Analysis of TB epidemic model with relapse and treatment

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Abstract. Tuberculosis (TB) is an infectious disease becoming a serious health problem that causes mortality and morbidity. A model of Tuberculosis spread by incorporating the effect of relapse and susceptible from recovery individuals, as well as treatment is studied. The existence of endemic equilibrium is shown through the basic reproduction ratio. The analysis results show that the non endemic equilibrium is global stable if the ratio value is less than unity, the endemic equilibrium the global stable if the ratio value is greater than unity. The results of study show that the relapse factor affects in the decrease of healthy individuals, and treatment of chemoprophylaxis is more significant in preventing the spread of TB disease compared to therapy.

1. Introduction
Tuberculosis (TB) is a one of diseases becoming the health problem in the worldwide due to mortality and morbidity for suffers. The disease is generated by the Mycobacterium Tuberculosis bacteria that infects lung [1]. The World Health Organization (WHO) has declared that TB disease becomes big health problem of infectious disease in the worldwide. The WHO reported that the death affected by TB reach 1.5 million people in 2018 [2].

Mathematics has become a tool to explore the dynamics of TB spread by modeling. A number of models has been developed to describe the transmission of TB disease by considering many aspects related to prevention and infection. Bowong et al. [3] proposed and analyzed a model by considering the effect of the losing sight for the infected individuals. They analyzed the dynamical global of equilibria for the proposed model. The global stability of equilibriums is characterized by the value of the threshold parameter. Mishra et al. [4], modeled TB disease by considering the effect of vaccine and quarantine class, and then studied the global dynamics by constructing Lyapunov function. By incorporating the effect of drugs, treatment and vaccine, the mathematical models were established and explored the behavior of the stability for these models [5, 6, 7, 8, 9, 10]. Egonmwan et al. [11] and Liu et al. [12] established mathematical models by taking into account the treatments to analyze the dynamical global of the model. The global dynamics is characterized by the basic reproduction number, it is shown by the values of this number larger or less than unity.

A mathematical model by considering relapse from recovery was explored by Ozcaglar et al. [13]. They introduced a model by incorporating the effect of re-infection return to active infectious and non-infectious from recovery and incorporating treatments. Yet, they only gave a review for mathematical models in different aspects of tuberculosis epidemic, and they have not yet given the dynamical analysis of proposed models. Zao et al. [14], established a model by dividing susceptible individuals into three groups of age, considering relapse from recovery individuals back to infectious and incorporating...
vaccine in children class. Willis [15] illustrated some examples mathematical models for intervention of TB epidemic related to reactive and relapse, yet he has not studied mathematically to analyze the dynamical behavior of the models. In the study, we propose a model by considering the effect of relapse resulted from recovery individuals return to exposed or latent stage, by incorporating the treatments for latent and infectious individuals, then explore the global dynamics and present the simulations to study numerically to compare the effect of treatments.

2. Methods

In the model contains of variable states, namely susceptible \((S)\), exposed \((E)\), infectious \((I)\), and recovery class \((R)\). The diagram transmission of TB spread including the relapse and treatments for latent and infectious compartments can be presented in Figure 1.

The mathematical model can be written as,

\[
\begin{align*}
\frac{dS}{dt} &= \lambda - \beta SI - \mu S + q\theta R \\
\frac{dE}{dt} &= \beta(1-p)SI + (1-q)\theta R - (\mu + \alpha)E \\
\frac{dI}{dt} &= \beta pSI + \alpha(1-r_I)E - \phi r_E I - (\mu + \delta)I \\
\frac{dR}{dt} &= \phi r_I I + \alpha r_E E - \phi R - \mu R
\end{align*}
\] (1)

Populations of susceptible are produced with a rate \(\lambda\). all individuals die naturally with the rate \(\mu\). Upon infection, the fraction of \(\beta(1-p)\) the susceptible individuals progress to latent class, while the fraction \(\beta pS\) move directly to infectious class. Due to chemoprophylaxis treatment for latent individuals, the part of \((1-r_I)\alpha\) in the latent individuals progress to infectious, while other the fraction of \(\alpha r_E E\) is cured. Due to therapy treatment for infectious individuals, the fraction \(\gamma r_E\) of these individuals returns to latent, while others fraction \(r_I I\) becomes cured. We consider that the fraction of \(q\theta\) from the cured individuals back to healthy and other fraction \((1-q)\theta\) of recovery individuals becomes latent. The individual die out due to TB infection with the constant rate \(\delta\). Next the dynamical behavior of the model and simulation results is discussed.

