A mathematical model for chemotherapy paradoxical reaction in Tuberculosis transmission

Febriana Tri Rahmawati\textsuperscript{1}, Alhadi Bustamam\textsuperscript{1}, and Dipo Aldila\textsuperscript{*1}

\textsuperscript{1}Department of Mathematics, Universitas Indonesia, 16424 Depok, Indonesia
E-mail: "aldiladipo@sci.ui.ac.id

Abstract. An SEIR with the age-class model is analyzed in this article to understand how paradoxical reaction in Tuberculosis (TB) treatment impact the success of TB control program. Mathematical model analysis of equilibrium points and the basic reproduction number of the model are analyzed. A numerical experiment about the dependency of basic reproduction number respect to the change of other parameters is given to give an illustration of how the paradoxical reaction might impact the success of chemotherapy intervention on TB. From the numerical investigation, we find that the paradoxical reaction plays an important role to determine the TB will coexist or disappear.

1. Recent facts about Tuberculosis (TB)
Tuberculosis (TB) is a contagious disease caused by the bacterium \textit{Mycobacterium tuberculosis}. The disease spreads with an airborne intermediate and is transmitted from an infected person to a healthy person through touch or sneezing \cite{1}. The transmission process occurs through small water particles released when infected people are coughing or sneezing and attached to the healthy person. When bacteria enter the body of a healthy person, there are two infection conditions, namely the situation when the bacteria are still passive, and when bacteria directly become active in the body. Passive bacterial conditions are also referred to as latent TB infection conditions. This latent condition does not show the visible characteristics of TB \cite{2}. TB symptoms that appear are fever, cough, shortness of breath, chest pain, and malaise \cite{3}.

TB prevention can be done by administering the Bacille Calmette-Guerin (BCG) vaccine, which until now is believed to reduce the potential for this disease. The primary purpose of this vaccine is to ward off bacterial infections. BCG vaccine is most useful for protecting infants and children, with an active period of approximately 15 years. TB treatment should include early and advanced stages. Treatment in the early stages is intended to kill bacteria effectively and given for two months. Advanced treatment is a crucial stage to kill the remaining bacteria in the body so that patients can recover and prevent recurrence. If the procedure is done in an orderly manner, then the standard of 6 months of the patient can be healed. The main anti-TB drugs commonly used are rifampicin and isoniazid \cite{4}.

Sometimes chemotherapy doesn’t always cure. Chemotherapy in patients with tuberculosis also has several problems, including paradoxical reactions. Paradoxical reaction (PR) during chemotherapy for tuberculosis (TB) has been defined as clinical or radiological worsening of preexisting TB lesions or the development of new lesions in a patient who has already received anti-TB therapy for several days and whose condition has been reported to be improving. This
paradoxical reaction usually occurs after initial treatment for 1-2 months after the beginning of the treatment period [5]. Symptoms that typically appear are high fever, deterioration of chest radiographs, and swollen lymph nodes [6]. Paradoxical reactions can be caused by an abnormal immune response or when the immune system decreases, but it is not known precisely what causes it [7]. Paradoxical reactions are more straightforward to attack children who do not have immunity against tuberculosis. Children with paradoxical reactions may show symptoms of TB more clearly than children without paradoxical reactions [5].

The spread of TB disease can be modeled mathematically. One commonly used mathematical model is the SIR epidemic model discovered by Kermack and McKendrick in 1927. In the range of TB disease spread, i.e., with age-class divisions [8] and with the effect of vaccines [2].

Unlike the articles mentioned earlier, in this article, we construct the mathematical model of TB involving two age class, i.e., children and adult classes. We also include the paradoxical reaction of TB intervention which impacts in a prolongation of the duration of human to be recovered from TB.

This paper is organized as follows. In section 2, we present the construction of the mathematical model. In section 3, we analyzed the model and followed with numerical experiments in section 4. Finally, in section 5, we give some conclusions and discussions.

