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ANALYSIS AND OPTIMAL CONTROL OF TUBERCULOSIS DISEASE SPREAD MODEL WITH VACCINATION AND CASE FINDING CONTROL (CASE STUDY: SURABAYA CITY)

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ABSTRACT

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Tuberculosis is a contagious disease that infects humans. It is caused by the bacterium Mycobacterium tuberculosis (M.tb). It is the largest infectious disease in the world and has become a major global health problem. Therefore, efforts are being made to control the spread of tuberculosis disease through vaccination and case finding, with the aim of reducing the population of latently infected and actively infected individuals. This study discusses the mathematical model of tuberculosis disease spread, disease-free and endemic equilibrium points, and stability analysis around the equilibrium points. Then, using Pontryagin's minimum principle, the optimal control problem is solved numerically by the 4th-order Runge-Kutta method. Based on the analysis and simulation results, the system is asymptotically stable around the disease-free and endemic equilibrium points. Furthermore, optimal control in the form of vaccination of susceptible individuals is required to further suppress the rate of change of susceptible individuals into latent individuals, while control in the form of case finding on latently infected individuals is required until the 9th year to minimize the population size, while on actively infected individuals, it is required until the 8th year to minimize the population size. Providing optimal control resulted in a 100% increase in the susceptible population and a 100% reduction in the latent and infected populations.



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1. INTRODUCTION

Tuberculosis (TB) is a contagious disease that infects humans and is caused by the bacteria Mycobacterium tuberculosis (M.tb). Infection occurs after a person inhales air or saliva droplets released by an actively infected patient. After inhalation, the bacteria enter the lungs and are engulfed by macrophages, multiplying and forming granulomas. At this point, the infection is able to damage body tissues and invade the lungs [1]. TB is one of the largest infectious diseases in the world and has become a significant global health problem. It is ranked second in the list of diseases causing the most deaths after COVID-19 [2]. Even this year, Indonesia is in second place with the highest number of cases in the world after India [3]. Control efforts continue to be made to reduce the number of cases of TB disease, one of which is optimal control. Optimal control is a model needed to assist in making decisions about achieving a goal while at the same time minimizing or maximizing several system performance criteria [4].

Modeling the spread of TB disease has been studied by several researchers, such as [5], who discussed mathematical models and efforts to mitigate TB disease in the Philippines. The compartments used are: Susceptible, individuals who are susceptible to disease; High-Risk Latent, individuals who are latently infected and at high risk of becoming infectious or actively infected; Infectious or Active TB, individuals who are infected with reduced immunity and may be at risk of transmission; and Low-Risk Latent, latently infected individuals who do not progress to an infectious state and individuals who recover naturally or due to treatment. This model provides four controls in the form of distance control or reducing direct contact, latent case finding, case management, and active case finding. Researchers considered eight scenarios when providing controls to determine the effectiveness of each control. Further, it became the foundational model in research on the dynamic model of the TB virus and the mathematical concept involved in [6] and [7]. In addition, other mathematical modeling was carried out by [8]. The compartments used are: Susceptible, individuals who are susceptible to the disease; Latent, latently infected individuals (asymptomatic, not contagious); Treatment infected latent, in the form of preventive treatment of individuals who are aware and receive treatment; Infected, infected individuals with a reduced immune system; Treatment infected active, in the form of curative treatment; and Recovered, individuals who recovered. The researcher formed a mathematical model of TBs disease spread by considering treatment as a new variable or compartment. This model also assumes that individuals in the system are aware of the existence of TB disease. Implementation of optimal control in TB models is important to research, such as [9], [10], [11], and [12].

This study will discuss the analysis and optimal control of the mathematical model of the spread of TB disease by providing control in the form of vaccination and case finding. Vaccination is one of the methods used to prevent the transmission of TB. The vaccine used is the BCG (Bacillus Calmette-Guérin) vaccine. The effectiveness of this vaccine varies and still does not provide perfect protection, especially for pulmonary TB patients. Thus, the development of a more effective vaccine is also important in efforts to control the spread [13]. Meanwhile, case finding is an important effort in identifying individuals who are infected with TB but undiagnosed or asymptomatic. However, this effort also needs to be made for individuals who are actively infected or feel symptoms but do not have the awareness to take treatment. Thus, the control used in this study is used as a variable whose value is obtained through optimal control theory using Pontryagin's Minimum Principle. This study also analyzed the stability and parameter estimation of the mathematical model of TB disease spread and performed numerical simulations using the 4th-order Runge-Kutta method.