3. Result and Discussion

In this section, the non endemic equilibriums for the model (1) is determined to explore the global dynamic.
3.1. The existence of equilibrium points

The nonendemic equilibrium of the model is $$E_0 = \left( \frac{\lambda}{\mu}, 0, 0, 0 \right)$$ and basic reproductive ratio can be defined by $$R_0 = \frac{\lambda\beta}{\mu(\mu + \alpha)(\mu + \delta + \phi_2)}$$ (see in [15]). The endemic equilibrium is $$E^* = (S^*, E^*, I^*, R^*)$$ related to this ratio (see in [16]) where,

$$S^* = \frac{(1-r_i)(\theta + \mu)\lambda + q_\theta(\delta r_i + \mu r_i + \phi r_i)I^*}{(1-r_i + pqr_i)\theta + (1-r_i)\mu}$$

$$E^* = \frac{I^* (r_i (\varphi (1-pq) + \mu) + (\mu + \theta)(\mu + \delta) \beta I^* - \lambda p(\mu + \theta) \beta + \mu r_i (\mu + \theta)(\mu + \delta))}{(1-r_i)(\mu + \theta) pqr_i \theta \beta I^* + (1-r_i)(\mu + \theta) \alpha}$$

$$R = \frac{r_i (\mu + \delta) r_i + \phi r_i)}{(1-r_i)(\mu + \delta)} \beta I^* + (1-r_i)(\mu + \theta) \alpha$$

and $$I^*$$ is the solution of the linear polynomial $$1 0 A I A 0$$, where $$A = (\mu r_i \phi r_i + \alpha (1-r_i + p r_i) (\mu + \delta) \beta \alpha + r_i \mu (\mu + \theta (1-pq)) + \mu (\mu + \theta)(\mu + \delta) \beta ,$$

$$A_0 = -K (R_0 - 1) - \frac{\alpha \mu (1-q)(1-r_i)\theta ((1-p)r_i (\mu + \delta) + r_\phi \alpha + \mu p \phi_2)}{\mu p + (1-r_i + p r_i)}$$

where, $$K = \frac{((1-r_i + p r_i)(\mu + \theta)) \alpha + \mu p (\mu + \theta))}{\mu p + (1-r_i + p r_i)}$$. It can be seen that $$A_0 > 0$$, the solution for endemic of the model is satisfied when $$A_0 < 0$$, it is hold if $$R_0 > 1$$.

3.2. Global stability of equilibria

The next theorems verify the stability of the system (1) concerning with the global dynamics.

**Theorem 1:** The non endemic equilibrium $$E_0$$ is global stable if $$R_0 < 1$$.

**Proof:**

The model (1) can be written by $$\frac{dY}{dt} = F(Y, Z), \frac{dZ}{dt} = G(Y, Z)$$, where $$Y = S, Z = (E, I, R)$$ and $$G(Y, 0) = 0, \ Y \in \bar{S}, Y \in \bar{I}$$ . It is seen that $$E_0 = (Y_0, 0)$$, where $$Y_0 = \frac{\lambda}{\mu}$$. Consider

$$(H_1). \quad F(Y, 0) = \lambda - \mu Y$$ , it means that for $$t \to \infty, Y = Y_0$$ is global asymptotically stable.

$$(H_2). \quad G(Y, Z) = AZ - \hat{G}(Y, Z)$$ , where

$$A = \begin{pmatrix} -\mu - \alpha & \frac{(1-p)\beta \lambda}{\mu} & (1-q)\theta \\ \alpha (1-r_i) & \frac{\beta \lambda}{\mu} & 0 \\ \alpha r_i & \phi r_i & -\mu - \alpha \end{pmatrix}$$

and $$\hat{G}(Y, Z) = \begin{pmatrix} \beta(1-p)I(\lambda - \mu S) \\ \frac{\beta p I(\lambda - \mu S)}{\mu} \\ 0 \end{pmatrix} \geq 0$$

It seen that $$A$$ is M-Matrix, so $$E_0$$ is global stable if $$R_0 < 1$$.

