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EFFECTS OF IMMMUNITY AND DRUGS RESISTANCE ON THE TRANSMISSION DYNAMICS OF TUBERCULOSIS

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ABSTRACT

SIER epidemiology model was modified to determine the effect of drug resistance and immunity on the transmission dynamics of tuberculosis. We obtained the existence and uniqueness of the solution of the model, the basic reproduction number R_0. The disease-free equilibrium point was determined and found to be locally asymptotically stable (LAS), when $R_0 < 1$ and globally asymptotically stable (GAS), when $R_0 < 1$ unstable if otherwise. The endemic equilibrium was also obtained and found to be locally asymptotically stable (LAS) when $R_0 > 1$ and globally asymptotically stable (GAS), when $R_0 > 1$. Numerical simulation carried out shows that there is less infected population with the first line of treatment when there is no drug resistance.

Keywords: Epidemiology, Tuberculosis, Drug, Resistance, Immunity, Dynamic

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 that led to the epidemic (Daniel, 2006).

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 (World Health Organization, 2014).

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 (WHO, 2016).

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 (WHO, 2016). Also, people suffering from malnutrition due to lifestyle, drug abuse or poverty equally are at risk of contracting tuberculosis. Another category of people largely at risk of contracting tuberculosis are those who work closely or live close to a person with active tuberculosis and they could include health care workers, people living in crowded living spaces or confined places such as schools or prisons (Zaman, 2010). The intensity of transmission depends on factors related to the bacteria, the human host, the environment and migration. Non-climatic factors such as environmental development and urbanization, population movement and migration affect the severity and incidence of tuberculosis. When it comes to environment and urbanization, the incidence of tuberculosis is generally lower in prime urban areas than in rural areas as there is difficulty in accessing proper medical care in rural villages compared to urban areas. However, rapid urbanization of areas within or on the outskirts of urban centers is commonly done in an uncontrolled fashion without thought or planning. The settlers are mainly migrant workers from rural villages and they tend to settle mostly in poor, overcrowded houses commonly known as slums with hardly any proper sanitation and this in turn leads to increased exposure of the population to MTB hence a possibility of amplification of the disease to epidemic proportions through lack of effective treatment (Mandal, 2013). Population movements have significant implications for tuberculosis transmission as migration introduces tuberculosis problem to the areas to which the migrants migrate to. Temporary migrant workers often bring the bacteria to lower prevalence areas and local transmission can be readily established (Semenza *et al.,* 2010). Tuberculosis is curable provided an early diagnosis is made and one follows the proper treatment regimen which could take six months up to two years for the active tuberculosis to clear (Trauer, Denholm & McBryde, 2014).

In 2015, there were an estimated 480, 000 new cases of multidrug-resistant TB (MDR-TB) 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 (WHO, 2016). In this we modify the model by Andam (2013) by incorporating to the first line of treatment drug resistance and immunity to study the

effects of drug resistance and immunity in the transmission dynamic of the tuberculosis model.

MATERIALS AND METHODS

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 η and ρ respectively. The susceptible class is decreased by natural death μ 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 μ. The exposed susceptible to MTB move to the exposed classes (E) with the force of infection being βI, resulting in an increase in the exposed class. Natural death μ 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 μ, disease induced death α, those who recover γ and also by those resistant to the first line of treatment σ. Thus, both the infected class (I) and the resistant class (R_{ES}) gain partial immunity at the rates γ and δ 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 μ and disease induced deaths α_1 while natural death μ and those who lose their partial immunity at the rate ρ reduce the recovered class.

Assumptions of the Model with Immunity and Drug Resistance

The following assumptions were made:

i. Parameters and variables are considered non-negative

ii. Recruitment into the susceptible compartment is variable.

iii. Transition into and out of any compartment is governed by a specified rate.

iv. Natural death and death due to tuberculosis occurs at variable rate.

v. The members of the study population interact freely.

