a\lambda + b = 0, \quad (8)$$

with

$$a = (\mu + \alpha + r_1) + (\mu + d_2 + \delta),$$

$$b = (\mu + \alpha + r_1)(\mu + d_2 + \delta) - \alpha\delta(1-p).$$

Since all parameters are assumed positive,  $\lambda_i < 0$ ,  $i = 1, \dots, 3$ . The other two eigenvalues are the roots of (8). Since  $a > 0$ , equation (8) has the roots with  $Re(\lambda) < 0$  if  $b > 0$ , i.e.

$$\frac{\alpha\delta(1-p)}{(\mu + \alpha + r_1)(\mu + d_2 + \delta)} < 1. \quad (9)$$

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Therefore, the disease-free equilibrium  $\hat{E}$  is locally asymptotically stable when the condition (9) is fulfilled.

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### 3.1.2. The basic reproduction number ( $R_0$ )

The basic reproduction number is defined as the expected number of new cases of infection or secondary cases produced by a single (typical) infected individual in a completely susceptible population. It can be calculated by distinguish new infections from all other changes in population.

Consider the infected compartments,  $E, I,$  and  $I_h$ . Let  $\mathcal{F}$  be the rate of appearance of new infections in compartment  $i$  and  $\mathcal{V}$  be the rate of transfer of individuals into and out compartment  $i$  by all other means. From system (1) we have

$$\mathcal{F} = \begin{pmatrix} \frac{\beta_1 S(I+I_h)}{N} + \frac{\beta_2 R(I+I_h)}{N} \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} (\mu + \alpha + r_1)E - \delta I \\ -\alpha(1-p)E + (\mu + d_2 + \delta)I \\ -\alpha p E + (\mu + d_1 + r_2)I_h \end{pmatrix}.$$

By differentiating  $\mathcal{F}$  and  $\mathcal{V}$  with respect to  $E, I,$  and  $I_h$  and evaluating at  $\hat{E}$  with  $N = \frac{\Lambda}{\mu}$ , we get

$$F(\hat{E}) = \begin{bmatrix} 0 & \beta_1 & \beta_1 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix},$$

and

$$V(\hat{E}) = \begin{bmatrix} (\mu + \alpha + r_1) & -\delta & 0 \\ -\alpha(1-p) & (\mu + d_2 + \delta) & 0 \\ -\alpha p & 0 & (\mu + d_1 + r_2) \end{bmatrix}.$$

Since  $V(\hat{E})$  is a non-singular matrix, we have

$$V^{-1}(\hat{E}) = \frac{1}{\phi_1 \phi_2 - \alpha \delta (1-p)} \begin{bmatrix} \phi_2 & \delta & 0 \\ \alpha(1-p) & \phi_1 & 0 \\ \frac{\alpha p \phi_2}{\phi_3} & \frac{\alpha \delta p}{\phi_3} & \frac{\phi_1 \phi_2 - \alpha \delta (1-p)}{\phi_3} \end{bmatrix},$$

where  $\phi_1 = (\mu + \alpha + r_1)$ ,  $\phi_2 = (\mu + d_2 + \delta)$ , and  $\phi_3 = (\mu + d_1 + r_2)$ . Therefore, we have the next generation matrix of system (1),

$$FV^{-1} = \frac{1}{\phi_1\phi_2 - \alpha\delta(1-p)} \begin{bmatrix} \beta_1\alpha(1-p) + \frac{\beta_1\alpha p\phi_2}{\phi_3} & \beta_1\phi_1 + \frac{\beta_1\alpha\delta p}{\phi_3} & \frac{\beta_1\phi_1\phi_2 - \alpha\delta(1-p)}{\phi_3} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Since the basic reproduction number is the spectral radius of  $FV^{-1}$ , we get

$$R_0 = \frac{\beta_1}{\phi_3} \left( \frac{\alpha(1-p)\phi_3 + \alpha p\phi_2}{\phi_1\phi_2 - \alpha\delta(1-p)} \right), \tag{10}$$

where  $\phi_1 = (\mu + \alpha + r_1)$ ,  $\phi_2 = (\mu + d_2 + \delta)$ , and  $\phi_3 = (\mu + d_1 + r_2)$ . It can be observed that the value of  $R_0$  is directly proportional to the infection contact rate  $\beta_1$ . It is not affected by the infection contact rate  $\beta_2$  which comes from the recovered class meaning that the endemic condition is controlled by the infection that comes from the susceptible class not from the recovered class who has TB recurred.

