Is the Recovery Rate in Latent Tuberculosis Infection Significant in Reducing Tuberculosis Transmission in Indonesia? : A Mathematical Model Study in Epidemiology

Novi Reandy Sasmita[1], Alan Frederick Geater[1], Athassawat Kammanee[2] and Virasakdi Chongsuvivatwong[1]

[1]Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Thailand
[2]Applied Analysis Research Unit, Department of Mathematics and Statistics, Faculty of Science, Prince of Songkla University, Thailand
[*]Corresponding author, E-mail: novireandys@gmail.com

Abstract

Tuberculosis (TB) is an infectious and airborne disease caused by Mycobacterium tuberculosis. TB kills more than 1 million people every year. In Indonesia, TB is the fourth leading cause of mortality. One of WHO's current focuses for eliminating TB is on Latent Tuberculosis Infection (LTBI). The recovery rate in LTBI needs to consider a long-term solution. Understanding the effect of the recovery rate in LTBI in the process of eliminating TB is important. In this study, SE3I3R model is used. The model has implemented in Indonesia based on data of 2018 obtained from several sources. The Fourth-order Runge-Kutta method is used to solve the model. This work uses the recovery rates of 3%, 10%, 20%, and 30%. Based on the simulation result, the number of LTBI tend to decline year by year. The higher the recovery rate in LTBI, the lower the number of TB cases occurs. In other words, the recovery rate in LTBI has a significant effect on reducing TB transmission in Indonesia. Although at increasingly higher recovery rate, the incremental reduction in a number of exposed becomes progressively smaller. Furthermore, the target of SDG to the end the TB cases by 2030 will not be reached.

Keywords: *Recovery rate, Latent tuberculosis infection, Tuberculosis transmission, Mathematical model.*

1. Introduction

Tuberculosis (TB), an infectious and airborne disease, is caused by Mycobacterium tuberculosis (Mtb) (Bansal, Sharma, & Singh, 2017). TB mainly affects the lungs and is a primordial infectious disease which is characterized by the formation of tubercles, often developing long after the initial infection (Moghaddam et al., 2016). As the ninth leading cause of death worldwide, TB is the leading cause of a single infectious agent, ranking above HIV/AIDS, and remains a public health problem (Kritski et al., 2018). An urgent action with new approaches is needed to achieve the WHO's elimination targets of an 80% reduction in TB cases and a 90% reduction in deaths by 2030 (Brooks-Pollock & Jacobson, 2018). TB kills people more than 1 million people every year and is a leading cause of morbidity and mortality, especially in low-income and lower-middle-income economic countries (LMIC) like Indonesia. According to the global tuberculosis report 2018, Indonesia (8%) is ranked as the country with the third burden of tuberculosis cases in the world after India (27%) and China (9%) (WHO, 2018).

TB is the fourth leading cause of mortality in Indonesia (IHME, 2018). Significant and persistent gaps in detection and treatment still exist until now. There are 3.6 million global gaps in TB in the world. 80% of the gaps are accounted for by India (26%), Indonesia (11%) and Nigeria (9%) as the top three (WHO, 2018). Furthermore, the gaps between the estimated number of new cases and the number reported are due to a mixture of underreporting of detected cases and underdiagnosing. In 2017, a national study in Indonesia found that although about 80% of new cases were detected, 41% of these cases were not reported. Actions to correct underreporting are being put in place (WHO, 2018). In 2018, WHO estimated that the number of TB incidence in Indonesia was 842,000 cases, the incidence of MDR/RR-TB was 23,000 cases and the TB mortality of 107,000 cases (WHO, 2018).

One of WHO's current focus in eliminating TB is therapy for latent tuberculosis infection (LTBI) as a form of TB prevention. Many studies have concluded that therapy of LTBI is an effective way of preventing future cases of tuberculosis disease (Cruz, Ahmed, Mandalakas, & Starke, 2018). Treatment for active TB involves four antibiotics to reduce the likelihood of acquired drug resistance while treating LTBI

only uses one or two antibiotics. Although preventive therapy for LTBI has been available and emphasized in industrialized nations, its use has been limited in most resource-limited settings (Cruz et al., 2018).

Furthermore, one of the essential things in eliminating TB is the recovery rate in LTBI. In this study, the recovery rate in LTBI defines as the rate at which an individual transforms from LTBI to a recovered individual because one of two possibilities has happened. The possibilities are that an LTBI individual has received and consumed drugs for a total of 6 months in preventive therapy, or that LTBI does not develop to be a TB disease after two years because his individual has good immunity. The value of the recovery rate in this study is the combined value of the two possibilities expressed as a percentage.

Besides, the eradication of TB in Indonesia depends not only on medical issues but also the ability to understand the transmission dynamics of TB. Unrecognized transmission is a major contributor to ongoing TB epidemics in high-burden, resource-constrained settings. One of the needs for recognizing transmission is to predict the TB case in the future. Modeling plays an essential role in epidemiology by providing a concrete mechanism for the understanding of disease transmission and suggesting effective control measures (Hugo, Makinde, Kumar, & Chibwana, 2017). Also, the main scope of mathematical modeling in epidemiology is to develop models that will assist the decision-making process by helping to evaluate the consequences of choosing one of the alternative strategies available (Liddo, 2016). Modeling studies can be considered in the process of developing guidelines, particularly in the evaluation of public health programs, long-term effectiveness or comparative effectiveness (Egger et al., 2017).

