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Abstract. Tuberculosis is one of the deadliest infectious diseases in the world. In 2020, 9.9 million people were infected and 1.5 million died. East Java province ranks third with 43,268 tuberculosis cases. The purpose of this research is to see the condition of the spread of TB without and given optimal control. The mathematical model SEIR is a model that can analyze the spread of the disease tuberculosis. In this study, we added a variable treatment compartment to the SEIR model. We used 4 antibiotics in the intensive phase and added isoniazid and rifampin in the advanced phase as the optimal control parameters. Optimal control uses Pontriagin's maximum principle as the derivative to modify the SEIR model and is described by a Runge-Kutta order 4 scheme. It shows both the useful parameters in the optimal control with a maximum value of 1 and plots where the effect of optimal control exists further constrained—the number of people infected the Tuberculosis.

Keywords: Optimal Control, Tuberculosis, Mathematics Model

1 Preliminary

1.1 Background

Tuberculosis, caused by Mycobacterium tuberculosis, remains the leading cause of death worldwide. Especially in 2020, 9.9 million people were infected and 1.5 million died. [8]. Indonesia is one of the developing countries with the highest number of tuberculosis cases in the world, with a total of 824,000 tuberculosis infections and 93,000 deaths per day. [20].East Java was chosen for this study because nonadherence to recommended medications in the community remained high, with patient abandonment and inconsistency, and the number of cases in 2021 was 43,268 live. [5] [21] [18]. It is necessary to divide the disease into two stages, an intensive stage, and an advanced stage, and to administer drugs regularly. [16]. Also in terms of carrying out multi-sectoral campaigns for various interest groups, for example Advocacy, standby work, and association with stakeholders [22].

1.2 Previous Research

The prevalence of tuberculosis disease has been discussed in several previous studies. In the first research, SEIR (Susceptible, Exposed, Infection, Recovery) models were used to generate independent effects from each compartment, analyzing tuberculosis transmission at the disease-free stable point and reproductive numbers for system performance equations within compartments [3]. Subsequent studies discussed deterministic and probabilistic differences demonstrating successful modeling of tuberculosis infection using the transmission dynamics of the stochastic SEIR (Susceptible, Exposed, Infection, Recovery) model over time[15]. As for studies that added treatment control parameters and chemoprophylaxis, their function is to reduce the population of latently infected and active infections to reduce the spread of TB, with the optimal control effect when used simultaneously, increasing [17].

The difference in this study was that 4 antibiotics in the form of Isoniazid, Rifampicin, Ethambutol, and Pyrazinamide were administered for the first 2 months, followed by the addition of a compartmental variable to the regimen containing optimal control parameters for the intensive phase to maximize the process of treatment. That was continuously every 2 weeks. The next step is to add the drugs Isoniazid and Rifampin. It kills persistent (dormant) bacteria and prevents them from reappearing but for a longer period [4][23]. It can include studies that help analyze optimal control models in the SIRC (Susceptibility, Infection, Recovery, Cross-Immunity) model of influenza [24]. This research uses the dynamic system as the control input and uses the Pontryagin Maximum Principle, an optimal control technique to determine the optimal control value. [10][11]. Various studies are available to support the Pontryagin maximum principle. Next, to analyze and formulate an age-classified structured tuberculosis transmission model and apply optimal control strategies by adding variables of prevention, latent chemoprophylaxis, and active treatment efforts also useful [6].

1.3 Research Purposes

This study provides the demographic prevalence of tuberculosis in East Java. Furthermore, by adding treatment subpopulation compartments with focused and extended optimal control parameters, the effects of strategies are discussed in more detail.

2 Formulation Model

2.1 Assumption Modification

In this study, we modify the TB SEIR model using the following assumptions: It is contracted only through close contact with people who are not immune to tuberculosis. The combination of age, sex, social class, race and climatic conditions does not affect the likelihood of human exposure. Mortality rates were assumed to be stable and similar in all individuals, and mortality rates were continuously

adjusted as data were completed. In this case, the population is fixed. Where μ is the proportion of non-immune humans born into the vulnerable class, and μS is the natural death of the vulnerable subpopulation. infections in confined spaces. No emigration, immigration, or both, or death within the population. Each plot has the same natural mortality rate for the population [3].

