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MODELING THE DYNAMICS OF TUBERCULOSIS WITH DRUG RESISTANCE IN NORTH SHOA ZONE, OROMIYA REGIONAL STATE, ETHIOPIA

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Abstract. Tuberculosis (TB) is a major public health concern in many developing countries. Mycobacterium tuberculosis is a major cause of morbidity and mortality in Africa. Tuberculosis infection is curable but in the cases of incomplete treatment, the remains of Mycobacterium tuberculosis in the human body usually results in the bacterium developing resistant to antibiotics. In this study we developed a model that explains the dynamics of tuberculosis infection in the presence of drug resistance. The basic reproduction number of the model was computed using the next generation matrix approach. The disease free equilibrium and endemic equilibrium were obtained and their stability analysis were carried out. It revealed that they were locally and globally asymptotically stable whenever the reproductive number was less than unity. Numerical simulation of the TB model was conducted and the result revealed that contact rate can reduce or eliminate the sensitive strain and reduce drug resistant of tuberculosis.

Keywords: tuberculosis; modeling; drug resistance; sensitivity analysis.

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1. INTRODUCTION

Tuberculosis infection has been in existence since time immemorial. The organism responsible for tuberculosis infection is Myco-bacterium tuberculosis (MTB) [1]. This disease has been found in relics from ancient China, Egypt and India. During the 8th century in Western Europe, the disease has reached its peak with prevalence as high as 900 deaths per $100,000$.

In most instances, Poor ventilation, overcrowding, poor sanitation and other risk factors can lead to the spread of Tuberculosis infection. Moreover, with development of advanced screening, diagnostic and treatment methods for tuberculosis infection, a larger population have been exposed to the disease [2, 3].

It has been estimated that, approximately 8.8 Million cases of the disease occurred globally in 2010. Africa and Asia are mostly at risk of Tuberculosis. According to the World Health Organisation Report in 2011, it was estimated that approximately 1.4 million people died of Tuberculosis (TB) infection [2, 3].

A study conducted by [4, 5] revealed that Tuberculosis affects the lungs and other parts of the body including the brain, lymph nodes, urinary tract and the joints. The infection easily spread via droplet when people with pulmonary TB expel the germ through coughing, talking and sneexing. In the absence of treatment, children, people with immune disorders, diabetics and pregnant women are mostly at risk of infections.

Generally, tuberculosis symptoms depends on the part of the body infected. Moreover, latent tuberculosis is symptomless. Active tuberculosis symptoms includes the following, coughing with mucus or blood, fatigue, loss of weight, fever, night sweatd and loss of appetite. The occurence of tuberculosis outside the lungs has varying symptoms. Tuberculosis can as well be spread to other parts of the body via blood stream [6, 7].

In a study conducted by [2, 4], tuberculosis is curable provided early diagnosis is conducted and the infected adheres to treatment regulations which usually takes up to six months or one year. An emerging ofrm of tuberclosis which is commonly called multi drug resistant (MDR) tuberculosis is the most effective antibiotic for active tuberculosis.

Ethiopia ranks seventh in the world's twenty two high risk countries with tuberculosis infection

and has an estimated incidence and prevalence of 300 to 470 per $100,000$ populations respectively. Moreover, case detection was 50% for all forms of tuberculosis (TB) [8]. In all new TB cases 35% were smear positive, 30% smear negative, 34% extra pulmonary and ,$<$ 1% smear unknown cases. Moreover, in the 2017 WHO data on tuberculosis deaths, Ethiopia has reached 24240 or 3.81% deaths and adjusted death rate was 45.57 per $100,000$ population [8].

In a quaterly report by the Health office in North Shoa Zone Oromiya region, annual achievement of tuberculosis of any form in Shoa Zone was 290 in the year 2017. Out of the 290 cases, 102 cases were pulmonary negative positive, 90 were negative and 98 were extra pulmonary. Moeover, 88 out of the 90 pulmonary negative cases successfully completed treatment and two died as indicated in Table (1). However, fatality rate was 312 per $100,000$ per population.

