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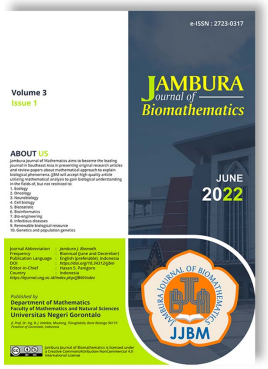

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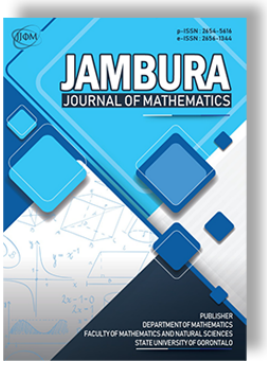

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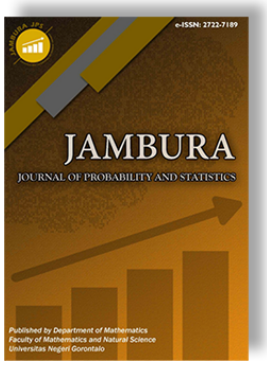

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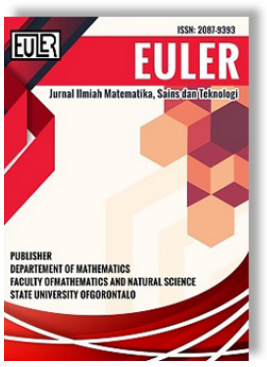

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Research Article

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Dynamical System for Tuberculosis Outbreak with Vaccination Treatment and Different Interventions on the Burden of Drug Resistance

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ABSTRACT. *Tuberculosis, a highly contagious and lethal infectious disease, remains a global health concern with challenging treatment options. To combat its widespread impact, prevention strategies, such as vaccination, are imperative. This research focuses on developing a mathematical model with the addition of a vaccination compartment to understand the dynamics of tuberculosis transmission with vaccination. Subsequently, the study proceeds to identify the equilibrium points and calculate the basic reproduction number ($\Re_0$). Following this, a comprehensive stability analysis is conducted, and a numerical simulation is executed to observe the population dynamics. Furthermore, parameter sensitivity analysis is undertaken to assess the extent to which these parameters impact $\Re_0$. Preliminary analysis shows that the modified model has a solution that remains in the non-negative and bounded region. Furthermore, model analysis reveals two equilibrium points, namely the disease-free equilibrium and the endemic equilibrium. It is established that the disease-free equilibrium exhibits local asymptotic stability when $\Re_0 < 1$. Remarkably, the numerical simulation aligns with the analytical findings, reinforcing the robustness of the results. Analysis of the sensitivity of the parameter to $\Re_0$ shows that the parameter of the proportion of susceptible population entering the vaccination class has a significant effect on the value of $\Re_0$. The parameter of proportion of susceptible population entering the vaccination class has a negative effect on the number of populations with infection.*

1. Introduction

Tuberculosis is a globally prevalent infectious disease characterized by a high mortality rate [1–3]. Tuberculosis (TB) is a persistent health condition triggered by the bacterium Mycobacterium tuberculosis [4–7] which is transmitted through direct contact with patients with active Tuberculosis when coughing, sneezing, screaming, or talking [8, 9]. The initial dynamics of tuberculosis infection is very difficult to detect and most are asymptomatic [10].

Tuberculosis remains a significant global threat to human health as one of the primary infectious diseases [9]. This is because Tuberculosis is difficult to cure [4] and easily creates resistance to multi-drugs [9]. In addition, the availability of TB drugs is still very limited and the cost of treatment is still very high [11, 12]. Therefore, it is important to take preventive and control measures against the transmission of tuberculosis such as vaccination [13–15].

It is important to conduct research on the mathematical modeling of the spread of Tuberculosis to determine the effect of vaccination on the population dynamics of Tuberculosis. Mathematical modeling of Tuberculosis itself has been carried out by many experts, such as Das et al. [7] examined the transmission model for the spread of Tuberculosis with time subordinate boundaries. Avilov et al. [10] assess the dynamics of the initial phases of active pulmonary tuberculosis using contemporary routine notification data.

Furthermore, Xu et al. [16] conducted research by dividing the population into drug-sensitive and drug-resistant populations. In this research, total population is divided into seven compartments, namely Susceptible population (S), drug-sensitive Exposed population (E_s), drug-sensitive Infected population (I_s), drug-sensitive Recovered population (R_s), drug-resistant Exposed population (E_r), drug-resistant Infected population (I_r), and drug-resistant Recovered population (R_s). Mishra and Srivastava [17] and Zhang et al. [9] who studied the effect of vaccination on the population dynamics of tuberculosis.

2. Methods

In this section, the mathematical models of the spread of Tuberculosis from previous researchers will be presented. Then will be explained about the Mathematical model of the spread of Tuberculosis disease used in this study.

2.1. Mathematical Models

The model in this study is the modified result of Xu et al. [16] by adding the Vaccination compartment based on the Mishra

