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# A MATHEMATICAL MODEL OF TUBERCULOSIS WITH EFFECTS OF IMMUNITY AND DRUG RESISTANCE

**By**

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## Abstract

*In this Paper, a Susceptible-Exposed-Infected-Recovered (SEIR) epidemiological model was modified to determine the effect of immunity and drug resistance on the transmission dynamics of tuberculosis. The equilibrium point was found and its stability was investigated. By analyzing the model, we found a threshold value* $R_0$, *the basic reproduction number and the existence of the disease free equilibrium* $(E_0)$ *point. The disease free equilibrium point of the model is locally stable* $(E_0)$ *since basic reproduction number* $R_0 < 1$, *which was obtained from the numerical simulation of the model. The Global stability analysis was obtained and shows that it is globally asymptotically stable. Numerical analysis for the model is done and demonstrated that in the case of patients with both active tuberculosis and MDR tuberculosis, both strains will be gradually eliminated from the population*.

## Introduction

Tuberculosis is an airborne disease caused by Mycobacterium tuberculosis (MTB) bacteria. It is an ancient disease with evidence of its existence being found in relics from ancient Egypt, India and China. In the eighteenth century, Western Europe suffered terribly from this disease with prevalence as high as 900 deaths per 100,000. This was largely due to poor ventilation, overcrowded housing, primitive sanitation and malnutrition among other risk factors [4].

Today, this disease ranks as the second leading cause of morbidity and mortality in the world from a single infectious agent, after the human immunodeficiency virus (HIV). Interestingly, about one-third of the world's population is infected with MTB with approximately nine million people developing active tuberculosis and up to nearly two million people worldwide died from the disease every year. In 2013, approximately nine million people contracted active tuberculosis and this included 1.1 million cases among people living with HIV and 550,000 children. Out of these nine million cases 1.5 million people succumbed to the disease and this included 360,000 among people who were HIV-positive, 510,000 were women out of which 180,000 were HIV-positive. Africa recorded the highest tuberculosis/HIV burden with three out of four Tuberculosis patients knowing their HIV status. Approximately 480,000 people developed multidrug-resistant (MDR) tuberculosis globally with 210,000 of those who developed MDR tuberculosis succumbing to it [10].

In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. People living with HIV accounted for 1.2 million (11%) of all new TB cases [11].

Six countries accounted for 60% of the new cases: India, Indonesia, China, Nigeria, Pakistan and South Africa. Global progress depends on major advances in TB prevention and

care in these countries. Worldwide, the rate of decline in TB incidence remained at only 1.5% from 2014 to 2015. This needs to accelerate to a 4% – 5% annual decline by 2020 to reach the first milestones of the End TB Strategy [11].

Psychosocial distress that communities go through is enormous. This involves thinking about the loss of their loved ones and the economic impact of taking care of the sick ones especially among the low-income individuals. This impacts not only the individuals, but also the economic progress of the country. Over the last twenty-five years, the mortality rate of tuberculosis has greatly decreased by forty-five percent, this is largely due to effective diagnosis and treatment [7].

Tuberculosis is curable provided an early diagnosis is made and one follows the proper treatment regimen which could take six months to two years for the active tuberculosis to clear [8].

In 2015, there were an estimated 480, 000 new cases of multidrug-resistant TB (MDRTB) and an additional 100, 000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment. India, China and the Russian Federation accounted for 45% of the combined total of 580, 000 cases [11].

Treatment for Tuberculosis uses antibiotics and requires much longer period of treatment (around 6 to 24 months) to entirely eliminate Mycobacterium from the body. The Directly Observed Treatment Shorts (DOTS) strategy as recommended by WHO makes sure diagnosis and medicine are available for all TB patients free of charge. It has helped in the control and management of tuberculosis [12].