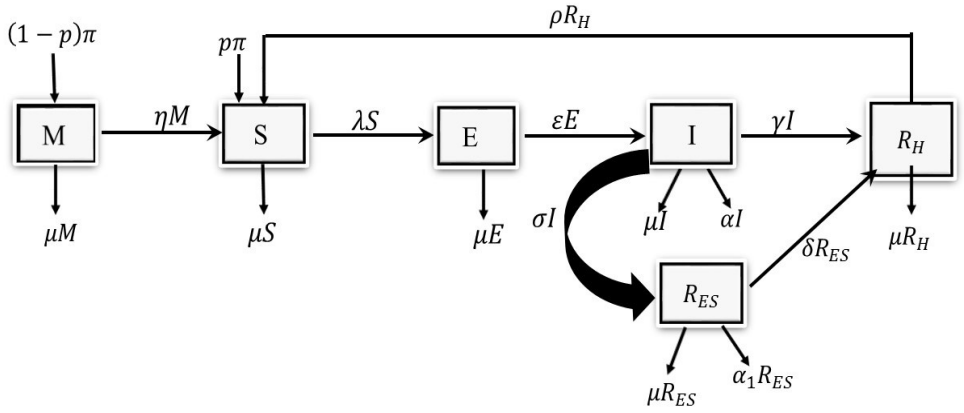

Figure 1: Compartmental diagram of the model

Model Equations

$$\begin{aligned}
\frac{dM}{dt} &= (1-p)\pi - (\mu+\eta)M \\
\frac{dS}{dt} &= p\pi + \eta M + \rho R_H - \beta SI - \mu S \\
\frac{dE}{dt} &= \beta SI - (\mu+\varepsilon)E \\
\frac{dI}{dt} &= \varepsilon E - (\mu+\alpha+\gamma+\sigma)I \\
\frac{dR_{ES}}{dt} &= \sigma I - (\mu+\alpha_1+\delta)R_{ES} \\
\frac{dR_H}{dt} &= \gamma I - (\mu+\rho)R_H + \delta R_{ES}
\end{aligned} \tag{2.3.1}$$

Where $S(0) = S_0,\ V(0) = V_0,\ E(0) = E_0,\ I(0) = I_0,\ R_{ES}(0) = R_{ES_0},\ R_H(0) = R_{H_0}$

Note that $N = S + M + E + I + R_{ES} + R_H$

Table 1: Parameters and variables

Symbols	Description
$M(t)$	Number of immune infants at time t
$S(t)$	Number of Susceptible individuals
$E(t)$	Exposed individual at time t
$I(t)$	Number of infected individuals at time t
$R_H(t)$	Number of Recovered humans from both active and MDR tuberculosis at time
$R_{ES}(t)$	Number of Resistant humans to first line of treatment
$p\pi$	Recruitment rate without immunity
$(1-p)\pi$	Birth rate with immunity

η	Rate at which immune infants become susceptible
α	Disease induced death rate due to active tuberculosis
μ	Natural death rate
α_1	Disease induced death rate due to active tuberculosis
σ	Rate at which infected humans become resistance to first line of treatment
ρ	Rate at which recovered humans become susceptible
δ	Recovery rate of infected humans from MDR tuberculosis

Existence and Uniqueness

Theorem 1

Let D denote the region $|t - t_0| \leq \alpha$ and $|x - x_0| \leq b$, where $x = (x_1, x_2, ..., x_n)$ and

$x_0 = (x_{0,1}, x_{0,2}, ..., x_{0,n})$. Suppose that $f(x,t)$ satisfies Lipchitz condition

$|f(t, x_1) - f(t, x_2)| \leq K |x_1 - x_2|$ Where the pair (t, x_1) and (t, x_2) belong to D and K is a positive constant. Thus, the following lemma.

Lemma 1

Let D denote the region $0 \leq N \leq K$, then system (2.3.1) has a unique solution.