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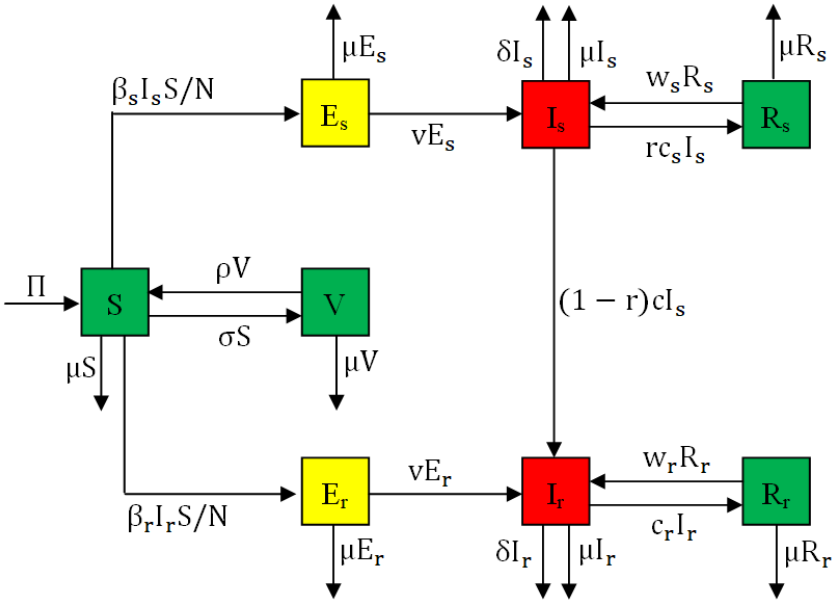

Figure 1. Modified Tuberculosis Spread Model Scheme

and Srivastava [17] and Zhang et al. [9]. So that in this study a model of the spread of Tuberculosis was obtained as can be seen in Figure 1. In this research, a more complex model was obtained compared to previous models. So that the model formed can better describe the effect of vaccination on the population dynamics of the spread of Tuberculosis. In this model, total population is divided into eight compartments, namely Susceptible population (S), Vaccinated population (V), drug-sensitive Exposed population (E_s), drug-sensitive Infected population (I_s), drug-sensitive Recovered population (R_s), drug-resistant Exposed population (E_r), drug-resistant Infected population (I_r), and drug-resistant Recovered population (R_s).

The diagram in Figure 1 corresponds to the following set of non-linear differential equations, representing the model:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi + \rho V - \frac{\beta_s I_s S}{N} - \frac{\beta_r I_r S}{N} - \sigma S - \mu S,\\
\frac{dV}{dt} &= \sigma S - \rho V - \mu V,\\
\frac{dE_s}{dt} &= \frac{\beta_s I_s S}{N} - \nu E_s - \mu E_s,\\
\frac{dI_s}{dt} &= \nu E_s + w_s R_s - (1-r)cI_s - rc_s I_s - \delta I_s - \mu I_s,\\
\frac{dR_s}{dt} &= rc_s I_s - w_s R_s - \mu R_s,\\
\frac{dE_r}{dt} &= \frac{\beta_r I_r S}{N} - \nu E_r - \mu E_r,\\
\frac{dI_r}{dt} &= \nu E_r + w_r R_r + (1-r)cI_s - c_r I_r - \delta I_r - \mu I_r,\\
\frac{dR_r}{dt} &= c_r I_r - w_r R_r - \mu R_r.
\end{aligned} \tag{1}$$

Parameter values used in this research can be seen in Table 1.

2.2. Positivity and Boundedness of Solutions

In this section, we will be proved that the model (1) has a non-negative and bounded solution region.

Theorem 1. *Set* $D = \left\{(S, V, E_s, I_s, R_s, E_r, I_r, R_r) \in \mathbb{R}^8_+ \mid 0 < N < \frac{\Pi}{\mu} + N_0\right\}$ *is the non-negative and bounded solution region of the model (1) where* N_0 *is the total population at* $t = 0$ *and* $N = S + V + E_s + I_s + R_s + E_r + I_r + R_r$.

Proof. Let t_f as in eq. (2) below:

$$\begin{aligned}
t_f = sup\Big\{t > 0 \mid S(t) > 0, V(t) > 0, E_s(t) > 0, I_s(t) > 0,\\
R_s(t) > 0, E_r(t) > 0, I_r(t) > 0, R_r(t) > 0 \in [0, t]\Big\}.
\end{aligned} \tag{2}$$

Hence, $t_f > 0$. The first equation in the model (1), can be written as follows

$$\begin{aligned}
\frac{dS}{dt} = \Pi + \rho V - \frac{\beta_s I_s S}{N} - \frac{\beta_r I_r S}{N} &\geq \Pi - \frac{\beta_s I_s S}{N} - \frac{\beta_r I_r S}{N}\\
-\sigma S - \mu S &\quad -\sigma S - \mu S
\end{aligned}$$

or

$$\frac{dS}{dt} \geq \Pi - \varphi S, \tag{3}$$

where

$$\varphi = \frac{\beta_s I_s}{N} + \frac{\beta_r I_r}{N} + \sigma + \mu.$$

By utilizing the integrating factor method [19, 20], eq. (3) can be represented as:

$$\frac{d}{dt}\left(S(t)\exp\left[\int_0^t \varphi(w)dw\right]\right) \geq \Pi \exp\left[\int_0^t \varphi(w)dw\right]$$

Hence,

$$S(t_f)\exp\left[\int_0^{t_f}\varphi(w)dw\right] - S(0) \geq \Pi\int_0^{t_f}\left(\exp\left[\int_0^{\theta}\varphi(w)dw\right]\right)d\theta$$

Table 1. Parameter Values in Tuberculosis Infection Model

Parameter	Description	Value	Source
Π	Monthly births	1,379,167	[16]
β_s	DS-TB transmission rate	0.6356	[16]
β_r	DR-TB transmission rate	0.3458	[16]
σ	The vaccination class receives a portion of the susceptible population	$0 < \sigma < 1$	Assumed
ρ	The rate at which individuals transition from the vaccination class to the susceptible class	$0 < \rho < 1$	Assumed
ν	Progression rate	7.99×10^{-5}	[16]
w_s	DS-TB relapse rate	3.90×10^{-4}	[16]
w_r	DR-TB relapse rate	1.96×10^{-4}	[16]
c	DS-TB to DR-TB conversion rate	0.0376	[16]
c_s	Cure rate of DS-TB	0.1299	[16]
c_r	Cure rate of DR-TB	0.0493	[16]
r	Proportion of DS-TB cured cases	0.85	[18]
δ	Monthly mortality rate due to TB	4.17×10^{-3}	[18]
μ	Monthly natural mortality rate	5.83×10^{-4}	[16]

so that

$$\begin{aligned} S(t_f) \quad &\geq \quad S(0)\exp\left[-\int_0^{t_f}\varphi(w)dw\right] + \Pi\exp\left[-\int_0^{t_f}\varphi(w)dw\right] \quad > \quad 0. \\ &\times \int_0^{t_f}\left(\exp\int_0^{\theta}\varphi(w)dw\right)d\theta \end{aligned}$$