2. Mathematical model derivation

To analyze the impact of the paradoxical reaction of chemotherapy in TB control program, we will use a deterministic SEIR model with two age class in each compartment (i = c denote children, while i = a denote adult class). We divide the human population in susceptible compartments \((S_c, S_a)\), infected by TB but not yet infectious, let call it as exposed TB \((E_c, E_a)\), infected compartments \((I_c, I_a)\), and recovered compartments \((R_c, R_a)\). The mathematical model is given below which constructed based on followed assumptions.

\[
\begin{align*}
\frac{dS_c}{dt} &= \theta - ((\rho_c + (1 - \rho_c)) \beta_c I_a + m + \mu) S_c, \\
\frac{dS_a}{dt} &= mS_c - ((\rho_a + (1 - \rho_a)) \beta_a I_a + \mu) S_a, \\
\frac{dE_c}{dt} &= ((1 - \rho_c) S_c + R_c) \beta_c I_a - (m + \mu + \varepsilon) E_c, \\
\frac{dE_a}{dt} &= ((1 - \rho_a) S_a + R_a) \beta_a I_a + mE_c - (\mu + \varepsilon) E_a, \\
\frac{dI_c}{dt} &= \rho_c \beta_c S_c I_a + \varepsilon E_c + \eta R_c - (q_c \gamma_1 + (1 - q_c) \gamma_2 + m + \mu) I_c, \\
\frac{dI_a}{dt} &= \rho_a \beta_a S_a I_a + \varepsilon E_a + \eta R_a + mI_c - (q_a \gamma_1 + (1 - q_a) \gamma_2 + \mu) I_a, \\
\frac{dR_c}{dt} &= (q_c \gamma_1 + (1 - q_c) \gamma_2) I_c - (\beta_c I_a + m + \mu + \eta) R_c, \\
\frac{dR_a}{dt} &= (q_a \gamma_1 + (1 - q_a) \gamma_2) I_a + mR_c - (\beta_a I_a + \mu + \eta) R_a.
\end{align*}
\]

Some explanation about the infection and treatment term in the model (1) is given as follows. Since infection of TB mainly only caused by adult people [9], the infection process only occurs when susceptible or recovered compartments made successful contact with infected adult compartment \((I_a)\). When susceptible human successfully gets infected, \(\rho_i\) proportion of them will go directly to infectious compartment caused by the fast infection progression, while
the rest of them, $1 - \rho_i$, goes to the exposed compartment. The chemotherapy treatment is given in the rate of $\gamma_j$, when $j = 1$ denote the recovery rate without paradoxical effect, while $j = 2$ is the recovery rate with paradoxical effect. We assume that the proportion of successful chemotherapy treatment as a constant parameter, let denote it as $q_i$. Therefore, the recovery rate without paradoxical effect is given by $q_i \gamma_1 I_i$, while $(1 - q_i) \gamma_2 I_i$ gives the recovery rate with paradoxical reaction. Please note that since the paradoxical reaction to chemotherapy intervention in TB will prolong the infection period, we have that $\gamma_2 < \gamma_1$.

3. Theoretical analysis of the model

There are two equilibrium points of the model (1), i.e., the disease-free equilibrium point which given by

$$\Omega_1 = \left( S_c = \frac{\theta}{m + \mu}, S_a = \frac{m \theta}{\mu (m + \mu)}, E_c = 0, E_a = 0, I_c = 0, I_a = 0, R_c = 0, R_a = 0 \right), \quad (2)$$

while the endemic equilibrium point is not in simple form to be shown. However, in a simpler model of system (1), i.e., when there are no age class involved in to the model $(m = 0, \rho_a = \rho_c = \rho, q_a = q_c = q, \beta_a = \beta_c = \beta)$, the endemic equilibrium point is given by

$$\Omega_2 = \left( S^* = \frac{\theta}{\beta I^* + \mu}, E^* = \frac{K (I^*)^3 + L (I^*)^2 + M I^*}{\varepsilon (\beta I^* + \mu) (\beta I^* + \eta + \mu)}, R^* = \frac{(q \gamma_1 + (1 - q) \gamma_2) I^*}{\beta I^* + \eta + \mu} \right), \quad (3)$$