The first publication addressing the mathematical model of epidemics dates back in 1766 (Siettos & Russo, 2013). A study that has a profound effect on the modeling of disease spread was reported by Kermack & McKendrick (Kermack & McKendrick, 1927). Mathematical models as quantitative analytical tools can play an essential role in informing The Sustainable Development Goals (SDGs) for 2030 and the End TB Strategy for 2035. Mathematical models have employed in the study of the epidemiology of TB since 1962 (Waaler, Geser, & Andersen, 1962). The phenomenon of TB transmission can be observed and analyzed through mathematical models. They can help us to predict and control TB transmission. A valid model can project the effects of interventions on the dynamics of disease for short or long periods. The mathematical model has become a powerful tool for analyzing epidemiological characteristics.

Some studies have used a mathematical model for TB transmission. Kim, Reyes, and Jung (2018) developed a mathematical model and intervention strategies for mitigating tuberculosis in the Philippines using susceptible (S), high-risk latent (E), infectious (I), and low-risk latent (L) group as a SEIL model. Egonmwan and Okuonghae (2018) used SE3IJ2T model which consist of susceptible (S), new latently infected (E1), diagnosed latently infected (E2), undiagnosed latently infected (E3), undiagnosed active infected (I), diagnosed actively-infected with prompt treatment (J1) and diagnosed actively infected with delayed treatment (J2) and treated (T).

Another study that used a mathematical model that of Zhao, Li & Yuan (2017). They conducted an analysis of transmission and control of tuberculosis in mainland China based on the age-structure mathematical model using S3EIR model. The model included a susceptible class which is divided into three age groups: childhood (S1), middle-aged (S2), and senior (S3), followed by exposed (E), infectious (I), and recovered (R) class. They also assumed that the latent, infectious, and recovered classes are the same for different age groups. Okuonghae and Ikhimwin (2016) developed an S2E2IJT model. They divided the susceptible and exposed classes into 2 categories, namely with a low level of awareness and high level of awareness, respectively. In their model, there are infectious as I, identified infectious (for treatment under DOTS) as J and the effectively treated individuals as T.

In this study, we will propose and analyze a deterministic mathematical model in epidemiology for TB transmission by simulating the recovery rates of 3%, 10%, 20%, and 30%. It is done to investigate the effect of the recovery rate in eliminating TB in the future. The basis of the model used is susceptible-exposed-infectious-recovered-susceptible (SEIRS) but we have modified that model to be SE3I3RS. The reason is that we want to develop a realistic model that is not only mathematically but also follows the pathogenesis of tuberculosis transmission. Indonesia is studying the setting and the newest data of TB transmission in Indonesia are used as baseline data in the mathematical model. We consider the types of

active TB and some crucial parameters in TB transmission such as different mortality rates in active TB, relapse rates and recovery rates from either LTBI or active TB in the model.

2. Objectives

This study aimed to investigate the effect of recovery rate in latent tuberculosis infection using a mathematical model to reduce tuberculosis transmission in Indonesia.

3. Materials and Methods

3.1 Assumption and Model Formulation

Mtb is carried in airborne particles called droplet nuclei. In the pathogenesis of TB, droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli in susceptible individuals. Susceptible individuals are those who can incur the disease but are not yet infected (Lahrouz, El Mahjour, Settati, & Bernoussi, 2018). We symbolize susceptible individuals as S. Further, tubercle bacilli will multiply in the alveoli in susceptible individuals. A small number of tubercle bacilli enter the bloodstream and spread throughout the body. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression (CDC, 2013). At this point, LTBI has been established. In this condition, susceptible individuals change to LTBI.

LTBI is a state of persistent immune response to stimulation by Mtb antigens with no evidence of clinically manifest active TB (WHO, 2018). We denote anyone who has LTBI as exposed individuals in the mathematical model. Exposed individuals cannot spread TB bacteria to other people. The vast majority of infected people have no signs or symptoms of TB but are at risk for active TB disease (WHO, 2018). We symbolize exposed individuals as E and his infection rate of susceptible individuals to exposed individuals as α. We divide E into three compartments according to transmission of each infectious individual; exposed individuals for drug-susceptible tuberculosis, exposed individuals for multidrug-resistant tuberculosis, and exposed individuals for extensively drug-resistant tuberculosis denoted consecutively E_1, E_2, and E_3.

Anyone who has a TB infection can develop TB disease. In this condition, exposed individuals will change to infectious individuals as active TB. Infectious individuals refer to infected individuals who developed the disease. This condition is characterized by signs or symptoms of active disease, or both, and is distinct from LTBI, which occurs without signs or symptoms of active disease (WHO, 2013). Infectious individuals can transmit Mtb to susceptible individuals through interpersonal contacts (Liddo, 2016). This model assumes that each susceptible individual has to pass the exposed compartment before that individual changes to be an infectious individual. Infectious individual comprised those with drug-susceptible tuberculosis (DS-TB) and drug-resistant tuberculosis (DR-TB).