In the same way, the remaining state variables $V(t) \geq 0$,$E_s(t) \geq 0$,$I_s(t) \geq 0$,$R_s(t) \geq 0$,$E_r(t) \geq 0$,$I_r(t) \geq 0$, and $R_r(t) \geq 0$ for all time $t > 0$. Hence, all the solutions of model (1) remain positive for all non-negative initial conditions.

Then, let $N = S + V + E_s + I_s + R_s + E_r + I_r + R_r$. The initial values at $t = 0$ for each population are $S(0) = S_0$, $V(0) = V_0$, $E_s(0) = E_{s0}$, $I_s(0) = I_{s0}$, $R_s(0) = R_{s0}$, $E_r(0) = E_{r0}$, $I_r(0) = I_{r0}$, and $R_r(0) = R_{r0}$.

The sum of the equations in the model (1) gives the change in the total population N over time t as follows:

$$\frac{dN}{dt} = \Pi - \mu N - \delta(I_s + I_r). \tag{4}$$

Since $\delta > 0$ and $I_s(t), I_r(t) \geq 0$, then eq. (4) can be written as

$$\begin{aligned} \frac{dN}{dt} \quad &\leq \quad \Pi - \mu N, \\ \frac{dN}{dt} + \mu N \quad &\leq \quad \Pi. \end{aligned}$$

Let c_1 as a positive constant such that

$$\frac{dN}{dt} + \mu N = \Pi - c_1.$$

By employing the integrating factor method with the initial value $N(0) = N_0$, is obtained as

$$N = \frac{\Pi}{\mu} + N_0 e^{-\mu t} - \frac{\Pi}{\mu}e^{-\mu t} - \frac{c_1}{\mu}(1 - e^{-\mu t}).$$

Since $0 \leq e^{-\mu t} \leq 1$ for each $t \geq 0$ and Π, μ, $c_1 > 0$, is obtained as

$$N \leq \frac{\Pi}{\mu} + N_0.$$

Since $S(t)$,$V(t)$,$E_s(t)$, $I_s(t)$,$R_s(t)$,$E_r(t)$, $I_r(t)$,$R_r(t) \geq 0$, then for each $t \geq 0$ is obtained as

$$0 \leq N \leq \frac{\Pi}{\mu} + N_0.$$

So, the solution region of the model (1) is non-negative and bounded. □

A non-negative and bounded solution region indicates that the population number in each compartment at time $t > 0$ is always non-negative and finite. This shows that the model that has been established is biologically reasonable.

3. Results and Discussion

In this section, we will explain about equilibrium points, basic reproduction number, equilibrium stability analysis, and parameter sensitivity analysis.

3.1. Equilibrium Points

Within the framework of the system defined in model (1), two distinct types of equilibrium points emerge, specifically the disease-free equilibrium, which is characterized by the conditions where $E_s = I_s = E_r = I_r = 0$ and the endemic equilibrium, which is characterized by the conditions where $E_s \neq 0$, $I_s \neq 0$, $E_r \neq 0$ and $I_r \neq 0$.

The disease-free equilibrium signifies a scenario in which all individuals within a specific population are in a healthy state, indicating the absence of the disease within that population [21, 22]. From the model (1), a disease-free equilibrium is obtained

$$T^0(S, V, E_s, I_s, R_s, E_r, I_r, R_r) = (S^0, V^0, 0, 0, 0, 0, 0, 0)$$

where

$$S^0 = \frac{\Pi(\mu + \rho)}{\mu(\mu + \rho + \sigma)} \text{ and } V^0 = \frac{\Pi\sigma}{\mu(\mu + \rho + \sigma)}.$$

The endemic equilibrium represents a situation in which there are still individuals within a given population who remain infected, indicating that the disease has not been eradicated from that population [21, 22]. From the model (1), the endemic equilibrum is obtained

$$\begin{aligned} S^* &= \frac{N(\Pi + \rho V)}{\beta_r I_r + \beta_s I_s + N(\rho + \mu)}, \\ V^* &= \frac{\rho S}{\rho + \mu}, \\ E_s^* &= \frac{\beta_s S I_s}{N(\nu + \mu)}, \\ I_s^* &= \frac{\nu E_s + w_s R_s}{(1 - c)r + c_s r + \delta + \mu}, \end{aligned}$$

$$
\begin{aligned}
R_s^* &= \frac{c_s r I_s}{w_s + \mu},\\
E_r^* &= \frac{\beta_r S I_r}{N(\nu + \mu)},\\
I_r^* &= \frac{(1-r)cI_s + \nu E_r + w_r R_r}{c_r + \delta + \mu},\\
R_r^* &= \frac{c_r I_r}{w_r + \mu}.
\end{aligned}
$$

3.2. Basic Reproduction Number

The basic reproduction number, often denoted as $(\Re_0)$, quantifies the average number of new infections generated by a single infected individual over a unit of time within a completely susceptible population. The computation of this crucial epidemiological metric involves employing the next generation matrix method [23, 24]. The calculation of the basic reproduction number focuses exclusively on the sequence of subpopulations responsible for transmitting infections [25], namely E_s, I_s, E_r and I_r as follows:

$$
\begin{aligned}
\frac{dE_s}{dt} &= \frac{\beta_s I_s S}{N} - \nu E_s - \mu E_s,\\
\frac{dI_s}{dt} &= \nu E_s + w_s R_s - (1-r)cI_s - rc_s I_s - \delta I_s - \mu I_s,\\
\frac{dE_r}{dt} &= \frac{\beta_r I_r S}{N} - \nu E_r - \mu E_r,\\
\frac{dI_r}{dt} &= \nu E_r + w_r R_r + (1-r)cI_s - c_r I_r - \delta I_r - \mu I_r.
\end{aligned}
\tag{5}
$$

