Available online at
https://mijuitm.com.my

e-ISSN: 2735-0703

Mathematical Sciences and Informatics Journal 6(2) 2025, 81 – 96.

Mathematical Sciences and Informatics Journal

Mathematical Modelling of Tuberculosis Disease Spread with Multidrug Resistance Effects

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ARTICLE INFO

Article history:
Received 10 August 2025
Revised 3 September 2025
Accepted 16 September 2025
Online first
Published 31 October 2025

Keywords:
Tuberculosis
MDR-TB
SVEITR
SVEITResR
Runge-Kutta

DOI:
10.24191/mij.v6i2.6245

ABSTRACT

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis, which affects the lungs and other organs. In East Java, there were 87,048 TB cases, and only 53% of regions achieved the 90% treatment success target. A major challenge in TB control is drug resistance, including Multidrug-Resistant Tuberculosis (MDR-TB). Prevention is implemented through BCG vaccination, while treatment is administered using anti-tuberculosis drugs. This research models the spread of tuberculosis in East Java using two models, SVEITR (without resistance) and SVEITResR (with resistance), to analyse the pattern of disease spread based on data obtained from the East Java Provincial Health Office. The basic reproductive number (R_0) is calculated using the next-generation method, and stability analysis is conducted at the Disease-Free Equilibrium (DFE) and Endemic Equilibrium (EE) to test the asymptotic stability of disease transmission The analysis of the SVEITResR mathematical model (R_0= 1.0987) shows it has a lower basic reproduction number than the SVEITR model (R_0= 1.3007.). Both models indicate that the spread of tuberculosis in the East Java region has the potential to cause an outbreak. Numerical simulations using the fourth-order Runge-Kutta method project a significant decrease in the number of exposed individuals after 2024, while the number of infected individuals is expected to increase until 2025 before reaching a stable condition thereafter. Vaccination and first and second-line treatment effectively reduce exposure to infection and increase cure rates over time.

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis, which infects the respiratory tract and spreads through airborne droplets when a person coughs, sneezes or talks. It usually begins with the lungs and can extend to the brain, skin, bones, and lymph nodes. If left untreated, TB

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https://doi.org/10.24191/mij.v6i2.6245

weakens the immune system and may be fatal, making it a serious health problem with far-reaching impacts (Rahmawati et al., 2024).

In 2023, Indonesia recorded the second-highest number of tuberculosis (TB) cases in the world after India (1,060,000 cases and 134,000 deaths, about 10% of global cases) (World Health Organization, 2023). One region in Indonesia that has drawn particular attention is the East Java Province, which recorded 87,048 cases up from 78,799 cases in 2022, with a low treatment success rate of 53% of districts not reaching the 90% treatment success target. Surabaya, Sidoarjo, and Jember are the areas with the highest cases, dominated by men (56%) compared to women (44%), largely due to risk factors such as smoking and alcohol use (Dinkes Jatim, 2023).

TB treatment success rates are assessed based on the percentage of patients who recover and complete treatment. In 2023, the TB treatment success rate in Indonesia was recorded at 86.5%, below the 90% target of the Ministry of Health. Complicated the resistance of Mycobacterium tuberculosis bacteria to anti-tuberculosis drugs such as isoniazid and rifampicin caused irregular treatment, bacterial mutations, and patient immunity (Kemenkes RI, 2023). This resistance will hamper treatment in cases of MDR-TB and XDR-TB, which require more complex treatment with a higher risk of failure. Controlling TB, including MDR-TB, requires a comprehensive approach such as administering the BCG vaccine to infants (Vyawahare et al., 2023). The spread of TB and the impact of MDR-TB in a population will be modelled as an epidemiological mathematical model. This model simulates the spread of disease by considering factors such as transmission rate, treatment effectiveness, vaccination, and drug resistance.

Classical epidemiological models SIR (Susceptible, Infected, Recovered) will analyse the dynamics of the spread of TB disease by assuming that individuals infected with TB can recover directly (Ergen et al., 2015). The SITR (Susceptible, Infected, Treatment, Recovered) model adds a treatment factor with the assumption that infected individuals will receive treatment before recovering (Side et al., 2016). The SVEIL (Susceptible, Vaccinated, Exposed, Infected, Latent) model adds the BCG vaccination factor for newborns by demonstrating the effectiveness of vaccination and treatment in TB control (Mengistu & Witbooi, 2019). The SEIResR (Susceptible, Exposed, Infected, Resistant, Recovered) model to analyse TB transmission including MDR-TB cases due to incomplete treatment resulting in disease outbreaks and an increase in new cases, hence the need for better control strategies (Ronoh et al., 2016).

This research aims to develop the previous epidemiological model of tuberculosis disease into the SVEITResR (Susceptible, Vaccination, Exposed, Infected, Treatment, Resistant, Recovered) model. This model adds the BCG vaccination component from the SVEIL model (Mengistu & Witbooi, 2019), the first-line OAT treatment aspect (isoniazid and rifampicin) from the SITR model (Side et al., 2016), and the concept of MDR-TB and the effectiveness of second-line OAT (fluoroquinolones and aminoglycosides) from the SEIResR model (Ronoh et al., 2016). This development aims to analyse the dynamics of TB spread, including MDR-TB cases, considering the effects of vaccination and various treatment strategies.

2. MATHEMATICAL MODEL OF EPIDEMIOLOGY

The epidemiological model analyses the spread of infectious diseases by dividing the population into several sub-populations. The movement of populations depends on disease characteristics (Yong, 2020). The SVEITR and SVEITResR epidemiological models are used to analyse tuberculosis spread under two scenarios: with and without drug resistance. This research incorporates the effects of vaccination and different treatments in controlling the spread of tuberculosis.