Proof

Let $x_1 = M$, $x_2 = S$, $x_3 = E$, $x_4 = I$, $x_5 = R_{ES}$ $x_6 = R_H$, and f_1, f_2, f_3, f_4, f_5 and f_6 be the respective equations in system (2.3.1). The goal is to show that $\frac{df_i}{dx_j}; i, j = 1, 2, 3, 4, 5, 6$ are continuous and bounded in *D*. Now $f_1 = (1 - p)\pi + (\mu + \eta)x_1$

$\left|\frac{df_1}{dx_1}\right| = |-(\mu + \eta)| < \infty$ $\left|\frac{df_1}{dx_2}\right| = \left|\frac{df_1}{dx_3}\right| = \left|\frac{df_1}{dx_4}\right| = \left|\frac{df_1}{dx_5}\right| = \left|\frac{df_1}{dx_6}\right| = 0 < \infty$;

Similarly, in same manner for f_2, f_3, f_4, f_5 and f_6 of model (2.3.1) above, we see that their partial derivatives exist for all equations and are continuous and bounded. Hence the system (2.3.1) has a unique solution.

Positivity of the Solution

Lemma 2

Let the initial solution set

$$\{M(0) > 0, S(0) > 0, E(0) > 0, I(0) > 0, R_{ES}(0) > 0, R_H(0) > 0\} \in \Re_+^6$$

Then the solution set $\{M(t), S(t), E(t), I(t), R_{ES}(t), R_H(t)\}$ is positive for all time $t > 0$

Proof

Consider the first equation in (2.3.1)

$$\frac{dM}{dt} = (1-p)\pi + (\mu+\eta)M$$
$$\geq -(\mu+\eta)M$$
$$\Rightarrow M(t) = M(0)e^{-\int(\mu+\eta)dt} > 0$$

Also, for the second equation (2.3.1)

$$\frac{dS}{dt} = p\pi + \eta M + \rho R_H - \beta SI - \mu S$$
$$\geq (\beta I + \mu)S$$
$$\Rightarrow S(t) = S(0)e^{-\int(\beta I+\mu)dt} > 0$$

In the same way, we found that $M(0) > 0, S(0) > 0, E(0) > 0, I(0) > 0, R_{ES}(0) > 0, R_H(0) > 0$ respectively. Hence the solution set is positive for all time $t > 0$.

Invariant Region

If a solution of a differential equation or a system of differential equations start on a given space, surface, or curve and remains within it for all time t, then the set is said to be invariant. Hence a positively invariant set will have solutions that are positive for all time. Now let $N = S + M + E + I + R_{ES} + R_H$ be the total population at any time t. Therefore,

$$\frac{dN}{dt} = \frac{dM}{dt} + \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR_{ES}}{dt} + \frac{dR_H}{dt}$$
$$\frac{dN}{dt} = \pi - \mu N - \alpha - \alpha_1 \qquad (*)$$
$$\frac{dN}{dt} \leq \pi - \mu N$$

Integrating (*) we have

$$N \leq N_0 e^{-\mu t} + \frac{\pi}{\mu}\left(1 - e^{-\mu t}\right)$$

Where N_0 is the initial population at time $t = 0$, thus as $t \to \infty$ we have $N \leq \frac{\pi}{\mu}$, which shows that the feasible solution of the system (2.3.1) as $N \to \frac{\pi}{\mu}$ is the system consist of six possible solutions and the solution model for this system is uniformly bounded in the subset of R_+^6 the feasible solution of the region Ω is positively invariant and attracting with respect to system(2.3.1) , the invariant region is;

$$\Omega = \left\{(M, S, E, I, R_{ES}, R_H) \in R_+^6; N \leq \frac{\pi}{\mu}\right\}$$

Equilibrium Points

The equilibrium state for the model is obtained by setting the model equations to zero.

i.e. $\frac{dM}{dt}+\frac{dS}{dt}+\frac{dE}{dt}+\frac{dI}{dt}+\frac{dR_{ES}}{dt}+\frac{dR_{H}}{dt}=0$

Disease Free Equilibrium (Eq^0)

Setting equation (2.3.1) equal to zero we have

$$M^{*}=\frac{(1-p)\pi}{(\mu+\eta)}\quad S^{*}=\frac{p\pi(\mu+\eta)+(1-p)\mu\pi}{\mu(\mu+\eta)}\quad\text{and}\quad E^{*}=I^{*}=R^{*}_{ES}=R^{*}_{H}=0$$