2. RESEARCH METHODS

The steps taken in this research are, first, a literature study. This stage aims to collect reference information to support the formation of mathematical models of TB disease spread, Pontryagin's Minimum Principle, and other matters related to this research. References are sought through several journals, research projects, and papers related to the research topic. The second step is data collection. The data was obtained from the Population and Civil Registration Service and Public Health Bureau in Surabaya City. The data was used to calculate parameters and initial values in the mathematical model of TB disease spread. Furthermore, the third step is model identification. This stage aims to identify the appropriate compartmental model to model the spread of TB disease. In this study, the SLIR model will be used, where the entire population is divided into four groups, namely: Susceptible (S), Latent (L), Infected (I), and Recovered (R). Susceptible (S) population is a vulnerable population. The Latent (L) population is a population that is latently infected,

meaning that they do not feel symptoms because the immune system successfully fights back. The Infected population (I) is a population that is actively infected, meaning that it feels symptoms because the immune system cannot successfully fight back. Meanwhile, the Recovered (R) population is the population that has recovered. After determining the compartment model used, the parameters used in the model will be used for the mathematical model construction of TB disease spread using the SLIR model. At this stage, a mathematical model of the spread of TB disease with the provision of control in the form of vaccination and case finding is also developed.

The next stage is to find the equilibrium points of the mathematical model of the spread of TB disease, and will do the linearization around the equilibrium point. The next step will be analyzed and determined the stability of the equilibrium point obtained previously. At this stage, optimal control is also solved using Pontryagin's Minimum Principle. After analyzing the system, numerical simulations will be carried out using the 4th-Order Runge-Kutta Method. The simulation is carried out to compare the number of populations before and after being controlled. We describe the methods on **Figure 1**.



Figure 1. Research Methods

3. RESULTS AND DISCUSSION

3.1 Mathematical Model

Mathematical modeling is a discussion of mathematical concepts that present and explain real-world problems in mathematical statements. The model used in this research is SLIR (Susceptible, Latent, Infected, Recovered). The compartments are: S, which is a susceptible individual; L, which is a latently infected individual or does not feel symptoms; I, which is an actively infected individual; and R, which is a recovered individual. The population in this system is assumed to be closed, meaning that individuals from each compartment do not immigrate. Additionally, each population is assumed to have the same natural mortality rate, μ . The relationship between the four compartments in the SLIR model is presented in the diagram in **Figure 2**.



Figure 2. Diagram of Mathematical Model of Tuberculosis Disease Spread

Figure 2 shows the compartments in the mathematical model of TB disease spread. Thus, the mathematical model is as follows:

$$\begin{cases} \frac{dS}{dt} = \theta N - \alpha \beta SI - \mu S \\ \frac{dL}{dt} = \alpha \beta (1 - m) SI - (\gamma + \mu) L \\ \frac{dI}{dt} = \alpha \beta m SI + \gamma h L - (\eta + \mu + \sigma) I \\ \frac{dR}{dt} = \eta I + \gamma (1 - h) L - \mu R \end{cases}$$
(1)

with initial conditions, $S(0) = S_0$, $L(0) = L_0$, $I(0) = I_0$, $R(0) = R_0$. The total population of individuals can be expressed as follows:

$$S(t) + L(t) + I(t) + R(t) = N$$
 (2)

where the parameters used are shown in Table 1.

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Table 1.	Parameter	Value of	Mathematical	Model of	Tuberculosis	Disease Spread
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Parameter	Description	Value
θ	Growth rate of susceptible individuals	0.0215
μ	Natural mortality rate	0.2959
σ	Death rate due to tuberculosis disease	0.8275
α	Rate of individuals leaving the susceptible class	0.0007
β	Rate of interaction of susceptible individuals with actively infected individuals	0.0006
m	Proportion of susceptible individuals to actively infected individuals	0.00008
h	Proportion of latently infected individuals to actively infected individuals	0.0038
γ	Rate of individuals leaving the latent class	0.0056
η	The rate of change from actively infected individuals to recovered individuals	0.0159