**Theorem 2:** The endemic equilibrium $$E^*$$ is global stable if $$R_0 > 1$$.

**Proof:**

Lyapunov function of the model can be define as
\[ V = (S - S' \ln S) + a_1 (E - E' \ln E') + a_3 (I - I' \ln I') + a_4 (R - R' \ln R') \]  

(3)

Differentiating this function to time related to the model (1) and manipulating the algebraic calculation is obtained,

\[
\frac{dV}{dt} = \frac{dV}{dt} \left[ 1 - \frac{S'}{S} \right] \frac{dS}{dt} + \left[ 1 - \frac{E'}{E} \right] \frac{dE}{dt} + a_2 \left[ 1 - \frac{I'}{I} \right] \frac{dI}{dt} + a_4 \left[ 1 - \frac{R'}{R} \right] \frac{dR}{dt}
\]

\[
= C - (\mu + \beta p I') S + (a_1 \beta (1 - p) + a_2 \beta p - \beta) S I + (a_3 \alpha (1 - r) + a_4 \alpha r - (\mu + \alpha)) E
\]

\[
+ \left( \beta S' - a_2 (\phi r + \delta + \mu) \right) I + (\phi q + a_1 (1 - q) - a_3 (\theta + \mu)) R - \lambda \frac{S'}{S} - q \phi S' \frac{R}{S}
\]

\[
- a_4 (1 - p) \beta E' \frac{S I}{E} - a_2 (1 - q) \theta E' \frac{R}{E} - a_3 (1 - r) E' \frac{I}{R} - a_4 \phi r R' \frac{I}{R} - a_4 \alpha r R' \frac{E}{R},
\]

(4)

where \( C = \lambda + \mu S' + a_1 (\mu + \alpha) E + a_2 (\phi r + \mu + \delta) I + a_3 (\phi q + \mu) R' \) . The values \( a_1, a_2 \) and \( a_3 \) are the solution from coefficients of \( S I, E I, I' R \) that are equal to zero, it is obtained the relationship \( a_1 (1 - p) + a_3 p = 1, a_2 \alpha (1 - r) + a_4 \alpha r = \mu + \alpha, a_2 (\phi r + \mu + \delta) = \beta S', a_3 (\phi q + \mu + \delta) = a_3 (\theta + \mu) \)

\[
a_4 (\phi r + \delta + \mu) = a_4 (\delta + \mu) \alpha.
\]

The equation (4) can be written as

\[
= C - (\mu + \beta p I') S - \lambda \frac{S'}{S} - q \phi S' \frac{R}{S} - (1 - p) \beta E' \frac{S I}{E} - a_2 (1 - q) \theta E' \frac{R}{E}
\]

\[
- a_3 (1 - r) E' \frac{I}{R} - a_4 \phi r R' \frac{I}{R} - a_4 \alpha r R' \frac{E}{R},
\]

(5)

Next, it is given the new notation, \( w = \frac{S}{S'}, x = \frac{E}{E'}, y = \frac{I'}{I'}, z = \frac{R}{R'} \) . So the equation (4) can be given as

\[
\frac{dV}{dt} = C - (\mu + \beta p I') S w - \lambda \frac{1}{w} - \phi q R' \frac{z}{w} - a_1 \beta \frac{1}{w} S' I' \frac{x y}{x}
\]

\[
- a_2 \frac{1}{w} \theta R' \frac{x}{x} - a_3 \frac{1}{w} \frac{r y}{z} - a_4 \frac{1}{w} \frac{r q r R' E' \frac{x}{z}}{z}
\]

(6)