Year	Population infected	Population resistant to drugs	Population recovered	Population who died from infection
2013	1259	8	1248	3
2014	1288	12	1275	2
2015	1575	17	1554	4
2016	1645	17	1621	7
2016	1326	22	1294	10
2017	1848	25	1809	14

TABLE 1. Total population infected by TB and drug resistant from 2013 to 2017

(Source: Oromiya Region North Showa Zone Health Office, Ethiopia.)

Figure (1) shows the population dynamics of people who died from Tuberculosis infection between 2013 to 2018 in Oromiya Region North Showa Zone, Ethiopia.

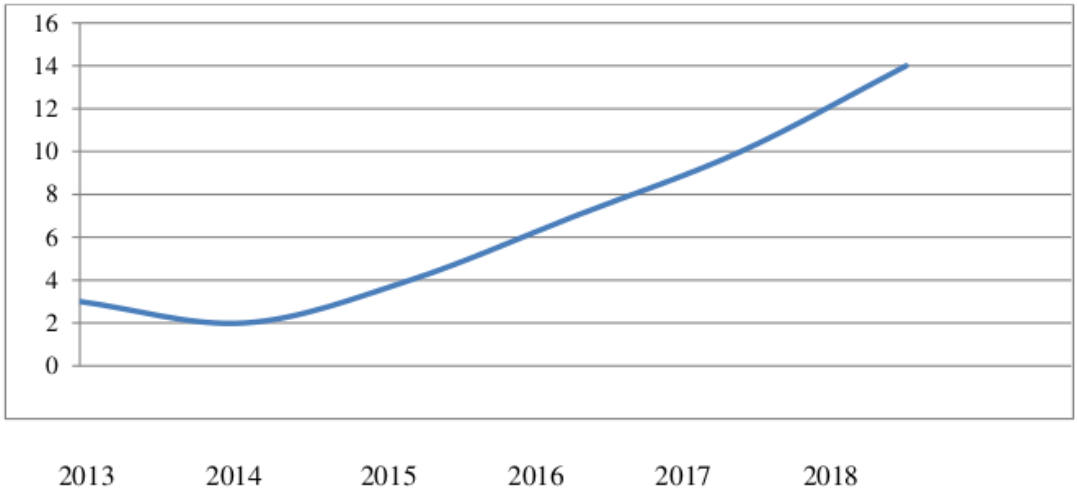

FIGURE 1. Population death due to TB Infection

Epidemic models generally explain the spread mechanism of diseases, determine the best optimal control mechanism and the most effective cost to be employed in combating the infections [9, 10, 11, 12, 13].

A real world phenomenon is translated by a disease model for optimal cost control and employ sensitivity analysis to determine the best control measure [14, 15, 16, 17]

The five basic hypothesis proposed by Danny Pascal Moualeu-gangue as follows:

- Tuberculosis is transmissible from human to human (for simplicity, we neglect the bovine tuberculosis);
- Only few among the infected become a source of infection (and among them, for simplicity only those who are coughing and have bacilli impute are considered);
- there is no vertical transmission (all new births are susceptible);
- ill infected individuals remain infected throughout their lives; this is still a simplification, since it seems that in the absence of re-infection, the initial infection eventually fades after a number of years not yet well defined;
- The vaccination of susceptible does not prevent infection. It prevents a proportion (variable with time) of infected to become infectious and contagious.

These hypothesis usually accounts for the structural differences in a number of tuberculosis models. These could be as a result of the disease history, the ordinary differential equations approach and the spatially structured models.

2. Model Formulation

2.1. Description of the Model. Human population is classified into five groups such as Susceptible (S), Exposed (E), Infected (I), Resistance to treatment (R_{ES}) and Recovered (R). We assumed that a fraction of the infected have been recovered before the disease outbreak at the rate of k. A fraction of the resistant population to first line treatment at a rate $(1-k)$.

Total human population is given by the relation; $N = S+E+I+R_{ES}+R$. Recruitment into the susceptible population is at a rate Θ and human poplation increases due to partial immunty in R after loss of immunity at a rate ρ.

Human population decreases due to natural death at a rate μ and tuberculosis induced death. The rate of force of infection is given by β and the exposed class is further decreased by natural deaths (μ) and the proportion who move to the infected class after developing active tuberculosis.