Based on the system of eq. (5), we obtain vectors F_i and V_i expressing the production of new-infection in compartment and transition part of the infectious compartment [17, 19], respectively as follows:

$$
\begin{aligned}
F_i &= \begin{pmatrix} \frac{\beta_s I_s S}{N} \\ 0 \\ \frac{\beta_r I_r S}{N} \\ 0 \end{pmatrix},\\
V_i &= \begin{pmatrix} \nu E_s + \mu E_s \\ -\nu E_s - w_s R_s + (1-r)cI_s + rc_s I_s + \delta I_s + \mu I_s \\ \nu E_r + \mu E_r \\ -\nu E_r - w_r R_r - (1-r)cI_s + c_r I_r + \delta I_r + \mu I_r \end{pmatrix}.
\end{aligned}
$$

Next, to determine the basic reproduction number $(\Re_0)$, a matrix F and V is formed which is evaluated at the disease-free equilibrium T^0. So that the matrices F and V are obtained as follows:

$$
\begin{aligned}
F &= \begin{pmatrix} 0 & \Omega\beta_s & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \Omega\beta_r \\ 0 & 0 & 0 & 0 \end{pmatrix},\\
V &= \begin{pmatrix} k_1 & 0 & 0 & 0 \\ -\nu & k_2 & 0 & 0 \\ 0 & 0 & k_3 & 0 \\ 0 & -(1-r)c & -\nu & k_4 \end{pmatrix}.
\end{aligned}
$$

where

$$
\begin{aligned}
\Omega &= \frac{\rho + \mu}{\sigma + \rho + \mu},\\
k_1 &= \nu + \mu,\\
k_2 &= (1-r)c + rc_s + \delta + \mu,\\
k_3 &= k_1 = \nu + \mu,\\
k_4 &= c_r + \delta + \mu.
\end{aligned}
$$

Then we get a matrix G, with $G = FV^{-1}$ as follows:

$$
\begin{aligned}
G &= \begin{pmatrix} 0 & \Omega\beta_s & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \Omega\beta_r \\ 0 & 0 & 0 & 0 \end{pmatrix} \cdot \begin{pmatrix} \frac{1}{k_1} & 0 & 0 & 0 \\ \frac{\nu}{k_1 k_2} & \frac{1}{k_2} & 0 & 0 \\ 0 & 0 & \frac{1}{k_3} & 0 \\ \frac{(1-r)c\nu}{k_1 k_2 k_4} & \frac{(1-r)c}{k_2 k_4} & \frac{\nu}{k_3 k_4} & \frac{1}{k_4} \end{pmatrix},\\
G &= \begin{pmatrix} \frac{\Omega\nu\beta_s}{k_1 k_2} & \frac{\Omega\beta_s}{k_2} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{(1-r)c\nu\Omega\beta_r}{k_1 k_2 k_4} & \frac{(1-r)c\Omega\beta_r}{k_2 k_4} & \frac{\nu\Omega\beta_r}{k_3 k_4} & \frac{\Omega\beta_r}{k_4} \\ 0 & 0 & 0 & 0 \end{pmatrix}.
\end{aligned}
$$

Based on the matrix G above, we get the spectral radius of a matrix G, as follows:

$$
\Re_0 = \sqrt{\Re_0^s \cdot \Re_0^r} \tag{6}
$$

where

$$
\Re_0^s = \frac{\Omega\nu\beta_s}{k_1 k_2} \text{ and } \Re_0^r = \frac{\Omega\nu\beta_r}{k_3 k_4}.
$$

3.3. Stability Analysis

In this section, we will present the proof of Theorem 2 which is the stability criterion for the disease-free equilibrium T^0.

Theorem 2. *If $\Re_0 < 1$ then the disease-free equilibrium T^0 for the model (1) is locally asymtotically stable.*

Proof. The stability property of $T^0(S, V, E_s, I_s, R_s, E_r, I_r, R_r) = (S^0, V^0, 0, 0, 0, 0, 0, 0)$ can be known by conducting linearization on model (1) around T^0, so that the Jacobian matrix for disease-free equilibrium T^0 is obtained as follows:

$$
J_{T^0} = \begin{pmatrix} J_{11} & J_{12} & 0 & J_{14} & 0 & 0 & J_{17} & 0 \\ J_{21} & J_{22} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & J_{33} & J_{34} & 0 & 0 & 0 & 0 \\ 0 & 0 & J_{43} & J_{44} & J_{45} & 0 & 0 & 0 \\ 0 & 0 & 0 & J_{54} & J_{55} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & J_{66} & J_{67} & 0 \\ 0 & 0 & 0 & J_{74} & 0 & J_{76} & J_{77} & J_{78} \\ 0 & 0 & 0 & 0 & 0 & 0 & J_{87} & J_{88} \end{pmatrix}
$$

where

$$\begin{aligned}
J_{11} &= -(\sigma+\mu), & J_{54} &= rc_s,\\
J_{12} &= \rho, & J_{55} &= -(w_s+\mu),\\
J_{14} &= -\frac{\beta_s(\rho+\mu)}{\sigma+\rho+\mu}, & J_{66} &= -k_1 = -k_3,\\
J_{17} &= -\frac{\beta_r(\rho+\mu)}{\sigma+\rho+\mu}, & J_{67} &= \frac{\beta_r(\rho+\mu)}{\sigma+\rho+\mu},\\
J_{21} &= \sigma, & J_{74} &= (1-r)c,\\
J_{22} &= -(\rho+\mu), & J_{76} &= \nu,\\
J_{33} &= -k_1 = -k_3, & J_{77} &= -k_4,\\
J_{34} &= \frac{\beta_s(\rho+\mu)}{\sigma+\rho+\mu}, & J_{78} &= w_r,\\
J_{43} &= \nu, & J_{87} &= c_r,\\
J_{44} &= -k_2, & J_{88} &= -(w_r+\mu).\\
J_{45} &= w_s,
\end{aligned}$$