We consider that infectious individuals (I) are divided into three compartments namely drug-susceptible TB (DS-TB) I_1, multidrug-resistant TB (MDR-TB) I_2 and extensively drug-resistant TB (XDR-TB) I_3. Both MDR-TB and XDR are DR-TB (Kurz, Furin, & Bark, 2016). DR-TB is caused by transmission of resistant strains of Mtb or by the acquisition of resistance through inadequate treatment (Seddon et al, 2012). Additionally, DR-TB is transmitted in the same way as DS-TB, and DS-TB is no more infectious than DR-TB. However, delay in recognition of drug resistance or prolonged periods of infectiousness may facilitate increased transmission and further development of drug resistance.

DS-TB refers to patients who do not have evidence of infection with strains resistant to rifampicin (i.e. not rifampicin-resistant (RR) or MDR-TB). MDR-TB, one of the DR-TB types, is defined as resistance to isoniazid and rifampicin, with or without resistance to other first-line drugs (FLD). XDR is resistant to any fluoroquinolone and at least one of three second-line injectable drugs (SLD) such as capreomycin, kanamycin, and amikacin, in addition to multidrug resistance (WHO, 2014). XDR-TB treatment is more toxic, more expensive, and less effective (CDC, 2013).

The rate at which exposed individuals become infectious is symbolized by β. If the immune system in susceptible individuals cannot keep the tubercle bacilli under control, the bacilli will begin to multiply rapidly. This process can cause exposed the individual to become an infectious individual as well.

Preventive therapy for exposed individuals in TB is essential for controlling and eliminating TB disease. The exposed individuals can move to recovered individuals because of the recovery rate. In this model, ρ is the recovery rate. The recovery in exposed individuals can occur either with or without treatment.

To make it clear, we define recovered individuals as people who have healed from infection. There are two ways to move to the recovered compartment namely through recovery rate of exposed individuals and treatment success rates of infectious individuals. If an individual becomes a recovered individual through the treatment success rate then the individuals have followed the treatment and get the outcome as cured or treatment completed from treatment outcomes. In this model, we give symbol recovered individuals as R.

DR-TB disease can develop in two different ways, called transmitted (or primary) or acquired (or secondary) resistance (Dheda et al., 2017). Primary resistance occurs in persons who are infected with resistant organisms initially. Secondary resistance develops during TB treatment because the patient either was treated with an inadequate regimen or did not take the prescribed regimen appropriately or because of other conditions such as drug malabsorption or drug-drug interactions that led to low serum levels (CDC, 2013). In this model, γ_1 is the symbol for the development rate from DS-TB to MDR-TB, γ_2 is the symbol of the development rate from MDR-TB to XDR-TB, and γ_3 is the symbol of development rate from DS-TB to XDR-TB. The development rate of DS-TB to XDR-TB is very low but possible. It occurs because of several possibilities; two of them are poorly compliant patients taking the drug for a very long time or inappropriate drug administration so that Mtb will develop as XDR-TB.

Treating and curing DR-TB is complicated and take longer than the treatment of TB with no resistance (Bule, 2017). Furthermore, the treatment success rate for each compartment in this mathematical model will be symbolized as δ. The treatment success rate is the sum of cured and treatment completed (WHO, 2014). Relapse continues to be a significant problem and is an essential indicator of the effectiveness of TB control. Relapse refers to patients who have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection) (WHO, 2014).

This study gives θ as the relapse rate. It seems that the higher the local incidence, the higher the proportion of reinfection (Wang et al., 2018). People who had TB once are at a strongly increased risk of developing TB when re-infected. Recovered individuals are assumed not to acquire permanent immunity; So, there is a transfer from recovered to susceptible compartment indicated by the loss of immunity rate. It occurs due to patients having no immunity after recovering and becoming susceptible individuals again. The loss of immunity rate of recovered to susceptible individuals is symbolized with φ.

In this mathematical model, N symbolizes the total population and Λ is the natural birth rate. We divide death rate into two components; μ is natural death rate in susceptible, exposed and recovered individuals, and μ_t is the rate of death that occurs before or during treatment in infected individuals. Based on all our assumptions, we evolved and partitioned the model with eight compartments according to their epidemiological status representing each group of the population. The eight compartments are susceptible, exposed for DS-TB, exposed for MDR-TB, exposed for XDR-TB, DS-TB, MDR-TB, XDR-TB and recovered compartment. The total population size at a time t is denoted by $N(t)$ and therefore we have:

$$N(t) = S(t) + E_1(t) + E_2(t) + E_3(t) + I_1(t) + I_2(t) + I_3(t) + R(t) \quad (1)$$

In our work, our model is a deterministic mathematic model so that we assume that all parameters in the mathematical model are positive constant. Based on these assumptions we can construct a flowchart for TB transmission in Indonesia as Figure 1. The model was developed under the following assumptions: the rate of change of any state is equal to the number entering into the state minus the number leaving the state per unit time. The growth of susceptible compartment depends on the natural birth rate. The susceptible compartment will increase because of the loss of immunity rate from the recovered

compartment. The condition occurs because the immunity in a recovered individual after completion of TB treatment wanes over time. Further, the susceptible compartment will be decreased because of infected rate as well. The exposed compartment will increase because of the infected rate of susceptible to the exposed compartment. On the other hands, over time, the exposed compartment will be decreased because exposed individuals will become infectious individuals because their immune system is weakened and because of the recovery rate from exposed to recovered individuals.

