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Dynamical System of the Mathematical Model for Tuberculosis with Vaccination

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Abstract **–** This research focused on the modification of deterministic mathematical models for tuberculosis with vaccination. It also aimed to see the effect of giving the vaccine. It was done by adding vaccine compartments to people who were given the vaccine in the susceptible compartment. The population was divided into nine different groups. Those were susceptible individuals (S), vaccine (V), new latently infected (E_1), diagnosed latently infected (E_2), undiagnosed latently infected (E_3), undiagnosed actively infected (I), diagnosed actively infected with prompt treatment (D_r), diagnosed actively infected with delay treatment (D_p), and treated (T). Basic reproduction number was constructed using next-generation matrix. Sensitivity analysis was also conducted. The results show that the model comprises two equilibriums: disease-free equilibrium (T^0) and endemic equilibrium (T^*). It also shows that there is a relationship between R_0 and two equilibriums. Moreover, the disease-free equilibrium point is asymptotically stable local when it is $R_0 < 1$. Then, the disease-endemic equilibrium point is asymptotically stable local when it is $R_0 > 1$. Furthermore, the parameters of β, ρ, and γ are the most important parameter.

Keywords: dynamical system, mathematical model, tuberculosis, vaccination

I. INTRODUCTION

Tuberculosis (TB) is the infectious diseases caused by Mycobacterium Tuberculosis. It is transmitted through the air (spits, coughing, or speaking) from a person suffering from active TB. Generally, it infects the lungs, but it can also affect other organs. Most people infected with TB have not shown symptoms known as latent types of infection. People with latent types cannot infect other people. However, if it is untreated, it will become an active disease. The common symptoms of active TB are chronic cough accompanied by blood, fever, night sweats, and weight loss. People who are infected in other organs can show various symptoms. Active infection is more common in people affected by HIV/AIDS and people who smoke (Lawn & Zumla, 2011).

Based on the WHO in 2018, it was estimated that a quarter of the world's population was infected by TB. Every year, new infections were occurred in about 1% of the population. In 2017, TB cases were the number one cause compared to other infectious diseases. This was because there were more than 10 million cases of active TB. It resulted in 1,3 million deaths as many as 95% occurring in developing countries. More than 50% happened in India, China, Indonesia, Pakistan, and Philippines. In Indonesia, there had been 842.000 cases of TB sufferers (World Health Organization (WHO), 2018).

An essential component of TB control is the diagnosis of latent TB infection and rapid treatment of active infection. When TB infection is not detected, there can be a delay in treatment of latent and active TB. Thus, it can cause more severe disease conditions resulting in a wider spread of the disease (Al-Darraji, Altice, & Kamarulzaman, 2016).

In addition, other efforts can be made to control the spread of developing and dangerous TB. One of them is by giving vaccines. The vaccine used for TB is the Bacillus Calmette-Guerin (BCG). It is the only vaccine or the most often used. It can reduce the risk of being infected with TB bacteria. BCG can only be given once to someone (newly born or has never been infected with TB). Currently, there are new vaccines under development (Lawn & Zumla, 2011).

The transmission of TB is still happening to this day. For this reason, a way is needed to study the pattern of the spread of TB. One tool that can be used is by making mathematical models. The mathematical model known as the epidemic model is created by Kermack and McKendrick (1927). They assumed a fixed population. It consisted of only three compartments. Compartments were divided into three classes. Those were susceptible populations (S), infected populations (I), and populations recovering from disease (R). It was also known as SIR models. Over time, the model continued to be developed (Roni, 2011; Side, Sanusi, & Setiawan, 2016).

Several mathematical models of TB transmission have been made and used to study the dynamics of the spread of TB in a population. For example, Aparicio and Casstillo-Chavez (2009) presented a mathematical model of TB epidemics. Okuonghae (2013) showed a mathematical model of TB transmission with heterogeneity and progression under a treatment regime for infectious cases. Next, Trauer, Denholm, and McBryde (2014) presented the construction of a mathematical model for TB transmission in highly endemic. Then, the model of Okuonghae and Ikhimwin (2016) classified the latently infected individuals by their level of TB awareness. Moreover, Egonmwan and Okuonghae (2019) had a mathematical model for TB with the diagnosis.

The model in this research is modifying the model of Egonmwan and Okuonghae (2019). It is because the previous model only pays attention to the circumstances of individuals who have interacted with infected individuals. The model of Egonmwan and Okuonghae (2019) is an epidemic model with eight compartments. The model is made by considering several conditions. Some patients are not diagnosed or diagnosed with latent or active TB infection. Then, there are delay and timeliness in the treatment of some active cases in patients.