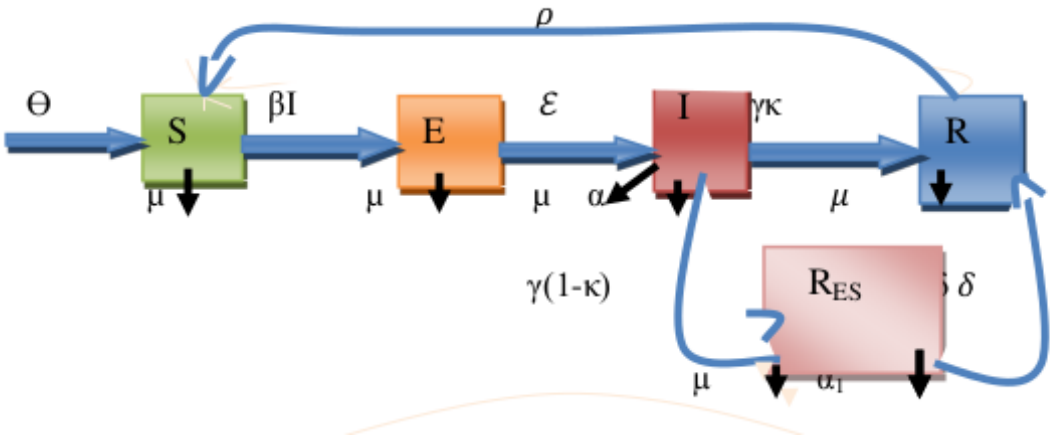

FIGURE 2. Flow diagram of the model

The infected compartment, I natural death and disease induced death rate are (μ) and (α) repectively. Rate of recovery is given by k and the probabilty of resistance is given by $1-k$.

Both the infected and resistance compartments gain partial immunity at rates γ and δ respectively.

R_{ES} class is reduced by natural death rate (μ) and disease induced death rate (α_1). Recovered class is reduced by natural deaths μ and those who lose their partial immunity at the rate ρ.

The above model description in Figure (2) gave rise to the following systems of differential equations.

$$
\begin{cases}
\frac{dS(t)}{dt} = \Theta - \beta SI - \mu S + \rho R \\
\frac{dE(t)}{dt} = \beta SI - (\mu + \varepsilon)E \\
\frac{dI(t)}{dt} = \varepsilon E - (\mu S + \alpha + \gamma)I \\
\frac{dR_{ES}}{dt} = (1-k)\gamma I - (\mu + \alpha_1 + \delta)R_{ES} \\
\frac{dR}{dt} = k\gamma I - (\mu - \rho)R + \delta R_{ES}
\end{cases} \tag{1}
$$

Where, $N(t) = S(t) + E(t) + I(t) + R_{ES}(t) + R(t)$ refers to total population at any given time t and with initial condition $S(0) = S_0 0, E(0) = E_0, I(0) = I_0, RES(0) = R_{ES(0)}, R(0) = R_0$.

2.2. Qualitative Model Analysis. In this section, we dwell on invariant region, positivity of the solution disease free equilibrium and the basic reproduction number.

2.2.1. *Invariant Region.* This refers to a region in which solutions of the model's system of equation is uniformly bounded. The solutions of our TB model must be a proper subset $\Omega \subset \mathbb{R}^s_+$.

Theorem 2.1. *The system of equation describes a deterministic model that all solutions are uniformly bounded on* $\Omega \subset \mathbb{R}^s_+$

Proof. We obtained the invariant region, in which the model solution is bounded. This is done by first considering the total human population (N), where

$$N = S + E + I + R_{ES} + R \tag{2}$$

By differentiating both sides with respect to t;

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR_{ES}}{dt} + \frac{dR}{dt} \tag{3}$$

Substituting the differential equation (2) in (3);

$$\frac{dN}{dt} = \Theta - \mu(S+E+I+R_{ES}) - \alpha I - \alpha_1 R_{ES} \tag{4}$$