2.1 SVEITR Model

The SVEITR model for modelling TB spread in East Java considers the effectiveness of BCG vaccination in infants as an early preventive measure and first-line treatment using anti-tuberculosis drugs.

https://doi.org/10.24191/mij.v6i2.6245

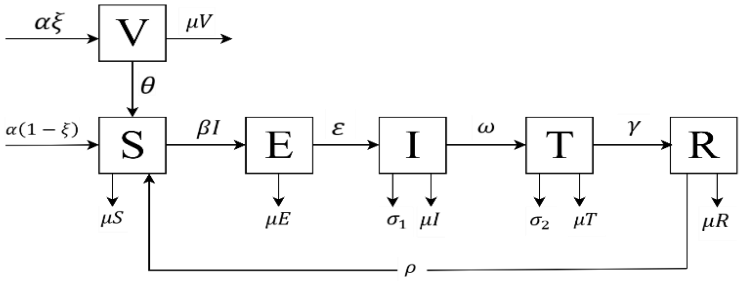

Fig. 1. SVEITR epidemic-model compartment

Based on the compartment diagram in Fig. 1, the SVEITR tuberculosis epidemic model is expressed mathematically as follows:

$$\frac{dS}{dt} = \alpha N(1-\xi) + \theta V + \rho R - \left(\frac{\beta I}{N} + \mu\right) S \tag{1}$$

$$\frac{dV}{dt} = \alpha N\xi - (\theta + \mu)V \tag{2}$$

$$\frac{dE}{dt} = \frac{\beta IS}{N} - (\varepsilon + \mu)E \tag{3}$$

$$\frac{dI}{dt} = \varepsilon E - (\omega + \sigma_1 + \mu)I \tag{4}$$

$$\frac{dT}{dt} = \omega I - (\gamma + \sigma_2 + \mu)T \tag{5}$$

$$\frac{dR}{dt} = \gamma T - (\rho + \mu)R \tag{6}$$

Research data and parameter values were obtained from the East Java Provincial Health Office, including the number of individuals with various TB infection statuses as mortality data, total population deaths, and deaths due to TB in various sub-populations. The parameters of the mathematical model are described in Table 1.

Table 1. Model-parameter estimation

Parameter	Description	Value	Parameter	Description	Value
N	Total population	40,530,954	σ_1	Infection death rate	0.03
α	Birth rate	0.01318	σ_2	Treatment death rate	0.048
β	TB transmission rate	0.8	ξ	Vaccination rate	0.9397
ε	Rate of exposed individuals becoming infected	0.34	ψ	Second-line treatment cure rate	0.51
π	Rate of infections that become resistant	0.1	θ	The rate of vaccination effectiveness decline	0.4
ω	First-line treatment rate	0.5	μ	Natural death rate	0.01387
γ	First-line treatment cure rate	0.892	σ_3	Resistant mortality rate	0.02
δ	Treatment-resistant rate	0.04613	ρ	Susceptible recovery rate	0.05

Source: *East Jawa Provincial Health Office*

https://doi.org/10.24191/mij.v6i2.6245

2.1.1 System Equilibrium Point

The tuberculosis-spread model can be represented through a system of differential equations. The equilibrium condition when the number of subpopulations does not change is determined by setting the right-hand side of each equation to zero. The equilibrium point is reached if the rate of change of each compartment in the system is equal to zero (Alam et al., 2020).

Disease-Free Equilibrium Point

The disease-free condition when there is no spread of tuberculosis in the population, assuming there are no infected individuals ($E = I = T = 0$). These values are substituted into equations (1) to (6) to the disease-free equilibrium point $P_0 = (S_0, V_0, E_0, I_0, T_0, R_0)$ as follows:

$$P_0 = \left(\frac{\alpha N(\theta + \mu - \mu\xi)}{\mu(\theta + \mu)}, \frac{\alpha N\xi}{\theta + \mu}, 0,0,0,0\right) \tag{7}$$

Substituting each parameter value in Table 1, the disease-free system of the SVEITR model is:

$$P_0 = (37.301.726;\ 1.212.907;\ 0;\ 0;\ 0;\ 0) \tag{8}$$

Endemic Equilibrium Point

The endemic condition occurs when infection continues in the system because transmission persists, so the disease remains endemic. The population assumes there are infected individuals ($E \neq I \neq T \neq 0$). These values are substituted into equations (1) to (6) to obtain the endemic equilibrium point $P_1 = (S_1, V_1, E_1, I_1, T_1, R_1)$ as follows:

$$\begin{gathered} P_1 = \frac{N(\varepsilon + \mu)(\omega + \sigma_1 + \mu)}{\beta\varepsilon}, \frac{\alpha N\xi}{\theta + \mu}, \frac{AN(\rho + \mu)(C - \mu D)(\omega + \sigma_1 + \mu)}{\varepsilon\big(A(\rho + \mu)(\beta D)\big) - \rho\omega N\gamma}, \\ \frac{AN(\rho + \mu)(C - \mu D)}{A(\rho + \mu)(\beta D) - \rho\omega N\gamma}, \frac{N\omega(\rho + \mu)(C - \mu D)}{A(\rho + \mu)(\beta D) - \rho\omega N\gamma}, \frac{N\omega\gamma(\rho + \mu)(C - \mu D)}{A(\rho + \mu)(\beta D) - \rho\omega N\gamma(\rho + \mu)} \end{gathered} \tag{9}$$

Substituting each parameter value in Table 1, the endemic system in the SVEITR model is:

$$P_1 = (37.301.726;\ 1.212.907;\ 0;\ 0;\ 0;\ 0) \tag{10}$$

2.1.2 Stability Analysis of Equilibrium Point

The dynamics of tuberculosis spread in the SVEITResR model are analysed by testing stability at each equilibrium point to determine whether TB will continue to spread or can be controlled in East Java Province.

Linearization

Linearization is the process of transforming a non-linear dynamical system into a linear differential system around the equilibrium point (Wulandari et al., 2023). Linearization of the system into equations (1) to (6) using the Taylor series and Jacobian matrix, as follows:

https://doi.org/10.24191/mij.v6i2.6245

$$|\dot{S}\,\dot{V}\,\dot{E}\,\dot{I}\,\dot{T}\,\dot{R}\,| = \left|-\left(\frac{\beta I}{N}+\mu\right)\,\theta\;0\;-\frac{\beta S}{N}\;0\;\rho\;0\;-(\theta+\mu)\;0\;0\;0\;0\;\frac{\beta I}{N}\;0\right.$$
$$-(\varepsilon+\mu)\;\frac{\beta S}{N}\;0\;0\;0\;0\;\varepsilon\;-(\omega+\sigma_1+\mu)\;0\;0\;0\;0\;0\;\omega \qquad (11)$$
$$\left.-(\gamma+\sigma_2+\mu)\;0\;0\;0\;0\;0\;\gamma\;-(\rho+\mu)\right|$$

The stability of the system can be analysed with the Jacobi matrix in equation (11), finding the eigenvalues of the linearization in the characteristic equation of the Routh-Hurwitz criterion to determine the stability condition.