The mathematical models by Egonmwan and Okuonghae (2019) do not consider preventive measures regarding the spread of TB. Therefore, a model is created by considering preventive measures. It is done by giving vaccines. The researchers modify the model by adding vaccination compartments as a precaution before interacting with infected individuals. Vaccination compartments are a collection of individuals who have been given a vaccine. This modification is made to see the effect of vaccine administration or vaccine effectiveness given to individuals who have never been infected with Mycobacterium Tuberculosis and parameters that influence to spread of tuberculosis.

II. METHODS

This research is a literature review. The method is a mathematical model from the transmission of TB disease. Then, the researchers modify it. The researchers also find the basic fixed points and reproduction number from the equation system to analyze the stability of the fixed points. It uses the Routh-Hurwitz criteria and center manifold theory. Then, a sensitivity analysis is performed to see which influential parameters raise or decrease the basic reproduction number.

III. RESULTS AND DISCUSSIONS

Egonmwan and Okuonghae (2019) made a deterministic epidemic model with ordinary differential equations. The population size was divided into eight special compartments. There was the total population at time (t). The N is the total population of individuals in each compartment. Moreover, there were susceptible individuals (S), new latently infected (E_1), diagnosed latently infected (E_2), undiagnosed latently infected (E_3), undiagnosed actively infected (I), diagnosed actively infected with prompt treatment (D_r), diagnosed actively infected with delay treatment (D_p), and individuals given treatment (T).

Assumed μ is the natural death rate that can occur in each class of the population. Each δ_1, δ_2, and δ_3 represents the mortality rate caused by active TB infection. Newborn individuals (A) belong to the population class (S). If individuals in S population interact with individuals population of I, D_r, and D_p, they will be infected. It is as much as the strength of infection λ. By β being the transmission rate, η_1 and η_2 are the modification parameters. It causes a reduced probability of disease transmission by individuals diagnosed with active TB with immediate treatment (D_r) and delay treatment (D_p).

Therefore, in this research, a model is made by modifying the previous models of Egonmwan and Okuonghae (2019). Individuals in vulnerable populations are given vaccines at rate of γ so they can be protected from the attack of Mycobacterium Tuberculosis. The commonly used vaccine is BCG. Giving vaccines only aims to increase the body's immune system. Therefore, individuals given vaccines can move into latently infected individuals with a rate of $\varepsilon\lambda$ when interacting with individuals with active TB infection. Then, ε is the effectiveness of vaccines against TB development by Kalu and Inyama (2012). In addition, the natural death rate can occur in the vaccination compartment. This modification is done to see the key parameters that have the greatest influence on the transmission dynamics of TB using the basic reproduction number of the model.

A vaccine can increase the body's resistance. Thus, the model is made with the assumption that when someone who is given a vaccine in interacting with someone who is actively infected with TB, the person enters the class of new latent infection (E_1) (Nainggolan, Supian, Supriatna, & Anggriani, 2013). Schematically, the pattern of tuberculosis spread modification models is depicted in the compartment diagram in Figure 1.

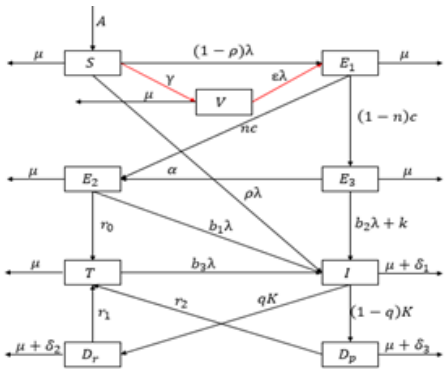


Figure 1 Diagram Modification
Equation (1) of the TB

Based on the diagram in Figure 1, the researchers have a system of ordinary differential equations as follows:

$$\frac{dS}{dt} = A - \lambda S - \gamma S - \mu S,$$

$$\frac{dV}{dt} = \gamma S - \lambda \varepsilon V - \mu V,$$

$$\frac{dE_1}{dt} = (1-\rho)\lambda(S + b_3 T) + \varepsilon\lambda V - c E_1 - \mu E_1,$$

$$\frac{dE_2}{dt} = c n E_1 + \alpha E_3 - b_1 \lambda E_2 - (r_0 + \mu) E_2,$$

$$\frac{dE_3}{dt} = c(1-n) E_1 - b_2 \lambda E_3 - (\alpha + k + \mu) E_3,$$

$$\frac{dI}{dt} = \rho\lambda S + b_1\lambda E_2 + (b_2\lambda + k)E_3 + \rho b_3\lambda T - (K + \delta_1 + \mu)I,$$

$$\frac{dD_r}{dt} = KqI - (r_1 + \delta_2 + \mu)D_r,$$

$$\frac{dD_p}{dt} = K(1-q)I - (r_2 + \delta_3 + \mu)D_p,$$

$$\frac{dT}{dt} = r_0E_2 + r_1D_r + r_2D_p - b_3\lambda T - \mu T,$$

with $\lambda = \frac{\beta(I + \eta_1 D_r + \eta_2 D_p)}{N}$,

and $N(t) = S(t) + V(t) + E_1(t) + E_2(t) + E_3(t) + I(t) + D_r(t) + D_p(t) + T(t)$ as the total population at time *t*. (1)