DS-TB compartment will increase due to the infectious rate of exposed individuals to DS-TB individuals and the relapse rate of recovered individuals to DS-TB individuals. It will decrease because of the developed rate of DS-TB to MDR-TB individuals, the developed rate of DR-TB to XDR-TB individuals and the treatment success rate of DS-TB individuals becoming recovered individuals.

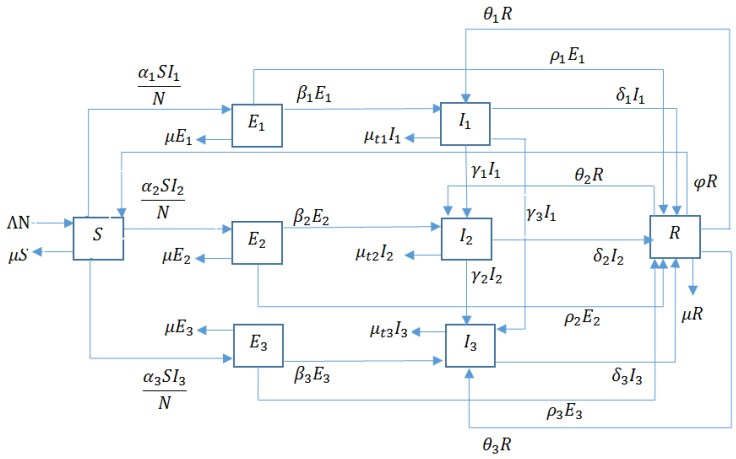


Figure 1 Flowchart of TB Transmission

The number of individuals in the MDR-TB compartment will increase due to the infectious rate of exposed to MDR-TB individuals, the developed rate of DS-TB to MDR-TB individuals and the relapse rate of recovered individuals to MDR-TB individuals. It will decrease because of the developed rate of MDR-TB to XDR-TB individuals and the treatment success rate of MDR-TB becoming recovered individuals. The number of individuals in the XDR-TB compartment will increase due to the infectious rate of exposed to XDR-TB individuals, the developed rate of MDR-TB to XDR-TB individuals and the relapse rate of recovered to XDR-TB individuals. It will decrease because of the treatment success rate of XDR-TB to recovered individuals.

The recovered compartment will increase due to the recovery rate of each exposed compartment and treatment success rate of each infectious compartment and will decrease due to loss of immunity rate and relapse rate. In this model, we assume that each compartment will be decreased because of the natural death rate as well. Another special assumption in the infectious compartment is that it will decrease because of the death rate which is caused by any reason before starting or during the course of treatment. Based on the assumption, we formulate the mathematical model in ordinary differential equation form as follows

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda N + \varphi R - \frac{S}{N}(\alpha_1 I_1 + \alpha_2 I_2 + \alpha_3 I_3) - \mu S \\
\frac{dE_1}{dt} &= \frac{\alpha_1 S I_1}{N} - E_1(\beta_1 + \rho_1 + \mu) \\
\frac{dE_2}{dt} &= \frac{\alpha_2 S I_2}{N} - E_2(\beta_2 + \rho_2 + \mu) \\
\frac{dE_3}{dt} &= \frac{\alpha_3 S I_3}{N} - E_3(\beta_3 + \rho_3 + \mu)
\end{aligned} \qquad (2)$$

$$\frac{dI_1}{dt} = \beta_1 E_1 + \theta_1 R - I_1(\delta_1 + \gamma_1 + \gamma_2 + \mu_{CI})$$
$$\frac{dI_2}{dt} = \beta_2 E_2 + \theta_2 R + \gamma_1 I_1 - I_2(\delta_2 + \gamma_2 + \mu_{CI})$$
$$\frac{dI_3}{dt} = \beta_3 E_3 + \theta_3 R + \gamma_2 I_1 + \gamma_2 I_2 - I_3(\delta_3 + \mu_{CI})$$
$$\frac{dR}{dt} = \delta_1 I_1 + \delta_2 I_2 + \delta_3 I_3 + \rho_1 E_1 + \rho_2 E_2 + \rho_3 E_3 - R(\varphi + \theta_1 + \theta_2 + \theta_3 + \mu)$$

In this study, there is an assumption that there is no difference in the recovery rate among the three classes of exposed individuals at any one time. Further, because equation (2), the ordinary differential equation, is too complicated to solve analytically, we will use the Fourth-order Runge-Kutta method to solve it. The duration in this study is 156 months starting from January 2018 and ending in December 2030.

3.2 State and Parameter Value

The initial values of state variables and parameters which are used in this study are obtained from the literature review including research articles, books, reports, and other research related to the study. Table 1 shows the initial values of state variables. The parameter values used in the study are chosen and calculated to be as close to Indonesia condition as possible, see Table 2.

