Mathematical Model Of Tuberculosis Transmission With Recurrent Infection And Vaccination

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Abstract: This paper presents a model of tuberculosis transmission with vaccination by explicitly considering the total number of recovered individuals, either from natural recovery or due to vaccination. In this paper the endemic and nonendemic fixed points, basic reproduction number, and vaccination reproduction number are given. Some results regarding the stability of the fixed points and the relation to the basic reproduction numbers are analysed. At the end of this study, the numerical computation presented and it shows that vaccination is capable to reduce the number of laten and infectious populations.

1. Introduction
Tuberculosis (TB) is an infection disease caused by \textit{Mycobacterium tuberculosis}. The disease is able to spread quickly through the air medium and becoming the second most killer among all transmission disease. It is also regarded to be the third grade in the list of the ten highest killer disease in Indonesia [13]. The World Health Organization (WHO) data in 2009 shows that the total number of tuberculosis victims in Indonesia reach up to 429,000 persons, and lies in the fifth position in the world after India, China, South Africa, and Nigeria [1]. Hence, TB is one of the disease that has been raising a serious problem for a long time in Indonesia [13].

Some researchers have been studying the tuberculosis transmission using modeling approach [2, 4, 9]. Some of them have include intervention to over come the spread of TB in their models [3, 4, 6]. An example of WHO recommended intervention is by giving BCG (\textit{Bacillus Calmette Guerin}) vaccination to newborn baby an in general population [1, 7, 13, 15, 16]. The person that is vaccinated with BCG could be protected 70% - 80% from tuberculosis infection [13].

In this paper, to evaluate the effectiveness of vaccination program we develop a mathematical model and use the concept of the \textit{basic reproduction number}. It is well known in the literature that, the free infection condition is globally stable if the \textit{basic reproduction number} value is less than one, but if the \textit{basic reproduction number} value is greater than one the tuberculosis disease will be endemic [5, 8]. In this paper we will show that in the present of vaccination, a modified \textit{threshold} parameter which is called the \textit{vaccine reproduction number} will have the value less than one for a certain level of vaccination. The vaccination model had been studied by some researchers in various forms, among others: vaccination in \textit{SVI} model [11], where \textit{S} is a \textit{susceptible} compartment, \textit{V} is a vaccination compartment, and \textit{I} is an infected compartment; vaccination in \textit{SVIR} model [12], where \textit{R} is a \textit{recovered} compartment; vaccination in \textit{SVIER} model by considering the existence of an \textit{exposed} phase of infected individuals (\textit{E})
In this paper we modify the model in [3] by considering that the recovered individuals can only be reinfected by making contact with the infectious individuals.

2. Dynamical System model of tuberculosis spreading with vaccination

State variable on the dynamical model is given as in [3] that is: The number of susceptible individual compartment on the time \( t \) denoted by \( S(t) \). The number of exposed individual compartment on the time \( t \) denoted by \( E(t) \). The number of infected individual compartment on the time \( t \) denoted by \( I(t) \), and the number of recovery individual compartment on the time \( t \) denoted by \( R(t) \). The model of tuberculosis transmission with recurrent infection is as follows:

\[
\begin{align*}
\frac{dS}{dt} & = \lambda - \lambda S - \mu S \\
\frac{dE}{dt} & = f \lambda S - \delta_1 \lambda E - (\mu + k)E + f_2 \delta_2 R \\
\frac{dI}{dt} & = (1-f) \lambda S + \delta_1 \lambda E + kE - (\mu + p + d)I + (1-f_1) \delta_2 \lambda R \\
\frac{dR}{dt} & = pI - \mu R - \delta_2 \lambda R
\end{align*}
\]  

(1)

where

\[
\lambda = \frac{\beta c I}{N}
\]