Eigenvalues for disease-free equilibrium T^0 are obtained by means

$$\begin{aligned}
0 &= |J_{T^0} - \lambda I|,\\
0 &= \begin{vmatrix}
J_{11} & J_{12} & 0 & J_{14} & 0 & 0 & J_{17} & 0\\
J_{21} & J_{22} & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & J_{33} & J_{34} & 0 & 0 & 0 & 0\\
0 & 0 & J_{43} & J_{44} & J_{45} & 0 & 0 & 0\\
0 & 0 & 0 & J_{54} & J_{55} & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & J_{66} & J_{67} & 0\\
0 & 0 & 0 & J_{74} & 0 & J_{76} & J_{77} & J_{78}\\
0 & 0 & 0 & 0 & 0 & 0 & J_{87} & J_{88}
\end{vmatrix}\\
&\quad - \begin{vmatrix}
\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & \lambda & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & \lambda & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & \lambda & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & \lambda & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & \lambda & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & \lambda & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \lambda
\end{vmatrix},
\end{aligned}$$

so that the characteristic equation is obtained as follows:

$$J_1 \cdot J_2 \cdot J_3 = 0$$

where

$$\begin{aligned}
J_1 &= \lambda^2 - (J_{11}+J_{22})\lambda + (J_{11}J_{22} - J_{21}J_{22}), \qquad (7)\\
J_2 &= \lambda^3 - (J_{33}+J_{44}+J_{55})\lambda^2 + (J_{33}J_{44} + J_{33}J_{55}\\
&\quad + J_{44}J_{55} - J_{34}J_{43} - J_{45}J_{54})\lambda + (J_{33}J_{45}J_{54}\\
&\quad + J_{34}J_{43}J_{55} - J_{33}J_{44}J_{55}), \qquad (8)\\
J_3 &= \lambda^3 - (J_{66}+J_{77}+J_{88})\lambda^2 + (J_{66}J_{77} + J_{66}J_{88}\\
&\quad + J_{77}J_{88} - J_{67}J_{76} - J_{78}J_{87})\lambda + (J_{66}J_{78}J_{87}\\
&\quad + J_{67}J_{76}J_{88} - J_{66}J_{77}J_{88}). \qquad (9)
\end{aligned}$$

Based on equation (7) is obtained $\lambda_1 + \lambda_2 = J_{11} + J_{22} = -(\sigma + \rho + 2\mu)$ and $\lambda_1 * \lambda_2 = J_{11}J_{22} - J_{21}J_{22} = (\sigma+\mu)(\rho+\mu) + \sigma(\rho+\mu)$. So it can be concluded that $\lambda_1 < 0$ and $\lambda_2 < 0$.

Furthermore, λ_3, λ_4 and λ_5 are obtained by solving equation (8) as follows:

$$J_2 = (\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3) = 0 \qquad (10)$$

where

$$\begin{aligned}
a_1 &= -(J_{33}+J_{44}+J_{55})\\
&= k_1 + k_2 + (w_s+\mu),\\
a_2 &= (J_{66}J_{77} + J_{66}J_{88} + J_{77}J_{88} - J_{67}J_{76} - J_{78}J_{87})\\
&= (k_3+k_4)(w_r+\mu) + (1-\Re_0^r)k_3k_4 - w_rc_r,\\
a_3 &= (J_{33}J_{45}J_{54} + J_{34}J_{43}J_{55} - J_{33}J_{44}J_{55})\\
&= -k_1w_src_s + (1-\Re_0^s)k_1k_2(w_s+\mu).
\end{aligned}$$

Based on Routh-Hurwitz criterion [26], eq. (10) at equilibrium T^0 is stable if it satisfies the following stability conditions:

$$a_1 > 0,\ a_3 > 0, \text{ and } a_1a_2 > a_3$$

Since all parameters are positive, then the coefficient a_1 is positive. The coefficient a_3 will be positive when $\Re_0^s < 1$. Furthermore, to show $a_1a_2 > a_3$, the parameter values in Table 1 are used.

Furthermore, λ_6, λ_7 and λ_8 are obtained by solving equation (9) as follows:

$$J_3 = (\lambda^3 + b_1\lambda^2 + b_2\lambda + b_3) = 0 \qquad (11)$$

where

$$\begin{aligned}
b_1 &= J_{66}J_{78}J_{87} + J_{67}J_{76}J_{88} - J_{66}J_{77}J_{88}\\
&= -k_1w_rc_r + (1-\Re_0^r)k_3k_4(w_r+\mu),\\
b_2 &= (J_{66}J_{77} + J_{66}J_{88} + J_{77}J_{88} - J_{67}J_{76} - J_{78}J_{87})\\
&= (k_3+k_4)(w_r+\mu) + (1-\Re_0^r)k_3k_4 - w_rc_r,\\
b_3 &= -(J_{66}+J_{77}+J_{88})\\
&= k_3 + k_4 + (w_r+\mu).
\end{aligned}$$

Based on Routh-Hurwitz criterion [26], eq. (11) at equilibrium T^0 is stable if it satisfies the following stability conditions:

$$b_1 > 0,\ b_3 > 0, \text{ and } b_1b_2 > b_3$$

Since all paramaters are positive, then the coefficient b_3 is positive. The coefficient b_1 will be positive when $\Re_0^r < 1$. Furthermore, to show $b_1b_2 > b_3$, the parameter values in Table 1 are used.