Table 1 Initial Value of State Variable for Tuberculosis Transmission in Indonesia

Sy	Unit	Value	Reference	Sy	Unit	Value	Reference
S	Persons	142,878,297	Data fitted[a]	I_1	Persons	836,879	Data fitted[c]
E	Persons	120,000,000	Houben & Dodd (2016)	I_2	Persons	5,070	WHO (2018)
E_1	Persons	119,270,166	Data fitted[b]	I_3	Persons	51	WHO, (2018)
E_2	Persons	722,565	Data fitted[b]	R	Persons	279,703	MoH RI (2018)
E_3	Persons	7,269	Data fitted[b]	N	Persons	264,000,000	WHO (2018)
I	Persons	842,000	WHO (2018)				

Sy : Symbol, WHO : World Health Organization, MoH RI : Ministry of Health of the Republic of Indonesia (2018). [a] value is estimated based on data from the MoH RI, WHO and Houben & Dodd data. [b] value is estimated based on data from the proportion of DS-TB, MDR-TB, and XDR-TB from WHO and Houben & Dodd data. [c] values is estimated based on WHO's data

Table 2 Value of Parameter for TB transmission

Sy	Description of parameters	Unit	Value	Reference
Λ	the natural birth rate	Per year	0,01888	World Bank (2018)
μ	the natural death rate	Per year	0.00712	World Bank (2018)
μ_{t1}	the natural death rate of I_1	Per year	0.2	Dheda et al. (2017)
μ_{t2}	the natural death rate of I_2	Per year	0.4	Dheda et al. (2017)
μ_{t3}	the natural death rate of I_3	Per year	0.6	Dheda et al. (2017)
α_1	the infected rate of S to E_1	Per year	0.0879	Data fitted[d]
α_2	the infected rate of S to E_2	Per year	0.00053	Data fitted[d]
α_3	the infected rate of S to E_3	Per year	5.354×10^{-6}	Data fitted[d]
β_1	the infectious rate of E_1 to I_1	Per year	0.05	WHO (2018)
β_2	the infectious rate of E_2 to I_2	Per year	0.05	WHO (2018)
β_3	the infectious rate of E_3 to I_3	Per year	0.05	WHO (2018)
γ_1	the developed rate of I_1 to I_2	Per year	0.05	Dheda et al. (2017)
γ_2	the developed rate of I_2 to I_3	Per year	0.1	Dheda et al. (2017)
γ_3	the developed rate of I_1 to I_3	Per year	0.05	Dheda et al. (2017)
δ_1	the treatment success rate of I_1 to R	Per year	0.86	WHO (2018)
δ_2	the treatment success rate of I_2 to R	Per year	0.47	WHO (2018)
δ_3	the treatment success rate of I_3 to R	Per year	0.28	WHO (2018)
θ_1	the relapse rate of R to I_1	Per year	1.6956×10^{-3}	Widyaningsih et al. (2018)
θ_2	the relapse rate of R to I_2	Per year	1.6956×10^{-3}	Widyaningsih et al. (2018)
θ_3	the relapse rate of R to I_3	Per year	1.6956×10^{-3}	Widyaningsih et al. (2018)
ρ_1	the recovery rate of E_1 to R	Per year	0.03, 0.1, 0.2, 0.3	Assumed[e]
ρ_2	the recovery rate of E_2 to R	Per year	0.03, 0.1, 0.2, 0.3	Assumed[e]
ρ_3	the recovery rate of E_3 to R	Per year	0.03, 0.1, 0.2, 0.3	Assumed[e]
φ	the loss immunity rate of R to S	Per year	0.9877	Data fitted[f]

[d] value is estimated based on data from the WHO's statement and calculation. [e] value is estimated based on assumed by researcher. [f]value is estimated based on data from residual calculations using a parameter in R compartment

The lower bound value is 3% and will be used as the baseline of the recovery rate. We assume that 3% is the level that has been achieved by the Indonesian government. While 30% is the highest possible value to be achieved by the Indonesian government and will be the upper bound value. Furthermore, 10% and 20% are assumed as representatives of other recovery rates between lower and upper bounds.

4. Results and Discussion

In this study, we used four values of recovery rate, namely 3%, 10%, 20%, and 30%, to see more clearly the differences among the conditions. The results are illustrated in Figure 2. Figure 2 (a) was a comparison of the recovery rate in DR-TB individuals. The recovery rate of 3% was used as a baseline and we assumed that this achievement will not decrease until 2030. Next, the baseline position was at the top with the highest number of DR-TB until 2030. This was followed by recovery rates of 10%, 20%, and 30%. If the Indonesian government can consistently achieve recovery rates of 10%, 20% and 30% then the total numbers of individuals that will avoid getting DS-TB are 1,106,871 (33.0%), 1,897,552 (56.6%) and 2,274,091 (67.8%), respectively.