### 3.2. Numerical results

This section deals with numerical simulations for the deterministic and stochastic model. Several control scenarios are designed to study the dynamical behavior of all individual classes. Adjusting parameters are chosen to study the behavior of the system such as the rate of the progression to infectious ( $\alpha$ ), the treatment rate of the latent individuals ( $r_1$ ), the treatment rate of hospitalized individuals ( $r_2$ ), and proportion of the infectious to hospitalized ( $p$ ). One parameter is varied and other parameters are fixed (the values of parameter are shown in Table 1). The initial conditions are chosen as  $(S(0), E(0), I(0), I_h(0), R(0)) = (896, 4, 100, 0, 0)$ , with total population  $N = 1000$ .

In the first simulation, we investigate the percentage of change of the number of individuals in each class by varied the chosen adjusted parameter. The percentage of change for the deterministic solutions is quantified as follows,

$$\Delta = \frac{x_{adjst}(T) - x_{fix}(T)}{x_{fix}(T)},$$

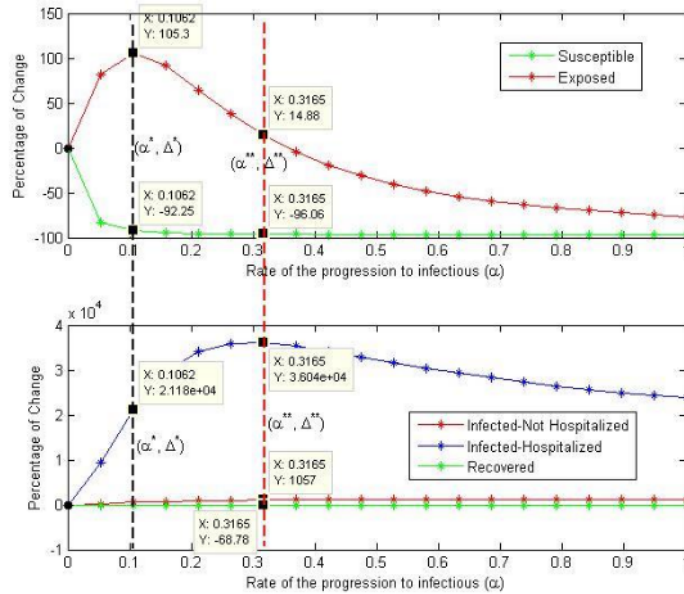
where  $x_{adjst}(T)$  refers to the solution of (1) at the final time  $T$  when one parameter is varied and others are fixed, while  $x_{fix}(T)$  refers to the solution of (1) at the final time  $T$  using parameter values in Table 1 with final time  $T = 50$  months. Figure 2 shows the percentage of changes of all classes when the rate of the progression of latent to the infectious class ( $\alpha$ ) is varied.

**Table 1.** Definition and Parameter values [11].

Parameter	Definition	Value
$\Lambda$	Recruitment rate	1
$\alpha$	The rate of the progression to infectious	0.03
$\beta_1$	Incidence rate of susceptible individuals	0.9875
$\beta_2$	Incidence rate of recovered individuals	0.2476
$p$	Proportion of infectious to hospitalized class	0.53
$r_1$	The treatment rate of latent individuals	0.2365
$r_2$	The treatment rate of hospitalized individuals	0.8608
$\delta$	Self-recovered rate of not hospitalized infectious	0.0001
$d_1$	Disease-induced rate of infectious and hospitalized	$12 \times 10^{-6}$
$d_2$	Disease-induced rate of infectious not hospitalized	0.025
$\mu$	Natural death rate	$3.91 \times 10^{-5}$

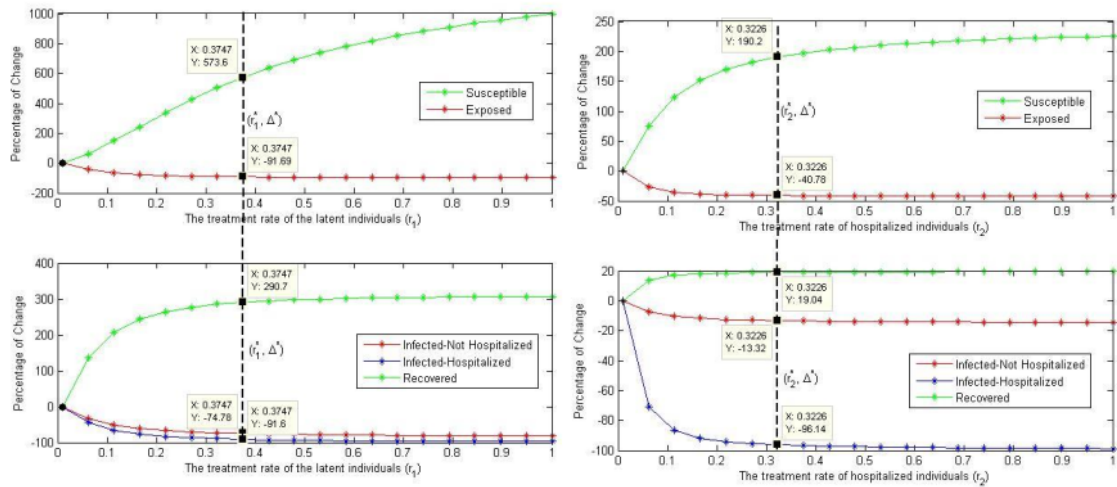
As  $\alpha$  is increased, the number of latent is also increased. There exists a certain  $\alpha$ , says  $\alpha^*$ , in which the value of  $\Delta$  reaches the maximum and then decreases as the number of susceptible also decreases (see top picture in Figure 2). The range in which the system should be controlled from high infectious is when the value of  $\alpha$  is defined in interval  $(\alpha^*, \alpha^{**})$ . In that interval, the value of  $\alpha$  generates high number of latent and infected even though the infected individuals are hospitalized (see the bottom picture in Figure 2). To prevent the high number of infection class, the progression rate to the latent class should be controlled below  $\alpha^*$ . It implies that an early treatment is needed to prevent the high infection rate.