Disease-Free Condition

The value of the disease-free equilibrium point will be substituted into the Jacobian matrix in equation (11) to the $J(P_0)$ matrix and eigenvalues to analyze its stability, as follows:

$$|J(P_0)-\lambda I\,| = |0\,|$$
$$\left|-\mu-\lambda\;\theta\;0\;-\frac{\beta C}{N}\;0\;\rho\;0\;-F-\lambda\;0\;0\;0\;0\;\frac{\beta I}{N}\;0\;-G-\lambda\;\frac{\beta C}{N}\;0\;0\;0\;0\;\varepsilon\;-H\right. \qquad (12)$$
$$\left.-\lambda\;0\;0\;0\;0\;0\;\omega\;-A-\lambda\;0\;0\;0\;0\;0\;\gamma\;-J-\lambda\right| = |0\,|$$

The matrix determinant in equation (12) produces an equation to calculate the eigenvalues of the matrix (P_0) is as follows:

$$\lambda_1 = -\mu; \quad \lambda_4 = -J$$
$$\lambda_2 = -F; \quad \lambda_5 = -\frac{GN+H_1N-\sqrt{4CN\beta\varepsilon+G^2N^2-2GH_1N^2+H_1^2N^2}}{2N} \qquad (13)$$
$$\lambda_3 = -A; \quad \lambda_6 = -\frac{GN+H_1N+\sqrt{4CN\beta\varepsilon+G^2N^2-2GH_1N^2+H_1^2N^2}}{2N}$$

The equilibrium point is to be asymptotically stable if all eigenvalues are negative ($\lambda_i < 0$).

$$\lambda_1 = -0.0139; \quad \lambda_2 = -0.4139; \quad \lambda_3 = -0.9539$$
$$\lambda_4 = -0.0639; \quad \lambda_5 = -0.9582; \quad \lambda_6 = 0.0604 \qquad (14)$$

The eigenvalues have negative values ($\lambda_{1,2,3,4,5} < 0$) and positive values ($\lambda_6 < 0$). Based on these results, the disease-free equilibrium point can be categorised as unstable.

Endemic Condition

The value of the endemic equilibrium point will be substituted into the Jacobian matrix in equation (11) to the $J(P_1)$ matrix and eigenvalues to analyze its stability, as follows:

$$|J(P_1)-\lambda I\,| = |0\,|$$
$$\left|-L-\lambda\;\theta\;0\;-\frac{\beta D}{N}\;0\;\rho\;0\;-F-\lambda\;0\;0\;0\;0\;\frac{\beta K}{N}\;0\;-G-\lambda\;\frac{\beta D}{N}\;0\;0\;0\;0\;\varepsilon\;-H\right. \qquad (15)$$
$$\left.-\lambda\;0\;0\;0\;0\;0\;\omega\;-A-\lambda\;0\;0\;0\;0\;0\;\gamma\;-J-\lambda\right| = |0\,|$$

The matrix determinant in equation (15) produces an equation to calculate the eigenvalues of the matrix (P_1) is as follows:

https://doi.org/10.24191/mij.v6i2.6245

$$\begin{array}{c|ccc} \lambda^5 & -1 & -7.97662 & -0.91322 \\ \lambda^4 & -5.57098 & -4.31816 & -0.01508 \\ \lambda^3 & -7.20073 & -1.68582 & \\ \lambda^2 & -6.67185 & & \\ \lambda & -1.68582 & & \\ \lambda^0 & -0.04430 & & \end{array} \tag{16}$$

The equilibrium point is to be asymptotically stable if all eigenvalues are negative ($\lambda_i < 0$).

$$\begin{gathered} \lambda_1 = -0.4139; \quad \lambda_2 = -3.7219; \quad \lambda_3 = -0.9860; \quad \lambda_4 = -0.4225 - 0.2232i \\ \lambda_5 = -0.4225 + 0.2232i; \quad \lambda_6 = -0.0180 \end{gathered} \tag{17}$$

Each value in the column shows that all are negative without any change in sign, and each eigenvalue has a negative value ($\lambda_i < 0$). Based on these results, the endemic equilibrium point can be categorised as asymptotically stable.

2.1.3 Basic Reproduction Number (R_0)

The basic reproduction number (R_0) represents the expected number of secondary infections caused by one infected individual in a wholly susceptible population (Resmawan & Nurwan, 2017). The value using the Driessche and Watmough method involves analysing the disease-free equilibrium point variables such as exposed (E), infected (I), and treated (T).

$$\begin{gathered} |K - \lambda I| = 0 \\ \left| \left[\frac{S\beta\varepsilon}{GHN} \; \frac{S\beta}{HN} \; 0\,0\,0\,0\,0\,0\,0 \right] - \lambda [1\,0\,0\,0\,1\,0\,0\,0\,1] \right| = 0 \\ \left| \frac{S\beta\varepsilon}{GHN} - \lambda \; \frac{S\beta}{HN} \; 0\,0 \; -\lambda\,0\,0\,0 \; -\lambda \right| = 0 \\ \left(\frac{S\beta\varepsilon}{GHN} - \lambda \right)(-\lambda)(-\lambda) = 0 \\ \lambda_{1,2} = 0\,, \lambda_3 = \frac{S\beta\varepsilon}{GHN} \end{gathered} \tag{18}$$

Based on the operation with eigenvectors through the calculation of the determinant of the $|K - \lambda I|$ matrix, the following characteristic equation is obtained:

$$R_0 = \frac{S\beta\varepsilon}{GHN} = \frac{\left(\frac{\alpha N(\theta + \mu - \mu\xi)}{\mu(\theta + \mu)} \right)\beta\varepsilon}{(\varepsilon + \mu)(\omega + \sigma_1 + \mu)(N)} \tag{19}$$

The basic reproduction number is the eigenvalue of the next-generation matrix. Substituting each parameter, the value of R_0 is obtained,

$$R_0 = 1.3007 \tag{20}$$

Based on the SVEITR model, the spread of tuberculosis in East Java has the potential to outbreak with each infected individual can transmit the disease to approximately 1.3007 others.

https://doi.org/10.24191/mij.v6i2.6245

2.2 SVEITResR Model

The SVEITResR epidemiological model is applied to the spread of tuberculosis disease considering multidrug resistant tuberculosis (MDR-TB) cases, vaccination BCG, and first-line treatment using anti-tuberculosis drugs.

