An epidemic model of tuberculosis with vaccine control in Yogyakarta region Indonesia

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Abstract. Recently, researchers in the health field are very interesting. The spread of disease begins from the susceptible population become infected population or from infected population become recovered population is necessary to be observed. Tuberculosis is one diseases that can be represented by mathematical model. The transmission is described by using mathematical models as a form of the nonlinear differential equation system. The stages are forming the mathematical model, determining equilibrium point, determining the basic reproduction number (Ro) with Next Generation Matrix method, analysing the stability of equilibrium points by Routh Hurwitz Criteria method, and perform numerical simulation using MAPLE Program based on data from health profile in Yogyakarta area. Based on data of tuberculosis sufferers in Yogyakarta region is still considered to need attention. Vaccines to prevent tuberculosis infection have been given, but there needs to be an optimal vaccine control strategy. So that the number of infected population related to the percentage of vaccine should be given to vulnerable populations affect the spread of disease will not occur. Mathematically, if basic reproduction number less than one, the disease free equilibrium point is local asymptotically stable. It means the disease does not spread. Meanwhile, if the basic reproduction number more than one then the endemic equilibrium point is local asymptotically stable. It means the disease is persisting in the population. Furthermore, the value of the basic reproduction number is influenced by contact rate and vaccination parameter. The greater the rate of contact with the percentage of fixed vaccines, the more the TB infected population. The greater the percentage of the vaccinated population with fixed contact rate parameters, the more decreasing the number of infected populations.

1. Introduction
Tuberculosis (TB) is the leading cause of death of infectious diseases [1]. TB is an infectious disease, which mainly affects the lung parenchyma. Tuberculosis is an infectious disease caused by the bacterium "Mycobacterium Tuberculosis". A disease is acidic and easily transmitted through the air.

Despite many researches had been done, vaccines are available widely and the highly visible efforts of the WHO to promote an integrated global control strategy, the TB pandemic remains one of the greatest public health problems of modern times [2]. In 2007, there were an estimated 13.7 million cases of chronic active TB, 9.3 million new cases and 1.8 million deaths, mostly occurred in developing countries [3]. In Yogyakarta, Indonesia is still a lot of individuals who suffer from TB disease. By 2014, according
to the 2015 health profile in the city of Yogyakarta, there are 491 cases of TB cases. The city of Yogyakarta at that time as many as 413,936 people with 202,296 male and 211,640 female souls. The number of cases of TB patients in Yogyakarta, which has proven to be a motivation to make efforts to prevent the spread of TB that can occur widespread and quickly.

TB patients are divided into active TB and latent (passive) TB where active TB can transmit disease. Both latent TB and active TB can be treated or prevented. Meanwhile, for early prevention carried out immunization with BCG vaccine. This vaccine will be effective if given to the baby immediately after birth or at least 2 months after birth (with the note during which the baby is not in contact with active TB patients). Children who have been immunized BCG, then infected with TB bacteria, generally do not develop into illness. Treatment for other diseases during TB treatment should also be arranged by a doctor to prevent more serious / dangerous side effects. TB disease can be prevented by: Reduce contact with people with active TB disease, Maintain a good standard of living, with nutritious food, healthy environment, and exercise [4].

Although the use of BCG vaccine and some TB treatment therapies are some successes, the overall incidence of TB increases as a result of drug-resistant TB strains and human immune deficiency virus and TB epidemics [5]. Most of the current spread of disease is present in Africa, parts of Europe and Asia [6].

Mathematical models have been used extensively to gain insight into the spread and control of the TB epidemic. The dynamics of these models tend to be generally determined entirely by a threshold called the basic reproduction number which is the average number of secondary cases caused by an infected individual during his or her infected period in the whole vulnerable population [7].