In the next simulation (see Figure 3), we variate the value of treatment <sup>3</sup> rate of the latent class and the treatment rate of the infectious-hospitalized class by changing the value of  $r_1$  and  $r_2$  along the interval(0,1). In the left picture of Figure 3 we can observe that there exists a certain <sup>55</sup> treatment rate for the latent class which can <sup>5</sup> reduce the number of infectious and increase the number of susceptible. The similar results are found for the variation of the treatment rate of the infected-hospitalized class. However, it only affects <sup>43</sup> to the reduction of the number of infected-hospitalized while the infected-non hospitalized is still high enough. On the other hand, the treatment applied in the latent class can reduce not only those who are hospitalized but also those who are not hospitalized. These results have the same implications as the previous simulation results that suggest applying treatment earlier, particularly in the latent individuals. Furthermore, when  $p\%$  of infected individuals is hospitalized, it also affects the increasing of susceptible and the decreasing of latent and infected-not hospitalized. There exists a certain hospitalized portion, says  $p^*$ , such that the number of infected is saturated (see Figure 4).



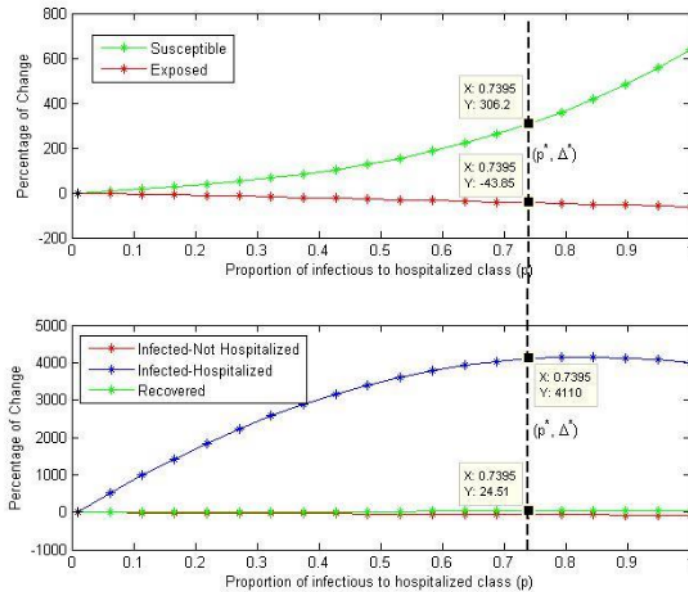
1  
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**Figure 2.** Percentage of changes of susceptible and exposed classes (top) and infected and recovered classes (bottom) when the rate of the progression of latent to the infectious class is varied,  $\alpha \in (0,1]$ .



5  
6  
7

**Figure 3.** Percentage of changes of all individual classes when the treatment rate of the latent individual (left) and infected-hospitalized individual (right) is varied,  $r_1, r_2 \in (0,1]$ .