There is an emerging form of tuberculosis commonly known as Multi-Drug Resistant (MDR) tuberculosis, it is defined as tuberculosis resistant to both of the two most effective first line of antibiotic treatment of active tuberculosis *i.e.*, Isoniazid (INH) and Rifampin (RIF), and it is harder and more expensive to treat. It is currently a major health concern to medical workers and researchers. One can get MDR tuberculosis by either spending time with an MDR patient or breathing in the MDR tuberculosis bacteria or those with active tuberculosis not following their prescribed treatment regimen or TB medicine not being readily available to them. MDR tuberculosis is much more difficult to treat and the mortality of persons with this form of tuberculosis is far much higher if the second line of antibiotic treatment is not affected promptly [3].

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Mathematical models of TB have played a key role in the formulation of tuberculosis prevention and control strategies and establishment of interim goals for intervention programmes. These models are based on the underlying transmission mechanism of TB to help public health administrative workers and our stakeholders in TB control understand better how the disease is spread. At this juncture, we review some past and recent works on tuberculosis.

[9] developed the first deterministic mathematical model to study the epidemiology of tuberculosis for the transmission dynamics of tuberculosis. This shows that with time, other models have been developed to help prevent the risk of transmission of tuberculosis.

[5] developed mathematical model for dynamics of TB disease with vaccination, taking into consideration the Passively Immune Infants (PII) and the vaccination of the susceptible. They considered a Susceptible-Exposed-Infectious- Recovered (SEIR) model by introducing the passively immune infants resulting to an MSEIR model. The dynamics of the compartments were described by system of ordinary differential equations which were solved algebraically, and

analyzed for stability. It was established that the disease free equilibrium state of the model is stable, when the basic reproduction number, $R_0 < 1,$ it was also established that the endemic states for the modified model is stable using Bellman and Cooke theorem. If efforts are made to ensure that more susceptible infants are vaccinated, the breakdown of the susceptible and progression to infectious state is reduced.

[2] used a deterministic model with isolation where they studied the transmission dynamics of three strains of Mycobacterium Tuberculosis (TB), namely; the Drug-Sensitive, Multi-Drug-Resistance (MDR) and Extensively Drug-Resistance (XDR) tuberculosis strains. Their result of the global sensitivity analysis indicated that the dominant parameters are the disease progression rate, the recovery rate, the infectivity parameter, the isolation rate, and the rate of cost to follow up and fraction of fast progression rates. They also found that an increase in isolation rate leads to a decrease in the total number of individuals who are to follow up. [17] used a mathematical model to simulate tuberculosis transmission in the highly endemic regions of the Asia-pacific. They found out that their model could not be calibrated to the estimated incidence rate without allowing for re-infection during latency and that even in the presence of a moderate fitness cost and a lower value of $R_0,$ MDR, tuberculosis becomes the dominant strain at equilibrium. Improved treatment of Drug-Susceptible tuberculosis did not result in decreased rates of MDR tuberculosis through prevention of the new Resistance but rather resulted in a modest increase in MDR tuberculosis. [11] formulated a model for global stability of the endemic equilibrium of tuberculosis with immigration and treatment. In their work, immigration was considered and ended up concluding that constant influx of latent TB can launch a TB epidemic itself irrespective of the initial conditions. Result simulation shows that a higher level of latent immigrants will produce a higher level of TB incidence.

[6] also presented an epidemiological model that tuberculosis can effectively be controlled or even be eradicated if effort is made to ensure that the total removal rate from both the latent and the infectious classes is always less than the product of total contraction and total breakdown of the susceptible class.

Assumptions of the Immunity and Drug Resistance
The following assumptions were made:

1. Parameters and variables are considered non-negative.
2. Recruitment into the susceptible compartment is variable.
3. Transition into and out of any compartment is governed by a specified rate.
4. Natural death and death due to tuberculosis occurs at variable rate.
5. The members of the study population interact freely.