Graphically, there was a significant difference between using the recovery rate of 3% and 10% even though the difference in the recovery rate between them is only 7%. Different results are shown between using the recovery rate of 20% and 30%. Graphically, there was not too much difference between them even though the recovery rate difference was 10%. Further, looking at the DS-TB compartment, we concluded that the recovery rate of 30% could significantly minimize the number of DS-TB until 2030. Using different recovery rate also gave different results on MDR-TB. It is illustrated in Figure 2 (b) in which, if the Indonesian government consistently can achieve the recovery rate until 2030 by 10%, 20%, and 30%, then the total numbers of individuals who avoid getting MDR-TB are 44 (0.03%), 4,277 (3.30 %)

and 9,112 (7.02%) individuals, respectively. Based on the simulation results, it was concluded that using the 10% recovery rate was not too different when compared to the baseline.

The simulation result from the mathematical model for XDR-TB is illustrated in Figure 2 (c). The use of the recovery rates of 10%, 20% and 30% as compared to the baseline significantly reduced the numbers of individuals getting XDR-TB by 7,658, 8,728, and 6,411, respectively. In this situation, the recovery rate of 20% was the best rate to avoid individuals from MDR-TB. Further, if we observe the proportions compared with the baseline, the proportions are not too different at 6.46%, 7.36% and 5.41% for the recovery rates of 10%, 20%, and 30%.

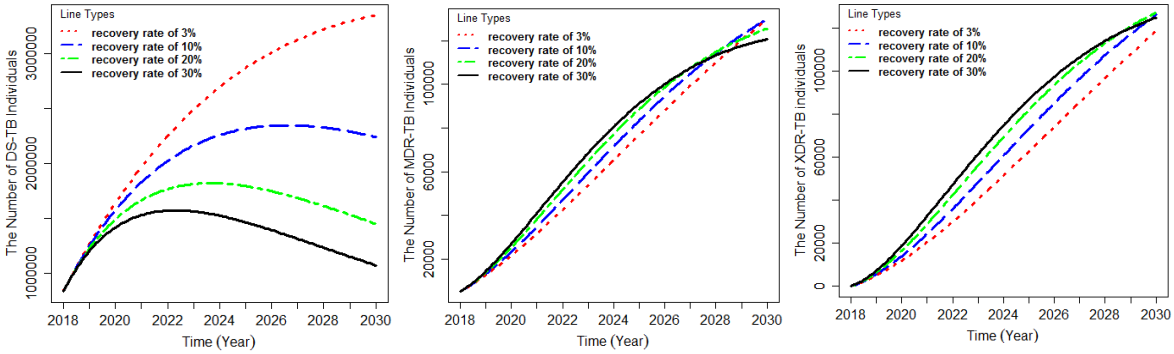


Figure 2 (a) Distribution of DR-TB individuals, **(b)** distribution of MDR-TB individuals, and **(c)** distribution of XDR-TB individuals

The recovery rate that occurs on exposed individuals has a positive effect on all exposed compartments. Graphically, in Fig. 2 (d) – 2 (f), it can be seen that the higher the recovery rate achieved, so, the greater is the decrease that occurs in each exposed compartment. Based on numerical simulation results there would be a decline in the number of exposed individuals for DS-TB by the amount of 45,349,049 individuals for the recovery rate of 10%, 67,733,164 individuals for the recovery rate of 20%, and 73,890,659 individuals for the recovery rate of 30% (Fig. 2 (d)). In exposed individuals, for the MDR-TB compartment, there are also significant declines of 274,471 individuals for the recovery rate of 10%, 409,883 individuals for the recovery rate of 20% and 447,096 individuals for the recovery rate of 30%.

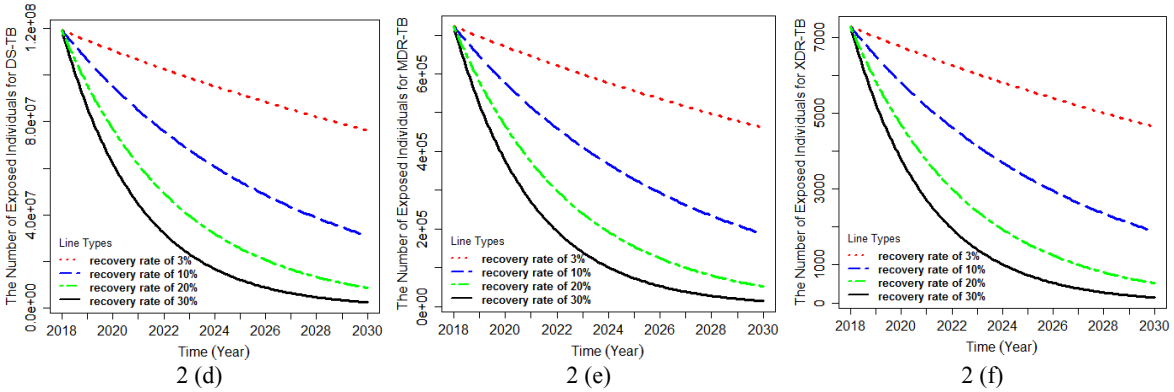
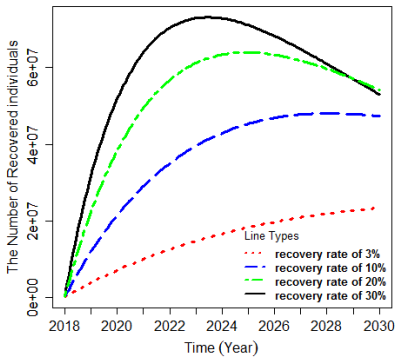