In particular, when the contact rate of the infected individual decreases it will not produce a large TB outbreak, the disease is not spread or even disappears mathematically as shown by the disease free equilibrium point of asymptotically stable. On the other hand, infection will occur or persist if the endemic equilibrium point is stable. The equilibrium point stability analysis is used Routh Hurwitz Criteria method. This method is used based on the sign of the eigenvalues of the Jacobian matrix of the mathematical model. In the Routh Hurwitz Criteria all the roots of the Jacobian matrix characteristic equation have negative real sections if and only if all elements in the first column of the Rough Hurwitz Table have the same mark (all positive or negative all) [8].

The previous researches about mathematical models model can be seen on the paper written by Waziri AS, et.al [9], C.C. Chavez and B.J. Sony. [10], and J.P. Aparico and C.C. Chavez. [11]. Meanwhile, epidemic model by using vaccine have been discussed by M.R. Taufik, et.al [12], and S.A. Egbetade, et.al [13]. Vaccine model which is given for susceptible population can be seen on the paper with author Mose Ongau Fred, et.al [14] and Ousmane [15]. Furthermore, about stability analysis of avian influenza and AIDS epidemic models have been researched by M. Derouich and A. Boutayeb [16], Cai LimingXue Chi Li, et.al. [17], and C.N. Wahyuda and D. Lestari [18].

In this paper will discuss about the spread of TB epidemic with vaccine control strategy in Yogyakarta region. Mathematically, it is done by proving the stability of equilibrium points, especially the disease free equilibrium point. The spread of TB epidemic also can be seen from the result of numerical simulation using data that shown in the last of this discussion.

2. Mathematical Models

In the formation of mathematical models it takes assumptions to simplify the model. Nevertheless, the assumptions taken still pay attention to the real condition the model formed so that the mathematical model is not far from the real problem. The assumptions of the models as follows

1. Population is closed which means the increase or decrease of population is only caused by birth and death, while the increase and reduction caused by other factors is ignored.
2. Population is homogeneous.
3. Death caused by factors other than TB infection is considered a natural death.
4. Individuals who have not attacked the disease belong to the susceptible class.
5. Infected individuals are divided into two groups: latent infected and active infected. The individual active infected can transmit TB disease.
6. Individuals on recovered classes will not return to be individuals on infected classes.
7. There was a death due to TB infection. 8. Vaccines are given to susceptible populations.

Meanwhile, variable and parameter of models can be seen on table 1.

Table 1. Variable and parameter of models.

| Notation | Definition                                      | Interval  | Dimension  |
|----------|-------------------------------------------------|-----------|------------|
| $N(t)$   | The number of population at time t.             | $N \geq 0$| People     |
| $S(t)$   | The number of susceptible population at time t. | $S(t) \geq 0$ | People     |
| $I_L(t)$ | The number of latent infected population at time t. | $I_L(t) \geq 0$ | People     |
| $I_A(t)$ | The number of active infected population at time t. | $I_A(t) \geq 0$ | People     |
| $R(t)$   | The number of recovered population at time t.   | $R(t) \geq 0$ | People     |
| $B$      | Recruitment rate                                | $B \geq 0$| People .Time$^{-1}$ |
| $\mu$    | The natural death rate                          | $\mu \geq 0$| Time$^{-1}$  |
| $\mu_t$  | The death rate caused by Tuberculosis.          | $\mu_t \geq 0$| Time$^{-1}$  |
| $\alpha$ | The contact rate of Tuberculosis.               | $\alpha \geq 0$| People$^1$.Time$^{-1}$ |
| $\gamma_1$ | The recovered rate of active TB after treatment given | $\gamma_1 \geq 0$ | Time$^{-1}$  |
| $\gamma_2$ | The recovered rate of latent TB after treatment given | $\gamma_2 \geq 0$ | Time$^{-1}$  |
| $\nu$    | Probability of susceptible population are not given vaccine | $0 \leq \nu \leq 1$ |
| $\rho$   | Proportion individual of susceptible population get active TB | $0 \leq \rho \leq 1$ |
| $\beta$  | The rate of latent TB becomes active TB         | $\beta \geq 0$| Time$^{-1}$ |
Based on the assumption and parameter, the following diagram describes the spread of TB epidemic.