Model (1) is a human population, so the variables and parameters must be positive at time t. Therefore, it will be shown that all variables are not negative. The initial values for each compartment are $S(0)\geq 0$, $V(0)\geq 0$, $E_1(0)\geq 0$, $E_2(0)\geq 0$, $E_3(0)\geq 0$, $I(0)\geq 0$, $D_r(0\geq 0$, $D_p(0)\geq 0$, $T(0)\geq 0$. It is with the positive value of all parameters in the system, and the description of each parameter is in Table 1.

Table 1 Parameter and Description of the Model

Parameter	Description	Unit
μ	Natural death rate	year^{-1}
A	Recruitment rate	year^{-1}
γ	Rate of vaccinating	year^{-1}
β	Transmission rate	year^{-1}
ε	Effective of vaccine $(0<\varepsilon<1)$	-
η_1	The rate of reduction in TB patients (D_r) in	year^{-1}
η_2	The rate of reduction in TB patients (D_p) in	year^{-1}
κ	Disease progression rate from the class of undiagnosed latently infected to active TB (I)	year^{-1}
α	The rate of latently infected individuals become diagnosed individuals.	year^{-1}
ρ	Fraction of fast TB progression $(0<\rho<1)$	-
b_1, b_2	Parameters of exogenous re-infection	year^{-1}
b_3	Modification parameters that result in a successful increase in reinfection after treatment	year^{-1}
n	Proportion of new latent TB that are diagnosed	-
c	Rate of diagnosis of latent TB infection	year^{-1}
q	Proportion of detected active TB cases who receive prompt treatment	-
K	Rate of detection of active TB cases	year^{-1}
$\delta_1, \delta_2, \delta_3$	The death rate for individuals of	year^{-1}
r_0, r_1, r_2	Treatment rates for individuals of	year^{-1}

Lemma 3.1 Set $\Omega = \{(S,V,E_1,E_2,E_3,I,D_r,D_p,T)\in \mathbb{R}^{+}_{9}: N(t)\leq \frac{A}{\mu}+N_0, S(t)>0\}$ is a non-negative and limited regional solution of system (1) with N_0 as the initial total population. Then, S_0 is the population of the susceptible individual at time $t = 0$ (Apriliani, 2016).

Proof Let $N=S+V+E_1+E_2+E_3+I+D_r+D_p+T$, and it is given the initial value for each population when $t = 0$, where $N(0)=N_0$, $S(0)=S_0$, $V(0)=V_0$, $E_1(0)=E_{1_0}$, $E_2(0)=E_{2_0}$, $E_3(0)=E_{3_0}$, $I(0)=I_0$, $D_r(0)=D_{r_0}$, $D_p(0)=D_{p_0}$

Summing the nine equations of the system of equation (1) gives a change in total population N to time t as follows:

$$\frac{dN}{dt} = \frac{d}{dt}(S + V + E_1 + E_2 + E_3 + I + D_r + D_p + T)$$
$$= A - \mu N - (\delta_1 I + \delta_2 D_r + \delta_3 D_p) \quad (2)$$

since $\delta_1, \delta_2, \delta_3 > 0$ and l, $D_r, D_p \geq 0$, the equation (2) can be written as:

$$\frac{dN}{dt} \leq A - \mu N \quad (3)$$

The equation (3) is solved using an integrating factor by Robinson (2004) with an initial value of $N(0) = N_0$. Then, it can be rewritten as:

$$N(t) = \frac{A}{\mu} + N_0 e^{-\mu t} - \frac{A}{\mu} e^{-\mu t} \quad (4)$$

$$S(t) + V(t) + E_1(t) + E_2(t) + E_3(t) + I(t) + D_r(t) + D_p(t) + T(t) \leq \frac{A}{\mu} + N_0 \quad (5)$$

Since it is $S(t) + V(t) + E_1(t) + E_2(t) + E_3(t) + I(t) + D_r(t) + D_p(t) + T(t) \geq 0$, then for each $t \to \infty$, it shows that

$$0 \leq N(t) \leq \frac{A}{\mu} + N_0 \quad (6)$$

With the same way, it will be shown that S is also limited. The first equation in the system of equation (1) is as follows:

$$\frac{dS(t)}{dt} = A - (\lambda + \gamma + \mu)S(t) \quad (7)$$

It can be rewritten as follows:

$$\frac{d}{dt}\left[S(t)\exp\left\{\gamma t + \mu t + \int_0^t \lambda(\tau)\,d\tau\right\}\right] = A\exp\left\{\gamma t + \mu t + \int_0^t \lambda(\tau)\,d\tau\right\} \quad (8)$$