The assumptions, compartment diagram model, and parameters used for the development of the above research are as follows: The population rate (α) is different from the natural mortality rate (μ), and Mortality from tuberculosis infection (ϕ) is different from natural mortality (μ). This is because the probability of dying from tuberculosis is 50% compared to natural death [19].

2.2 TB Model & Parameters

Below are the modified tuberculosis models from the [3] study and the parameters used:

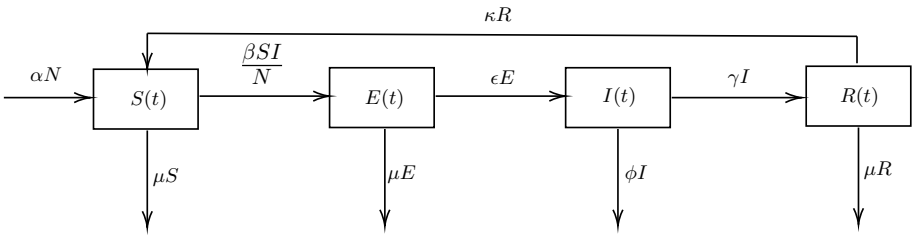

Fig. 1. *Susceptible, Exposed, Infected, Recovery* (SEIR) TB Model

Based on the compartment diagram in Fig. (1), We can write the following equation :

$$\begin{aligned} S^{\bullet}(t) &:= \frac{dS(t)}{dt} = \alpha N + \kappa R(t) - S(t)\Big(\frac{\beta I(t)}{N} + \mu\Big) \\ E^{\bullet}(t) &:= \frac{dE(t)}{dt} = \frac{\beta S(t) I(t)}{N} - E(t)\Big(\epsilon + \mu\Big) \\ I^{\bullet}(t) &:= \frac{dI(t)}{dt} = \epsilon E(t) - I(t)\Big(\gamma + \phi\Big) \\ R^{\bullet}(t) &:= \frac{dR(t)}{dt} = \gamma I(t) - R(t)\Big(\mu + \kappa\Big) \end{aligned} \tag{1}$$

where : $N = S(t) + E(t) + I(t) + R(t)$

: $S(0) = S_0 \geq 0; E(0) = E_0 \geq 0; I(0) = I_0 \geq 0; R(0) = R_0 \geq 0$

Table 1. Table of Parameters

Parameter	Description
α	Rate of the population
μ	Rate of natural deaths
β	Comparison of TB-infected population and susceptible TB rate
ϵ	Rate of the exposed population who have been infected with TB
ϕ	Mortality from TB infection
γ	The rate at which the infected population can recover
κ	The proportion of recovered patients who are susceptible to getting TB

3 Formulation of Optimal Control

3.1 Optimal Control Model

This section presents the problem of optimal control of the population dynamic of the prevalence of tuberculosis disease using optimal control parameters for the intensive care stage (u_1) in the compartment between the TB-infected population and the treatment population. increase. Moreover, the optimal control parameters for advanced stage (u_2) lie in the range between the subpopulations receiving treatment and those recovering from TB. All these optimal controls can be modeled as follows:

$$\begin{aligned}
S^{\bullet}(t) &:= \frac{dS(t)}{dt} = \alpha N + \kappa R(t) - S(t)\Big(\frac{\beta I(t)}{N} + \mu\Big) \\
E^{\bullet}(t) &:= \frac{dE(t)}{dt} = \frac{\beta S(t) I(t)}{N} - E(t)\Big(\epsilon + \mu\Big) \\
I^{\bullet}(t) &:= \frac{dI(t)}{dt} = \epsilon E(t) - I(t)\Big(u_1(t) + \phi\Big) \\
T^{\bullet}(t) &:= \frac{dT(t)}{dt} = u_1(t) I(t) - T(t)\Big(u_2(t) + \phi\Big) \\
R^{\bullet}(t) &:= \frac{dR(t)}{dt} = u_2(t) T(t) - R(t)\Big(\mu + \kappa\Big)
\end{aligned} \tag{2}$$

where : $N = S(t) + E(t) + I(t) + T(t) + R(t)$
: $S(0) = S_0 \geq 0; E(0) = E_0 \geq 0; I(0) = I_0 \geq 0; T(0) = T_0 \geq 0; R(0) = R_0 \geq 0$

3.2 Hamiltonian Function

From the above equation (2), we can implement the optimal control strategy by minimizing the value weighting function as:

$$J[u_1(t), u_2(t)] = \int_{t_0}^{t_f} \left(A_1 I(t) + A_2 T(t) + C_1 u_1^2(t) + C_2 u_2^2(t)\right)\, dt \tag{3}$$

where :