Data source: Population and Civil Registration Service and Public Health Bureau in Surabaya City

3.2 System Analysis

3.2.1 Equilibrium Points

Equilibrium point is a state where the population size remains constant over time [14]. The equilibrium point of the mathematical model of TB disease, as follows.

a. The disease-free equilibrium point occurs when there are no actively infected individuals in a population, or I = 0. In the absence of actively infected individuals, there is no spread of bacteria, causing latent and recovered individuals to also not exist or L = 0 dan R = 0.

$$E_0 = (S^0, L^0, I^0, R^0) = \left(\frac{\theta N}{\mu}, 0, 0, 0\right)$$

b. The endemic equilibrium point occurs when there is a spread of the disease,

$$E_1 = (S^*, L^*, I^*, R^*)$$

where:

$$S^* = \frac{\gamma h - \eta - \mu - \sigma}{\alpha \beta m}$$

$$L^* = \frac{(\theta N \alpha \beta m + \gamma h \mu - \eta \mu - \mu^2 - \mu \sigma)(1 - m)}{\alpha \beta m (\gamma + \mu)}$$

$$I^* = \frac{\theta N \alpha \beta m + \gamma h \mu - \eta \mu - \mu^2 - \mu \sigma}{\alpha \beta (\eta + \mu + \sigma - \gamma h)}$$

$$R^* = \frac{(\theta N \alpha \beta m + \gamma h \mu - \eta \mu - \mu^2 - \mu \sigma)}{\alpha \beta m (\gamma + \mu) (\gamma h - \eta - \mu - \sigma) \mu} (\gamma^2 h^2 (m - 1) + \gamma^2 h (1 - m) - \gamma h m (\eta + \mu + \sigma) + \gamma h (\eta + \mu + \sigma) - \eta m \mu - \gamma (\eta + \mu + \sigma))$$

3.2.2 Stability Analysis

The mathematical model of the spread of TB in **Equation** (1) is a nonlinear differential system. Therefore, before carrying out stability analysis, it is necessary to carry out linearization. Linearization of the system can be done through Taylor expansion around the equilibrium point. By using this approach, the Jacobian Matrix of the system **Equation** (1), as follows

$$J = \begin{bmatrix} -\alpha\beta I - \mu & 0 & -\alpha\beta S & 0\\ \alpha\beta(1-m)I & -\gamma - \mu & \alpha\beta(1-m)S & 0\\ \alpha\beta mI & \gamma h & \alpha\beta mS - \eta - \mu - \sigma & 0\\ 0 & \gamma(1-h) & \eta & -\mu \end{bmatrix}_{(S_0, L_0, I_0, R_0)}$$

a. Linearization around the disease-free equilibrium point with Jacobian Matrix, i.e.

$$J_{E_0} = \begin{bmatrix} -\mu & 0 & -\frac{\alpha \beta \theta N}{\mu} & 0 \\ 0 & -\gamma - \mu & \frac{\alpha \beta (1-m) \theta N}{\mu} & 0 \\ 0 & \gamma h & \frac{\alpha \beta m S \theta N}{\mu} - \eta - \mu - \sigma & 0 \\ 0 & \gamma (1-h) & \eta & -\mu \end{bmatrix}$$

Based on the J_{E_0} matrix, the characteristic equation can be formed by using $|J_{E_0} - \lambda I| = 0$, thus obtained

$$(-\mu - \lambda)^2 (A_0 \lambda^2 + A_1 \lambda + A_2) = 0$$

where $A_0 = 1$, $A_1 = \gamma + \mu - \frac{\alpha\beta mS\theta N}{\mu}$ and $A_2 = -\frac{\gamma\alpha\beta mS\theta N}{\mu} + \gamma\eta + \gamma\mu + \gamma\sigma - \frac{\mu\alpha\beta mS\theta N}{\mu} + \mu\eta + \mu^2 + \mu\sigma + \eta\lambda + \mu\lambda + \sigma\lambda - \frac{\gamma h\alpha\beta(1-m)\theta N}{\mu}$. Based on the characteristic equation, the following eigenvalues are obtained, $\lambda_1 = -\mu$, $\lambda_{2,3} = \frac{-A_1 \pm \sqrt{A_1^2 - 4A_0A_2}}{2A_0}$. Because the values of all parameters are positive, λ_1 is negative. The TB disease spread model around the disease-free equilibrium point is asymptotically stable if $Re(\lambda_2)$ and $Re(\lambda_3)$ are also negative by taking the value $A_1 > 0$, because the values of all parameters are positive, $A_1 > 0$ is verified.

b. Linearization around the endemic equilibrium point with Jacobian Matrix, i.e.