(2)

is the force of infection. The parameters used in the model are as follow. \( \Lambda \) is recruitment rate into susceptible compartment, \( c \) is the per capita contact rate, and \( \beta \) is the probability that one susceptible individual becomes infected by an infectious individual. Susceptible individuals infected with Mycobacterium tuberculosis bacteria (Mtb) moved to latently infected compartment at a rate \( f \lambda \), where \( f \) is the probability that the infected enters the latent compartment. Susceptible individuals infected with Mtb move into the infective compartment at a rate \((1-f)\lambda\). The latently infected progress to active TB at rates \( k \) for endogenous reactivation and \( \delta_1 \lambda \) for exogenous re-infection respectively. Once in active compartment of the disease, an individual may recovered naturally at rate \( p \) and move into the recovered compartment \( R \). Individuals in \( R \) are not totally immune to Mtb infection and are infected at rate \( f_1 \delta_1 \lambda \) and move into \( E \), where \( f_1 \) is the probability that relapse back into the latent compartment, \((1-f_1)\delta_2 \lambda \) relapse back into the active infected compartment. Infectives have an additional TB induced death rate \( d > 0 \), and the natural death rate in each class is assumed to be \( \mu > 0 \).

In this paper we extend the model above to include vaccination compartment \( (V) \) as expressed on the schematic transmission diagram in Figure 1, with the description of the parameters given in Table 1.
Based on the schematic diagram on the Figure 1, we have the following model

\[
\begin{align*}
\frac{dS}{dt} & = \Lambda - \lambda S - (\mu + \theta)S \\
\frac{dV}{dt} & = \theta S - (1 - \sigma)\lambda V - (\mu + r)V \\
\frac{dE}{dt} & = f\lambda S + (1 - \sigma)\lambda V - \delta_1\lambda E - (\mu + k)E + f_1\delta_2 R \\
\frac{dI}{dt} & = (1 - f)\lambda S + \delta_1\lambda E + kE - (\mu + p + d)I + (1 - f_1)\delta_2\lambda R \\
\frac{dR}{dt} & = rV + pI - \mu R - \delta_2\lambda R
\end{align*}
\]

Here we assume that BCG vaccine moves individuals from the susceptible compartment to the vaccinated compartment at a rate \(\theta\), and an individual into recovered compartment because immune due to vaccination at a rate \(r\). In this case, the effective contact rate, \(\beta_c\) is multiplied by a scaling factor \((1 - \tau)\), where \(0 \leq \tau \leq 1\) is the efficacy of the vaccine.

The nonendemic equilibrium point of the equation (3) is given by

\[
Q_0 = \left( \frac{\Lambda}{\mu + \theta}, \frac{\Lambda \theta}{(\mu + \theta)(\mu + r)}, 0, 0, \frac{\Lambda \theta r}{\mu(\mu + \theta)(\mu + r)} \right)
\]

The endemic equilibrium point of the equation (3) is given by

\[
Q_1 = (S_1, V_1, E_1, I_1, R_1)
\]

\[
Q_1 = \left( \frac{\Lambda}{\mu + \theta + \lambda_i}, \frac{\Lambda \theta}{(\mu + \theta + \lambda_i)(\mu + r + [1 - \sigma]\lambda_i)}, E_1, I_1, R_1 \right)
\]

where:

\[
\lambda_i = \frac{\beta c}{N}, \quad R_i = \frac{r\theta \lambda + p(\mu + \theta + \lambda_i)(\mu + r + [1 - \sigma]\lambda_i)I_i}{(\mu + \delta_2\lambda_i)(\mu + \theta + \lambda_i)(\mu + r + [1 - \sigma]\lambda_i)}
\]

\[
E_i = \frac{f\lambda\lambda_i(\mu + r + [1 - \sigma]\lambda_i)(\mu + \delta_2\lambda_i)(\mu + \theta + \lambda_i)}{(\mu + \delta_2\lambda_i)(\mu + \delta_1\lambda_i)(\mu + \theta + \lambda_i)(\mu + r + [1 - \sigma]\lambda_i)}
\]

\[
I_i = \frac{(1 - f)\lambda S_i + (\delta_1\lambda_i + k)E_i + (1 - f_1)\delta_2\lambda_i R_i}{\mu + p + d}
\]