Thus, it is:

$$S(t)\exp\left\{\gamma t + \mu t + \int_0^t \lambda(\tau)d\tau\right\} - S_0 = \int_0^t A\left[\left\{\exp\left\{\gamma y + \mu y + \int_0^y \lambda(\tau)d\tau\right\}\right\}\right]dy \quad (9)$$

So, it can be:

$$S(t) = S_0\exp\left\{-\gamma t - \mu t - \int_0^t \lambda(\tau)d\tau\right\} + \left[\exp\left\{-\gamma t - \mu t - \int_0^t \lambda(\tau)d\tau\right\} \times \int_0^t A\left\{\exp\left\{\gamma y + \mu y + \int_0^y \lambda(\tau)d\tau\right\}\right\}\right]dy > 0 \quad (10)$$

Similarly, it can be shown that $V(t)>0$, $E_1(t)>0$, $E_2(t)>0$, $E_3(t)>0$, $l(t)>0$, $D_r(t)>0$, $D_p(t)>0$, $T(t)>0$ for all time $t > 0$. Thus, all solutions of system (1) remain positive for all non negative initial conditions.

Table 2 Parameters Values of the Model

Parameter	Ranges of Values	Source
A	1000-2000	Apriliani (2016)
γ	0,2-0,005	Apriliani (2016)
μ	0,0222	Apriliani (2016)
ρ	0,1- 0,2	Egonmwan and Okuonghae (2019)
β	6,55-15	Egonmwan and Okuonghae (2019)
η_1	0,5	Egonmwan and Okuonghae (2019)
η_2	0,7	Egonmwan and Okuonghae (2019)
η	0,3	Egonmwan and Okuonghae (2019)
c	1,2	Egonmwan and Okuonghae (2019)
α	1	Egonmwan and Okuonghae (2019)
b_1	0-0,7	Egonmwan and Okuonghae (2019)
b_2	0-0,8	Egonmwan and Okuonghae (2019)
b_3	0-1	Egonmwan and Okuonghae (2019)
r_0	0,5	Egonmwan and Okuonghae (2019)
r_1	1,5	Egonmwan and Okuonghae (2019)
r_2	0,5	Egonmwan and Okuonghae (2019)
k	0-0,0005	Egonmwan and Okuonghae (2019)
K	1,6	Egonmwan and Okuonghae (2019)
δ_1	0,413	Egonmwan and Okuonghae (2019)
δ_2	0,139	Egonmwan and Okuonghae (2019)
δ_3	0,3	Egonmwan and Okuonghae (2019)
q	0,4	Egonmwan and Okuonghae (2019)
ε	0,6	Apriliani (2016)

Next, the disease free equilibrium of the model (1) is $T^0(S, V, E_1, E_2, E_3, I, D_r, D_p, T) = (S_0, V_0, 0, 0, 0, 0, 0, 0, 0)$, which is as follows:

$$S_0=\frac{A}{\gamma+\mu}, V_0=\frac{\gamma S_0}{\mu} \tag{11}$$

The local asymptotic stability of disease-free equilibrium is shown by determining the eigenvalue from the Jacobi matrix. Based on the procedure in Anderson and May (1991), the basic reproductive number related to the system (1) is

$$R_0=\beta\frac{[a_{11}a_{22}+a_{22}Kq\eta_1-a_{11}K(q-1)\eta_2]}{a_{11}a_{22}a_{44}a_{66}a_{77}a_{88}N}\frac{[-ck(n-1)a_{33}+a_{44}a_{66}A\rho]}{} \tag{12}$$

Where, those are $a_{11}=(r_1+\delta_2+\mu)$, $a_{22}=(r_2+\delta_3+\mu)$, $a_{33}=(\gamma\varepsilon N+A(1-\rho))$, $a_{44}=(k+\alpha+\mu)$, $a_{55}=(kn+\alpha+\mu)$, $a_{66}=(c+\mu)$, $a_{77}=(\gamma+\mu)$, $a_{88}=(\delta_1+K+\mu)$, and $a_{99}=r_0+\mu$.

Lemma 3.2 The disease-free equilibrium (T^0) in equation (1) is a local asymptotic if it is $R_0<1$. Meanwhile, it is unstable if it is $R_0>1$ (Egonmwan & Okuonghae, 2019).

