Tuberculosis transmission with relapse in Indonesia: susceptible vaccinated infected recovered model

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Abstract. Tuberculosis (TB) is a contagious disease prevented by the vaccination of Bacillus Calmette-Geurin (BCG). The sufferer is treated by giving the Directly Observed Treatment Shortcourse (DOTS). The patients sometimes do not take the medicine regularly so that the TB-bacteria do not completely vanish from their body. The bacteria only weaken so the patients can be re-infected (relapse). Mathematical modelling can be used to determine TB transmission based on changes in the number of TB patients. By concerning vaccination and relapse factors, a susceptible vaccinated infected recovered (SVIR) model with relapse in TB transmission need to be developed. Indonesia got the second rank in the new case of TB in the world. In the national program of TB prevention, Indonesia has three indicators i.e. prevalence, incidence, and mortality rate. In this article, we derive SVIR model with relapse in TB transmission, then apply the model in Indonesia and measure its accuracy. Furthermore, we also predict the three indicators of TB in Indonesia. The model is nonlinear first-order differential equations. The model is applied in Indonesia by estimating parameters based on 2004-2014 data. Model accuracy is measured based on relative errors in 2015 and 2016. Absolute values of relative error S, V, I, R, and TB incidence are less than 0.1. Thus, the model is said to be quite accurate and can be used to predict the prevalence, incidence, and mortality rates of TB in Indonesia. The prediction of these three indicators shows a decline year by year with an average decrease of 1.90% for prevalence and mortality rates and 1.68% for incidence rates.

1. Introduction
Tuberculosis (TB) is a contagious disease caused by Mycobacterium tuberculosis. It is transmitted by the bacteria spreading through the air in the form of sputum (droplet) from coughing, sneezing, or spitting. Though the illness commonly infects the pulmonary system, it also can attack other organs, such as lymphatic, brain, spinal, and renal systems (Indonesia Health Ministry [1]). On 2015, WHO [2] reported 10.4 million new TB cases at global level, in which 60% of them happened in India, Indonesia, China, Nigeria, Pakistan, and South Africa. Moreover, this illness also belongs to the top ten causes of death world widely for the year 2015 by WHO version [2]. There were 1.4 million deaths caused by TB and 0.4 million HIV positive TB death cases. TB prevention is conducted through Bacillus Calmette-Geurin (BCG) vaccination. Besides, TB treatment is done via Directly Observed Treatment Shortcourse (DOTS), which is the direct monitoring of drug consumption (Data and Information Center [3]). During this process, some patients may not take it steadily since they feel like healthy. Thus, the bacteria are not completely killed and they only weaken, causing the cured patients to get infected again (relapse). The vaccination and relapse are two affecting factors of the TB transmission. A mathematical model can be applied as a mode to analyze the spread of tuberculosis disease regarding to the changing number of the patients. Enagi & Ibrahim [4] and Shahid et al. [5] examine the transmission model of TB by observing the BCG vaccination. Shahid et al. [5] named it as vaccinated susceptible infected recovered (VSIR) model in which the targets are the newborns.
Taking a different idea with the previous researchers, the method in examining the time of the vaccination—which is several days after birth till one month—categorizes the newborns as healthy individuals yet susceptible of the infection. Thus, these individuals become the vaccination target. Concerning this matter, the susceptible vaccinated infected recovered (SVIR) model is constructed. Asides, the occurring relapse are also monitored to conduct further SVIR model research of this case. By the year of 2015, Indonesia ranked second for TB new cases discovery. In the National Tuberculosis Control Programme, this country targets to decrease the cases for 1 per million citizen (TB elimination) on 2035 and Indonesia tuberculosis-free on 2050. Besides, the three indicators – the prevalence, incidence, and mortality rates – are required and predicted to observe the successfulness of the program. Here, the SVIR model with relapse along with the interpreted results is also involved in determining the TB transmission patterns in Indonesia.

2. SIR model

On 1989, Hethcote [6] introduces three basic models in epidemiology, and one of them is susceptible infected recovered (SIR) model. Hethcote [6] divides the population (N) into three categories: healthy individuals yet susceptible (S) of the infection, infected (I) individuals, and the cured patients who have permanent immunity (recovered/R).

Hethcote [6] states that this model assumes to have only one disease within a population – which considered as constant – thus the natality and mortality have the same value which is \( \mu \). Furthermore, it also assumes that the newborns are healthy yet vulnerable to disease. The number of birth is \( \mu N \) thus the number of S individuals increase for \( \mu N \). The individual groups of S, I, and R have death rate thus each of them decreases for \( \mu S \), \( \mu I \), and \( \mu R \). The S group can get infected after having contact with I group. If \( \beta \) is the contact rate, S decreases for \( \beta \frac{SI}{N} \) and I increases for \( \beta \frac{SI}{N} \). Here, the I members might heal and get permanent immunity. If \( \gamma \) is the healing rate, the individuals of I reduce for \( \gamma I \) and R raise for \( \gamma I \). Therefore, the SIR model can be written as:

\[
\frac{dS}{dt} = \frac{SI}{N} - \mu S - \beta \frac{SI}{N} \\
\frac{dI}{dt} = \beta \frac{SI}{N} - \gamma I - \mu I \\
\frac{dR}{dt} = \gamma I - \mu R
\]  

(2.1)

with \( S(0) \geq 0 \), \( I(0) > 0 \), \( R(0) \geq 0 \), \( \mu, \beta, \gamma > 0 \). The (2.1) model is nonlinear first-order differential equations.