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The reproduction number of vaccination by using Next Generation Matrix [5, 8] is given by:

\[
R_v = \frac{\beta c \Lambda (\mu [\mu + r][1 - f] + [1 - f_i] \mu + k)] \delta, \theta r + (1 - \sigma) \kappa \theta \mu}{\mu N (\mu + r)(\mu + k)(\mu + \theta)(\mu + d + p)}
\]  

(6)

To be biologically meaningful, the initial condition of the model are given by \(S(0) = S_0 \geq 0, V(0) = V_0 \geq 0, E(0) = E_0 \geq 0, I(0) = I_0 \geq 0, \) and \(R(0) = R_0 \geq 0.\) It can be shown that the solution of the model defined for all the time \(t \geq 0.\) Since the equation (3) have the solution in the nonnegative area

\[
\left\{(S, V, E, I, R) \in R^5: S + V + E + I + R \leq \frac{\Lambda}{\mu + \theta}\right\}
\]

(7)

where \(\frac{\Lambda}{\mu + \theta}\) is the number of total population at nonendemic time.

**Table 1.** Definition of parameter used in the model.

| Parameters | Description                                      | Estimation         |
|------------|--------------------------------------------------|--------------------|
| \(\Lambda\) | Recruitment rate                                | 3500 per year      |
| \(\theta\) | Vaccination rate from \(S\)                     | 0.2 per year        |
| \(\mu\)   | Natural mortality rate                          | 0.01 per year       |
| \(c\)     | Contact rate of \(S\) with \(I\)               | 21 per day          |
| \(\sigma\) | Vaccination effectiveness                      | 0.8 per year        |
| \(d\)     | Death rate of \(I\)                             | 0.05 per year       |
| \(\beta\) | Transmission probabilities                     | 0.17 per year       |
| \(k\)     | Natural rate of progression to \(I\)            | 0.00013 per year    |
| \(p\)     | Natural recovery rate from \(I\)               | 0.15 per year       |
| \(r\)     | Natural recovery rate from \(V\)               | 0.35 per year       |
| \(\delta_1\) | Probability of the individul entering \(I\) from \(E\) that recontact with \(I\) | 0.2 per year       |
| \(\delta_2\) | Probability of the individual to be passive infected from \(R\) | 0.15 per year |
| \(f\)     | Probability of \(S\) entering into \(E\)       | 0.99 per year       |
| \(f_i\)   | Probability of \(R\) entering into \(E\)       | 0.7 per year        |

The solution of equation (3) with the positive initial condition is bounded for every \(t \geq 0.\) Further we have the following proposition for the equilibrium and its stability analysis

**PROPOSITION 1**

*The disease-free equilibrium of the system (3) is locally asymptotically stable when the vaccination reproduction number \(R_v < 1\) and unstable when \(R_v > 1.\)*
Proof:
Let \( \frac{dS}{dt} = F, \frac{dV}{dt} = G, \frac{dE}{dt} = H, \frac{dI}{dt} = K, \frac{dR}{dt} = L, \) be the Jacobian matrix on the point \( P \) is