1. t_0 = initial condition for first year, and
2. t_f = final condition for seventh year

Where C_1 and C_2 are cost weights for reducing the number of tuberculosis infections and treatment failure deaths. The next step is to find the optimal control values such that:

$$\begin{aligned}
J(u_1^{\star}, u_2^{\star}) &= min\{J(u_1, u_2) : u \in U\} \\
U &= \{u(t) : 0 \leq u_i(t) \leq 1, \forall t \in [t_0, t_f]\}; i \ = 1,\ 2
\end{aligned} \tag{4}$$

If the optimal control value is 0 within this interval, this has no effect on the control performed. Also, when the value is 1, the optimal control cost is maximized.

3.3 Pontryagin Maximum Principle

Optimal control $u_1^\star$ and $u_2^\star$ are model constraints (3) using *Pontryagin maximum principle* [9][13][6]. This principle combines the equations (3) and (4) to solve the problem of minimizing the Hamiltonian H with respect to u_1 and u_2 such as:

$$\mathcal{H}(S(t), E(t), I(t), T(t), R(t), u_1(t), u_2(t), \lambda_i(t), t) = \Big(A_1 I(t) + A_2 T(t) + C_1 u_1^2(t) + C_2 u_2^2(t)\Big) + \sum_{i=1}^{5} \lambda_i f_i \quad (5)$$

If f_i is specified on the right side of the model 2, the variable *adjoint* satisfies the *co-state* system of equations as:

$$\begin{aligned}
\lambda_1^{\bullet\star}(t) &:= -\Big(\frac{\partial \mathcal{H}^\star(t)}{\partial S^{\bullet\star}(t)}\Big) = -\Big(\lambda_1^\star(t)\Big[-\frac{\beta I^\star(t)}{N} - \mu\Big] + \lambda_2^\star(t)\frac{\beta I^\star(t)}{N}\Big)\\
\lambda_2^{\bullet\star}(t) &:= -\Big(\frac{\partial \mathcal{H}^\star(t)}{\partial E^{\bullet\star}(t)}\Big) = -\Big(\lambda_2^\star(t)\Big[-\epsilon - \mu\Big] + \lambda_3^\star(t)\epsilon\Big)\\
\lambda_3^{\bullet\star}(t) &:= -\Big(\frac{\partial \mathcal{H}^\star(t)}{\partial I^{\bullet\star}(t)}\Big) = -\Big(A_1 + \Big[\frac{\beta S^\star(t)}{N}\Big]\Big(\lambda_1^\star(t) - \lambda_2^\star(t)\Big) + \lambda_3^\star(t)\Big[-u_1^\star(t) - \phi\Big] + \lambda_4^\star u_1^\star(t)\Big)\\
\lambda_4^{\bullet\star}(t) &:= -\Big(\frac{\partial \mathcal{H}^\star(t)}{\partial T^{\bullet\star}(t)}\Big) = -\Big(A_2 + \lambda_4^\star(t)\Big[-u_2^\star(t) - \phi\Big] + \lambda_5^\star(t)u_2^\star(t)\Big)\\
\lambda_5^{\bullet\star}(t) &:= -\Big(\frac{\partial \mathcal{H}^\star(t)}{\partial R^{\bullet\star}(t)}\Big) = -\Big(\lambda_1^\star(t)\kappa + \Big[\mu - \kappa\Big]\lambda_5^\star(t)\Big)
\end{aligned} \quad (6)$$

with transverse initial condition: $\lambda_i(t_f) = 0; i = 1, 2, 3, 4, 5$
The next step is needed to satisfy the optimal control $u = (u_1^\star, u_2^\star)$ by minimizing the Hamiltonian with respect to U as:.

$$u_1^\star(t) = \begin{cases} 0, & u_1(t) \le 0 \\ \frac{\Big(\lambda_3(t) - \lambda_4(t)\Big) I(t)}{2C_1}, & 0 < u_1(t) < 1 \\ 1, & u_1(t) \ge 1 \end{cases} \quad (7)$$

$$u_2^\star(t) = \begin{cases} 0, & u_2(t) \le 0 \\ \frac{\Big(\lambda_3(t) - \lambda_4(t)\Big) I(t)}{2C_1}, & 0 < u_2(t) < 1 \\ 1, & u_2(t) \ge 1 \end{cases} \quad (8)$$

Next, solve the system *state* $x^\bullet(t) = \frac{\partial \mathcal{H}}{\partial \lambda}$. where $x = (S, E, I, T, R), \lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5)$ (using initial condition $x_{0)}$. Finally, the system of equations *co-state* $\lambda^\bullet(t) = -\frac{\partial \mathcal{H}}{\partial x}$ using the transverse condition $\lambda_i(t_f) = 0, i = 1, 2, 3, 4, 5$.