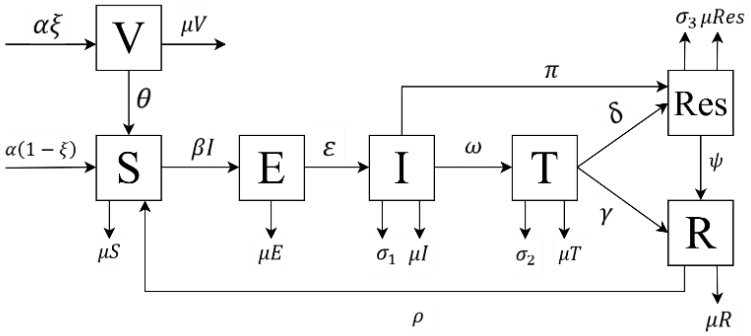

Fig. 2. SVEITResR epidemic model compartment

Based on the compartment diagram in Fig. 2, the SVEITResR tuberculosis epidemic model can be compiled into a mathematical form as follows:

$$\frac{dS}{dt} = \alpha N(1-\xi) + \theta V + \rho R - \left(\frac{\beta I}{N} + \mu\right) S \tag{21}$$

$$\frac{dV}{dt} = \alpha N\xi - (\theta + \mu)V \tag{22}$$

$$\frac{dE}{dt} = \frac{\beta IS}{N} - (\varepsilon + \mu)E \tag{23}$$

$$\frac{dI}{dt} = \varepsilon E - (\pi + \omega + \sigma_1 + \mu)I \tag{24}$$

$$\frac{dT}{dt} = \omega I - (\delta + \gamma + \sigma_2 + \mu)T \tag{25}$$

$$\frac{dRes}{dt} = \pi I + \gamma T - (\psi + \ \sigma_3 + \mu)Res \tag{26}$$

$$\frac{dR}{dt} = \gamma T + \psi Res - (\rho + \mu)R \tag{27}$$

2.2.1 System Equilibrium Point

Disease-Free Equilibrium Point

The disease-free condition when there is no spread of tuberculosis in the population assuming there are no infected individuals ($E = I = T = Res = 0$). These values are substituted into equations (21) to (27) to the disease-free equilibrium point $P_0 = (S_0, V_0, E_0, I_0, T_0, Res_0, R_0)$ as follows:

https://doi.org/10.24191/mij.v6i2.6245

$$P_0 = \left(\frac{\alpha N(\theta+\mu-\mu\xi)}{\mu(\theta+\mu)}, \frac{\alpha N\xi}{\theta+\mu}, 0,0,0,0,0\right) \tag{28}$$

Substituting each parameter value in the Table 1, the disease-free condition system in the SVEITResR model is:

$$P_0 = (37.301.726;\ 1.212.907;\ 0;\ 0;\ 0;\ 0;0) \tag{29}$$

Endemic Equilibrium Point

The population assumes there are infected individuals ($E \neq I \neq T \neq Res \neq 0$). These values are substituted equations (21) to (27) the endemic equilibrium point $P_1 = (S_1, V_1, E_1, I_1, T_1, Res_1, R_1)$ as follows:

$$\begin{gathered} P_1 = \frac{N(\varepsilon+\mu)(\pi+\omega+\sigma_1+\mu)}{\beta\varepsilon}, \frac{\alpha N\xi}{\theta+\mu}, \frac{ABN(\rho+\mu)(C-\mu D)(\pi+\omega+\sigma_1+\mu)}{AB\varepsilon(\rho+\mu)(\beta D)-N\varepsilon(\pi\psi A+\gamma\omega B+\delta\omega\psi)}, \\ \frac{ABN(\rho+\mu)(C-\mu D)}{AB(\rho+\mu)(\beta D)-N(\pi\psi A+\gamma\omega B+\delta\omega\psi)}, \frac{BN\omega(\rho+\mu)(C-\mu D)}{AB(\rho+\mu)(\beta D)-N(\pi\psi A+\gamma\omega B+\delta\omega\psi)} \\ \frac{N(A\pi+\delta\omega)(\rho+\mu)(C-\mu D)}{AB(\rho+\mu)(\beta D)-N(\pi\psi A+\gamma\omega B+\delta\omega\psi)}, \frac{N(\rho+\mu)(C-\mu D)(A\pi\psi+B\gamma\omega+\delta\omega\psi)}{AB(\rho+\mu)(\beta D)-N(\pi\psi A+\gamma\omega B+\delta\omega\psi)(\rho+\mu)} \end{gathered} \tag{30}$$

Substituting each parameter value in the Table 1, the endemic condition system in the SVEITResR model is:

$$P_1 = (33.951.569;\ 1.212.907;\ 230.497;\ 121.715;\ 60.857;\ 27.541;\ 68.331) \tag{31}$$

2.2.2 Stability Analysis of Equilibrium Point

The dynamics of tuberculosis spread in the SVEITResR model through stability analysis at each equilibrium point aims to tuberculosis will continue to spread or can be controlled in East Java Province.

Linearization

Linearization of the system into equations (21) to (27) using the Taylor series and Jacobian matrix, as follows:

$$\begin{vmatrix} \dot{S} & \dot{V} & \dot{E} & \dot{I} & \dot{T} & \dot{Res} & \dot{R} \end{vmatrix} = \begin{vmatrix} -\left(\frac{\beta I}{N}+\mu\right) & \theta & 0 & -\frac{\beta S}{N} & 0 & 0 & \rho \\ 0 & -(\theta+\mu) & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta I}{N} & 0 & -(\varepsilon+\mu) & \frac{\beta S}{N} & 0 & 0 & 0 \\ 0 & 0 & \varepsilon & -(\pi+\omega+\sigma_1+\mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \omega & -(\delta+\gamma+\sigma_2+\mu) & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \delta \\ 0 & 0 & 0 & 0 & \gamma & \psi & -(\rho+\mu) \end{vmatrix} \tag{32}$$

The stability of the system can be analysed with the Jacobi matrix in equation (32), finding the eigenvalues of the linearization in the characteristic equation of the Routh-Hurwitz criterion to determine the stability condition.