\[
J(P) = \begin{bmatrix}
\frac{\partial F}{\partial S} & \frac{\partial F}{\partial V} & \frac{\partial F}{\partial E} & \frac{\partial F}{\partial I} & \frac{\partial F}{\partial R} \\
\frac{\partial G}{\partial S} & \frac{\partial G}{\partial V} & \frac{\partial G}{\partial E} & \frac{\partial G}{\partial I} & \frac{\partial G}{\partial R} \\
\frac{\partial H}{\partial S} & \frac{\partial H}{\partial V} & \frac{\partial H}{\partial E} & \frac{\partial H}{\partial I} & \frac{\partial H}{\partial R} \\
\frac{\partial K}{\partial S} & \frac{\partial K}{\partial V} & \frac{\partial K}{\partial E} & \frac{\partial K}{\partial I} & \frac{\partial K}{\partial R} \\
\frac{\partial L}{\partial S} & \frac{\partial L}{\partial V} & \frac{\partial L}{\partial E} & \frac{\partial L}{\partial I} & \frac{\partial L}{\partial R}
\end{bmatrix}
\]

\[
J(P) = \begin{bmatrix}
\frac{\partial F}{\partial S} & \frac{\partial F}{\partial V} & \frac{\partial F}{\partial E} & \frac{\partial F}{\partial I} & \frac{\partial F}{\partial R} \\
\frac{\partial G}{\partial S} & \frac{\partial G}{\partial V} & \frac{\partial G}{\partial E} & \frac{\partial G}{\partial I} & \frac{\partial G}{\partial R} \\
\frac{\partial H}{\partial S} & \frac{\partial H}{\partial V} & \frac{\partial H}{\partial E} & \frac{\partial H}{\partial I} & \frac{\partial H}{\partial R} \\
\frac{\partial K}{\partial S} & \frac{\partial K}{\partial V} & \frac{\partial K}{\partial E} & \frac{\partial K}{\partial I} & \frac{\partial K}{\partial R} \\
\frac{\partial L}{\partial S} & \frac{\partial L}{\partial V} & \frac{\partial L}{\partial E} & \frac{\partial L}{\partial I} & \frac{\partial L}{\partial R}
\end{bmatrix}
\]

The Jacobian matrix on a point \( P_0 \) is

\[
J(P_0) = \begin{bmatrix}
\frac{\partial F}{\partial S} & \frac{\partial F}{\partial V} & \frac{\partial F}{\partial E} & \frac{\partial F}{\partial I} & \frac{\partial F}{\partial R} \\
\frac{\partial G}{\partial S} & \frac{\partial G}{\partial V} & \frac{\partial G}{\partial E} & \frac{\partial G}{\partial I} & \frac{\partial G}{\partial R} \\
\frac{\partial H}{\partial S} & \frac{\partial H}{\partial V} & \frac{\partial H}{\partial E} & \frac{\partial H}{\partial I} & \frac{\partial H}{\partial R} \\
\frac{\partial K}{\partial S} & \frac{\partial K}{\partial V} & \frac{\partial K}{\partial E} & \frac{\partial K}{\partial I} & \frac{\partial K}{\partial R} \\
\frac{\partial L}{\partial S} & \frac{\partial L}{\partial V} & \frac{\partial L}{\partial E} & \frac{\partial L}{\partial I} & \frac{\partial L}{\partial R}
\end{bmatrix}
\]

Det\[J(P_0)] = \beta c A \left( \mu \right) \left( \mu + r \right) \left[ (1 - f) \mu + k \right] + \left[ (1 - f_1) \mu + k \right] \delta_2 \theta r + \left( 1 - \sigma \right) k \theta \mu \cdot \mu N \left( \mu + r \right) \left( \mu + k \right) \left( \mu + \theta \right) \left( \mu + d + p \right)
\]

Det\[J(P_0)] = 0 when

\[
\beta c A \left( \mu \right) \left( \mu + r \right) \left[ (1 - f) \mu + k \right] + \left[ (1 - f_1) \mu + k \right] \delta_2 \theta r + \left( 1 - \sigma \right) k \theta \mu \cdot \mu N \left( \mu + r \right) \left( \mu + k \right) \left( \mu + \theta \right) \left( \mu + d + p \right)
\]

The real part of eigen value of Det\[J(P_0) - \lambda \] = 0 are all negative when \( R_V < 1 \) [3, 10]. As a result, the disease-free equilibrium point \( P_0 \) is locally asymptotically stable whenever \( R_V < 1 \). On the contrary, the real part of eigen value of Det\[J(P_0) - \lambda \] = 0 is positive when \( R_V > 1 \) [3, 10]. As a result, the disease-free equilibrium point \( P_0 \) is locally asymptotically unstable whenever \( R_V > 1 \).