Proof With the Jacobi matrix on the system around T^0 and eigenvalue, the characteristic equation is produced as follows:

$$(J_{11}-\lambda)(J_{22}-\lambda)(J_{44}-\lambda)(J_{99}-\lambda)$$
$$(\lambda^5+a_1\lambda^4+a_2\lambda^3+a_3\lambda^2+a_4\lambda+a_5)=0 \tag{13}$$

So, it obtains:

$$\lambda_1=J_{11}=-(\gamma+\mu),\ \lambda_2=J_{22}=-\mu,\ \lambda_3=J_{44}=-(r_0+\mu),$$
$$\text{and } \lambda_4=J_{99}=-\mu \tag{14}$$

Five eigenvalues are used to complete the following equation form with Routh-Hurwitz criteria (Edelstein-Keshet, 2005). It is as follows:

$$(\lambda^5+a_1\lambda^4+a_2\lambda^3+a_3\lambda^2+a_4\lambda+a_5)=0 \tag{15}$$

With using Routh-Hurwitz criteria, T^0 will be stable if it fulfills these conditions:

$$a_1>0,\ a_2>0,\ a_3>0,\ a_4>0,\ a_5>0,$$
$$a_1a_2>a_3,\ a_1a_2a_3+a_1a_5>a_3^2+a_1^2a_4,$$
$$\alpha_1\alpha_2\alpha_3\alpha_4+\alpha_2\alpha_3\alpha_5+2\alpha_1\alpha_4\alpha_5>\alpha_5^2+\alpha_3^2\alpha_4+$$
$$\alpha_1^2\alpha_4^2+\alpha_1\alpha_2^2\alpha_5 \tag{16}$$

So, using the parameter values in Table 2 fulfill these conditions. Thus, the disease-free equilibrium (T^0) is stable asymptotic local if it is $R_0<1$.

Moreover, the disease-endemic equilibrium of the model (1) is as follows:

$$S^*=\frac{AN}{\beta(I^*+\eta_1D_r^*+\eta_2D_p^*)+(\gamma+\mu)N} \tag{17}$$

$$V^*=\frac{\gamma S^*N}{\beta\varepsilon(I^*+\eta_1D_r^*+\eta_2D_p^*)+\mu N} \tag{18}$$

$$E_1^*=\frac{\beta(I^*+\eta_1D_r^*+\eta_2D_p^*)(S^*+b_3T^*+V^*\varepsilon-(S^*+b_3T^*)\rho)}{(c+\mu)N} \tag{19}$$

$$E_2^*=\frac{(cnE_1^*+\alpha E_3^*)N}{b_1\beta(I^*+\eta_1D_r^*+\eta_2D_p^*)+(r_0+\mu)N} \tag{20}$$

$$E_3^*=\frac{cE_1^*(n-1)N}{b_2\beta(I^*+\eta_1D_r^*+\eta_2D_p^*)+(k+\alpha+\mu)N} \tag{21}$$

$$I^*=-\frac{(\eta_1 D_r^*+\eta_2 D_p^*)(b_1\beta E_2^*+b_2\beta E_3^*+\beta(S^*+b_3T^*)\rho)+kE_3^*N}{b_1\beta E_2^*+b_2\beta E_3^*-(\delta_1+K+\mu)N+\beta(S^*+b_3T^*)\rho} \quad (22)$$

$$D_r^*=\frac{qKI^*}{r_1+\delta_2+\mu} \quad (23)$$

$$D_p^*=\frac{(1-q)KI^*}{r_2+\delta_3+\mu} \quad (24)$$

$$T^*=\frac{(r_0E_2^*+r_1D_r^*+r_2D_p^*)N}{b_3\beta(I^*+\eta_1D_r+\eta_2D_p)+\mu N} \quad (25)$$

Lemma 3.3 The disease-endemic equilibrium (T^*) in model (1) is local asymptotic if it is $R_0>1$.

Proof Lemma 3.3 is proven by using theorem of Castillo-Chavez and Song (2004). Let $\varphi=\beta$ be a bifurcation parameter at $R_0=1$ and $x_1=S$, $x_2=V$, $x_3=E_1$, $x_4=E_2$, $x_5=E_3$, $x_6=I$, $x_7=D_r$, $x_8=D_p$, $x_9=T$. Then, it is:

$$\varphi=\varphi^*=\frac{a_{11}a_{22}a_{44}a_{66}a_{77}a_{88}N}{(a_{22}Kq\eta_1+a_{11}a_{22}-a_{11}K(q-1)\eta_2)(a_{44}a_{66}A\rho-ck(n-1)a_{33})} \quad (26)$$