Since $\Re_0^s < 1$ and $\Re_0^r < 1$, it must be $\Re_0 = \sqrt{\Re_0^s \cdot \Re_0^r} < 1$. So, it is proved that the disease-free equilibrium T^0 for the model (1) is locally asymtotically stable if $\Re_0 < 1$. □

3.4. Numerical Simulations

Numerical simulations are conducted on the adjusted model to illustrate its stability characteristics, with parameter values taken from Table 1. Subsequently, additional numerical simulations are employed to investigate the dynamics of the system and observe its behavior. The initial values used are $S(0) = 721,500,000$, $E_s(0) = 404,950,000$, $I_s(0) = 70,000$, $E_r(0) = 173,550,000$, $I_r(0) = 30,833$ [16] and it is assumed that $V(0) = R_s(0) = R_r(0) = 0$.

The model (1) when $\Re_0 < 1$ has one disease-free equilibrium which can be represented by a numerical solution. Disease-free equilibrium is obtained by using the parameter values in Table 1 with $\Re_0 = 0.466331 < 1$ and disease-free equilibrium $T^0(S = 1.5776 \times 10^9, V = 7.88036 \times 10^8, E_s = 0, I_s = 0,$

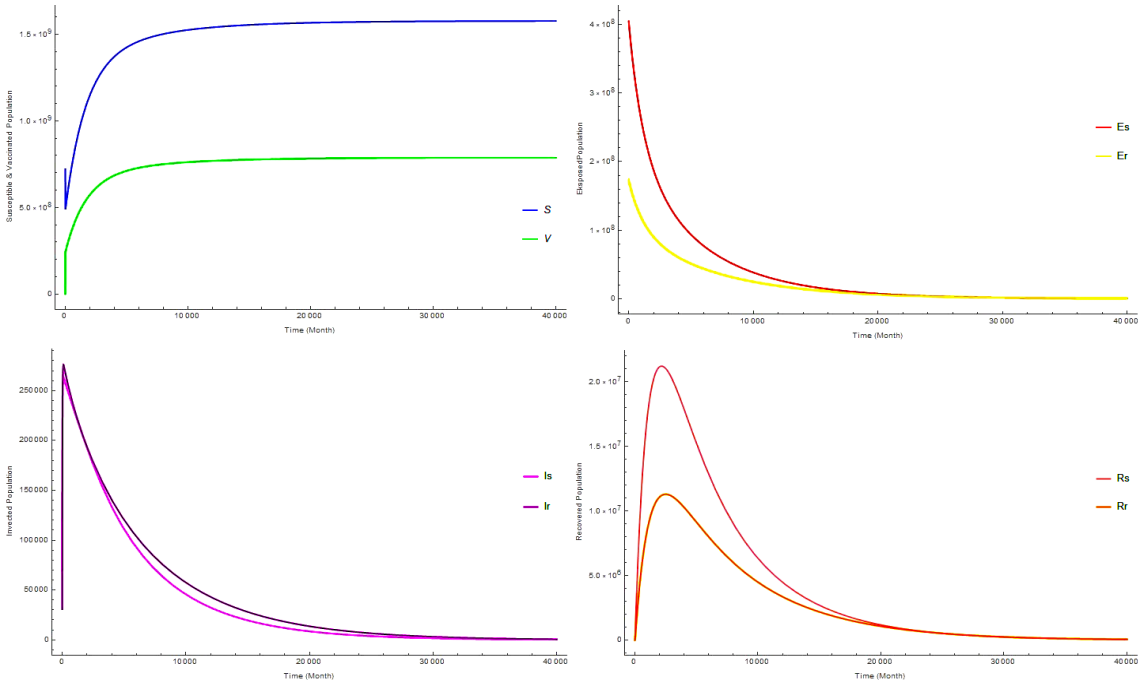

Figure 2. The Population Dynamics at Condition $\Re_0 < 1$

$R_s = 0$, $E_r = 0$, $I_r = 0$, $R_r = 0$). Through linearization and computation of the system described in model (1) around the disease-free equilibrium, the Jacobian matrix and eigenvalues associated with this equilibrium are determined. The observed outcome indicates the stability of the disease-free equilibrium, as all eigenvalues exhibit negativity, ie $\lambda_1 = -0.900583$, $\lambda_2 = -0.121446$, $\lambda_3 = -0.0545744$, $\lambda_4 = -0.00083638$, $\lambda_5 = -0.0007444$, $\lambda_6 = -0.000583$, $\lambda_7 = -0.000176093$ and $\lambda_8 = -0.000161682$.

Population dynamics with Susceptible population (S), Vaccinated population (V), drug-sensitive Exposed population (E_s), drug-sensitive Infected population (I_s), drug-sensitive Recovered population (R_s), drug-resistant Exposed population (E_r), drug-resistant Infected population (I_r), and drug-resistant Recovered population (R_s) towards disease-free equilibrium T^0 as can be seen in Figure 2. The simulation results are in accordance with Theorem 2 that if $\Re_0 < 1$, the disease-free equilibrium is locally asymtotically stable.

3.5. Sensitivity Analysis

The dynamics of tuberculosis transmission within a population are significantly shaped by the values assigned to various parameters. Alterations in these parameter values lead to corresponding changes in simulation outcomes. However, the impact of each parameter varies, contingent upon its sensitivity level. Consequently, a thorough analysis of parameter sensitivity concerning the basic reproduction number $\Re_0$ is imperative. The objective of sensitivity analysis is to identify the parameters exerting the most substantial influence on the value of $\Re_0$. This analysis is executed by evaluating the parameter sensitivity index denoted as $(\gamma_p^{R_0})$.