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Relation of the vaccination reproduction number to the basic reproduction number

The reproduction number without vaccination or the basic reproduction number is given by

$$R_0 = \frac{\beta c \Lambda((1-f)\mu+k)}{\mu N(\mu+k)(\mu+d+p)}.$$  \hspace{1cm} (8)

As a result,

$$R_v = R_0 \left( \frac{(\mu+r)((1-f)\mu^2+k\mu)+(1-f)\mu+k)]\delta r + (1-\sigma)k\theta \mu}{(\mu+r)(\mu+\theta)((1-f)\mu+k)} \right) < R_0,$$

since $$(\mu+r)((1-f)\mu^2+k\mu)+[(1-f)\mu+k]\delta r + (1-\sigma)k\theta \mu < (\mu+r)(\mu+\theta)((1-f)\mu+k).$$ Hence, for $(\theta > 0$ and $0 < \sigma \leq 1)$, the effect of vaccine will always reduce the basic reproduction number from the disease.

Furthermore, let $R_v = 1$ and solve for $\theta$ so that the solution is $\theta^\ast$. This solution is a critical vaccination level that given by:

$$\frac{\beta c \Lambda(\mu(\mu+r)((1-f)\mu+k)] + [(1-f)\mu+k]\delta r + (1-\sigma)k\theta \mu}{\mu N(\mu+r)(\mu+k)(\mu+d+p)} = 1$$

$$\beta c \Lambda(\mu(\mu+r)((1-f)\mu+k)] + [(1-f)\mu+k]\delta r + (1-\sigma)k\theta \mu = \mu N(\mu+r)(\mu+k)(\mu+d+p)$$

$$\theta^\ast = \frac{\mu N(\mu+r)(\mu+k)(\mu+d+p) - \beta c \Lambda(\mu(\mu+r)((1-f)\mu+k)]}{\beta c \Lambda(\mu(\mu+r)((1-f)\mu+k)] - \mu N(\mu+r)(\mu+k)(\mu+d+p)}$$

$$= \frac{\mu(1-R_v)}{((1-f)\mu+k)\delta r + (1-\sigma)k\mu R_v - 1}.$$  \hspace{1cm} (9)

We can see that if $\theta < \theta^\ast$ vaccination will not effective in eliminating the disease, and if $\theta > \theta^\ast$ vaccination will effectively eliminate the endemic condition. The following numerical example gives an illustration for this result.

3. Numerical Simulation

Numerical simulation for the model of the equation system (3) is done using Matlab with the four order Runge-Kutta numerical scheme. The parameter values are given in Table 1 (most of them taken from [3]) and the initial conditions $S(0) = 95703$, $V(0) = 35703$, $E(0) = 13670$, $I(0) = 2000$, and $R(0) = 0$. The trend of exposed, infected, and recovered populations are given in Figure 2, Figure 3 and Figure 4 below.
Assuming vaccination is effective in protecting susceptibles individuals, Figures 2 and 3 show that vaccination can reduce the peak of exposed and infected compartment drastically. Figure 4 shows different dynamics of recovered compartment with vaccination and without vaccination.

4. Conclusion
In this paper we have developed a mathematical model for the transmission of tuberculosis disease by considering recurrent infection and vaccination. The disease free equilibrium and its stability is presented and its relation to the basic reproduction number and vaccination reproduction number is discussed. Numerical examples show that vaccination is able to prevent the disease from spreading. Further study can be done for the optimal vaccination level (currently under investigation) as the function of recurrent rate of reinfection.
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