**Description of the Model**

The human population is categorized into six compartments such that at time $t \geq 0$ there are (S), susceptible humans, (M), immune infants, (E), exposed humans to tuberculosis, (I), infected humans with active tuberculosis, ($R_{ES}$), resistant humans to the first line of treatment, ($R_H$) , recovered humans. Thus the size of the human population is given as $N = S + M + E + I + R_{ES} + R_H$. In our model, the recruitment into the susceptible human population is by birth $P\pi$. The size of the susceptible class is further increased by the immune infants in (M), partially immune humans in ($R_H$) after they lose their immunity at the rate $\eta$ and $\rho$ respectively. The susceptible class is decreased by natural death $\mu$ and exposed to MTB. The immune class (M) is increased by birth with immunity at a rate (1-P) $\pi$ and decreased by natural death $\mu$. The exposed susceptible to MTB move to the exposed classes (E) with the

force of infection being $\beta$, resulting in an increase in the exposed class. Natural death $\mu$ and the proportion that move to the infected class (I) after developing active tuberculosis further decreased the exposed class. The infected class (I) is also reduced by natural death $\mu$, disease induced death $\alpha$, those who recover $\gamma$ and also by those resistant to the first line of treatment $\sigma$. Thus, both the infected class (I) and the resistant class $R_{ES}$ gain partial immunity at the rates $\gamma$ and $\delta$ respectively thus moving to the recovered class (R) thus reducing their respective classes and also increasing the recovered class. The resistant class $R_{ES}$ is also reduced by natural deaths $\mu$ and disease induced deaths $\alpha_1$ while natural death $\mu$ and those who lose their partial immunity at the rate $\rho$ reduce the recovered class.

**Model Diagram**

The flow diagram of the model with Immunity and Drug Resistance on the Transmission Dynamics of Tuberculosis is given in figure below.

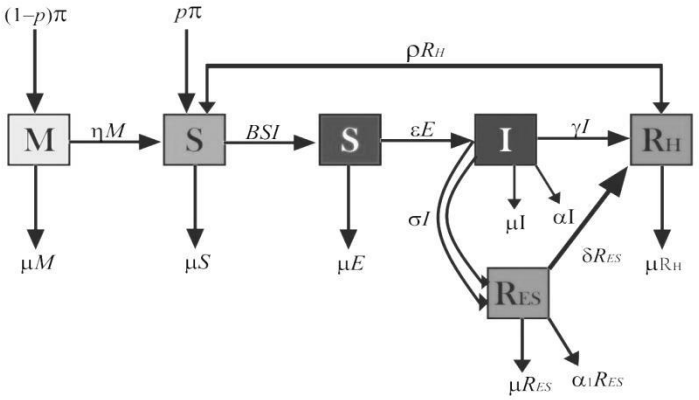


Figure 1: Model with immunity and drug resistance effect on the transmission.

Model Equations

$$\left.\begin{aligned}
\frac{dM}{dt} &= (1-P)\pi - (\mu+\eta)M \\
\frac{dS}{dt} &= P\pi + \eta M - \beta SI - \mu S + \rho R_H \\
\frac{dE}{dt} &= \beta SI - (\mu+\varepsilon)E \\
\frac{dI}{dt} &= \varepsilon I - (\mu+\alpha+\gamma+\sigma)I \\
\frac{dR_{ES}}{dt} &= \sigma I - (\mu+\alpha_1+\delta)R_{ES} \\
\frac{dR_H}{dt} &= \gamma I - (\mu+\rho)R_H + \delta R_{ES}
\end{aligned}\right\} \qquad (1)$$

Where $M(0)=M_0, S(0)=S_0, E(0)=E_0, I(0)=I_0, R_{ES}(0)=R_{ES0}, R_H(0)=R_{H0}$. Note that $N = M+S+E+I+R_{ES}+R_H$.