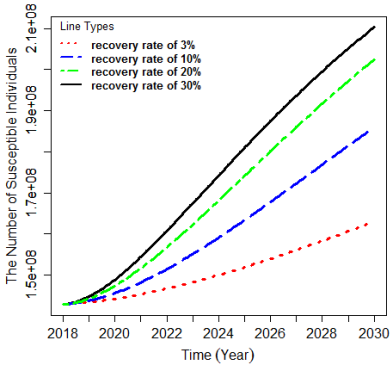
Figure 2 (d) distribution of exposed individuals for DR-TB, **(e)** distribution of exposed for MDR-TB, and **(f)** distribution of exposed individual for XDR-TB

In recovered compartments, it is seen that the recovery rate of 30% could maximize the number of recovered individuals from TB for 13 years. However, at the end of that period, the result is almost the

same as that for a recovery rate of 20%. This is illustrated in Figure 2 (g). If we observe graphically and numerically, there is information that the recovery rate of 30% until 2030 is the best recovery rate for increasing the number of susceptible individuals. This is clearly seen in Figure 2 (h).



2 (g)



2 (h)

Figure 2 (g) Distribution of recovered individuals and **(h)** distribution of susceptible individuals

Completely, the simulation results on the number of individuals in 2030 based on each compartment can be seen in Table 3.

Table 3 The simulation results that use different recovery rates (the number of individuals)

Com	January, 2018	December, 2030			
	Initial value	The first rate[g]	The second rate[h]	The third rate[i]	The fourth rate[j]
S	142,878,297	163,036,244	185,996,850	202,430,423	210,276,873
E_1	119,270,166	76,239,712	30,890,662	8,506,547	2,349,052
E_2	722,565	461,207	186,735	51,324	14,111
E_3	7,269	4,640	1,879	516	142
I_1	836,879	3,349,501	2,242,631	1,451,950	1,075,410
I_2	5,070	129,798	129,842	125,521	120,686
I_3	51	118,530	126,188	127,258	124,941
R	279,703	23,439,526	47,296,499	54,259,295	53,040,989
N	264,000,000	266,779,158	266,871,285	266,952,834	267,002,204

Com : Compartment, [g] the simulation used the recovery rate of 3%, [h] the simulation used the recovery rate of 10%, [i] the simulation used the recovery rate of 20%, and [j] the simulation used recovery rate of 30%.

5. Conclusion

To eliminate TB cases in Indonesia, the recovery of LTBI needs to be done with maximum effort because the recovery rate has a significant impact on eradicating TB in the future. If we observe the result of the simulation, the higher the recovery rate achieved, the greater the number of individuals can avoid getting TB disease. Based on the simulation result, the target of SDG to the end the TB cases by 2030 will not be reached.

Generally, the recovery rate of 30% can reduce the number of DS-TB significantly. As a recommendation, to increase the recovery rate, Indonesia must carry out health programs to increase awareness of the population such as a healthy life campaign so that the population in Indonesia, especially LTBI individuals, have good immunity system in the body. The strong immune system in exposed individuals (LTBI) will help LTBI individuals reduce bacterial growth in the body. Then, the Indonesian government must be able to provide logistics and the best services in TB preventive therapy for the LTBI in remote areas. Another recommendation for eliminating TB in the future is by considering effort and costs; the Indonesia government must achieve a minimum recovery rate of 10%.

6. Acknowledgments

This research was conducted through TB/MDR-TB Research Training Program at The Epidemiology Unit, Prince of Songkla University, under the support of Fogarty International Center, National Institute of Health (Grant number D43TW009522).

7. References

Bansal, R., Sharma, D., & Singh, R. (2017). Tuberculosis and its treatment: An Overview. *Mini-Reviews in Medicinal Chemistry*, *18*(1), 58–71.

Brooks-Pollock, E., & Jacobson, K. R. (2018). Rethinking tuberculosis control by targeting previously treated individuals. *The Lancet Global Health*, *6*(4), e361–e362.

Bule, M. H., Maqbool, F., Ahmad, I., Dhama, K., & Iqbal, H. M. N. (2017). Advances in the treatment options towards drug-resistant tuberculosis. *International Journal of Pharmacology*, *13*(7), 746–761.

CDC. (2013). *Core curriculum on tuberculosis : What the Clinician Should Know*. (Sixth). Atlanta, USA: Centers for Disease Control and Prevention.

Cruz, A. T., Ahmed, A., Mandalakas, A. M., & Starke, J. R. (2018). Treatment of latent tuberculosis infection in children. *Pediatric Latent TB Infection Therapy*, *2*(3), 248–258.

Dheda, K., Gumbo, T., Maartens, G., Dooley, K. E., Mcnerney, R., Murray, M., … Warren, R. M. (2017). The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant , and incurable tuberculosis. *The Lancet Respiratory Medicine*, *5*(17), 1–71.

Egger, M., Johnson, L., Althaus, C., Schöni, A., Salanti, G., Low, N., & Norris, S. L. (2017). Developing WHO guidelines: Time to formally include evidence from mathematical modelling studies. *F1000Research*, *6*(0), 1584.

