Stability analysis of a tuberculosis epidemic model with nonlinear incidence rate and treatment effects

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Abstract. We present a tuberculosis epidemic model with nonlinear incidence rates. The mathematical model consists of five variables that are susceptible, exposed, infectious, and recovered. Where infectious is divided into two categories, the first is latent infectious and the second categories is MDR (Resistant). The parameters on infectious describe the level of tuberculosis’s treatments are the treatment for the prevention of epidemic tuberculosis is by chemoprohylaxis for the the exposed individuals. Whereas treatment for infected individuals uses anti-tuberculosis drug therapy with the directly observed treatment short course strategy (DOTS). The research method uses analytical (using the MAPLE) and numerical (using the MATLAB application) analysis. The steps in the analytical analysis include making a tuberculosis disease model, determining the point of equilibrium, and analyzing stability. Meanwhile, numerical analysis is used to explain the dynamic simulation of the spread of tuberculosis and the effectiveness of the treatment. The results of this research obtained are two equilibrium points (endemic and non-endemic) with a condition of conditional stability for each point. The stability will apply if the conditions proposed are met, namely local stability at a point of non-endemic equilibrium is stable if \( R_0 \) less than 1 and endemic equilibrium point \( (e^*) \) will be stable if \( R_0 \) more than 1. From the results of analytic calculations and numerical simulations, by using Ruth-Hurwitz Method \( R_0 = 0.312 \) at the non-endemic point and Centre Manifold method on endemic point is \( R_0 = 1.302 \). So it can be concluded that the treatment on the first stage is more important to protect on TB spread.

1. Introduction
Tuberculosis is caused by Mycobacterium tuberculosis (MTb) infection [1]. This disease is one of the deadliest communicable diseases in the world [2]. It was transmitted by the air and through the saliva of an infected person [3]. Some of the symptoms are cough, fever, loss of appetite, shortness of breath, chest pain, chills, and fatigue, weight loss [4]. Without treatment, mycobacterium tuberculosis continues to develop and destroy the tissues. Some with involuntary TB are infected instantly, and other will develop dormant later if their immune are weak [5].

Based on a report from (WHO) the World Health Organization that the death caused by tuberculosis disease stays as the highest infectious disease in the wide lead to mortality [7]. The death toll from Indonesia’s TB by 2020 reached 11.993. A concerted worldwide effort is urgently needed to end tuberculosis which has become a global target at 2030. More than 4.000 people die from TB and nearly 30.000 people get sick with TB every year. In the world, Indonesia was in the third rank after India and...
China, with sufferer reaching 845,000 cases[8]. The development of medical science has a very important role in overcoming tuberculosis. The problem of tuberculosis spread and its treatment are very complex, it is necessary to make calculations and estimation so that the world’s target to end tuberculosis achieves results as expected. The mathematical model is used to analyze and simulate the dynamics of the spread of tuberculosis and the effects of its treatment.

The dynamics of tuberculosis spread model has been studied by many researchers, they are Sutimin (2020) and Marilyn Ronoh (2016). In Sutimin’s research, the epidemic model was used in the saturated infection force and only used one type of infectious. In Marilyn Ronoh’s research, the model used was SEIR, but there was no treatments effect. Now, we study new mathematical model from the tuberculosis (TB) epidemic in Indonesia using nonlinear incidence rate and treatments effect. In this research, infectious is divided into two categories, the first is latent infectious and the second categories is MDR (Resistant). The parameters on infectious describe the level of tuberculosis treatments. They are the treatment for the prevention of epidemic tuberculosis is by chemoprophylaxis for the exposed individuals. Whereas treatment for infected individuals uses anti-tuberculosis drug therapy with the directly observed treatment short course strategy (DOTS). The difference between therapy in first TB and second TB(MDR) are the duration of treatment.

2. Model formulation
The diagram of TB disease spread can be presented in the following figure 1.

\[ \beta_1 p I_1 + \beta_2 q I_2 \]

\[ S \quad \beta_1 (1-p)S I_1 \quad \beta_2 (1-q)S I_1 \]

\[ E \quad \alpha \]

\[ I_1 \quad \beta(1-r_1) \]

\[ I_2 \quad \mu + \delta_2 \]

\[ R \quad \mu + \delta_1 \]

\[ \phi_1 \quad \phi_2 \]

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\[
\frac{dS}{dt} = \lambda - \beta_1 S I_1 - \beta_2 S I_2 - \mu S \\
\frac{dE}{dt} = \beta_1 p_1 S I_1 + \beta_2 q S I_2 - (\mu + \alpha) E \\
\frac{dI_1}{dt} = p \beta_1 S I_1 + q \beta_2 S I_2 + \alpha E - (\phi + \mu + \delta) I_1 \\
\frac{dI_2}{dt} = \phi (1 - r) I_1 - (\mu + \delta) I_2 - \varphi r I_2 \\
\frac{dR}{dt} = \varphi r I_1 + \varphi r I_2 - \mu R
\]