| VAR/PAR | DESCRIPTION |
|---|---|
| $N(t)$ | Total Population |
| $M(t)$ | Number of immune infants at time t |
| $S(t)$ | Number of Susceptible individuals at time t |

| | |
|---|---|
| $E(t)$ | Number of Exposed individuals at time t |
| $I(t)$ | Number of infectious individuals at time t |
| $R_H(t)$ | Number of Recovered Humans from both active and MDR tuberculosis at time t |
| $R_{Es}(t)$ | Number of Resistant Humans to first of treatment at time t |
| $P\pi$ | Birth rate without immunity |
| $(1-P)\pi$ | Birth rate with immunity |
| $\eta$ | Rate at which immune infants become Susceptible |
| $\alpha$ | Disease induced death rate due to active tuberculosis |
| $\alpha_1$ | Disease induced death rate due to MDR tuberculosis |
| $\delta$ | Recovery rate of infected humans from MDR tuberculosis |
| $\sigma$ | Rate at which infected humans become resistance to first line of treatment |
| $\rho$ | Rate at which infected humans become Susceptible |
| $\varepsilon$ | Infectious Rate |
| $\beta$ | Contact Rate |
| $\mu$ | Death Rate |
| $\gamma$ | Recovery Rate |

Disease Free Equilibrium $(E_0)$

The disease free equilibrium point of a system represents the state at which there are no infections in the whole population. Now, considering the two compartments $\frac{dM}{dt}.$ and $\frac{dS}{dt}.$

$$\frac{dM}{dt}. = (1-P)\pi - (\mu+\eta)M$$

$$(1-P)\pi - (\mu+\eta)M = 0$$

$$M^0 = \frac{(1-P)\pi}{\mu+\eta}$$

$$\frac{dS}{dt}. = P\pi + \eta M - \beta SI - \mu S + \rho R_H = 0$$

$$P\pi + \eta M - \beta SI - \mu S + \rho R_H = 0$$

$$S^0 = \frac{P\pi(\mu+\eta) + (1-P)\eta\pi}{\mu(\mu+\eta)}$$

$$E^0 = I^0 = R^0{}_{ES} = R^0{}_H = 0$$

.

Therefore, the disease free equilibrium state for the model is

$$E_0\left(M^0, S^0, E^0, I^0, R^0{}_{ES}, R^0{}_H,\right) = \left(\frac{(1-P)\pi}{\mu+\eta}\right). \qquad (2)$$

**Basic Reproduction Number**

The reproduction number $R_0$ is defined as the average number of secondary cases of infection generated by one primary case in a whole susceptible population. The basic reproduction number is used to predict whether the epidemic will spread or die out. In this

model, we will adopt the method of the next generation on the equations (1) in the form of matrices $F$ and $V$.

Let $F_i$ be the rate of approach of the new infection in a compartment.

$V_i$ be the transfer of individuals out of compartment by another means.

$X_0$ be the disease-free equilibrium $(E_0)$

The basic reproduction number, $R_0$ is obtained by setting; $R_0 = \rho(FV^{-1})$; where $F = \left[\frac{\partial F_I(x_0)}{\partial x_j}\right]$ and $V = \left[\frac{\partial V_I(x_0)}{\partial x_j}\right]$ for $i \geq 1$ for the number of compartments and $1 \leq j \leq m$ for the infected compartments only.

$\rho(FV^{-1})$ denotes the spectral radius of the matrix $F$ and $V$ are $m \times m$ matrices, where $m$ is the number of infected classes (Diekmann, & Heesterbeek, 2000).

Considering the infected compartments;

$$\left.\begin{aligned} \frac{dE}{dt} &= \beta SI - (\mu+\varepsilon)E \\ \frac{dI}{dt} &= \varepsilon E - (\mu+\alpha+\gamma+\sigma)I \\ \frac{dR_{ES}}{dt} &= \sigma I - (\mu+\alpha_1+\delta)R_{ES} \end{aligned}\right\} \qquad (4)$$

$$F = \begin{bmatrix} \beta SI \\ 0 \\ 0 \end{bmatrix}, \Delta F = \begin{bmatrix} 0 & \beta S & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} 0 & \frac{\beta(P\pi(\mu+\eta)+(1-P)\eta\pi)}{\mu(\mu+\eta)} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} 0 & A_1 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \text{ and}$$

$$F = \begin{bmatrix} (\mu+\varepsilon)E \\ (\mu+\alpha+\gamma+\sigma)I - \varepsilon E \\ (\mu+\alpha_1+\delta)R_{ES} - \sigma T \end{bmatrix}, \Delta V = \begin{bmatrix} (\mu+\varepsilon) & 0 & 0 \\ -\varepsilon & (\mu+\alpha+\gamma+\sigma) & 0 \\ 0 & -\sigma & (\mu+\alpha_1+\delta) \end{bmatrix}$$