The equation (6) contains the state variables in the set \( \left\{ w, \frac{1}{w}, \frac{x y}{x}, \frac{x}{z} \right\} \), and \( \left\{ \frac{1}{u}, \frac{1}{y}, \frac{u y}{x} \right\} \). So

\[
\frac{dV}{dt} = b_1 \left( 2 - w - \frac{1}{w} \right) + b_2 \left( 2 - x - \frac{z}{x} \right) + b_3 \left( 3 - \frac{1}{w} - x - \frac{w y}{x} \right) + b_4 \left( 4 - \frac{1}{x} - u - \frac{w y}{v} \right) - q \theta R' \frac{z}{w}.
\]

(7)

The values \( b_1, b_2 \) and \( b_3 \) are computed by equating the coefficients of the equation (7) and the equation (6) and with the relationship \( 2b_1 + 2b_2 + 3b_3 = C, b_1 = (\mu + \beta p I') S', b_1 + b_2 = \lambda, b_2 = a_3 (1 - r) = a_1 (\beta (1 - p) S' I'), b_3 = a_1 \alpha r E' = a_3 (1 - q) \theta R' \). By considering the inequality of geometric mean and the arithmetic mean, it can be seen that \( \frac{dV}{dt} \leq 0 \) for \( x, y, u, v > 0 \), and \( \frac{dV}{dt} = 0 \) if \( x = y = z = w = 1 \). So the
maximum invariant set of the model (1) of the set \( \{ (x,y,u,v) | \frac{dV}{dt} = 0 \} \) is the solution (1,1,1,1). By considering LaSalle principle, \( E^* \) is global stable.

3.3. Simulation results
For simulations, we explain numerically the effect of treatment and relapse for the evolution of susceptible and infectious populations. The chemoprophylaxis treatment is used for latent individuals, whereas therapy is used for infectious individuals. We also investigate numerically to explain the implication of relapse factor.

In the simulation of treatment effect, \( r_1, r_2 \) are the efficacy values of chemoprophylaxis and therapy. The efficacy of treatment combination \( r_1, r_2 \) is determined as \( \varepsilon = 1 - (1 - r_1)(1 - r_2) = 0.7 \). For the simulations, we consider the scenarios of treatment as follows. The first scenario, it is taken with \( r_1 = 0.5 \) and \( r_2 = 0.4 \), the second scenario is for \( r_1 = 0.4 \) and \( r_2 = 0.5 \), and the third scenario, it is chosen \( r_1 = r_2 = 0.45 \). We take the values of parameter from [12], with \( \beta = 0.00005, \mu = 0.022, \alpha = 0.0003, \delta = 0.13, \phi = 0.058 \), and we choose \( p = q = 0.1, \lambda = 50 \) and \( \theta = 0.002 \).

\[ \text{Figure 2. The population of healthy and infectious in scenarios of treatment} \]

In the Figure 2, it seen that therapy is less effective for increasing the healthy population compared to chemoprophylaxis treatment. Converse, this therapy is slower in reducing the population of infectious compared to chemoprophylaxis treatment. It can be considered that chemoprophylaxis treatment is significant in reducing the TB transmission.

The effect of relapse with respect to outcome the number of healthy and infectious populations can be simulated in Figure 3 with giving the different values \( \theta \). It can be seen that when the relapse factor is high, the number of healthy individuals is low and vice versa. On the other hand, the infectious population increases when the relapse factor is high. It shows that the relapse factor relapse has significant effect for increasing the TB epidemic.

\[ \text{Figure 3. The population of healthy and infectious under relapse level} \]
4. Conclusion
A mathematical model of TB epidemic by considering the effect of relapse from recovery individuals to exposed individuals as well as treatments effect provided for exposed and infectious population was studied. The global stable for non-endemic equilibrium is satisfied if $R_0 < 1$, whereas for the endemic is satisfied when $R_0 > 1$.

From simulations, by comparing the implication of the chemoprophylaxis treatment and therapy, it can be concluded that the treatment of chemoprophylaxis may be more significant in reducing of TB epidemic compared to therapy. The relapse factor has significant effect in increasing the TB spread. Upon the weak individual immune system, the recovery individuals may be occurred TB re-infection that result in increasing the TB spread.

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