3. Result and discussion

3.1. SVIR model with relapse

Three engaged indicators in TB treatment are the prevalence, incidence, and mortality rates. The first rate belongs to the proportion of TB patients to the citizens of an area living in a certain time period, while the incidence rate is the proportion of the new and recurrent patients to the citizens of an area who are risky of getting infected in a certain time period (Indonesia Health Ministry [7]). Those three indicators are usually presented per 100000 people (Sutopo et al. [8]) and their numbers are affected by the amount of patients. A mathematical model can be employed in examining the changing number of the patients occasionally, which is called as TB transmission model.

The characteristic of tuberculosis transmission is through direct contact of the vulnerable individuals with the patients. Besides, it is a curable disease. Those aspects can be modelled mathematically as SIR. The constant population assumption on the SIR model (2.1) is unalike from Hethcote [6] this research the population is not constant. This assumption affects the natality and mortality to be different. If \( \theta \) stands for the birth rate, the \( \mu N \) for death rate changes to be \( \theta N \).

Related with mortality as the treatment indicator, this study classifies the death into 2 sorts – caused by TB and others (natural). If \( \delta \) stands for the mortality caused by TB, the I number of individuals reduces as \( \delta I \). If \( \mu \) is for the natural cause, the individuals of S, I, R decrease as \( \mu S, \mu I, \) and \( \mu R \).
TB transmission model with BCG vaccination has been studied by Enagi and Ibrahim [4] and Shahid et al. [5]. Shahid et al. [5] defines the individuals with the vaccine as vaccinated (V). Enagi and Ibrahim [4] assumed that BCG vaccines are given to newborns at their birth. TB prevention can be done through BCG vaccination which is given to babies under one month old with 0.01ml dosage one time (Pusdiklatnakes [9]). Different from Enagi and Ibrahim [4] and based on Pusdiklatnakes [9], in this article the newborns are assumed as healthy yet susceptible to TB. Hence, the vaccination target is the S group. If \( \alpha \) stands for BCG vaccination rates, \( S \) will reduce for \( \alpha S \) and \( V \) will raise for \( \alpha S \).

At its best time, BCG has 80% efficacy which is effective in preventing TB for 15 years (CDC [10]). Widyaningsih et. al [11] stated that the efficacy provide loss immunity. The loss immunity change the group of R and S. Different from Widyaningsih et. al [11], the efficacy indicates that the attempt of TB does not prevent the vaccinated individuals totally and they may be recurrent. If \( \lambda \) is the vaccine effectivity rate, the individuals of \( V \) reduce for \( \lambda V \) and \( S \) raise for \( \lambda V \). Also, \( V \) can get fatality thus it reduces for \( \mu V \).

TB is a recurring disease happened when the patients do not steadily taking the medication. It does not completely kill the bacteria - only weaken - which can make a relapse. Considering this matter, the individuals in \( V \) group need to be redefined as the cured individuals. If \( \sigma \) stands for the relapse rate, the individuals in R group reduce for \( \sigma R \) and I increase for \( \sigma R \). So, the SVIR model with relapse cases on TB transmission can be expressed as

\[
\begin{align*}
\frac{dS}{dt} &= \theta N - \beta \frac{SI}{N} - (\mu + \alpha)S + \lambda V \\
\frac{dV}{dt} &= \alpha S - (\lambda + \mu)V \\
\frac{dI}{dt} &= \beta \frac{SI}{N} - (\gamma + \mu + \delta)I + \sigma R \\
\frac{dR}{dt} &= \gamma I - (\sigma + \mu)R
\end{align*}
\]  

(3.1)

with \( S(0) \geq 0, V(0) \geq 0, I(0) > 0, R(0) \geq 0 \), and \( \theta, \beta, \gamma, \mu, \delta, \alpha, \lambda, \sigma > 0 \). Those eight parameters are the rates of birth, contact, recovery, natural-causes death, TB-causes death, BCG vaccination, vaccine effectiveness, and the relapse. The (3.1) model is nonlinear first-order differential equations. The solution of the (3.1) model can be used to determine the prevalence, incidence, and mortality rates.

3.2. Application

The model of (3.1) is applied in Indonesia by using data from Data and Information Center [3], World Bank [12], and WHO [13] from 2004-2016. They include the population, crude birth rate, crude death rate, new and relapse TB cases, TB-causes deaths, individuals who just got BCG vaccination and recovered. The data from 2004-2014 are used to estimate the parameters while data from 2015-2016 are used to measure the accuracy of the model.