Therefore,

$$V^{-1} = \begin{bmatrix} \frac{1}{(\mu+\varepsilon)} & 0 & 0 \\ \frac{\varepsilon}{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)} & \frac{1}{(\mu+\alpha+\gamma+\sigma)} & 0 \\ \frac{\varepsilon\sigma}{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)(\mu+\alpha_1+\delta)} & \frac{\sigma}{(\mu+\alpha+\gamma+\sigma)(\mu+\alpha_1+\delta)} & \frac{1}{(\mu+\alpha_1+\delta)} \end{bmatrix} = \begin{bmatrix} B_1 & 0 & 0 \\ B_2 & B_4 & 0 \\ B_3 & B_5 & B_6 \end{bmatrix}$$

where

$$A_1 = \frac{\beta\left(P\pi(\mu+\eta)+(1-P)\eta\pi\right)}{\mu(\mu+\eta)}$$

$$B_1 = \frac{1}{(\mu+\varepsilon)}$$

$$B_2 = \frac{\varepsilon}{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)}$$

$$B_3 = \frac{\varepsilon\sigma}{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)(\mu+\alpha_1+\delta)}$$

$$B_4 = \frac{1}{(\mu+\alpha+\gamma+\sigma)}$$

$$B_5 = \frac{\sigma}{(\mu+\alpha+\gamma+\sigma)(\mu+\alpha_1+\delta)}$$

$$B_6 = \frac{1}{(\mu+\alpha_1+\delta)}$$

We then obtain the spectral radius of $\rho\left(FV^{-1}\right)$, which is defined as the largest Eigen value of $FV^{-1}$. The reproduction number for the model is given as:

$$R_0 = \frac{\beta\varepsilon\left(P\pi(\mu+\eta)+(1-P)\eta\pi\right)}{\mu(\mu+\varepsilon)(\mu+\eta)(\mu+\alpha+\gamma+\sigma)}$$

Local Stability Analysis of the Disease Free Equilibrium of the Model

The Jacobian of system of differential equation (1) at disease free is

$$J = \begin{bmatrix} -(\mu+\eta) & 0 & 0 & 0 & 0 & 0 \\ \eta & -(\beta I+\mu) & 0 & -\beta S & 0 & \rho \\ 0 & \beta I & -(\mu+\varepsilon) & \beta S & 0 & 0 \\ 0 & 0 & \varepsilon & -(\mu+\alpha+\gamma+\sigma) & 0 & 0 \\ 0 & 0 & 0 & \sigma & -(\mu+\alpha_1+\delta) & 0 \\ 0 & 0 & 0 & \gamma & \delta & -(\mu+\rho) \end{bmatrix}$$

At disease free equilibrium $\left(E_0\right)$, we have

$$J(E_0) = \begin{bmatrix} -(\mu+\eta) & 0 & 0 & 0 & 0 & 0 \\ \eta & -\mu & 0 & -\frac{\beta\left(P\pi(\mu+\eta)+(1-P)\eta\pi\right)}{\mu(\mu+\eta)} & 0 & \rho \\ 0 & 0 & -(\mu+\varepsilon) & \frac{\beta\left(P\pi(\mu+\eta)+(1-P)\eta\pi\right)}{\mu(\mu+\eta)} & 0 & 0 \\ 0 & 0 & \varepsilon & -(\mu+\alpha+\gamma+\sigma) & 0 & 0 \\ 0 & 0 & 0 & \sigma & -(\mu+\alpha_1+\delta) & 0 \\ 0 & 0 & 0 & \gamma & \delta & -(\mu+\rho) \end{bmatrix}$$