![Diagram of TB epidemic model.](image)

**Figure 1.** Diagram of TB epidemic model.

Based on the assumption and parameter, the following diagram describes the spread of TB epidemic.

Based on figure 1, obtained the mathematical models as follows:

\[
\begin{align*}
\frac{dS}{dt} &= vB - \alpha I_A S - \mu S \\
\frac{dI_L}{dt} &= (1 - \rho)\alpha I_A S - \beta I_L - \mu I_L - \gamma_2 I_L \\
\frac{dI_A}{dt} &= \rho \alpha I_A S + \beta I_L - \mu I_A - \mu I_A - \gamma_1 I_A \\
\frac{dR}{dt} &= (1 - \nu)B + \gamma_1 I_A + \gamma_2 I_L - \mu R \\
\end{align*}
\]

(1)

where

\[
\frac{dN}{dt} = B - \mu N - \mu I_A .
\]

The model in the system (1) is epidemiologically and mathematically well posed in the domain,

\[
\Omega = \{(S, I_L, I_A, R) | S \geq 0, I_L \geq 0, I_A \geq 0, S + I_L + I_A + R = N \leq B / \mu \}.
\]

We introduce the following proportions: \( s = \frac{S}{B / \mu}, i_L = \frac{I_L}{B / \mu}, i_A = \frac{I_A}{B / \mu}, r = \frac{R}{B / \mu} \)

where \( s + i_L + i_A + r = n \), we obtain the system (1) become:
A. L. A. T.

ds

\frac{dt}{dt} = \nu \mu - \alpha i_A s - \mu s

di_A

\frac{dt}{dt} = (1 - \rho) \alpha i_A s - \beta i_L - \mu i_L - \gamma j_L

di_L

\frac{dt}{dt} = \rho \alpha i_A s + \beta i_L - \mu i_A - \mu i_A - \gamma i_A

dr

\frac{dt}{dt} = (1 - \nu) \mu + \gamma i_A + \gamma j_L - \mu r

\text{with the domain } \Omega = \{(s, i_L, i_A, r) \mid s \geq 0, i_L \geq 0, i_A \geq 0, s + i_L + i_A + r = n \leq 1\}.

3. Equilibrium Points

Disease-free equilibrium points are steady state solutions where there is no disease. The system (2) has two equilibrium points such in theorem as follows:

**Theorem 3.1:**

If \( i_A = 0 \), The System (1) has a disease free equilibrium point \( E_0 = (s, i_L, i_A, r) = (s, 0, 0, 1 - \nu) \). If \( i_A \neq 0 \), the endemic equilibrium point \( E_1 = (s^*, i_L^*, i_A^*, r^*) \) is in the \( \Omega^* \).

**Proof:**

We get the equilibrium points from the following equations:

\( \nu \mu - \alpha i_A s - \mu s = 0 \) \hspace{1cm} (3)

\( (1 - \rho) \alpha i_A s - \beta i_L - \mu i_L - \gamma j_L = 0 \) \hspace{1cm} (4)

\( \rho \alpha i_A s + \beta i_L - \mu i_A - \mu i_A - \gamma i_A = 0 \) \hspace{1cm} (5)

\( (1 - \nu) \mu + \gamma i_A + \gamma j_L - \mu r = 0 \). \hspace{1cm} (6)

If \( i_A = 0 \), from the equation (3) we obtain

\( s = \nu \), \hspace{1cm} (7)

and the equation (5) yield

\( i_L = 0 \). \hspace{1cm} (8)

Then from the equation (6), (7), and (8) we have

\( r = 1 - \nu \). \hspace{1cm} (9)

So the disease free equilibrium point is \( E_0 = (s, 0, 0, 1 - \nu) \).