Disease-Free Condition

The value of the disease-free equilibrium point will be substituted into the Jacobian matrix in equation (32) to the $J(P_0)$ matrix and eigenvalues to analyze its stability, as follows:

$$|J(P_0) - \lambda I| = 0 \tag{33}$$

https://doi.org/10.24191/mij.v6i2.6245

$$\begin{vmatrix} -\mu-\lambda & \theta & 0 & -\frac{\beta C}{N} & 0 & 0 & \rho & 0 & -F-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -G-\lambda & \frac{\beta C}{N} & 0 & 0 & 0 & 0 & 0 & \varepsilon & -H \\ & & & & & & & & -\lambda & 0 & 0 & 0 & 0 & 0 & 0 & \omega & -A-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & \delta & -B-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & \gamma & \psi & -J \\ & & & & & & & & -\lambda & & & & & & & & & & & & & & & & & & & & & & & & \end{vmatrix} = 0$$

The matrix determinant in equation (33) produces an equation to calculate the eigenvalues of the matrix (P_0) is as follows:

$$\begin{gathered} \lambda_1 = -\mu; \quad \lambda_5 = -J \\ \lambda_2 = -F; \quad \lambda_6 = -\frac{GN + H_2N - \sqrt{4CN\beta\varepsilon + G^2N^2 - 2GH_2N^2 + H_2^2N^2}}{2N} \\ \lambda_3 = -A; \quad \lambda_7 = -\frac{GN + H_2N + \sqrt{4CN\beta\varepsilon + G^2N^2 - 2GH_2N^2 + H_2^2N^2}}{2N} \\ \lambda_4 = -B; \end{gathered} \tag{34}$$

The equilibrium point is to be asymptotically stable if all eigenvalues are negative ($\lambda_i < 0$).

$$\begin{gathered} \lambda_1 = -0.0139; \quad \lambda_2 = -0.4139; \quad \lambda_3 = -1; \quad \lambda_4 = -0.5439 \\ \lambda_5 = -0.0639; \quad \lambda_6 = -0.0198; \quad \lambda_7 = 0.0220 \end{gathered} \tag{35}$$

The eigenvalues have negative values ($\lambda_{1,2,3,4,5,6} < 0$) and positive values ($\lambda_7 < 0$). Based on these results, the disease-free equilibrium point can be categorized as unstable.

Endemic Condition

The value of the endemic equilibrium point will be substituted into the Jacobian matrix in equation (32) to the $J(P_1)$ matrix and eigenvalues to analyze its stability, as follows:

$$|J(P_1) - \lambda I| = 0$$

$$\begin{vmatrix} -\mu-\lambda & \theta & 0 & -\frac{\beta D}{N} & 0 & 0 & \rho & 0 & -F-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -G-\lambda & \frac{\beta D}{N} & 0 & 0 & 0 & 0 & 0 & \varepsilon & -H \\ & & & & & & & & -\lambda & 0 & 0 & 0 & 0 & 0 & 0 & \omega & -A-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & \delta & -B-\lambda & 0 & 0 & 0 & 0 & 0 & 0 & \gamma & \psi & -J \\ & & & & & & & & -\lambda & & & & & & & & & & & & & & & & & & & & & & & & \end{vmatrix} = 0 \tag{36}$$

The matrix determinant in equation (36) produces an equation to calculate the eigenvalues of the matrix (P_1) is as follows:

$$\begin{array}{c|cccc} \lambda^6 & -1 & -4.4727 & -0.9199 & -0.003018 \\ \lambda^5 & -3.4598 & -2.7868 & -0.1462 & \\ \lambda^4 & -1.5976 & -0.1371 & -0.1423 & \\ \lambda^3 & -0.6231 & -0.003 & & \\ \lambda^2 & -0.1293 & & & \\ \lambda & -0.0115 & & & \\ \lambda^0 & -0.0369 & & & \end{array} \tag{37}$$

https://doi.org/10.24191/mij.v6i2.6245

The equilibrium point is to be asymptotically stable if all eigenvalues are negative ($\lambda_i < 0$).

$$\begin{gathered}\lambda_1 = -0.4139; \quad \lambda_2 = -1.2998; \quad \lambda_3 = -1.0336; \quad \lambda_4 = -0.2766 - 0.3064i \\ \lambda_5 = -0.2766 + 0.3064i; \quad \lambda_6 = -0.0240; \quad \lambda_7 = -0.5492\end{gathered} \tag{38}$$

Each value in the column shows that all are negative without any change in sign, and each eigenvalue has a negative value ($\lambda_i < 0$). Based on these results, the endemic equilibrium point can be categorised as asymptotically stable.

2.2.3 Basic Reproduction Number (R_0)

The value using the Driessche and Watmough method involves analysing the disease-free equilibrium point variables such as exposed (E), infected (I), treated (T), and resistant (Res).

$$\begin{gathered}|K - \lambda I| = 0 \\ \left|\begin{bmatrix} \frac{S\beta\varepsilon}{GHN} & \frac{S\beta}{HN} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}\right. \\ \left. - \lambda\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 \end{bmatrix}\right| = 0 \\ \left|\begin{matrix} \frac{S\beta\varepsilon}{GHN} - \lambda & \frac{S\beta}{HN} & 0 & 0 & 0 & -\lambda & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda & 0 & 0 & -\lambda \end{matrix}\right| = 0 \\ \left(\frac{S\beta\varepsilon}{GHN} - \lambda\right)(-\lambda)(-\lambda)(-\lambda) = 0 \\ \lambda_{1,2,3} = 0\,, \lambda_4 = \frac{S\beta\varepsilon}{GHN}\end{gathered} \tag{39}$$

Based on the operation with eigenvectors through the calculation of the determinant of the $|K - \lambda I|$ matrix, the following characteristic equation is obtained:

$$R_0 = \frac{S\beta\varepsilon}{GHN} = \frac{\left(\frac{\alpha N(\theta + \mu - \mu\xi)}{\mu(\theta + \mu)}\right)\beta\varepsilon}{(\varepsilon + \mu)(\pi + \omega + \sigma_1 + \mu)(N)} \tag{40}$$

The basic reproduction number is the eigenvalue of the next-generation matrix. Substituting each parameter, the value of R_0 is obtained,

$$R_0 = 1.0987 \tag{41}$$

Based on the SVEITResR model, the spread of tuberculosis with the Multidrug Resistance Effect (MDR-TB) in East Java has the potential to outbreak with each infected individual can transmit the disease to approximately 1.3007 others.