Given $\left|J\left(E_0-\lambda I\right)=0\right|$

$$\begin{vmatrix} -(\mu+\eta)-\lambda & 0 & 0 & 0 & 0 & 0 \\ \eta & -\mu-\lambda & 0 & -\frac{\beta\left(P\pi(\mu+\eta)+(1-P)\eta\pi\right)}{\mu(\mu+\eta)} & 0 & \rho \\ 0 & 0 & -(\mu+\varepsilon)-\lambda & \frac{\beta\left(P\pi(\mu+\eta)+(1-P)\eta\pi\right)}{\mu(\mu+\eta)} & 0 & 0 \\ 0 & 0 & \varepsilon & -(\mu+\alpha+\gamma+\sigma)-\lambda & 0 & 0 \\ 0 & 0 & 0 & \sigma & -(\mu+\alpha_1+\delta)-\lambda & 0 \\ 0 & 0 & 0 & \gamma & \delta & -(\mu+\rho)-\lambda \end{vmatrix} = 0$$

The Eigen values of $J(E_0)$ are $\lambda_1 = -(\mu+\eta) < 0, \lambda_2 = -\mu < 0, \lambda_3 = -(\mu+\rho) < 0$ and $\lambda_4 = -(\mu+\alpha_1+\delta) < 0$ and

$$\begin{vmatrix} -d_1 - \lambda & c_1 \\ \varepsilon & -d_2 - \lambda \end{vmatrix} = 0 \quad (1)$$

Where

$$c_1 = \frac{\beta\left(P\pi(\mu+\eta)+(1-P)\eta\pi\right)}{\mu(\mu+\eta)}$$

$$d_1 = (\mu+\varepsilon)$$

$$d_2 = (\mu+\alpha+\gamma+\sigma)$$

From ()

$a_2\lambda^2 + a_1\lambda + a_0 = 0$

where

$$a_2 = 1$$

$$a_1 = d_1 + d_2$$

$$a_0 = d_1 d_2 - \varepsilon c_1 = (\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma) - \frac{\beta\varepsilon\left(P\pi(\mu+\eta)+(1-P)\eta\pi\right)}{\mu(\mu+\eta)}$$

$$= (\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)\left(1 - \frac{\beta\varepsilon\left(P\pi(\mu+\eta)+(1-P)\eta\pi\right)}{\mu(\mu+\eta)}\right)$$

$$= (\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)(1-R_0)$$

We apply Routh-Hurwitz criterion which states that all roots of the polynomial (18) have negative real part iff the coefficients $a_i$, are positive and the determinant of the matrices $H_i > 0$ for $i = 0,1,2.$ therefore,

$H_1 = a_1 = d_1 + d_2 > 0$

$$H_2 = \begin{vmatrix} a_1 & 0 \\ 1 & a_0 \end{vmatrix} = a_1^2 a_2 + a_1 a_2^2 - \varepsilon c_1 (d_1 + d_2) > 0, \text{ iff } \; a_1^2 a_2 + a_1 a_2^2 > \varepsilon c_1 (d_1 + d_2)$$

Therefore, all the Eigen values of the polynomial (18) have negative real parts, implying that $\lambda_5 < 0$ and $\lambda_6 < 0.$ since all the values of $\lambda_i < 0,$ for $i = 1,2,3,4,5,6.$ when $R_0 < 1,$ we conclude that the disease-free equilibrium point is locally asymptotically stable.