(1)

The variable \( R \) is not involved in the previous four equations so that the fifth equation can be ignored. Thus the equations of the model (1) reduced to model (2):

\[
\frac{dS}{dt} = \lambda - \beta_1 S I_1 - \beta_2 S I_2 - \mu S \\
\frac{dE}{dt} = \beta_1 p_1 S I_1 + \beta_2 q S I_2 - (\mu + \alpha) E \\
\frac{dI_1}{dt} = p \beta_1 S I_1 + q \beta_2 S I_2 + \alpha E - (\phi + \mu + \delta) I_1 \\
\frac{dI_2}{dt} = \phi (1 - r) I_1 - (\mu + \delta) I_2 - \varphi r I_2
\]

(2)

Next, we were analysing the local stability on model (2).

3. Model analysis

Linearization of the model is used because finding solutions to nonlinear systems is not easy. Looking for solutions of linear nonlinear differential systems by substituting equilibrium values into the jacobian matrix. Then, we analyze the existence of model (2)'s equilibriums and local stability to explain the local dynamics of model. Local stability is enough for analyzing this model so global stability is not shown in this paper. They are:

3.1. Existence of equilibriums

Non endemic state is \( e_0 = (S, E, I_1, I_2) = \left( \frac{\lambda}{\mu}, 0, 0, 0 \right) \). and

The endemic equilibrium is given by \( e^* = (S^*, E^*, I_1^*, I_2^*) \) where,

\[
S^* = \frac{\lambda (\mu + \delta_2 + \varphi r)}{I_1^* (\mu + \delta_2 + \varphi r) \beta_1 + \mu^2 + \mu \delta_2 + \mu \varphi r_2 + \beta_2 \phi r I_1^*}
\]

\[
E^* = \frac{\lambda I_1^* (\beta_1 q \phi r + \beta_2 p (\mu + \delta_2 + \varphi r))}{I_1^* \phi r (\mu + \alpha) \beta_1 + (\mu + \alpha) (\mu + \delta_2 + \varphi r_2) (\mu + \beta_1 I_1^*)}
\]

\[
I_2^* = \frac{\phi r I_1^*}{\mu + \delta_2 + \varphi r_2}
\]

(3)
where $p_1 = (1 - p)$, $q_1 = (1 - q)$ and $r = (1 - r_i)$. The value of parameters $p$ and $q$ are between 0 and 1. $I_i^*$ is the solution of the linear polynomial $A_i I_i + A_o = 0$ where $A_o = K_i^*(1 - R_o) < 0$ when $R_o > 1$

$$A_i = (\phi r(\phi + \mu + \delta_i)\mu + \mu r)\beta_i + \beta_i(\mu + \delta_i + \phi r)\beta_i + \mu\beta_i(\mu + \delta_i + \phi r)(\phi + \mu + \delta_i) > 0$$

by using the Next Generation Matrix of the model (2) we get a value of basic reproduction ratio $(R_o)$, that is

$$R_o = \frac{(p\mu + \alpha)\lambda\beta_1}{\mu(\mu + \alpha)(\mu + \delta_i)\mu}$$

(4)

3.2 Local Stability(LS) of Equilibrium Points

We use the Ruth-Hurwitz method to analyze local stability(LS) at $\varepsilon_0$ and center manifold’s method for LS at $\varepsilon^*$.

**Theorem 1.** If value $R_o$ is less than 1 on the $\varepsilon_0$, so, $\varepsilon_0$ of model (2) will locally asymptotically stable and if $R_o$ more than 1 is unstable.

**Proof:**

Jacobian’s matrix on the $DFE(\varepsilon_0)$ can be given by:

$$J_{DFE} = \begin{pmatrix}
-\mu & 0 & \frac{\beta_1}{\mu} & 0 \\
0 & -\mu - \alpha & \frac{\beta_1}{\mu} & \frac{\alpha}{\mu} \\
0 & 0 & -\phi - \mu - \delta_i & \frac{\alpha}{\mu} \\
0 & 0 & \phi r & -\mu - \delta_i - \phi r
\end{pmatrix}$$

(5)

JDFE’s matrix gets a bunch of eigenvalue, they are $X_1 = -\mu$, $X_2 = -\mu - \delta_i - \phi r$ and other fill up the quadratic polynomial $a_0 X^2 + a_1 X + a_0 = 0$, where

$$a_0 = -(\mu + \delta_i + \phi r)(\alpha p_1 + \mu + \alpha p)\beta_i - \lambda r(\alpha q_1 + \mu + \alpha q)\beta_i + \mu(\mu + \alpha)(\mu + \delta_i + \phi r)(\phi + \mu + \delta_i)$$

we assumed that $a_0 > 0$ if $R_o < 1$. $a_i = -\lambda(\alpha p_1 + \delta_i + \phi r + \alpha p_1 + 2p\mu)\beta_i + \alpha\mu\delta_i + \alpha\delta_i\mu + 2\phi^2 + 2\mu^2\delta_i + 2\delta_i\mu^2 + 2\mu\delta_i + \delta_i\phi r + 2\mu^2\phi r + \alpha\delta_i\mu + 3\mu^2 < 0$, and

$$a_2 = \mu\phi r + \mu\delta_i + \phi r + \delta_i\mu + \alpha\mu - \mu\beta_1^* + 3\mu^2 > 0$$. This polynomial has both negative roots when $a_0 > 0$. It is fulfilled when $R_o < 1$.