Therefore, the disease-free equilibrium state for the model is

$$Eq^{0}\left(M^{*},S^{*},E^{*},I^{*},R^{*}_{ES},R^{*}_{H}\right)=\left(\frac{(1-p)\pi}{(\mu+\eta)},\frac{p\pi+(1-p)\mu\pi}{\mu(\mu+\eta)},0,0,0,0\right)$$

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. The method of the next generation on the system (2.3.1) in the form of matrices F and V was adopted. 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 Eq^0.The basic reproduction number is 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 (P. Van den Driessche and James Watmough (2002)) . We have that

$$F=\begin{pmatrix}0 & \beta S^{*}\\ 0 & 0\end{pmatrix}\quad\text{and}\quad V=\begin{pmatrix}\mu+\varepsilon & 0\\ -\varepsilon & \mu+\alpha+\gamma+\sigma\end{pmatrix}$$

$$V^{-1}=\begin{pmatrix}\frac{1}{\mu+\varepsilon} & 0\\ \frac{\varepsilon}{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)} & \frac{1}{\mu+\alpha+\gamma+\sigma}\end{pmatrix}$$

$$FV^{-1}=\begin{pmatrix}\frac{\beta\varepsilon S^{*}}{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)} & \frac{\beta S^{*}}{(\mu+\alpha+\gamma+\sigma)}\\ 0 & 0\end{pmatrix}$$

$$\rho\left(FV^{-1}\right)=\begin{vmatrix}\dfrac{\beta\varepsilon S^{*}}{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)}-\lambda & \dfrac{\beta S^{*}}{(\mu+\alpha+\gamma+\sigma)}\\ 0 & -\lambda\end{vmatrix}=0$$

$$\left(\frac{\beta\varepsilon S^{*}}{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)}-\lambda\right)(-\lambda)=0$$

$$\lambda_1=0 \text{ and } \lambda_2=\frac{\beta\varepsilon S^{*}}{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)}$$

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

where $S^{*}=\dfrac{p\pi(\mu+\eta)+(1-p)\eta\pi}{\mu(\mu+\eta)}$

Local Stability Analysis of the Disease-Free Equilibrium

Lemma 2: The disease-free equilibrium points Eq^{0} of the model (2.3.1) is locally asymptotically stable (LAS) if $R_0<1$ and unstable if $R_0>1$

Proof

Using the trace method, i.e. if the trace $Tr\left(Eq^{0}\right)<0$ and the determinant $Det\left(Eq^{0}\right)>0$ whenever $R_0<1$then the model (2.3.1) is LAS. The Jacobian matrix of the system of equations (2.3.1) is given as;

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

At disease free equilibrium Eq^{0} the component is given as

$$J\left(Eq^{0}\right)=\begin{pmatrix}-(\mu+\eta) & 0 & 0 & 0 & 0 & 0\\ \eta & -(\mu) & 0 & -\beta\dfrac{p\pi(\mu+\eta)+(1-p)\eta\pi}{\mu(\mu+\eta)} & 0 & \rho\\ 0 & 0 & -(\mu+\varepsilon) & \beta\dfrac{p\pi(\mu+\eta)+(1-p)\eta\pi}{\mu(\mu+\eta)} & 0 & 0\\ 0 & 0 & \varepsilon & -(\mu+\alpha+\gamma+\sigma) & 0 & 0\\ 0 & 0 & 0 & \sigma & -(\mu+\alpha_1+\delta) & 0\\ 0 & 0 & 0 & \gamma & \delta & -(\mu+\rho)\end{pmatrix}$$

Now, the trace is determined as; $Tr\left(Eq^{0}\right)=-(6\mu+\eta+\varepsilon+\alpha+\gamma+\sigma+\alpha_1+\delta+\rho)<0$

$Det\left(Eq^{0}\right)=\mu(\mu+\eta)(\mu+\varepsilon)(\mu+\rho)(\mu+\alpha+\gamma+\sigma)(\mu+\alpha_1+\delta)(1-R_0)>0$

Hence, the disease-free equilibrium point Eq^{0} is locally asymptotically stable $R_0<1$.