with

$$K = \beta^2 q \gamma_1 + (1 - q) \beta^2 \gamma_2 + \beta^2 \mu, \quad L = (1 - q) 2 \beta \mu \gamma_2 - \beta^2 \rho \theta + 2 \beta \mu q \gamma_1 + \beta \eta \mu + 2 \beta \mu^2, \quad M = \mu^2 q \gamma_1 + (1 - q) \mu^2 \gamma_2 - \beta \eta \rho \theta - \beta \mu \rho \theta + \eta \mu^2 + \mu^3,$$

and $I^*$ is taken from the positive root of the two-degree polynomial in the form of:

$$A_2 (I^*)^2 + A_1 (I^*) + A_0 = 0, \quad (4)$$

with

$$A_2 = \beta^2 \mu (q (\gamma_1 - \gamma_2) + \varepsilon + \mu + \gamma_2), \quad A_1 = (R_0^\ast - \mathcal{K})(\mu (\mu + \varepsilon) (q (\gamma_1 - \gamma_2) + \eta + \mu + \gamma_2)), \quad A_0 = (1 - R_0^\ast)(\mu^2 (\mu + \varepsilon) (q (\gamma_1 - \gamma_2) + \eta + \mu + \gamma_2))$$

where $R_0^\ast = \frac{\beta \theta (q \gamma_1 + (1 - q) \gamma_2 + \epsilon + \mu + \gamma_2)}{\mu (\mu + \varepsilon) (q \gamma_1 - \gamma_2 + \eta + \mu + \gamma_2)}$, and $\mathcal{K} = \mu \left( 1 + \frac{\mu^2 (q (\gamma_1 - \gamma_2) + \epsilon + \mu + \gamma_2)}{\mu^2 (\mu + \varepsilon) (q \gamma_1 - \gamma_2 + \eta + \mu + \gamma_2)} \right)$. The existence of the endemic equilibrium $\Omega_2$ given in the following theorem.

**Theorem 1.** Endemic equilibrium $\Omega_2$ will

(i) have a unique positive endemic equilibrium ($\Omega_2 \in \mathbb{R}_4^1$) whenever $R_0^\ast > 1$, and

(ii) have two positive endemic equilibrium ($\Omega_2 \in \mathbb{R}_4^+$) whenever $\mathcal{K} < R_0^\ast < 1$ & $A_2^2 - 4A_2A_0 \geq 0$.

The proof of Theorem 1 is simple. Theorem 1(i) appears from the consequence that polynomial 4 will have exactly one positive root of $I^*$ when the multiplication of the root is negative, i.e., $\frac{A_0}{A_2} < 0$ which led us into a condition of $R_0^\ast > 1$. In the other hand, theorem 1(ii)
will have two positive root if and only if \( \frac{dK}{ds} > 0 \), \( -\frac{dK}{ds} > 0 \), and the discriminant of 4 should be non negative to guarantee the non-imaginary roots which gave us \( K < R_0^\ast \) and \( A_1^2 - 4A_2A_0 \geq 0 \).

Next, we analyze the basic reproduction number \( (R_0) \) of model (1) using the next-generation matrix method to determine \( R_0 \). The basic reproduction matrix of model (1) is the spectral radius of the next-generation matrix \( K_{sa} \) which taken by

\[
K_{sa} = -BS^{-1}C,
\]

where \( B, \Sigma \) and \( C \) are in the following form.