**Theorem 2:** $\varepsilon^*$ of model(2) is stable if $R_o > 1$.

**Proof.** centre manifold is used to prove the stability of local[12]. We determine the parameter of bifurcation $\beta_1^* = \beta_1^*$ that is obtained from $R_o = 1$, so we have

$$\beta_1^* = \frac{\phi r(\alpha q_1 + \mu + \alpha q)\beta_i}{(\mu + \delta_i + \phi r)(\alpha p_1 + \mu + \alpha p)}$$

Substitution $\beta_1 = \beta_1^*$ into $J(\varepsilon_0)$, we get
The eigen values of matrix $J(\epsilon_0, \beta_1^*)$ are $X_1 = -\mu$, $X_2 = -\mu - \delta_2 - \phi r_2$, $X_3 = 0$, and $X_4 = -(2\mu + \delta_2 + \phi + \alpha)$ in centre manifold theorem we compute that are given as follows:

\[
a = -\frac{2(p-q)\lambda((-1+p)\alpha + \mu q(-1+p))\beta_2^2}{(\alpha + p\mu)^2} + \frac{2(\mu + \alpha)(\mu + \delta_2 + \phi r_2)(\phi + \mu + \delta_1)((-1+p)\alpha^2 - \mu(3q - 2pq - 2p + p^2)\alpha + \mu^2 p(p-q))\beta_2}{\phi(-1+r_1)(\alpha + p\mu)^2 \alpha \mu} - \frac{2(\alpha^2 + 2\alpha \mu + \mu^2)(\mu + \delta_2 + \phi r_2)^2 (\phi + \mu + \delta_1)^2 ((-2-p)\alpha + \mu \mu)}{(\alpha + p\mu)^2 \lambda \alpha \phi^2 (-1+r_1)^2} < 0
\]

on condition that $q > p$, and $b = \frac{(\mu + \delta_2 + \phi r_2)(1-p)\lambda}{\phi r \mu} > 0$. Thus, the endemic equilibria are stable if $\Re_0 > 1$

4. Simulation results
We illustrate the evolution of dynamic of tuberculosis epidemic for a long time to investigate numerically the condition of nonendemic and endemic states. The illustrations are given in the following figure 1.

![Simulation results](image)

**Figure 2.** The evolution of population for endemic ($\Re_0>1$) and nonendemic states ($\Re_0<1$)
The simulation illustration stratified the condition when $R_0 > 1$ and $R_0 < 1$. In the figure 2(a) the value of $R_0 = 1.302$ and figure 2(b) $R_0 = 0.312$. Thus, according to the Fig.1 locally stable of endemic equilibrium on this model is achieved when $R_0 > 1$. And the local stability of $DFE$ also qualified to $R_0 < 1$. Then, the following parameters are used to simulate the effects of treatments. The parameters on fig.3 (a) are: $\lambda = 30, \beta_1 = 0.0002, \beta_2 = 0.0001, \mu = 0.0101, \alpha = 0.03, \delta_1 = 0.02272, \delta_2 = 0.02272, \phi = 0.5, \varphi = 0.25, p = 0.1,$ and $q = 0.002$

![Figure 3](image_url)

**Figure 3.** The evolution of susceptible and infectious populations in different treatments

We define the simulation of efficacy treatments by using $E = 1 - (1 - r_1)(1 - r_2) = 0.68$. Three scenarios used are: $r_1 = 0.6, r_2 = 0.2; r_1 = 0.2, r_2 = 0.6 ;$ and $r_1 = r_2 = 0.43$. Figure 3(a) shows that first line treatment is more effective in reducing TB epidemic rate. And In Figure 3(b), it shows that the second line treatment can significantly reduce the number of infectious populations. It is seen that for increasing value of $r_1$ implying the increasing the number of susceptible individuals, but not for the values of $r_2$.

5. Conclusion

We study about a dynamical model of tuberculosis epidemic spread with bilinear incidence rate and treatment effects with $SEI_1I_2 R$ epidemic model on this paper. The local dynamics is proven in the analysis, and it is shown that the stability depends on the basic reproduction number. The local stability of non endemic state is fulfilled when $R_0 < 1$. The endemic state is local stable when $R_0 > 1$. Numerical simulation has shown that first line treatment can decrease the infected population numbers and increasing the susceptible individuals. It can be concluded that the treatment for the first stage of the infected individuals may be more important in protecting the TB spread.

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