Based on the J_{E_1} matrix, the characteristic equation can be formed by using $|J_{E_1} - \lambda I| = 0$, thus obtained $A_0\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_2\lambda + A_4 = 0$

where:

$$A_{0} = 1$$

$$A_{1} = 2\mu + a_{1} - a_{4} - a_{9}$$

$$A_{2} = \mu^{2} + a_{1}\mu - 2a_{4}\mu - 2a_{9}\mu - a_{1}a_{4} - a_{1}a_{9} + a_{3}a_{7} + a_{4}a_{9} - a_{5}a_{8}$$

$$A_{3} = (-a_{4} - a_{9})\mu^{2} + (-a_{1}a_{4} - a_{1}a_{9} + a_{3}a_{7} + 2a_{4}a_{9} - 2a_{5}a_{8})\mu$$

$$+ (a_{1}a_{4}a_{9} - a_{1}a_{5}a_{8} + a_{2}a_{5}a_{7} - a_{3}a_{4}a_{7})$$

$$A_{4} = (a_{4}a_{9} - a_{5}a_{8})\mu^{2} + (a_{1}a_{4}a_{9} - a_{1}a_{5}a_{8} + a_{2}a_{5}a_{7} - a_{3}a_{4}a_{7})\mu$$

Using the Routh-Hurwitz criterion, the characteristic equation has negative characteristic roots if and only if A_1, b_1, c_1, d_1 are positive. That is, $A_1, A_2, A_3, A_4 > 0, A_1A_2 > A_3$ and $(A_1A_2 - A_3)A_3 > A_1^2A_4$. Therefore, the TB disease spread model around the endemic equilibrium point is asymptotically stable by fulfilling the three conditions above, i.e., $A_1, A_2, A_3, A_4 > 0, A_1A_2 > A_3$ and $(A_1A_2 - A_3)A_3 > A_3$ $A_1^2 A_4$.

3.3 The Optimal Control Conditions

Optimal control is a model required to assist in making decisions about obtaining a goal [15]. The objective to be obtained from this study is to minimize the number of latent and infected individuals and operational costs in the control efforts used. The objective function is defined as follows:

$$J(u_1, u_2) = \min \int_{t_0}^{t_f} \left[a_1 S + a_2 L + a_3 I + \frac{1}{2} \left(b_1 u_1^2(t) + b_2 u_2^2(t) + b_3 u_3^2(t) \right) \right] dt$$

with constraints:

$$\frac{dS}{dt} = \theta N - \alpha \beta SI - \mu S + u_1 S$$

$$\frac{dE}{dt} = \alpha \beta (1 - m) SI - (\gamma + \mu + u_2) L$$

$$\frac{dI}{dt} = \alpha \beta m SI + \gamma h L - (\eta + \mu + \sigma + u_3) I$$

$$\frac{dR}{dt} = \eta I + \gamma (1 - h) L + u_2 L + u_3 I - \mu R$$

with the description as shown in Table 2.

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where:

Parameter	Description
u_1	Control for the presence of vaccination
u_2	Control for latent case finding
u_3	Control in the form of infected case finding
a_1	Weight on susceptible individuals
a_2	Weight on latent individual
<i>a</i> ₃	Weight on infected individual
b_1	Weight on vaccination control
b_2	Weight on latent case finding control
b_3	Weight on infected case finding control

 Table 2. Control Parameter

 a_i and b_i is the parameter weight coefficient to minimize the population of Latent and Infected individuals based on the costs incurred in each control effort, where $a_i, b_i > 0$ for each i = 1,2,3. t_0 and t_f are the start time and end time.