\[
B = \begin{bmatrix}
0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix}, \quad C = \begin{bmatrix}
\rho_c \beta_c S_c & 0 & 0 \\
\rho_a \beta_a S_a & 0 & 0 \\
(1 - \rho_c) \beta_c S_c + \beta_c R_c & \beta_c I_a & 0 \\
(1 - \rho_a) \beta_a S_a + \beta_a R_a & 0 & \beta_a I_a \\
-\beta_c R_c & -\beta_c I_a & 0 \\
-\beta_a R_a & 0 & -\beta_a I_a
\end{bmatrix},
\]

\[
\Sigma = \begin{bmatrix}
-q_a \gamma_1 - (1 - q_a) \gamma_2 - m - \mu & 0 & \varepsilon & 0 & \eta & 0 \\
 m & -q_a \gamma_1 - (1 - q_a) \gamma_2 - m - \mu & \varepsilon & 0 & \eta & 0 \\
0 & -m - \mu - \varepsilon & 0 & 0 & 0 & 0 \\
0 & 0 & -m - \mu - \varepsilon & 0 & 0 & 0 \\
q_a \gamma_1 + (1 - q_a) \gamma_2 & 0 & 0 & 0 & -\eta - m - \mu & 0 \\
0 & q_a \gamma_1 + (1 - q_a) \gamma_2 & 0 & 0 & m & -\eta - m - \mu
\end{bmatrix}.
\]

Although the \( R_0 \) of the complete model (1) cannot be shown analytically in this paper, the simpler form of \( R_0 \) for a simpler model, i.e., when \( m = 0, \rho_a = \rho_c = \rho, q_a = q_c = q, \beta_a = \beta_c = \beta \) is given by

\[
R_0 = \frac{\beta \theta (\mu \rho + \varepsilon) (\eta + \mu)}{\mu^2 (\mu + \varepsilon) (q \gamma_1 - q \gamma_2 + \eta + \mu + \gamma_2)}.
\]

Please note that this \( R_0 \) is the same with \( R_0^\ast \) which becomes the requirement to guarantee the existence of endemic equilibrium \( \Omega_2 \).

### 4. Numerical experiments

From the results in the previous section, it is indicated that \( R_0 \) hold a vital role to determine whether the TB will exist or vanish from the field, which also stated from many authors in other epidemiological models [11, 12, 13, 14]. They found that the disease will exist whenever \( R_0 > 1 \) and will vanish when \( R_0 < 1 \). Therefore, the numerical experiment in this section will be shown to see how the \( R_0 \) impact the dynamic of the model (1) and how it fluctuates depend on many parameters.

For the following simulations, we use set of parameters : \( \theta = \frac{10000}{65}, \beta_c = 1 \times 10^{-5}, \beta_a = 2.73 \times 10^{-5}, \gamma_1 = 0.3, \gamma_2 = 0.1, \rho_c = 0.1, \rho_c = 0.7, \eta = 0.0341, m = \frac{1}{15}, \varepsilon = 6, \mu = \frac{1}{65} \). The first simulation is performed to see how \( q_a \) and \( q_c \) determine the magnitude of \( R_0 \). From Figure 1, we can see that enlarging the proportion who do not get a paradoxical effect of TB chemotherapy (\( q_a \) and \( q_c \)) will reduce \( R_0 \). With this relation in hand between \( q_a \) and \( q_c \), determining \( R_0 \), we can determine how large is \( q_a \) or \( q_c \) to achieve the disease-free equilibrium condition. For an example, let \( q_c = 0.5 \), therefore it is needed \( q_a = 1 \) so that \( R_0 = 0.8746568876 < 1 \) while if
\(q_a = 0.8\) it is needed \(q_c = 0.7\) so that \(R_0 = 0.9981619276 < 1\). To confirm how the dynamic of susceptible compartments and infected compartments will change respect to the change of \(q_c\) and \(q_a\), the autonomous simulation of model (1) is given in Figure 2.

\[\text{Figure 1: Sensitivity of } R_0 \text{ respect to paradoxical parameters of chemotherapy (} q_a \text{ and } q_c).\]

\[\text{Figure 2: (a) The dynamic of susceptible compartments and infected compartments in system (1) with the fixed value of } q_a = 0.8 \text{ and the changed value of } q_c = 0, \text{ unsuccess chemotherapy treatment in children (blue) and } q_c = 0.7 \text{ (red). (b) The dynamic of susceptible compartments and infected compartments in system (1) with the fixed value of } q_c = 0.5 \text{ and the changed value of } q_a = 0.6 \text{ (blue) and } q_a = 1, \text{ success chemotherapy treatment in adult (red).}\]