Global Stability Analysis of DFE (Eq^0)

Lemma 3. The DFE $\left(Eq^0\right)$ of the model (2.3.1) is globally asymptotically stable in D whenever $R_0 < 1$

Proof

Consider the function $V = \varepsilon E + (\mu + \varepsilon) I$ (2.9.1)

With derivative $\dot{V} = \varepsilon \dot{E} + (\mu + \varepsilon) \dot{I}$ (2.9.2)

Substituting the values of $\dot{E}$ and $\dot{I}$ in (2.9.2)

$$\dot{V} = \varepsilon(\beta SI) - (\mu + \varepsilon)\varepsilon E + (\mu + \varepsilon)\varepsilon E - (\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma) I$$

$$\dot{V} = \beta\varepsilon SI - (\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma) I$$

Since $S \le S^*$ in D

$$\dot{V} = \beta\varepsilon S^* I - (\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma) I$$

$$\dot{V} \le I(\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma)\left[\frac{\beta\varepsilon\left[p\pi(\mu + \eta) + \pi\eta(1 - p)\right]}{\mu(\mu + \varepsilon)(\mu + \eta)(\mu + \alpha + \gamma + \sigma)} - 1\right]$$

$$\dot{V} \le I(\mu + \varepsilon)(\mu + \alpha + \gamma + \sigma)[R_0 - 1]$$

Therefore $\dot{V} \le 0$ if $R_0 \le 1$ and $\dot{V} = 0$ if $I = 0$. Since all the parameters are non-negative it follows that $\dot{V} = 0$ if and only if $I = 0$. Hence V is a Lyapunov function on D. Furthermore, the largest compact invariant set in $\{(M(t), S(t), E(t), I(t), R_{ES}(t), R_H(t)) \in D : \dot{V}$ is the singleton set $\{Eq^0\}$. Therefore, by LaSalle's Invariant Principles every solution to the model with initial condition in D, approaches Eq^0 as $t \to \infty$ whenever $R_0 < 1$ so that Eq^0 is GAS in D if $R_0 < 1$.

RESULT

Endemic Equilibrium Point

From the model equation we the endemic point as;

$$M^{**} = \frac{(1-p)\pi}{(\mu+\eta)} \qquad S^{**} = \frac{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)}{\beta\varepsilon}$$

$$I^{**} = \frac{\begin{array}{l}\beta\varepsilon\, p\pi\,(\mu+\eta)(\mu+\rho)(\mu+\alpha_1+\delta)+\eta\pi\,(1-p)(\mu+\rho)(\mu+\alpha_1+\delta)\\ -\mu(\mu+\varepsilon)(\mu+\rho)(\mu+\alpha_1+\delta)(\mu+\alpha+\gamma+\sigma)\end{array}}{\beta(\mu+\varepsilon)(\mu+\rho)(\mu+\eta)(\mu+\alpha_1+\delta)(\mu+\alpha+\gamma+\sigma)-\beta\varepsilon\rho(\mu+\eta)\left(\gamma(\mu+\alpha_1+\delta)+\delta\sigma\right)}$$

$$I^{**} = \frac{K_1(R_0-1)}{K_2}, \text{ where } K_1 = \mu(\mu+\varepsilon)(\mu+\rho)(\mu+\alpha_1+\delta)(\mu+\alpha+\gamma+\sigma)$$

$$K_2 = \beta(\mu+\varepsilon)(\mu+\rho)(\mu+\alpha_1+\delta)(\mu+\alpha+\gamma+\sigma)-\beta\varepsilon\rho\left[\left(\gamma(\mu+\alpha_1+\delta)+\delta\sigma\right)\right]$$

$$R_{ES}{}^{**} = \frac{K_1\sigma(R_0-1)}{K_2(\mu+\alpha_1+\delta)} \qquad R_{ES}{}^{**} = \frac{\mu(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)\left[\gamma(\mu+\alpha_1+\delta)+\delta\sigma\right](R_0-1)}{K_2}$$

$$E^{**} = \frac{K_1(\mu+\alpha+\gamma+\sigma)(R_0-1)}{\varepsilon K_2}$$

And we clearly see that

$$\beta(\mu+\varepsilon)(\mu+\rho)(\mu+\alpha_1+\delta)(\mu+\alpha+\gamma+\sigma) > \beta\varepsilon\rho\left[\left(\gamma(\mu+\alpha_1+\delta)+\delta\sigma\right)\right]$$