The steps used in solving optimal control of the spread of TB using the Pontryagin Minimum Principle are as follows [16]:

Step 1: Form the Hamiltonian function, such as

$$H = a_{1}S + a_{2}L + a_{3}I + \frac{1}{2} \left(b_{1}u_{1}^{2}(t) + b_{2}u_{2}^{2}(t) + b_{3}u_{3}^{2}(t) \right) + \lambda_{1} \left[\theta N - \alpha\beta SI - \mu S + u_{1}S \right] + \lambda_{2} \left[\alpha\beta(1-m)SI - (\gamma + \mu + u_{2})L \right] + \lambda_{3} \left[\alpha\beta mSI + \gamma hL - (\eta + \mu + \sigma + u_{3})I \right] + \lambda_{4} \left[\eta I + \gamma(1-h)L + u_{2}L + u_{3}I - \mu R \right]$$
(3)

Step 2: Compute the Hamiltonian function (*H*) over all controls u, Stationary conditions can be obtained by lowering Equation (3) to each control variable u_1, u_2 and u_3 .

• Equation H is derived against u_1 , is obtained

$$u_1^*(t) = \frac{\lambda_1}{b_1} S$$

• Equation *H* is derived against u_2 , is obtained

$$u_2^*(t) = \frac{(\lambda_2 - \lambda_4)}{b_2} h$$

• Equation *H* is derived against u_3 , is obtained

$$u_3^*(t) = \frac{(\lambda_3 - \lambda_4)}{b_3}h$$

Step 3: Form the optimal Hamiltonian function (H^*) by substituting $u^*(t)$ into the Hamiltonian function (H),

$$\begin{split} H^* &= a_1 S + a_2 L + a_3 I + \frac{1}{2} \left(-\frac{\lambda_1}{b_1} S^2 + \frac{(\lambda_2 - \lambda_4)^2}{b_2} L^2 + \frac{(\lambda_3 - \lambda_4)^2}{b_3} I^2 \right) + \lambda_1 \left[\theta N - \alpha \beta S I - \mu S - \frac{\lambda_1}{b_1} S^2 \right] \\ &+ \lambda_2 \left[\alpha \beta (1 - m) S I - \left(\gamma + \mu + \frac{(\lambda_2 - \lambda_4)}{b_2} L \right) L \right] \\ &+ \lambda_3 \left[\alpha \beta m S I + \gamma h L - \left(\eta + \mu + \sigma + \frac{(\lambda_3 - \lambda_4)}{b_3} I \right) I \right] + \lambda_4 [\eta I + \gamma (1 - h) L + \frac{(\lambda_2 - \lambda_4)}{b_2} L^2 \\ &+ \frac{(\lambda_3 - \lambda_4)}{b_3} I^2 - \mu R] \end{split}$$

Step 4: Determining the state $\dot{x}^*(t)$ and costate equation $\lambda^*(t)$,

• The state equation under optimal conditions is obtained by deriving the optimized Hamiltonian function with regard to λ ,

$$\dot{x}^*(t) = + \left(\frac{\partial H}{\partial \lambda}\right)_*$$

is obtained

$$\dot{S}^{*}(t) = \frac{\partial H^{*}}{\partial \lambda_{1}} = u_{1}^{*}S + \theta N - \alpha\beta SI - \mu S$$

$$\dot{L}^{*}(t) = \frac{\partial H^{*}}{\partial \lambda_{2}} = -u_{2}^{*}L + \alpha\beta(1-m)SI - (\gamma+\mu)L$$

$$\dot{I}^{*}(t) = \frac{\partial H^{*}}{\partial \lambda_{3}} = -u_{3}^{*}I + \alpha\beta mSI + \gamma hL - (\eta+\mu+\sigma)I$$

$$\dot{R}^{*}(t) = \frac{\partial H^{*}}{\partial \lambda_{4}} = u_{2}^{*}L + u_{3}^{*}I + \eta I + \gamma(1-h)L - \mu R$$

• The costate equation under optimal conditions is obtained by deriving the optimized Hamiltonian function for each state variable,

$$\dot{\lambda}^*(t) = -\left(\frac{\partial H}{\partial x}\right)_*$$

is obtained

$$\dot{\lambda}_1^*(t) = -a_1 - \lambda_1 [-\alpha\beta I - \mu + u_1^*] - \lambda_2 \alpha\beta(1-m)I - \lambda_3 \alpha\beta mI$$

$$\dot{\lambda}_2^*(t) = -a_2 - \lambda_2(\gamma + \mu + u_2^*) - \lambda_3 \gamma h - \lambda_4(\gamma(1-h) + u_2^*)$$

$$\dot{\lambda}_3^*(t) = -a_3 - \lambda_1 \alpha\beta S - \lambda_2 \alpha\beta(1-m)S - \lambda_3 [\alpha\beta mS - (\eta + \mu + \sigma + u_3^*)] - \lambda_4 [\eta + u_3^*]$$

$$\dot{\lambda}_4^*(t) = \mu\lambda_4$$

Step 5: Using the previous state and costate solutions, the optimal control $u^*(t)$ is obtained from step 2.