**Global stability of the DFE of the model**

The local dynamics of a general MSEIR model is determined by the reproduction number $R_0$ . If $R_0 \leq 1,$ then each infected individual in its entire period of infectiousness will produce less than one infected individual on average. This means that the disease will be wiped out of the population. If $R_0 > 1$, then each infected individual in its entire infectious period having contact with susceptible individuals will produce more than one infected individual implying that the disease persists in the population. If $R_0 = 1$ and this is defined as

the disease threshold, then one individual infects one more individual. For $R_0 \le 1$, the disease free equilibrium is locally asymptotically stable while for $R_0 > 1$, the disease free equilibrium becomes unstable. By using the theory of Lasalle-Lyapunov function $V$, we will show the global asymptotic stability. The disease free equilibrium point is $(E, I, R_{ES}) = (0,0,0)$.

**Theorem 2:**

If $R_0 \le 1$, then the disease-free equilibrium $(E, I, R_{ES}) = (0,0,0)$ of the system is globally asymptotically stable on $\Omega$. We construct the following Lasalle-Lyapunov function $V(E, I, R_{ES})$ on the positively invariant compact set $\Omega$. Thus on $\Omega$, $V(E, I, R_{ES})$ is continuous and non-negative. We define $V(E, I, R_{ES}) = \varepsilon E + (\mu + \varepsilon) I$. The system of ordinary differential equations is given by equation (2) can be written as

$$\begin{pmatrix} \dot{E} \\ \dot{I} \\ R_{ES} \end{pmatrix} = \begin{pmatrix} -(\upsilon + \mu) & \dfrac{\beta\left(P\pi(\mu+\eta) + (1-P)\eta\pi\right)}{\mu(\mu+\eta)} & 0 \\ \varepsilon & -(\mu + \alpha + \gamma + \sigma) & 0 \\ 0 & \sigma & (\mu + \alpha_1 + \delta) \end{pmatrix} \begin{pmatrix} E \\ I \\ R_{ES} \end{pmatrix} \qquad (5)$$

Thus, equation (4) can be written as $\dot{I} = A(I)$ where

$$A = \begin{pmatrix} -(\upsilon + \mu) & \dfrac{\beta\left(P\pi(\mu+\eta) + (1-P)\eta\pi\right)}{\mu(\mu+\eta)} & 0 \\ \varepsilon & -(\mu + \alpha + \gamma + \sigma) & 0 \\ 0 & \sigma & (\mu + \alpha_1 + \delta) \end{pmatrix} \quad \text{and} \quad I = \begin{pmatrix} E \\ I \\ R_{ES} \end{pmatrix}$$

If we define $V^T = [\varepsilon, \mu + \varepsilon, 0]$, then the derivative along the trajectories is given by $\dot{V} = V^T A(I)$ as

$$V^T A(I) = [\varepsilon, \mu + \varepsilon, 0] \begin{bmatrix} -(\upsilon + \mu) & \dfrac{\beta\left(P\pi(\mu+\eta) + (1-P)\eta\pi\right)}{\mu(\mu+\eta)} & 0 \\ \varepsilon & -(\mu + \alpha + \gamma + \sigma) & 0 \\ 0 & \sigma & (\mu + \alpha_1 + \delta) \end{bmatrix} \qquad (6)$$

Simplifying equation (5), we have

$$= \begin{bmatrix} 0 \\ (\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma)\left[\dfrac{\beta\varepsilon\left(P\pi(\mu+\eta) + (1-P)\eta\pi\right)}{\mu(\mu+\eta)(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)} - 1\right] \\ 0 \end{bmatrix}$$

$$= \begin{bmatrix} 0 \\ (\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)[R_0-1] \\ 0 \end{bmatrix}$$

which is strictly decreasing when $R_0 < 1$. Thus, $\dot{V} \le (\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)(R_0-1)$. We define the set $K = \left\{ (E, I, R_{ES}) \in \Omega / \dot{V}(E, I, R_{ES}) = 0 \right\}$. The largest invariant set is contained in the set $K$ for which $E = 0$ or $I = 0$ or $R_{ES} = 0$. Thus $\dot{V} < 0$ when $R_0 < 1$. If $I = 0$ or $R_0 = 1, \dot{V} = 0$. Thus, by Lasalle's invariance principle the disease free equilibrium is globally asymptotically stable on $\Omega$.