Based on all the above steps, the optimal control $(u_1^\star, u_2^\star)$ obtains the following theorem.

Theorem 1. Optimal control $(u_1^\star, u_2^\star)$ minimizing value weightness for $J(u_1^\star, u_2^\star)$ to U is

$$u_1^\star(t) = max\left\{0, min\left\{1, \frac{\Big(\lambda_3(t) - \lambda_4(t)\Big)I(t)}{2C_1}\right\}\right\}$$

$$u_2^\star(t) = max\left\{0, min\left\{1, \frac{\Big(\lambda_4(t) - \lambda_5(t)\Big)T(t)}{2C_2}\right\}\right\}$$

4 Result and Discussion

4.1 Parameter Value

The parameters used in this study are: $\alpha = 0.70$ [2]; $\mu = 0.0047$ [12]; $\beta = 0.5853$ [14]; $\epsilon = 0.2007$ [1]; $\phi = 0.09$ [7]; $\gamma = 0.75$ [6]; and $\kappa = 0.02$ [14], with initial condition $S(0) = 38{,}606{,}470$; $E(0) = 199{,}574$; $I(0) = 48{,}739$; $T(0) = 2{,}458$; and $R(0) = 17{,}320$. To complete this simulation, first, use Runge-Kutta Order 4 *Forward* in the *state* equations. A second eventuality is to use *Backward* of RKO4 in the *co-state* equations.

The assumption used in this study is that if the value of C_1 based on the intensive care stage is greater than C_2, 4 antibiotics are required to prevent the emergence of drug immunity. Then. in advanced stages, he only needs two antibiotics. Of course, it helps prevent relapses and reduce the number of TB infections [4]. Therefore, the weights used in the objective function of the 3 equation are $C_1 = 90$ and $C_2 = 70$ [6].

4.2 Numerical Simulation

Below are the simulation results for the TB model without and with optimal control, consisting of: optimal control simulation diagram; simulation chart of subpopulations susceptible to TB, subpopulations exposed to TB, TB-infected subpopulation, and subpopulation recovery of TB, except in the treatment subpopulation it is not shown because there are no different charts without and with optimal control.

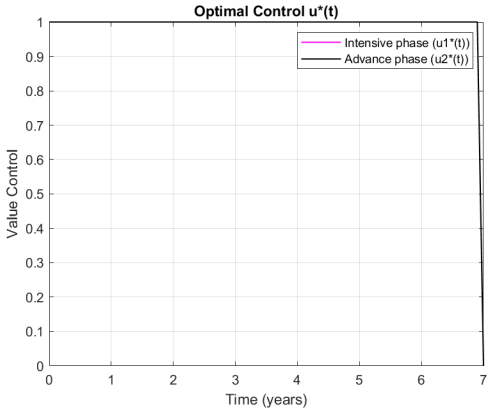

Fig. 2. Optimal Control $u^{\star}$

From the figure (2) we can see that the best-fit control plots for the four intensive and advanced antibiotic stages from day 1 to day 7 are congruent and the value obtained for each is 1. This indicates that two optimal controls can have a large impact on reducing the number of TB infections.

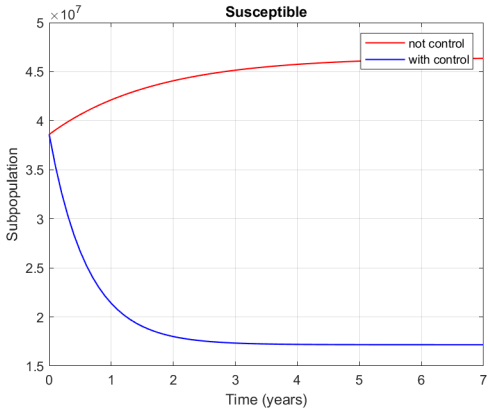

Fig. 3. Susceptible Subpopulation

Based on the figure above (3) for the optimal uncontrolled graph with a large increase from year 1 to year 7, with additional subpopulations added each year thereafter. Unlike optimal control charts, there is a sharp decline, resulting in a decreasing number of subpopulations each year. This is due to the optimal control action to control the number of people moving to the next step.