3.4 Numerical Simulation

In this discussion, the initial conditions of each population are given, such as S(0) = 2.818.595, L(0) = 56.675, I(0) = 6.391, R(0) = 3.054. The initial values of the variables were obtained from the Public Health Bureau in Surabaya City. The parameter values used to simulate the optimal control problem in an effort to reduce the spread of TB disease by controlling the operational costs of providing control in the form of vaccination, latent and infected case findings are obtained from the calculation of data obtained from the population development profile of Population and Civil Registration Service and Public Health Bureau in Surabaya City in 2018-2022. Furthermore, simulations were carried out using the 4th-order Runge Kutta Method so that the following results like the explanation on the next paragraph.

In **Figure 3**(a), the simulation results of Susceptible individuals without and with control are obtained. It is known that Susceptible individuals, after being given control, increased when compared to before being controlled with an increase of 3.316.465.420 people. This happens because the provision of control in the form of vaccination (u_1) can suppress the rate of Susceptible population to Latent. In **Figure 3**(b), the simulation results of Latent individuals without and with control are obtained. It is known that Latent individuals after being given control, decreased when compared to before control. The Latent population before control amounted to 3.115 people in the 10th year. However, after the control, in 9th year and before 4^{th} year there will be no Latent individuals. This happens because the provision of control in the form of latent case finding (u_2) can suppress the Latent population rate.



Figure 3. Comparison of Changes in Population Size without and with Control (a) Susceptible Individual, (b) Latent Individual



Figure 4. Comparison of Changes in Population Size without and with Control (a) Infected Individual, (b) Recovered Individual

The simulation results of Infected individuals without and with control are described in Figure 4(*a*). It is known that in the 10th year before and after being given control, there are no Infected individuals in the system. However, after giving control in the form of infected case finding (u_3) , it can increase the rate of change of Infected individuals to Recovered individuals. Before being controlled, the system will have no Infected individuals in the 8th year of 6th month. After being given control, the system will not have any Infected individuals into Recovered individuals is faster than before being controlled. In Figure 4(*b*), the simulation results of Recovered individuals without and with control are obtained. It is known that Recovered individuals after being given control increase of 5,964 people. This happens because the provision of control in the form of latent case finding (u_2) on Latent individuals and infected case finding (u_3) on Infected individuals can increase the population of Recovered individuals.



Figure 5. Change Graph of Providing Control

The amount of control u_1, u_2 and u_3 with the weighted cost of each control is 0,33. It can be seen in **Figure 5** that at u_1 when t = 0 to t = 10 the maximum is 1 because the Susceptible population must continue to be vaccinated to prevent the spread of TB. In the control u_2 when t = 0 to t = 9,3 the maximum is 1, because there is still a Latent population. While starting from t = 9,3 the minimum control is 0 where at this time u_2 control is no longer needed because the Latent population is minimal. Similarly, in u_3 control when t = 0 to t = 8,5 the maximum is 1, because there is still an Infected population. While starting from t = 8,5 the minimum control is 0 where at this time control u_3 is no longer needed because the Individual population is minimal.

4. CONCLUSIONS

Based on the simulation results that have been conducted, it shows the effectiveness of the control in controlling the spread of TB disease in Surabaya City so that it can increase the number of Susceptible individuals or retired individuals by 100%. In addition, it can reduce the number of Latent infected individuals by 100% and the number of actively infected or Infected individuals by 100%. This is done with minimum control operational costs with a cost weight on each control of 0,33. Optimal control aims to minimize the latent and active infected population, as well as the weight of the control process. Finally, numerical simulations show that optimal control has been performed to suppress the spread of TB disease, and this is in line with the regulated objective function.

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