The basic reproducibility number sensitivity index $\Re_0$ depending on the parameter p is obtained by $\gamma_p^{R_0} = \dfrac{\partial \Re_0}{\partial p} \times \dfrac{p}{\Re_0}$, where $\Re_0$ is the eq. (6) which depends on the parameter models [27, 28]. The parameter values used are the parameter values in Table 1. So that the sensitivity index values are obtained which can be seen in Table 2.

Table 2. Sensitivity Indices of the Model

Parameter	Sensitivity Index
Π	0
β_s	0.5
β_r	0.5
σ	-0.333118
ρ	0.332794
ν	0.879469
w_s	0
w_r	0
c	-0.0233428
c_s	-0.456985
c_r	-0.456034
r	-0.324709
δ	-0.055832
μ	-0.886951

Based on Table 2, it can be concluded that the parameters that have the greatest influence are β_s, β_r, ν, and μ respectively DS-TB transmission rate, DR-TB transmission rate, progression rate, and monthly natural mortality rate. A positive sign in the sensitivity index signifies that an increase in the parameter value will result in a corresponding increase in the $\Re_0$ value. Conversely, a negative sign in the sensitivity index indicates that an increase in the parameter value will lead to a decrease in the $\Re_0$ value. For a comprehensive overview of these sensitivity index values for model parameters, please refer to Figure 3.

In addition, it can be seen that the parameters σ and ρ have a considerable influence. Next, a numerical simulation will be carried out to show the effect of the parameters σ and ρ on populations with Tuberculosis infection.

The effect of proportion of vaccination class receives a por-

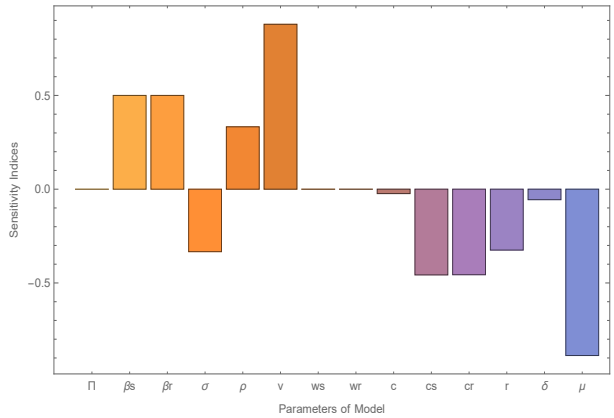

Figure 3. Sensitivity Indices of the Model

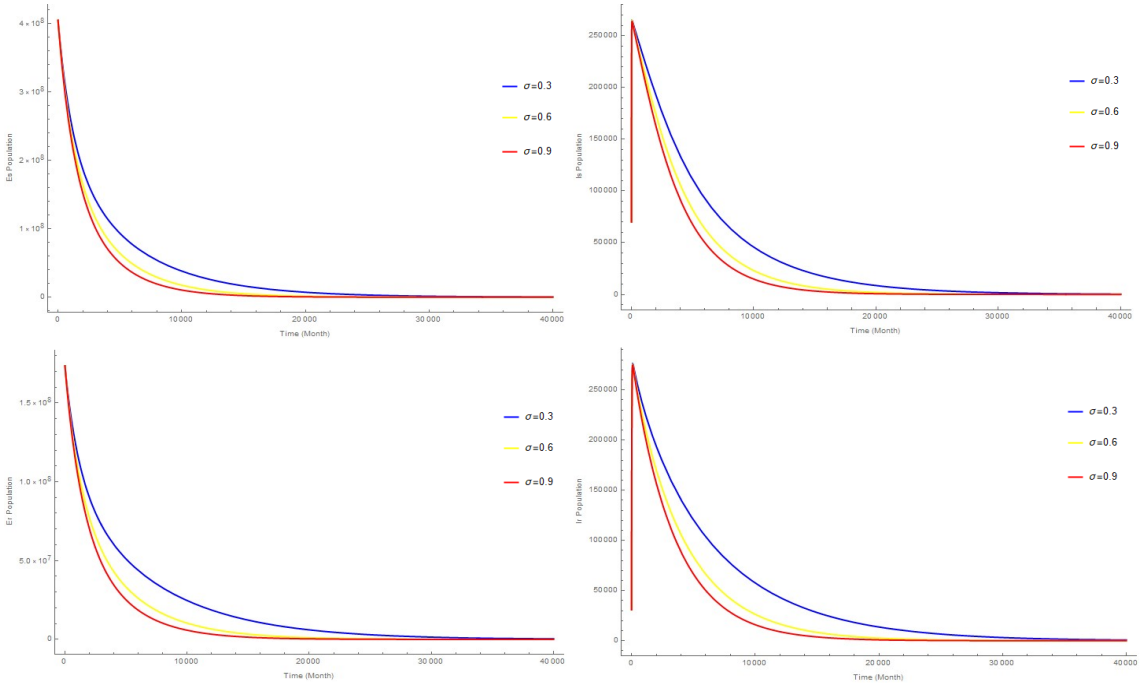

Figure 4. Population Dynamics with Variations in σ Values

tion of the susceptible population (σ) on population dynamics is known using the following equation:

$$\frac{\partial \Re_0}{\partial \sigma} = -\frac{\Omega\nu\sqrt{\dfrac{\beta_s\beta_r}{k_1k_2k_3k_4}}}{(\sigma+\rho+\mu)} \tag{12}$$

Based on eq. (12), $\dfrac{\partial \Re_0}{\partial \sigma} < 0$ means that if vaccination class receives a portion of the susceptible population (σ) increases while the other parameters are held constant, the basic reproduction number $\Re_0$ will decrease. Changes in the value of (σ) that cause changes in the value of $\Re_0$ can be seen in Table 3.