Local Stability of the Endemic Equilibrium Point

Theorem. The endemic equilibrium point (Eq_1) is locally asymptotically stable if the trace $Tr(Eq^0) < 0$ and the determinant $Det(Eq^0) > 0$ when $R_0 > 1$.

Proof

The Jacobian matrix of the system (2.3.1) is given as;

$$J(Eq_1) = \begin{pmatrix} -(\mu+\eta) & 0 & 0 & 0 & 0 & 0 \\ \eta & -\left(\beta\frac{K_1(R_0-1)}{K_2}+\mu\right) & 0 & -\beta\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)}{\beta\varepsilon} & 0 & \rho \\ 0 & \beta\frac{K_1(R_0-1)}{K_2} & -(\mu+\varepsilon) & \beta\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma+\sigma)}{\beta\varepsilon} & 0 & 0 \\ 0 & 0 & \varepsilon & -(\mu+\alpha+\gamma+\sigma) & 0 & 0 \\ 0 & 0 & 0 & \sigma & -(\mu+\alpha_1+\delta) & 0 \\ 0 & 0 & 0 & \gamma & \delta & -(\mu+\rho) \end{pmatrix}$$

The trace and determinant is given as

$$Tr\left(Eq^{0}\right) = -\left((\mu+\eta) + \frac{\beta K_1 (R_0 - 1)}{K_2} + \mu + (\mu+\varepsilon) + (\mu+\alpha+\gamma+\sigma) + (\mu+\alpha_1+\delta) + (\mu+\rho) \right) < 0$$

$$Det\left(Eq^{0}\right) = \mu(\mu+\eta)(\mu+\varepsilon)(\mu+\rho)(\mu+\alpha_1+\delta)(\mu+\alpha+\gamma+\sigma)(R_0 - 1)$$

We clearly observed that $Tr\left(Eq_1\right) < 0$ and the determinant $Det\left(Eq_1\right) > 0$ if and only if $R_0 > 1$. Hence the endemic equilibrium point is locally asymptotically stable when $R_0 > 1$.

Global Stability of the Endemic Point

Theorem 2. The endemic equilibrium points $\left(Eq_1\right)$ of the model (2.3.1), is GAS in D_1 if $R_0 > 1$.

Proof

Consider the Lyapunov function

$$V = \left(M - M^{**} - M^{**} \ln \frac{M^{**}}{M} \right) + \left(S - S^{**} - S^{**} \ln \frac{S^{**}}{S} \right) + \left(E - E^{**} - E^{**} \ln \frac{E^{**}}{E} \right) + A\left(I - I^{**} - I^{**} \ln \frac{I^{**}}{I} \right)$$

whose derivative is

$$V' = \left(1 - \frac{M^{**}}{M}\right) M' + \left(1 - \frac{S^{**}}{S}\right) S' + \left(1 - \frac{E^{**}}{E}\right) E' + A\left(1 - \frac{I^{**}}{I}\right) I' \qquad (3.1.1)$$

Substituting the values of M', S', E' and I' in (3.1.1), we have

$$\begin{aligned} V' = {} & \left(1 - \frac{M^{**}}{M}\right)\left[(1-p)\pi - (\eta+\mu)M\right] + \left(1 - \frac{S^{**}}{S}\right)\left[p\pi + \eta M + \rho R_H - \beta SI - \mu S\right] \\ & + \left(1 - \frac{E^{**}}{E}\right)\left[\beta SI - (\mu+\varepsilon)E\right] + A\left(1 - \frac{I^{**}}{I}\right)\left[\varepsilon E - (\mu+\alpha+\gamma+\sigma)I\right] \end{aligned} \qquad (3.1.2)$$