2.2.4 Numerical Simulation

Fourth-order Runge-Kutta simulation in tuberculosis spread SVEITResR model involves complex differential equations. This method provides accurate results to analyse the population (susceptible, vaccine, exposed, infected, treated, resistant, and recovered) and predict the impact of interventions such as treatment and vaccination. The solution of the tuberculosis spread model using the system of equations (21) to (27) carried with the initial values of variables and parameters presented in Table 1 and the system of equations is formulated in the Runge-Kutta scheme.

$$S_{n+1} = S_n + \frac{h}{6}(k_{1S} + 2k_{2S} + 2k_{3S} + k_{4S}) \tag{42}$$

https://doi.org/10.24191/mij.v6i2.6245

$$V_{n+1} = V_n + \frac{h}{6}(k_{1V} + 2k_{2V} + 2k_{3V} + k_{4V})$$
$$E_{n+1} = E_n + \frac{h}{6}(k_{1E} + 2k_{2E} + 2k_{3E} + k_{4E})$$
$$I_{n+1} = I_n + \frac{h}{6}(k_{1I} + 2k_{2I} + 2k_{3I} + k_{4I})$$
$$T_{n+1} = T_n + \frac{h}{6}(k_{1T} + 2k_{2T} + 2k_{3T} + k_{4T})$$
$$Res_{n+1} = Res_n + \frac{h}{6}(k_{1Res} + 2k_{2Res} + 2k_{3Res} + k_{4Res})$$
$$R_{n+1} = R_n + \frac{h}{6}(k_{1R} + 2k_{2R} + 2k_{3R} + k_{4R})$$

The coefficient value of equation (42) is obtained as follows:

$$\begin{aligned} k_{1S} &= \alpha(1-\xi) + \theta V_n + \rho R_n - (\beta I_n + \mu) S_n \\ k_{1V} &= \alpha\xi - (\theta + \mu) V_n \\ k_{1E} &= \beta I_n S_n - (\varepsilon + \mu) E_n \\ k_{1I} &= \varepsilon E_n - (\pi + \omega + \sigma_1 + \mu) I_n \\ k_{1T} &= \omega I_n - (\delta + \gamma + \sigma_2 + \mu) T_n \\ k_{1Res} &= \pi I_n + \delta T_n - (\psi + \sigma_3 + \mu) Res_n \\ k_{1R} &= \gamma T_n + \psi Res_n - (\rho + \mu) R_n \end{aligned} \tag{43}$$

The initial slope value k_2 for each variable is obtained from the equation k_1 is modified as follows:

$$\begin{aligned} k_{2S} &= \alpha(1-\xi) + \theta\left(V_n + \frac{k_{1V}}{2}\right) + \rho\left(R_n + \frac{k_{1R}}{2}\right) - \left(\beta\left(I_n + \frac{k_{1I}}{2}\right) + \mu\right)\left(S_n + \frac{k_{1S}}{2}\right) \\ k_{2V} &= \alpha\xi - (\theta + \mu)\left(V_n + \frac{k_{1V}}{2}\right) \\ k_{2E} &= \beta\left(I_n + \frac{k_{1I}}{2}\right)\left(S_n + \frac{k_{1S}}{2}\right) - (\varepsilon + \mu)\left(E_n + \frac{k_{1E}}{2}\right) \\ k_{2I} &= \varepsilon\left(E_n + \frac{k_{1E}}{2}\right) - (\pi + \omega + \sigma_1 + \mu)\left(I_n + \frac{k_{1I}}{2}\right) \\ k_{2T} &= \omega\left(I_n + \frac{k_{1I}}{2}\right) - (\delta + \gamma + \sigma_2 + \mu)\left(T_n + \frac{k_{1T}}{2}\right) \\ k_{2Res} &= \pi\left(I_n + \frac{k_{1I}}{2}\right) + \delta\left(T_n + \frac{k_{1T}}{2}\right) - (\psi + \sigma_3 + \mu)\left(Res_n + \frac{k_{1Res}}{2}\right) \\ k_{2R} &= \gamma\left(T_n + \frac{k_{1T}}{2}\right) + \psi\left(Res_n + \frac{k_{1Res}}{2}\right) - (\rho + \mu)\left(R_n + \frac{k_{1R}}{2}\right) \end{aligned} \tag{44}$$

The initial slope value k_3 for each variable is obtained from the equation k_2 is modified as follows:

$$\begin{aligned} k_{3S} &= \alpha(1-\xi) + \theta\left(V_n + \frac{k_{2V}}{2}\right) + \rho\left(R_n + \frac{k_{2R}}{2}\right) - \left(\beta\left(I_n + \frac{k_{2I}}{2}\right) + \mu\right)\left(S_n + \frac{k_{2S}}{2}\right) \\ k_{3V} &= \alpha\xi - (\theta + \mu)\left(V_n + \frac{k_{2V}}{2}\right) \\ k_{3E} &= \beta\left(I_n + \frac{k_{2I}}{2}\right)\left(S_n + \frac{k_{2S}}{2}\right) - (\varepsilon + \mu)\left(E_n + \frac{k_{2E}}{2}\right) \\ k_{3I} &= \varepsilon\left(E_n + \frac{k_{2E}}{2}\right) - (\pi + \omega + \sigma_1 + \mu)\left(I_n + \frac{k_{2I}}{2}\right) \\ k_{3T} &= \omega\left(I_n + \frac{k_{2I}}{2}\right) - (\delta + \gamma + \sigma_2 + \mu)\left(T_n + \frac{k_{2T}}{2}\right) \\ k_{3Res} &= \pi\left(I_n + \frac{k_{2I}}{2}\right) + \delta\left(T_n + \frac{k_{2T}}{2}\right) - (\psi + \sigma_3 + \mu)\left(Res_n + \frac{k_{2Res}}{2}\right) \end{aligned} \tag{45}$$