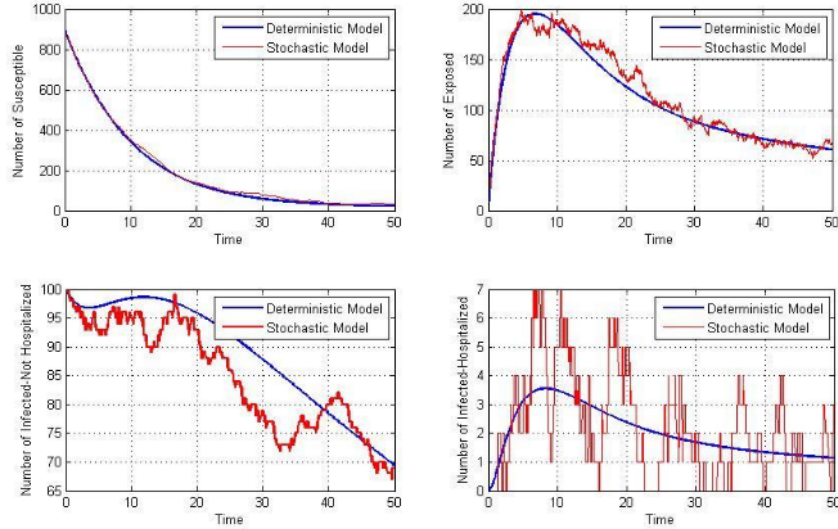


8

9 **Figure 4.** Percentage of changes of all individual classes when the proportion of the infectious to  
 10 hospitalized is varied,  $p \in (0,1]$ .

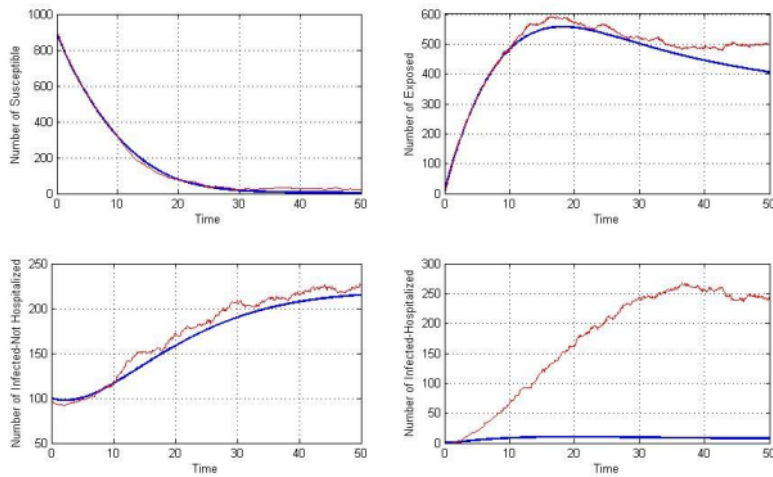
11 We next simulate the numerical solution of the stochastic model. We investigate the sample  
 12 paths of the stochastic model to study the random process in the tuberculosis infection. The random  
 13 process will change the state according to the random variable, and then move to the different state  
 14 as specified by the probabilities of the stochastic matrix. Figure 5 shows how the sample path of  
 15 each compartment changes in time. Using the parameters in Table 1, we found that randomness in  
 16 the infected population was clearly observed. While the randomness does not affect to the  
 17 susceptible population. The highest randomness observes in the infected-hospitalized population  
 18 with high amplitude. Different behavior observed when we decrease the treatment rate of latent  
 19 individuals. In the latent class, deterministic solution shows a decreasing rate of the latent  
 20 individual at the final time of observation while the stochastic solution shows reverse behavior.  
 21 Sample path of the latent class increases at the final time of observation. It affects the increasing  
 22 in the infected-hospitalized individuals. These phenomena were not observed by the deterministic  
 23 solution. In the deterministic solution, number of infected-hospitalized decreasing at the final time

24 of observation. These results imply that some parameters are sensitive to the change of sample  
 25 path and the **deterministic solution**.



26

27 **Figure 5.** The comparison of the **deterministic solution** with the sample path of stochastic  
 28 solution using parameter values in Table 1.



29

30 **Figure 6.** Deterministic solution vs sample path of stochastic solution when the treatment rate of  
 31 latent individuals is decreased to  $r_1 = 0.01$ .

#### 32 4. CONCLUSIONS

33 In this paper we have studied mathematically transmission of tuberculosis infection from  
34 susceptible compartment, infected compartment (latent class and infectious class), and recover  
35 compartment using an epidemiology model called SEIIR model. We analytically found <sup>32</sup> the basic  
36 reproduction number of the model which showed the multiplication rate of new cases of infectious  
37 tuberculosis. Some parameters were investigated their sensitivity to the percentage of change of  
38 each class. We found there exists a critical parameter value that affected the decreasing of  
39 infectious class and increasing the susceptible class. For a certain treatment rate of latent individual,  
40 the stochastic model captured different behavior at the final time which was different with the  
41 deterministic solution. Furthermore, effects of randomness were observed clearly in the infected  
42 class but not for the susceptible class. It implied that the infected class should be closely watched  
43 compared with the susceptible class due to its high of randomness factor.

44

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48

#### 49 <sup>28</sup> CONFLICT OF INTERESTS

50 The author(s) declare that there is no conflict of interests.

51

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