**Numerical Simulation**

The numerical simulation of the model was carried out using MATLAB. The estimated parameter values used in the simulation of this model are presented in table 2. Since the parameter values are known, then we can solve our system of differential equation (1), since the model uses six separate differential equations, one must use a numerical solver to plot the solution.

This is easier with MATLAB. We used the parameter values (2) in MATLAB and plot the graph. The numerical simulation result is displayed in figure 2.

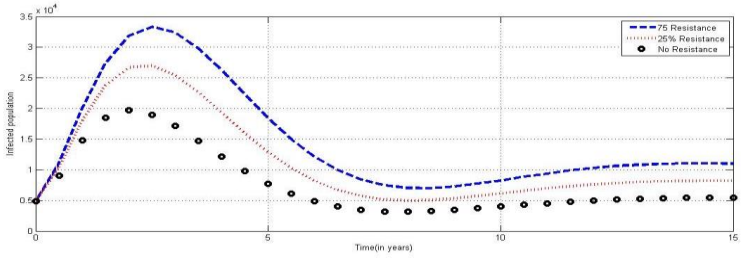


Figure 2: Numerical Simulation of Infected Individual against time.

| Parameters | value |
|---|---|
| N | 1000 |
| $\Pi$ | 5000 |
| $\mu$ | 0.9 |
| P | 0.04 |
| $B$ | 0.05 |
| $E$ | 0.06 |
| $\Gamma$ | 0.65 |

| | |
|---|---|
| $A$ | 0.6 |
| $\Lambda$ | 0.3 |
| $\alpha_1$ | 0.04 |
| $H$ | 0.088 |
| $\Sigma$ | 0, 0.25, 0.75 |

**Table 2**: Estimation of Parameter and Constant

The graph of figure (2) represent three cases from table (2), the first case when $\sigma = 0$ that is the initial state, second case when $\sigma = 0.25$ and the third case when $\sigma = 0.75$. We can see that there was less number of infected population when there is no resistance and infection is increased as we increase the resistance from 25% to 75% with respect to time.

**Discussion of Results**

From the numerical simulation of the condition in figure (2) above, it shows that there was less number of infected population when there is no resistance and infection is increased as we increase the resistance from 25% to 75%. This was achieved by first choosing $\sigma = 0$ simulation gives $R_0 = 0.865116 < 1$, secondly when $\sigma = 0.25$ simulation gives $R_0 = 0.907885 < 1$ and lastly when $\sigma = 0.75 < 1$ simulation gives $R_0 = 0.751353 < 1$, showing that the disease free equilibrium point $(E_0)$ of the model is locally stable in all the three (3) different values of $\sigma$. Since the basic reproduction number $R_0 < 1$, it implies that the disease will gradually die out in the population when there are no resistances and the disease will increase when there is resistance to first line of treatment.

**Conclusion**

Mathematical model is a useful technique for solving real life problems, a deterministic model to study the effect of immunity and drug resistance on the transmission dynamics of tuberculosis was modeled and analyzed in order to see the effect of resistance to first line of treatment in a population. The analysis and numerical simulation of the model revealled that the disease free equilibrium $(E_0)$ is locally stable since $R_0 < 1$ which implies that TB disease will be gradually eliminated from the population. The numerical simulation of the model was carried out using MATLAB.

**Recommendation**

In line with this research finding, the following recommendations are made;

1. Encourage the use of mathematical models to model real life problems which simplifies problems in the society.
2. The government should integrate TB programmes into other existing health services such as outreach, maternal and child welfare programmes among others in order to increase its awareness.
3. The government should intensify the education on TB in schools, community gathering, worship centers etc to sensitize the individuals in the communities of its existence, free access to medical care and treatment duration.
4. TB patients who migrate must be given referral to the clinics in such areas for continuation of treatment.

5. Further research work is also recommended in order to help develop other suitable models to help public health professionals to adopt other strategies to control and eradicate the disease.

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