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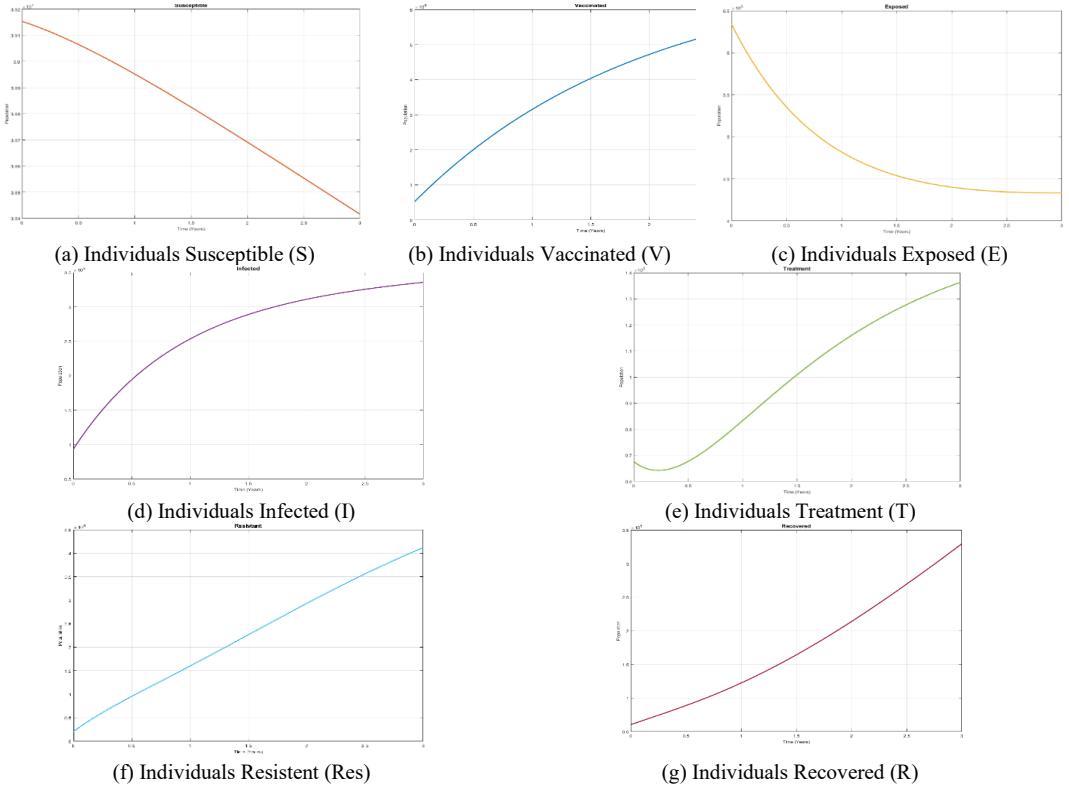
$$k_{3R} = \gamma\left(T_n + \frac{k_{2T}}{2}\right) + \psi\left(Res_n + \frac{k_{2Res}}{2}\right) - (\rho + \mu)\left(R_n + \frac{k_{2R}}{2}\right)$$

The initial slope value k_4 for each variable is obtained from the equation k_3 is modified as follows:

$$\begin{gathered} k_{4S} = \alpha(1-\xi) + \theta(V_n + k_{3V}) + \rho(R_n + k_{3R}) - (\beta(I_n + k_{3I}) + \mu)(S_n + k_{3S}) \\ k_{4V} = \alpha\xi - (\theta + \mu)(V_n + k_{3V}) \\ k_{4E} = \beta(I_n + k_{3I})(S_n + k_{3S}) - (\varepsilon + \mu)(E_n + k_{3E}) \\ k_{4I} = \varepsilon(E_n + k_{3E}) - (\pi + \omega + \sigma_1 + \mu)(I_n + k_{3I}) \\ k_{4T} = \omega(I_n + k_{3I}) - (\delta + \gamma + \sigma_2 + \mu)(T_n + k_{3T}) \\ k_{4Res} = \pi(I_n + k_{3I}) + \delta(T_n + k_{3T}) - (\psi + \sigma_3 + \mu)(Res_n + k_{3Res}) \\ k_{4R} = \gamma(T_n + k_{3T}) + \psi(Res_n + k_{3Res}) - (\rho + \mu)(R_n + k_{3R}) \end{gathered} \tag{46}$$

Equation (42) is simulated with MATLAB 2023 to produce the graph as follows:



(a) Individuals Susceptible (S) (b) Individuals Vaccinated (V) (c) Individuals Exposed (E)

(d) Individuals Infected (I) (e) Individuals Treatment (T)

(f) Individuals Resistent (Res) (g) Individuals Recovered (R)

Fig. 3. Distribution Dynamics of Each Population in the SVEITResR Model

Based on Fig. 3 (a), the individuals in the susceptible sub-population (*S*) in the first year is 39.112.100. This decreases over time due to natural mortality and movement of individuals to the exposed sub-population (*E*) until it reaches 37.243.600 in the third year. Fig. 3 (b) an increase in the number of BCG vaccinated individuals (*V*) from 523.994 to 998.400, influenced the birth rate and the effectiveness of the vaccination program. Fig. 3 (c) and the number of exposed (*E*) sub-populations increased from 631.493 individuals and then decreased to 517.857 due to the transfer of individuals to the infected (*I*) and treated (*T*) sub-populations.

https://doi.org/10.24191/mij.v6i2.6245

Fig. 3 (d), result in infected sub-population (I) initially amounted to 100.795 individuals decreased due to the transfer of individuals to the resistant sub-population (Res) and treatment (T), then increased to 251.409 individuals due to the increase in the number of exposed individuals. Fig. 3 (e), experiencing an increase in the number of individuals in the first-line treatment (T) sub-population due to the movement of infected individuals (I), will stabilize significantly after treatment (T) is completed and move to the recovered (R) sub-population. Optimal treatment duration helps reduce drug resistance. In Fig. 3 (f), the number of individuals in the resistant (Res) sub-population increased significantly from 2.112 in the first year to 7.516 in the third year. This increase was due to treatment failure in some individuals who then switched to the resistant (Res) sub-population and received second-line treatment to recover or moved to the recovered (R) sub-population. The rate of increase is influenced by factors such as non-adherence to treatment or bacterial mutations that increase resistance.

In Fig. 3 (g), the number of individuals in the recovered (R) sub-population increased from 63.080 in year one to 264.871 in year three. This indicates successful treatment of individuals from the treatment (T) and resistant (Res) sub-populations, reflecting adherence to therapy, drug effectiveness, and disease control programs. Individuals recovered (R) remain at risk of re-exposure and enter the susceptible (S) sub-population due to loss of immunity.