Furthermore, when \( i_A \neq 0 \) we get

\( s^* = \frac{\nu \mu}{\alpha i_A^* + \mu} \), \hspace{1cm} (10)

and then from the equation (5) we have
By substituting the equation (10) and (11) into (5) obtained

\[ i_A^* = \frac{\beta i_s^*}{\mu + \mu_i + \gamma_1 - \rho \alpha s^*}. \] (12)

While from the equation (6), (11), and (12) yield

\[ r^* = \frac{(1 - \nu)\mu_i i_A^* + \gamma_1 i_L^*}{\mu}. \] (13)

The endemic equilibrium point of the system (2) can be seen in the equation (10)-(13).

4. The Basic Reproduction Number

The basic reproduction number, \( R_0 \), is the expected number of secondary infections that one infectious individual (human) would create over the duration of the infectious period provided that all other members of both populations are susceptible. By using next generation matrix, The system (2) has the basic reproduction number as follows [7]:

\[ R_0 = \frac{\beta(1 - \rho)\alpha \nu + \rho \alpha \nu(\beta + \mu + \gamma_2)}{(\beta + \mu + \gamma_2)(\mu + \mu_i + \gamma_1)}. \] (14)

5. Stability Analysis

**Theorem 5.1:**

The disease free equilibrium point \( E_0 = (n, 0, 0, 1 - v) \) is locally asymptotically stable if \( R_0 < 1 \) and unstable if \( R_0 > 1 \).

**Proof:**

The System (2) has a Jacobian matrix (by linearization) as follows:

\[ J = \begin{bmatrix}
-(\alpha i_A + \mu) & 0 & -\alpha s & 0 \\
(1 - \rho)\alpha i_A & -(\beta + \mu + \gamma_2) & (1 - \rho)\alpha s & 0 \\
\rho \alpha i_A & \beta & -(\mu + \mu_i + \gamma_1) & 0 \\
0 & \gamma_2 & \gamma_1 & -\mu
\end{bmatrix}. \] (15)

The Jacobian matrix for \( E_0 = (n, 0, 0, 1 - v) \) is giving by substituting into equation (15)

\[ J(E_0) = \begin{bmatrix}
-(\alpha i_A + \mu) & 0 & -\alpha \nu & 0 \\
0 & -(\beta + \mu + \gamma_2) & (1 - \rho)\alpha \nu & 0 \\
0 & \beta & -(\mu + \mu_i + \gamma_1) & 0 \\
0 & \gamma_2 & \gamma_1 & -\mu
\end{bmatrix}. \] (16)

Then the characteristic polynomial of \( J(E_0) \) from \( | J(E_0) - \lambda I | = 0 \) is written by:

\[ P(\lambda) = (\lambda + \mu)^2[\lambda^2 + ((\beta + \mu + \gamma_2) + (\mu + \mu_i + \gamma_1))\lambda + (\beta + \mu + \gamma_2)(\mu + \mu_i + \gamma_1) - (1 - \rho)\alpha \nu \beta] = 0 \]

which has eigen values \( \lambda_{1,2} = -\mu \), and other eigen values obtained by solving the following equation

\[ P'(\lambda) = \lambda^2 + ((\beta + \mu + \gamma_2) + (\mu + \mu_i + \gamma_1))\lambda + (\beta + \mu + \gamma_2)(\mu + \mu_i + \gamma_1) - (1 - \rho)\alpha \nu \beta = 0. \] (17)

It can be seen equation (17) have negative eigen values by using Routh Hurwitz criteria. We need to show

\[ P'(\lambda) = a_0 \lambda^2 + a_1 \lambda + a_2 = 0 \]
where $a_0 = 1 > 0$, 

$$a_k = (\beta + \mu + \gamma_2) + (\mu + \mu_1 + \gamma_1) > 0$$

(18)
because all of parameters are positive.