Egonmwan, A. O., & Okuonghae, D. (2018). Analysis of a mathematical model for tuberculosis with diagnosis. *Journal of Applied Mathematics and Computing*, 1–34.

Houben, R. M. G. J., & Dodd, P. J. (2016). The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLOS Medicine*, *13*(10), e1002152.

Hugo, A., Makinde, O. D., Kumar, S., & Chibwana, F. F. (2017). Optimal control and cost effectiveness analysis for newcastle disease eco-epidemiological model in Tanzania. *Journal of Biological Dynamics*, *11*(1), 190–209.

IHME. (2018). *Indonesia's Health Data*. Retrieved February 17, 2019, from http://www.healthdata.org/indonesia

Kermack, W. O., & McKendrick, A. G. (1927). A Contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*, *115*(772), 700–721.

Kim, S., Reyes, A. A. De Los., & Jung, E. (2018). Mathematical model and intervention strategies for mitigating tuberculosis in the Philippines. *Journal of Theoretical Biology*, *443*, 100–112.

Kritski, A., Andrade, K. B., Galliez, R. M., Maciel, E. L. N., Cordeiro-Santos, M., Miranda, S. S., … Croda, J. (2018). Tuberculosis: Renewed challenge in Brazil. *Revista Da Sociedade Brasileira de Medicina Tropical*, *51*(1), 2–6.

Kurz, S. G., Furin, J. J., & Bark, C. M. (2016). Drug-Resistant tuberculosis. *Infectious Disease Clinics of North America*, *30*(2), 509–522.

Lahrouz, A., El Mahjour, H., Settati, A., & Bernoussi, A. (2018). Dynamics and optimal control of a non-linear epidemic model with relapse and cure. *Physica A: Statistical Mechanics and Its Applications*, *496*, 299–317.

Liddo, A. Di. (2016). Optimal control and treatment of infectious diseases. The Case of Huge Treatment Costs. *Mathematics*, *4*(2), 27.

Ministry of Health of the Republic of Indonesia. (2018). *Data and information: indonesian health profile 2017*. Jakarta: Ministry of Health of the Republic of Indonesia.

Moghaddam, H. T., Moghadam, Z. E., Khademi, G., Bahreini, A., & Saeidi, M. (2016). Tuberculosis: Past, present and future. *Int J Pediatr*, *4*(125), 1243–1255.

Okuonghae, D., & Ikhimwin, B. O. (2016). Dynamics of a mathematical model for tuberculosis with variability in susceptibility and disease progressions due to difference in awareness level. *Frontiers in Microbiology*, *6*(January), 1–23.

Seddon, J. A., Warren, R. M., Enarson, D. A., Beyers, N., & Simon Schaaf, H. (2012). Drug-resistant tuberculosis transmission and resistance amplification within families. *Emerging Infectious Diseases*, *18*(8), 1342–1345.

Siettos, C. I., & Russo, L. (2013). Mathematical modeling of infectious disease dynamics. *Virulence*, *4*(4), 295–306.

The World Bank. (2018). *Death rate, crude (per 1,000 people)*. Retrieved from https://data.worldbank.org/indicator/SP.DYN.CDRT.IN?locations=ID

Waaler, H., Geser, A., & Andersen, S. (1962). The use of mathematical models in the study of the epidemiology of tuberculosis. *American Journal of Public Health and the Nations Health*, *52*(6), 1002–1013.

Wang, J., Lee, L., Lai, H., Hsu, H., Liaw, Y., Hsueh, P., & Yang, P. (2018). Prediction of the tuberculosis reinfection proportion from the local incidence. *The Journal of Infectious Diseases*, *196*(7), 281–288.

WHO. (2013). *Systematic screening for active tuberculosis: principles and recommendations*. Geveva, Switzerland: World Health Organization. Retrieved https://www.ncbi.nlm.nih.gov/books/NBK294083/pdf/Bookshelf_NBK294083.pdf

WHO. (2014). *Definitions and reporting framework for tuberculosis – 2013 revision*. *World Health Organization*. Geneva, Switzerland: World Health Organization.

WHO. (2018). *Global Tuberculosis Report 2018*. France. Retrieved from http://apps.who.int/iris/bitstream/handle/10665/274453/9789241565646-eng.pdf?ua=1

WHO. (2018). *Latent Tuberculosis Infection : updated and consolidated guidelines for programmatic management*. *World Health Organization*. Geneva, Switzerland: World Health Organization.

WHO. (2018). *What is TB? How is it treated?*. Retrieved from http://www.who.int/features/qa/08/en/

Widyaningsih, P., Nugroho, A. A., & Saputro, D. R. S. (2018). Susceptible infected recovered model with vaccination, immunity loss, and relapse to study tuberculosis transmission in Indonesia. *ICSAS 2018* (pp. 020121-1 - 020121-6). Solo: International Conference on Science and Applied Science.

World Bank. (2018). *Birth rate, crude (per 1,000 people)*. Retrieved from https://data.worldbank.org/indicator/SP.DYN.CBRT.IN