3. RESULT AND DISCUSSION

Based on the SVEITResR model, the rate of individuals first-line treatment with rifampicin and isoniazid is denoted as ω. The results that a treatment for 2 months with a parameter value of $\omega = 0.167$, resulted in a basic reproduction number (R_0) of 2.2756. If a 6-month treatment procedure with a parameter value of $\omega = 0.5$ reduced the basic reproductive rate (R_0) to 1.0987. Treatment duration can reduce the basic reproduction number (R_0), prevent resistance and control the spread of the disease. The duration of first-line treatment and adherence to that duration is very important to prevent the occurrence of resistance in the spread of tuberculosis in the East Java region.

The SVEITResR model has a lower basic reproduction number (R_0) than the SVEITR model, despite including a resistant population. Second-line treatment is effective in reducing transmission from resistant individuals and vaccination prevents infection, reducing the number of individuals who become resistant. With intensive treatment and appropriate medical interventions, the proportion of resistant individuals can be reduced, and the R_0 value remains low even when resistance is considered. The importance of effective medical intervention to control the tuberculosis outbreak.

The basic reproduction number (R_0) SVEITResR model of 1.0987 indicates that tuberculosis will still spread in East Java, Indonesia. In comparison, research by Ronoh et al., (2016) with case studies in Africa and South Asia, the SVEIResR model a basic reproduction number (R_0) of 10.4348 due to ineffective treatment drug resistance (MDR-TB) extends the infection period and increases the transmission rate (β) if the model assumes contacts of 5-10 people/day (high β), then the value of R_0 can increase.

Research by Ochieng, (2024) with case studies in Kenya, the SVEITRS model produced a reproduction number (R_0) of 1.005341. TB can still spread at a low rate, estimating the time to double cases to 5-10 years. The SIR model in Kazakhstan research by Kalizhanova et al., (2024) R_0 value of 0.2960 indicates the epidemic is a phase of decreasing susceptible population and recovered over time. The success of Kazakhstan's health programs rapid diagnosis, vaccination, and treatment of MDR-TB with a success rate of 82.5% contributed to reducing the spread of the disease and increasing the number of cured patients.

The SVEIR-I model in China research by Liu et al., (2023) R_0 value of 1.8605 indicates the disease has the potential to become endemic if no increase in vaccination or treatment. The model is a nonlinear incidence rate (the transmission rate is not constant) and depends on the number of infected and susceptible individuals. Complex interactions between susceptible and infected populations increase the likelihood of

https://doi.org/10.24191/mij.v6i2.6245

transmission, especially in densely populated areas. Research by Tamhaji & Hamdan, (2023) with case studies in Malaysia, the BSEIR model produced a reproduction number (R_0) of 1.955. The addition of the immigration parameter in the model suggests that the arrival of new individuals from areas with high TB prevalence increases the number of susceptible and infected individuals in Malaysia.

4. CONCLUSION

4.1 Concluding Remarks

The stability analysis of the SVEITR model system the existence of two equilibrium points, the disease-free equilibrium point with $P_0 = (37.301.726; 1.212.907; 0; 0; 0; 0; 0)$ is not stable, and the endemic equilibrium point $P_1 = (28.678.522;\ 1.212.907;\ 956.482;\ 597.944;\ 313.430; 103.050)$ asymptotically stable with the value of the basic reproduction number (R_0 = 1.3007). It can be concluded that the spread of tuberculosis in East Java has the potential to outbreak with each infected individual can transmit the disease by 1.3007 to other individuals.

The stability analysis of the SVEITResR model system the existence of two equilibrium points, the disease-free equilibrium point with $P_0 = (37.301.726;\ 1.212.907;\ 0;\ 0;\ 0;\ 0; 0)$ is not stable, and the endemic equilibrium point with $P_1 = (33.951.569;\ 1.212.907;\ 230.497;\ 121.715;\ 60.857;\ 27.541;\ 68.331)$ is asymptotically stable with the value of the basic reproduction number (R_0 = 1.0987). It can be concluded that the spread of tuberculosis disease with Multidrug Resistance Effect (MDR-TB) in East Java has the potential to outbreak with each infected individual can transmit the disease by 1.0987 to other individuals.

Simulation results using 4th-order Runge-Kutta show the number of individuals exposed (E) to tuberculosis will decrease significantly after 2024, while the number of infected (I) individuals is projected to continue increasing until 2025 before reaching a steady state the next year. The effectiveness of vaccination as well as first- and second-line treatment an important role in reducing the number of exposed and infected individuals and significantly increasing the number of recovered (R) individuals.

The tuberculosis (TB) situation in Indonesia contributes to the spread of the epidemic, and it is important to ensure that the value of the basic reproduction number ($R_0 < 1$) to stop the spread of the disease. Numerical and sensitivity analysis of the R_0 parameter way to reduce the number of infected individuals is to increase the transmission rate (β) and recovery rate (γ). A comparison between models with and without resistance shows that TB infection with resistance decreases due to second-line treatment. Control strategies such as increased vaccination, early diagnosis, and effective treatment are critical to controlling or eliminating the disease from the population, as TB is still a health problem that has not been fully eradicated in Indonesia.

4.2 Suggestion

After analysing the mathematical model of tuberculosis disease spread, the author proposes several development suggestions for further research, such as adding new parameters and populations, such as HIV-TBC and advanced resistance such as extensively drug-resistant tuberculosis (XDR-TB) that requires third-line treatment. SVEITResR model can be developed by adding optimal control with the use of antibiotic parameters in accelerating the healing of infected individuals and shortening the spread of tuberculosis disease. Methods that can be applied include the Minimum Pontryagin Principle (MPP) or Linear Quadratic Regulator (LQR).

https://doi.org/10.24191/mij.v6i2.6245

5. ACKNOWLEDGEMENT/FUNDING

The author expresses gratitude for the support of UIN Sunan Ampel Surabaya and the Division of Infectious Disease Prevention and Control (P2P) of the East Java Health Department have provided data and input during the process so that the author can complete this research properly.

6. CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this paper. All data, analyses, and conclusions presented in this research are based on objective findings and are not influenced by personal or financial interests.

7. AUTHORS' CONTRIBUTIONS

Dian Puspita Sari conducted the research, conceptualized the main research idea, provided the theoretical framework, and revised the article. Aris Fanani and Ahmad Hanif Asyhar designed the research, supervised its progress, reviewed the work, and approved the submission of the article.

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