Based on Jacobi matrix (J^*), disease free equilibrium (T0) has nine eigenvalues. The one and eight eigenvalues are negative if it is R0 = 1 or $\varphi=\varphi^*$. Using Centre Manifold Theory (Dushoff, Huang, & Castillo-Chavez, 1998), J^* has a right eigenvector given by $u=(n_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8, u_9)$ where,

$$u_1=-\left(\frac{\beta\mu(r_1+\delta_2+\mu)}{(\gamma+\mu)^2qK}+\frac{\beta\mu\eta_1}{(\gamma+\mu)^2}+\frac{\beta\mu\eta_2(r_1+\delta_2+\mu)(\delta_1+K+\mu)}{qK(1-q)K}\right)u_7<0,$$

$$u_2=-\left(\frac{\beta\gamma\varepsilon(r_1+\delta_2+\mu)}{\mu(\gamma+\mu)qK}+\frac{\beta\gamma\varepsilon\eta_1}{\mu(\gamma+\mu)}+\frac{\beta\gamma\varepsilon\eta_2(r_1+\delta_2+\mu)}{\mu(\gamma+\mu)qK(1-q)K}\right)u_7<0,$$

$$u_3=\frac{k+\alpha+\mu}{c(1-n)}u_5>0,$$

$$u_4=\left(\frac{n(k+\alpha+\mu)}{(1-n)(r_0+\mu)}+\frac{\alpha}{(r_0+\mu)}\right)u_5>0, \quad u_5>0,$$

$$u_6=\left(\frac{r_1+\delta_2+\mu}{qK}\right)u_7>0, \quad u_7>0,$$

$$u_8=\left(\frac{K(1-q)(r_1+\delta_2+\mu)}{qK(1-q)K}\right)u_7>0$$

$$u_9=\left(\frac{r_2(\delta_1+K+\mu)(r_1+\delta_2+\mu)}{qK(1-q)\mu K}\right)u_7>0$$

Similarly J^* has left eigen vector $v=(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)$ in satisfying u.v = 1 , with:

$$v_1=v_2=0 \quad (27)$$

$$v_3=\frac{c(1-n)}{c+\mu}v_5>0,\ v_4=0\ ,\ v_5>0,\ v_6=\frac{k+\alpha+\mu}{k}v_5>0 \quad (28)$$

$$v_7=\frac{\varepsilon\beta\eta_1\gamma A+(1-\rho)\mu\beta\eta_1\gamma Ac(1-n)}{(c+\mu)(\gamma+\mu)(r_1+\delta_2+\mu)}+\frac{\beta\eta_1\rho A(k+\alpha+\mu)}{N(\gamma+\mu)k(r_1+\delta_2+\mu)}v_5>0 \quad (29)$$

$$v_8=\frac{\varepsilon\beta\eta_2\gamma+(1-\rho)\mu\beta\eta_2c(1-n)}{(c+\mu)(\gamma+\mu)(r_2+\delta_3+\mu)}+\frac{\beta\eta_2\rho\mu(k+\alpha+\mu)}{(\gamma+\mu)k(r_2+\delta_3+\mu)}v_5>0,\ v_9=0 \quad (30)$$

Based on the theorem of Castillo-Chavez and Song (2004), it evaluates disease-free equilibrium (T^0) with $\varphi=\varphi^*$. It associates with bifurcation coefficients (a and b) given by:

$$a=\sum_{k,i,j=1}^{7}v_ku_iu_j\frac{\partial^2f_k}{\partial x_i\partial x_j}(T^0,0) \quad (31)$$

$$b=\sum_{k,i,j=1}^{7}v_ku_i\frac{\partial^2f_k}{\partial x_i\partial\varphi}(T^0,0) \quad (32)$$

So it becomes:

$$a=\frac{2\varphi^*v_6}{N}[b_1Q_{22}+b_2Q_{33}]-\frac{2\varphi^*}{N}[(1-\rho)v_3Q_{11}+\rho v_6Q_{11}+b_2v_5Q_{33}+\varepsilon v_3Q_{44}] \quad (33)$$

$$b=(u_6+u_7\eta_1+u_8\eta_2)(\rho v_6+((1-\rho)+\varepsilon)v_3)>0 \quad (34)$$

Where,

$$Q_{11}=u_1u_6+u_1u_7\eta_1+u_1u_8\eta_2-u_1u_6b_3-u_1u_7\eta_1b_3-u_1u_8\eta_2b_3$$

$$Q_{22}=b_1(u_4u_6+u_4u_7\eta_1+u_4u_8\eta_2,$$

$$Q_{33}=b_2(u_5u_6+u_5u_7\eta_1+u_5u_8\eta_2,$$

$$Q_{44}=(u_2u_6+u_2u_7\eta_1+u_2u_8\eta_2$$

The value of Q_{22}, Q_{33}, and *b* are positive. Then, Q_{44} is negative for all biologically feasible parameters. Meanwhile, the value of α depends on the parameter values used. If the number is exogenous re-infection (b_1, b_2, b_3) is a positive number that is large enough. The positive part dominates the negative part so that there will be a backward bifurcation in the equation model (1) (Esmail, Barry, Young, & Wilkinson, 2014).