From the 2004-2014 data, we obtain the birth rate (\( \theta \)) is 0.0210, contact rate (\( \beta \)) is 0.34080, recovery rate (\( \gamma \)) is 0.16001, natural-causes death rate (\( \mu \)) is 0.00663, TB-causes death rate (\( \delta \)) is 0.13198, BCG vaccination rate (\( \alpha \)) is 0.02120 and the relapse rate (\( \sigma \)) is 0.00522. Meanwhile, the vaccine effectiveness rate (\( \lambda \)) is determined from the effectivity period of 15 years, thus \( \lambda \) value is \( 1/15 \approx 0.06667 \). By substituting the parameter values to the (3.1), the TB transmission with relapse in Indonesia is
\[
\frac{dS}{dt} = 0.02108N - 0.34080 \quad \frac{SI}{N} - 0.02783S + 0.06667V \\
\frac{dV}{dt} = 0.021205 - 0.0733V \\
\frac{dI}{dt} = 0.34080 \frac{SI}{N} - 0.29862I + 0.00522R \\
\frac{dR}{dt} = 0.16001I - 0.01185R
\] (3.2)

The solution of (3.2) model is determined using the fourth-order Runge-Kutta algorithm. The algorithm requires initial values. The initial values refer to the number of individuals S, V, I, and R in 2004 (t = 0), that are

\[
S (0) = 217890382 \\ V (0) = 4169722 \\ I (0) = 985000 \\ R (0) = 119545
\] (3.3)

The solution of the (3.2) model with the initial values (3.3) for the first 12 years (2005-2016), in which the solution on the 11th and 12th years are compared with the data from the 2015-2016. Moreover, the TB incidence (new and relapse cases) can also be compared within the same year. The relative error for S, V, I, R, and TB incidence is shown in Table 1.

**Table 1.** The relative error for S, V, I, R and TB incidence

| Year | $S$  | $V$    | $I$   | $R$  | TB Incidence |
|------|------|--------|-------|------|--------------|
| 2015 | -0.00495 | -0.02795 | -0.01163 | -0.09538 | -0.02103 |
| 2016 | -0.00755 | -0.03117 | -0.05235 | -0.03145 | 0.05543 |

Table 1 indicates that the relative error for S, V, I, and R individual groups is on the interval $[-0.09538, -0.00495]$. Meanwhile, the relative error of TB incidence is less than 0.06. This means that the relative error is small. Thus the (3.2) model is quite accurate. So, this model can be used to predict the individuals of the four groups and the TB incidence. The solution of the model is implemented in establishing the transmission pattern in Indonesia shown by the numbers of $I$. The number of the $I$ individuals in the first 46 years, based on the solution of (3.2) model, is shown in Figure 1.
Figure 1 shows an increase in the first 10 years, in which the number of individuals on the 10th year (2004) was 1129247 people. After that, it declines until the 39th year (2043) and increases again for the next 7 years (2050). This indicates that on 2050, there is still quite large number of TB patients, 1004945 people, thus the target for Indonesia tuberculosis-free on 2050 has not achieved yet.

Apart for deciding the transmission pattern in Indonesia, the solution of (3.2) model can be used to determine the prediction of TB treatment indicators. The prevalence and mortality rates are affected by I thus the model is quite accurate in predicting the rates. The incidence rate prediction can also be determined. Figure 2 shows the prediction of all indicators during 2017-2035.

Figure 2. The prediction of all indicators during 2017-2035

Figure 2 indicates that the three indicators have a decline through the years. The annual average percentage decrease for the prevalence is 1.90% and for mortality rates is also 1.90%, while for the incidence rate is 1.68%. Figure 2 also shows that Indonesian prevalence rate prediction on 2035 is 296 per 100000 residents. This means that with the (3.2) model, the TB elimination target on 2035 also has not achieved yet.

4. Conclusion
Based on the discussion, there are three conclusions.
1) The SVIR model with relapse cases on TB transmission can be written as (3.1) where $S(0) \geq 0$, $V(0) \geq 0$, $I(0) > 0$, $R(0) \geq 0$, and $\theta, \beta, \gamma, \mu, \delta, \alpha, \lambda, \sigma$ have positive values.
2) The SVIR model with relapse cases on TB transmission is applied in Indonesian by estimating parameters based on 2004-2014 data. The solution model is compared with the 2015-2016 data. Absolute values of relative error $S$, $V$, $I$, $R$, and TB incidence are less than 0.1. So, the model is said to be quite accurate and can be used to predict the TB prevalence, incidence, and mortality rates in Indonesia.
3) The transmission pattern shows that the target for Indonesia tuberculosis-free on 2050 has not achieved yet. Meanwhile, the indicators rate prediction for 2017-2035 declines through the years with the annual average percentage decrease is 1.90% for the prevalence and mortality rates and 1.68% for the incidence rate. Even so, the TB elimination target on 2035 also has not achieved yet.

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