5. Conclusions and discussion
In this paper, a mathematical model is made to look at the effect of the paradoxical reactions of chemotherapy on TB, which play an essential role in determining TB to coexist or disappear. From the model (1), we can get two equilibrium point, i.e., the disease-free equilibrium point and the endemic equilibrium point, and the basic reproduction number \(R_0\). We find that two conditions have to be fulfilled for the endemic equilibrium point to exist. Based on the numerical
simulation of the autonomous model, we see that Paradoxical reactions can make people with tuberculosis a longer time in their recovery. It appears that the smaller the proportion of individuals affected by the paradoxical reaction will increase $R_0$ and make the total susceptible individuals decrease as the total number of infected individuals increases due to longer treatment duration. Then, the higher the proportion of individuals who are not exposed to a paradoxical reaction will decrease $R_0$ and make total susceptible individuals accrue together with reduced total infected individuals due to no treatment duration as long as the individual is affected by a paradoxical reaction. Further development of the model could be involved an optimal control problem to see how the limitation of the budget for TB chemotherapy will impact the optimal intervention that can be implemented in the field.

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References
[1] World Health Organization 2018 Tuberculosis Fact sheet Reviewed January 2018
[2] Liu S, Li Y, Bi Y and Huang Q 2017 Mixed vaccination strategy for the control of tuberculosis: A case study in China Mathematical Biosciences and Engineering 14(3) 695-708
[3] Sudoyo A W, Setiyohadi B, Alwi I, Simadibrata M and Setiati S 2009 Buku Ajar Ilmu Penyakit Dalam (vol 3) (Jakarta: Interna Publishing)
[4] Kementrian Kesehatan Republik Indonesia Pedoman Nasional Pengendalian Tuberkulosis 2014 Kementrian Kesehatan RI Jakarta
[5] Olive Carole, Mouchet Franoise, Toppet Vronique, Haelterman Edwige and Levy Jack 2013 Paradoxical Re-actionDuring Tuberculosis Treatment in Immuno competentChildren: Clinical Spectrum and Risk Factors The Pediatric Infectious Disease Journal 32 446-449
[6] Centre for Disease Control and Prevention 2003 Treatment for Tuberculosis CDC United States
[7] Bloch S, Wickremasinghe M, Wright A, Rice A, Thompson M, & Kon O M 2009 Paradoxical reactions in non-HIV tuberculosis presenting as endobronchial obstruction European Respiratory Review 18(114) 295-299
[8] Zhao Y, Li M, & Yuan S 2017 Analysis of Transmission and Control of Tuberculosis in Mainland China 20052016 Based on the Age-Structure Mathematical Model International Journal of Environmental Research and Public Health 14(10) 1192
[9] Donald P R, Marais B J and Barry C E 2010 Age and the epidemiology and pathogenesis of tuberculosis The Lancet 375 pp 1852-1854
[10] Diekmann O, Heesterbeek J A P, and Roberts M G 2010 The Construction of Next-Generation Matrices For Compartmenal Epidemic Models J. R. Soc. Interface 7 873-885
[11] Aldila D., Agustin M. R., 2018 A Mathematical Model Of Dengue-Chikungunya Co-Infection In A Closed Population. J. Phys.: Conf Ser 974 012001(1)-13
[12] Aldila D, Nuraini N, Soewono E 2014 Optimal control problem in preventing of swine flu disease transmission Applied Mathematical Sciences (69-72) pp 3501-3512
[13] Bustamam A, Aldila D, Yuwanda A 2018 Understanding Dengue Control for Short-Term and Long-Term Intervention with a Mathematical Model Approach Journal of Applied Mathematics 2018 9674138(1)-14
[14] Putri Y E, Rozi S, Tasman H, Aldila D 2017 Assessing the effect of extrinsic incubation period (EIP) prolongation in controlling dengue transmission with wolbachia-infected mosquito intervention AIP Conf Proc Vol 1825 020019(1)-9