This study leads to a special case, namely ignoring the number of reinfection exogen ($b_1=b_2=b_3=0$) so that it does not occur backward bifurcation due to exogenous reinfection as has been done by several previous researchers Egonmwan and Okuonghae (2019) and Okuonghae and Omosigho (2011). Thus, the value is as follows:

$$a=\frac{2\varphi^*}{N}[(1-\rho)v_3Q_{11}+\rho v_6Q_{11}+\varepsilon v_3Q_{44}]<0 \quad (35)$$

When it is $b_1=b_2=b_3=0$, it obtains a<0, b>0. According to Castillo-Chaves theorem, φ changes from negative to positive, so T^0 changes its stability from stable to unstable. Similarly, the negative fixed point of unstable changes to positive and stable local asymptotic.

Moreover, the researchers conduct a sensitivity analysis for all the parameters in the treatment model (1). It uses the three active populations for the simulation and basic reproduction number (R_0) as the response function. Sensitivity analysis of R_0 aims to determine the parameters regarding their influences on R_0. Numerical simulation of sensitivity using parameters values in Table 2 and the formula (Chitnis, Hyman, & Cushing, 2008) as follows:

$$Y_\rho^{R_0}=\frac{\partial R_0}{\partial\rho}\times\frac{\rho}{R_0} \quad (36)$$

Based on Table 3, it can be concluded that the parameters that have more influence for R_0 are *β, A, ρ,* and γ. The human birth rate (*A*) is not an influential parameter.

However, the rate of transmission of the disease (β), a fraction of fast TB progression (ρ), and the rate of vaccination in susceptible individuals (γ) are parameters that can be controlled to achieve a certain condition. A positive sign on the sensitivity index shows that if the parameter value is increased, the value of R_0 will also increase. Meanwhile, the negative sign on the sensitivity index shows that if the parameter value is increased, the value of R_0 will decrease.

Table 3 Sensitivity Index of Parameters

Parameter	Sensitivity Index
B	1
q	−0,175252
η_1	0,0958391
K	−0,283688
η_2	0,406636
A	1
ρ	1
C	$7{,}7 \times 10^{-10}$
K	$4{,}2 \times 10^{-8}$
n	$-1{,}81 \times 10^{-8}$
γ	−0,90009
E	$3{,}6 \times 10^{-8}$
r_1	−0,086539
δ_1	−0,202928
M	−0,123078
r_2	−0,247286
δ_1	−0,00801928
δ_1	−0,148371
A	$-4{,}14 \times 10^{-8}$

Next, the researchers analyze the effects of the disease transmission rate (β), vaccination (γ), and fraction of fast TB progression (ρ) on basic reproduction number. The β value is changed with the fixed value of other parameters. Then, the basic reproduction number also changes. If it is β=6,55, it is R_0 = 0,064. If it is β=8, it is R_0 = 0,079. Then if it is β=10, it will be R_0 = 0,098. This show that the greater the β value is, it will increase the basic reproductive number. The simulation can see in Figure 2. It shows that the greater β value is, the slower disease-free state will be. Each line will go to the point of remaining disease-free because the basic reproductive number values obtained are still at the level of R_0<1.

The same thing also happens in applying ρ value which has a positive value of sensitivity index in Table 3. It is different with γ value. When γ is increased, the basic reproduction number will decrease. This happens because of the gamma sensitivity index value in Table 3. If it is γ=0,02 it will be R_0=0,037. If there is γ=0,08, it will be R_0=0,139. Then, if it is γ=0,2, it will be R_0=0,06.