Obtaining the values of, A, $(1-p)\pi$, πp, $(\mu+\varepsilon)$, and $(\mu+\alpha+\gamma+\sigma)$ as below

$$A = \frac{\beta S^{**} I^{**}}{\varepsilon E^{**}}, \quad (1-p)\pi = (\eta+\mu)M^{**}, \quad \pi p = -\eta M^{**} - \rho R^{**}_H + \beta S^{**} I^{**} + \mu S^{**}$$

$$(\mu+\varepsilon) = \frac{\beta S^{**} I^{**}}{E^{**}}, \quad (\mu+\alpha+\gamma+\sigma) = \frac{\varepsilon E^{**}}{I^{**}} \qquad (3.1.3)$$

Substituting (3.1.3) in (3.1.2) and further Simplification gives

$$V' \le \mu M^{**}\left(2-\frac{M}{M^{**}}-\frac{M^{**}}{M}\right)+\mu S^{**}\left(2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\right)+\rho R_H\left(1-\frac{S}{S^{**}}\right)+\rho {R_H}^{**}\left(1-\frac{S^{**}}{S}\right)$$
$$+\beta S^{**}I^{**}\left(4-\frac{I}{I^{**}}-\frac{S^{**}}{S}-\frac{EI^{**}}{IE^{**}}-\frac{SIE^{**}}{ES^{**}I^{**}}\right)$$

Since the arithmetic mean exceeds the geometric mean the following inequality hold:

$$2-\frac{M}{M^{**}}-\frac{M^{**}}{M}\le 0,\ 2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\le 0,\ \text{and}\ 4-\frac{I}{I^{**}}-\frac{S^{**}}{S}-\frac{EI^{**}}{IE^{**}}-\frac{SIE^{**}}{ES^{**}I^{**}}\le 0$$

Furthermore, since all the model are non-negative, thus $V' \le 0$ if $S \le S^{**}$, then the largest compact invariant set in D_1 such that $V' \le 0$ is the singleton set $\{Eq_1\}$ then by LaSalle Invariant Principle (C.C Mccluskey (2006)) then it implies Eq_1 is globally asymptotically stable (GAS) in the interior of D_1.

Numerical Simulation

The numerical simulation was carried out using MATLAB. The estimated parameters values used in the simulation of model are presented in table 2.

The graph in Figure 2 represent three (3) cases from Table 2. The first case when $\sigma = 0$, that is the initial stage second case when $\sigma = 0.25$ and the third when $\sigma = 0.75$. We can see that there was a smaller number of infected population when there is no drug resistance and infection increase when we increase the resistance from 25% to &75%.

Table 2: Parameters values used in the simulation

Parameter	***value***
N	10000
π	5000
μ	0.9
p	0.04
β	0.05
ε	0.06
γ	0.65
α	0.6
δ	0.3
σ	0, 0.25.
0.75	
α_1	0.04