Figure 4 shows that if the vaccination class receives a portion of the susceptible population (σ) is increase, the total population of drug-sensitive Exposed population (E_s), drug-sensitive Infected population (I_s), drug-resistant Exposed population (E_r), and drug-resistant Infected population (I_r) will decrease.

The effect of rate at which individuals transition from the vaccination class to the susceptible class (ρ) on population dynamics is known using the following equation:

Table 3. The Effect of Vaccination Class Receives a Portion of the Susceptible Population (σ) on the Basic Reproduction Number

Parameter σ	Basic Reproduction Number
$\sigma = 0.3$	$\Re_0 = 0.466331$
$\sigma = 0.6$	$\Re_0 = 0.349805$
$\sigma = 0.9$	$\Re_0 = 0.279871$

$$\frac{\partial \Re_0}{\partial \rho} = \frac{\sigma\nu\sqrt{\dfrac{\beta_s\beta_r}{k_1k_2k_3k_4}}}{(\sigma+\rho+\mu)^2} \tag{13}$$

Based on eq. (13), $\dfrac{\partial \Re_0}{\partial \rho} > 0$ means that if rate at which individuals transition from the vaccination class to the susceptible class (ρ) increases while the other parameters are held constant, the

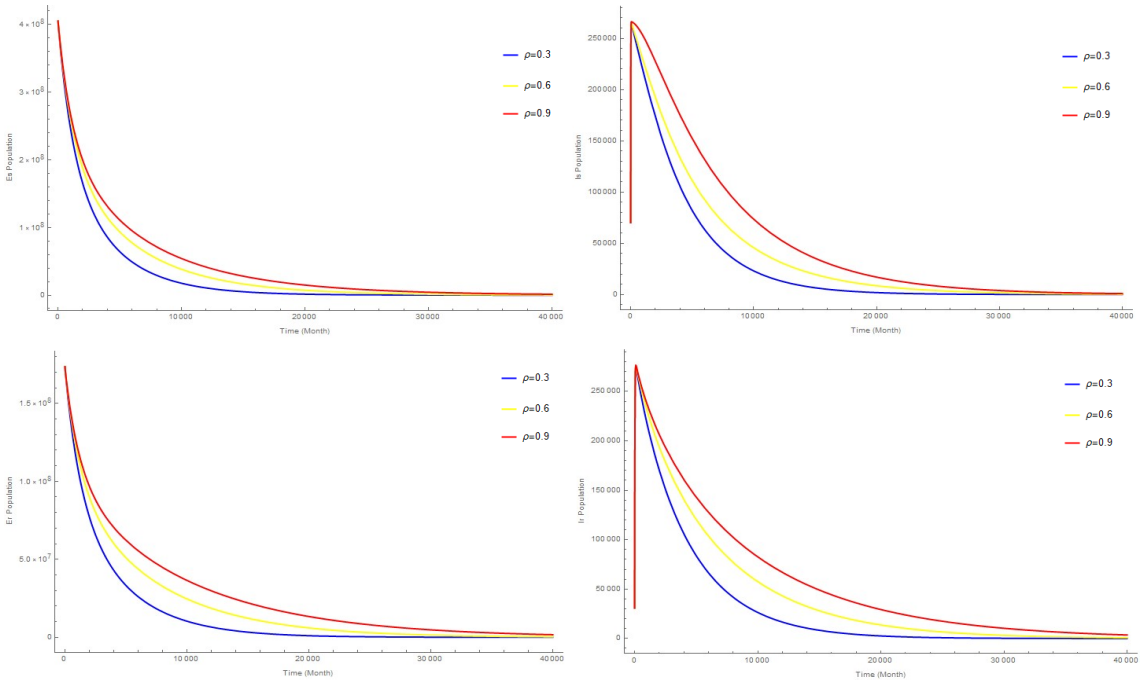

Figure 5. Population Dynamics with Variations in ρ Values

basic reproduction number $\Re_0$ will increase. Changes in the value of ρ that cause changes in the value of $\Re_0$ can be seen in Table 4.

Table 4. The Effect of Rate at Which Individuals Transition from the Vaccination Class to the Susceptible Class (ρ) on the Basic Reproduction Number

Parameter ρ	Basic Reproduction Number
$\rho = 0.3$	$\Re_0 = 0.349975$
$\rho = 0.6$	$\Re_0 = 0.466331$
$\rho = 0.9$	$\Re_0 = 0.524538$

Figure 5 shows that if the value of the rate at which individuals transition from the vaccination class to the susceptible class (ρ) is increase, the total population of drug-sensitive Exposed population (E_s), drug-sensitive Infected population (I_s), drug-resistant Exposed population (E_r), and drug-resistant Infected population (I_r) will increase.

4. Conclusion

This study involves the adaptation of an existing mathematical model for tuberculosis transmission, incorporating vaccination for susceptible individuals. The resultant model successfully characterizes the tuberculosis spread dynamics. The analysis conducted on this modified model reveals the presence of two equilibrium points, namely the disease-free equilibrium and the endemic equilibrium. Notably, the disease-free equilibrium is proven to be asymptotically stable when the basic reproduction number is less than one. Furthermore, the numerical simulations of population dynamics consistently corroborate the stability of the disease-free equilibrium.

Sensitivity analysis produces parameters β_s, β_r, ν, and μ with the highest absolute value of the sensitivity index. Then a numerical simulation is carried out on parameter σ and parameter ρ. Proportion of vaccination class receives a portion of the susceptible population (σ) has a significant effect on the total population of drug-sensitive Exposed population (E_s), drug-sensitive Infected population (I_s), drug-resistant Exposed population (E_r), and drug-resistant Infected population (I_r). If the value of σ is increased, then the total population of drug-sensitive Exposed population (E_s), drug-sensitive Infected population (I_s), drug-resistant Exposed population (E_r), and drug-resistant Infected population (I_r) will decrease.

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