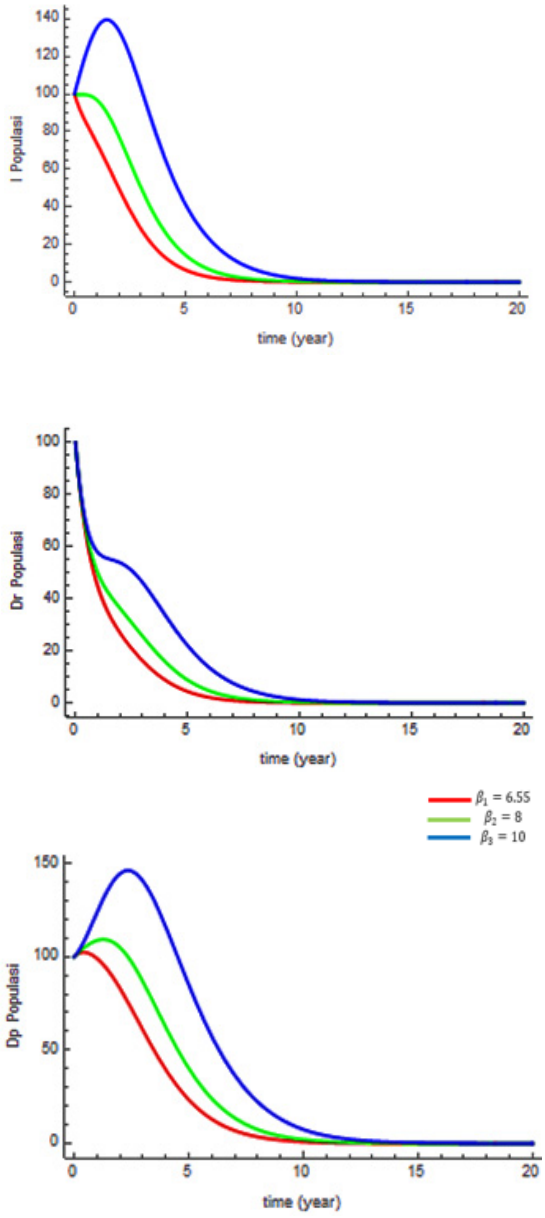
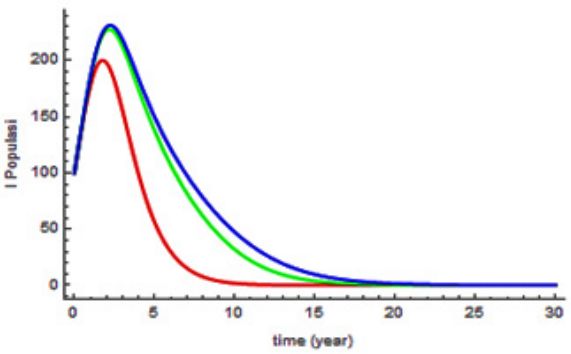


Figure 2 Effects of Disease Transmission Rate on Basic Reproduction Number



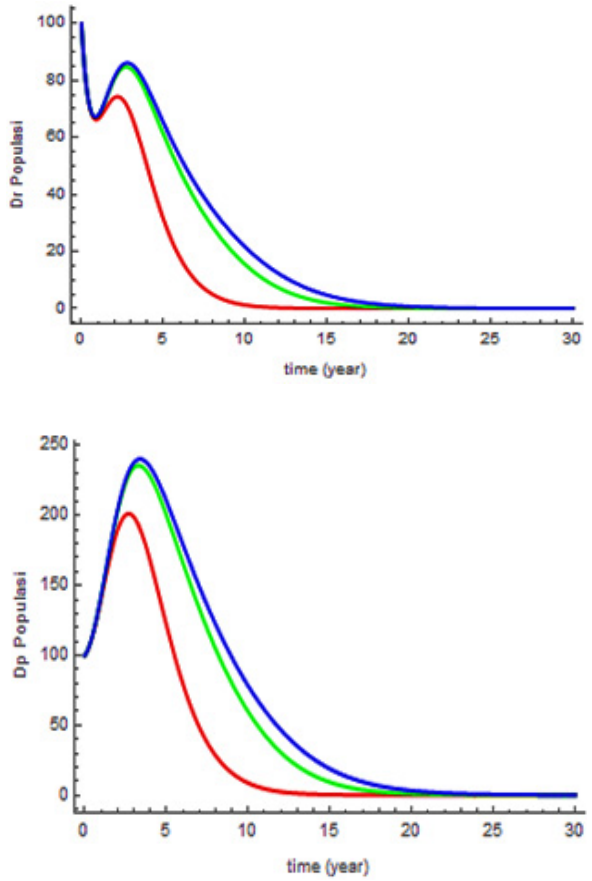


Figure 3 Influence of Vaccination

Figure 3 shows that that if γ value increases, it will quickly reach the point of being free of disease. Each line will go to the point of remaining disease-free because the basic reproduction number is still at a level of R_0<1. Based on the results of the sensitivity analysis, three parameters have a significant influence on the transmission of TB. These three parameters are the rate of transmission of disease, the individual who has fast progression on TB, and the rate of the vaccine.

IV. CONCLUSIONS

This research is a modification of the mathematical model from the transmission of TB by adding a vaccine. Vaccination is done by adding vaccine compartments to individuals who are given the vaccine in the susceptible compartment. This model is divided into nine different groups. Two fixed points of the model are disease-free equilibrium and disease-endemic equilibrium. Disease-free equilibrium is locally stable asymptotic if the basic reproduction number is less than unity. Then, disease-endemic equilibrium is locally stable asymptotic if the basic reproduction number is more than unity. The exogenous re-infection are ignored (b_1, b_2, b_3 = 0) because of the backward bifurcation phenomenon. Sensitivity analysis shows that the top three parameters that have influences of TB are the transmission rate (β), a fraction of fast TB progression (ρ), and the rate of vaccinating (γ). Thus, it is important to give the vaccine to prevent the spread of TB. This research can be continued by using real data in a certain area. The future research can consider the effect of the environment on the spread of disease.

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