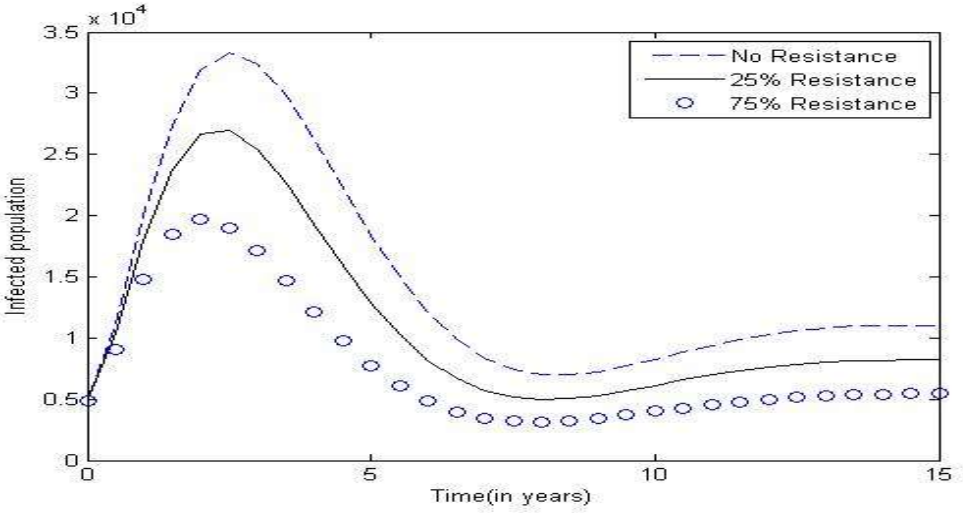

Figure 2: Numerical Simulation of Infected Individual against time when, $\sigma = 0$, $\sigma = 0.25$ and $\sigma = 0.75$. Parameter values in Table 2 were used in the simulation.

DISCUSSION

From the numerical simulation of the condition in Figure (4.1) above, it shows that there was less number of infected population when there is no resistance and infection is increased as we increases 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 points $\left(Eq^0\right)$ of the model is locally stable in all the three (3) different values of σ. Since the basic reproduction number $R_0 < 1$, it implies that the disease will gradually die out in the population when there are no resistance and the disease will increase when there is resistance to first line of treatment.

CONCLUSION

A deterministic model to study the effect of immunity and drug resistance on the transmission dynamics of tuberculosis was modelled and analysed in order to see the effect of resistance to first line of treatment in a population. The DFE is obtained and found to be locally asymptotically stable and globally asymptotically stable when $R_0 < 1$. The EEP was also determined and found out to be LAS and GAS when $R_0 > 1$. The analysis and numerical simulation of the model reveal that the disease-free equilibrium $\left(Eq^0\right)$ 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, which shows that the disease will die out when there is no drug resistance.

REFERENCES

Andam E. P. (2013). *Analysis of transmission dynamics of tuberculosis using differential equations*. A case study of Amansie West District Ghana.

Brooks-Pollock, E; Cohen, T; Murray, M (2010). *The impact of realistic age structure in simple models of tuberculosis transmission*. Plos.one, 5(1).

Bhunu C. P.,Garira W., Mukandavire Z., Zimba M. (2008). Tuberculosis transmission model with chemoprophylaxis and treatment. *Bull. Math. Biol*. 70: 1163-1191.

Dye C, Garnett G.P, Sleemank, Williams B.G (1998), Global Tuberculosis Programme. Evans C.C. (1994) History background In: Davies PDO (ed). *Clinical tuberculosis London*: Chapman and Hall, PP. 1-18.

Agusto F. B., Cook J., Shelton P.D, Wickers M.G. (2015). Mathematical model of Mdrtb and Xdr-tb with isolation and loss of follow-up.

Gupta K.B, Atreja A. (2006). *Transmission of tuberculosis infection and its control in health*. Cave facilities NTI Bulletin.

Mandal A, Singh A (2017). *Recent changes in tuberculosis guidelines for children*. Mycobact Dis 7: 237.

Mariam S.H., Werngren J., Aronsson J., Hoffner S., Andersson D.I. (2011). *Dynamics of antibiotic resistant mycobacterium tuberculosis during long term infection and antibiotic treatment*.

Murna P. (2015). *The transmission of tuberculosis and its prevalence on age and gender*: (A case study of infectious disease hospital (IDP) Bayara Bauchi).

Egbetade S. A, Ibrahim M. O (2012). *Existence of solution of tuberculosis epidemic model*; Journal of Mathematics IOSR, 4(1): 50- 52.

Van-Den Dreissche, P., and Watmough, J. (2002). Reproduction numbers and sub threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, *180* (1-2), 29-48.

Waaler and Anderson (1962). *The use of mathematical models in the study of the epidemiology of tuberculosis*, American journal of public health and nation's health.

World Health Organization [WHO] (2017). Guidelines for treatment of drug-susceptible tuberculosis and patient care.

Ziv E., Daley C. L., Blower S.M. (2001). Early therapy for latent tuberculosis infection, *American journal of epidemiology*, 153(4), 381-385.