Then we will prove $a_2 > 0$ given by

$$a_2 = (\beta + \mu + \gamma_2)(\mu + \mu_1 + \gamma_1) - (1 - \rho)\alpha \beta$$

$$= \left(1 - \frac{(1 - \rho)\alpha \beta}{(\beta + \mu + \gamma_2)(\mu + \mu_1 + \gamma_1)}\right) (\beta + \mu + \gamma_2)(\mu + \mu_1 + \gamma_1)$$

$$= (1 - R_0) + \frac{\rho \alpha \beta}{\mu + \mu_1 + \gamma_1} (\beta + \mu + \gamma_2)(\mu + \mu_1 + \gamma_1).$$

(19)

(20)

Since $R_0 < 1$, equation (20) is positive. So, equation (17) has all of negative eigen values. Therefore the characteristic polynomial of $J(E_0)$ has all of negative eigen values such that $E_0 = (v, 0, 0, 1 - v)$ is locally asymptotically stable. Meanwhile, if $R_0 > 1$, $E_0$ is unstable.

6. Numerical Simulation

In 2014, based on data from healthy profile of Yogyakarta city, there are 491 cases of TB cases. The city of Yogyakarta at that time as many as 413,936 people with 202,296 male and 211,640 female souls. Therefore, the initial value are obtained $s(0) = 0.998$, $i_L(0) = 0.0005$, $i_A(0) = 0.0007$, and $r(0) = 0.0006$. The number of death caused by Tuberculosis are 10 people in a year, so $\mu = \frac{10}{49112} = \frac{5}{2946} = 1.697216565 \times 10^{-3}$. It assumes that $\mu = \frac{1}{840} = 1.19047619 \times 10^{-3}$.

6.1. Simulation for $R_0 < 1$

For $\alpha = 0.0641, \beta = 0.61, \rho = 0.86, \gamma_1 = 0.074, \gamma_2 = 0.08, \nu = 0.72, R_0 = 0.098$

Figure 2. Simulation $R_0 < 1$.

Figure 3. Simulation $R_0 > 1$. 
Figure 2 shows the susceptible population decreased, but the recovered population increased. While the latent TB and active TB are decreased for a long time even does not exist in the population.

6.2. Simulation Ro > 1
For $\alpha = 0.641, \beta = 0.61, \rho = 0.6, \gamma_1 = 0.574, \gamma_2 = 0.048, \nu = 0.9, R_0 = 1.05898$. Figure 3 describes for a long time the latent and active TB are increased caused by the greater contact rate. Meanwhile, the susceptible and recovered population is decreased.

Based on the figures 2 and 3, the value of the basic reproduction number is influenced by contact rate ($\alpha$) and vaccination parameter ($1-\nu$). The greater the rate of contact with the percentage of fixed vaccines, the more the TB infected population. The greater the percentage of the vaccinated population with fixed contact rate parameters, the more decreasing the number of infected populations. From stability analysis, we obtain if basic reproduction number less than one, the disease free equilibrium point is local asymptotically stable. It means the disease does not spread. Meanwhile, if the basic reproduction number more than one then the endemic equilibrium point is local asymptotically stable. It means the disease is persisting in the population.

7. Conclusion
In this research, we get the epidemic model of TB in the form of a system of nonlinear differential equations with four sub-populations. The TB infected population is divided into two, namely latent TB and active TB. Vaccination are given to vulnerable populations. Mathematically, if the basic reproduction number is less than one then the disease free equilibrium point is stable. This means biologically that for a long time TB disease does not spread even disappear from the population. If the basic reproduction number is more than one then the endemic equilibrium point is stable. It means biologically that for a long time the spread of TB disease persists in the population. The value of the basic reproduction number is influenced by contact rate and vaccination parameter. The greater the rate of contact with the percentage of fixed vaccines, the more the TB infected population. The greater the percentage of the vaccinated population with fixed contact rate parameters, the more decreasing the number of infected populations. Furthermore, the next study can discuss the predicted population of each compartment in the future to be associated with vaccine control. Besides, sensitivity analysis also important to be discussed in order to some of influential parameter can be known.

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