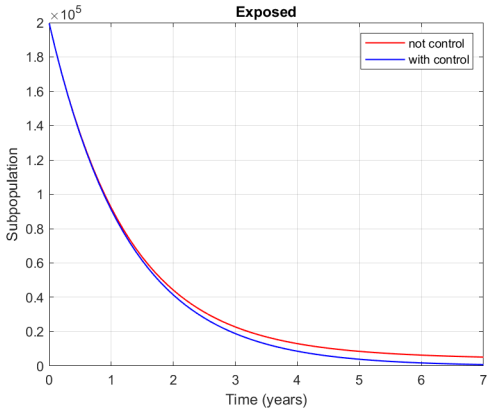

Fig. 4. Exposed Subpopulation

From the figure (4), we can see that the plots without and with optimal control converge at year 1 and start to spread out from year 2 to year 7. This suggests that TB-exposed subpopulations exist only in enclosed areas and are best controlled in other compartments, thus affecting population numbers and preventing them from entering the next compartment. It can be concluded that the population will decrease significantly in.

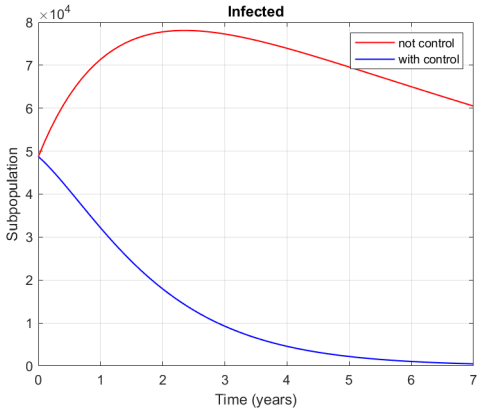

Fig. 5. Infected Subpopulation

There is a big difference in the figure (5). We observe that the uncontrolled graph increases. Optimal control occurs in this compartment in the form of four powerful antibiotics. At this stage, infected patients are given drugs such as: Isoniazid, Rifampicin, Ethambutol, and Pyrazanamide and will be directly monitored daily to prevent the emergence of drug resistance. The presence of optimal controls reduces the peak number of highly influential individuals before moving on to the next compartment.

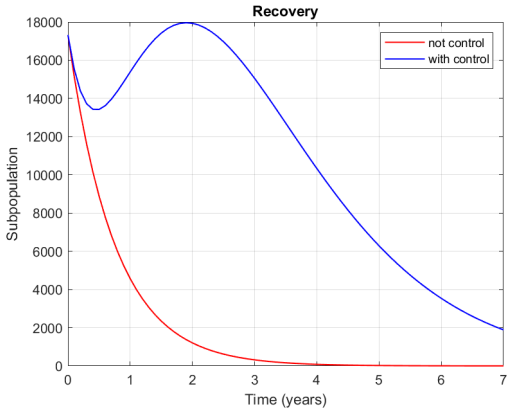

Fig. 6. Recovery Subpopulation

The figure (6) shows that there is a large difference between the figures without and with optimal control. Without optimal control, the curve decreased dramatically from his 1st year to his 7th year, and not a single person recovered from TB. This differs from the best control, where the patient continues to follow existing treatment protocols to declare cure, Isoniazid and Rifampin for 4 months. The difference between the two plots is that the change in infection rate in individuals does not decrease significantly compared to no controls before individuals who recover from TB and become susceptible to TB again become ill. There is an optimal contrast such as .

5 Conclusion

Numerical results show that the presence of the treatment compartment can reduce the number of TB infections. In addition, the infected compartment has two phases of TB treatment that must be followed to affect and follow changes in population rates to reduce the number of infected TB. Parameters are also combined. Affected individuals have recovered from TB, and the number of TB infections has increased slightly.

In addition, the government intends to mandate the administration of anti-tuberculosis drugs for drug-resistant TB in the form of 2RHZE/4RH (Isoniazid, Rifampin, Pyrazinamide, Ethambutol due to 2 months; and Isoniazid and Rifampin due to 4 months) and support from short courses of treatment by direct observation [4].

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