This yields;

$$\frac{dN}{dt} = \Theta - \mu N - \alpha I - \alpha_1 R_{ES} \tag{5}$$

In the absence of mortality due to TB infection; $(\alpha = \alpha_1 = 0)$, and (5) becomes;

$$\frac{dN}{dt} \leq \Theta - \mu N \implies \frac{dN}{\Theta - \mu N} \leq dt \tag{6}$$

By integrating; (6),

$$\int \frac{dN}{\Theta - \mu N} \leq \int dt \implies -\frac{1}{\mu}\ln(\Theta - \mu N) \leq t + c \implies \ln(\Theta - \mu N) \geq -\mu t - \mu c \tag{7}$$

Multiplying both sides by $-\mu$:

$$\begin{aligned} \ln(\Theta - \mu N) &\geq -\mu t - \mu c \\ e^{\ln(\Theta - \mu N)} &= e^{-\mu t - \mu c} \end{aligned} \tag{8}$$

By simplification;

$$\Theta - \mu N = Ce^{-\mu t} \tag{9}$$

Where C is constant. As $t \to \infty$ in (9), $Ce^{-\mu t} \to 0$, then;

$$\Theta - \mu N \leq 0 \tag{10}$$

and from (10), we have the population size ;

$$N \leq \frac{\Theta}{\mu} \implies 0 \leq N \leq \frac{\Theta}{\mu} \tag{11}$$

Hence, feasible solution set of the system enters and remains in the region:

$$\left\{(S,E,I,R_{ES}) \in \mathbb{R}^s_+ : N \leq \frac{\Theta}{\mu}\right\} \tag{12}$$

Hence, model is well posed epidemiologically and mathematically. Sufficient evidence to study the dynamics of the model in Ω [18, 19, 20]. □

2.2.2. *Positivity of the Solution.* For the model system (2) to be epidemiologically meaningful, all solution of the model with positive initial data ought to remain positive for all $t > 0$. Deriving the positivity solution for our system.

Theorem 2.2. *Each solution $(S(t),E(t),I(t),R_{ES}(t),R(t))$ of model (2) with the non negative initial condition is non-negative for all $t > 0$.*

Proof. Checking the positivity;

$$\begin{aligned} \frac{dS}{dt} &= \Theta - (\beta I + \mu)S + \rho R \\ \frac{dS}{dt} &\geq (\beta I + \mu)S \\ \frac{dS}{S} &\geq -(\beta I + \mu)dt \\ \ln S &\geq -\int (\beta I + \mu)S \end{aligned} \tag{13}$$

$$S(t) \geq S_0 \exp(-(\beta I + \mu)t) \geq 0 \tag{14}$$

Similarly we obtained

$$E(t) \geq E_0 \exp(-(\mu + \varepsilon)t) \geq 0 \tag{15}$$

$$I(t) \geq I_0 \exp(-(\mu + \alpha + \gamma)t) \geq 0 \tag{16}$$

$$R_{ES} \geq I_0 \exp(-(\mu + \alpha_1 + \delta)t) \geq 0 \tag{17}$$

$$R(t) = R_0 \exp(-(\mu + \rho)t) \geq 0 \tag{18}$$

Thus; $S(t),E(t),I(t),R_{ES}(t)$ and $R(t))$ are positive $\forall t \geq 0$ □

2.2.3. *The disease free Equilibrium, DFE.* The DFE is an equilibrium point at which the epidemic is eradicated from the population. In determining DFE, we equate the right hand side of model(2) to zero, evaluating at $E = I = R_{ES} = 0$.

First equation of model (2)$\Theta - \beta SI - \mu S + \rho R = 0$, since $E = I = R_{ES} = R = 0$ Therefore; $\text{DFE}_t = 0$

$$\Theta - \mu S = 0 \quad \text{from this} \quad S = \frac{\Theta}{\mu} \quad \text{and} \quad \text{DFE} = \left(\frac{\Theta}{\mu}, 0, 0, 0, 0\right) \tag{19}$$

2.2.4. *Basic Reproductive number, R_0.* This number, $(\mathscr{R}_0)$ defines the average number of secondary infections or cases arising from an average primary case in an entirely susceptible population [2, 21, 22].

Considering the system in (2);

$$\begin{cases} \dfrac{dE}{dt} = \beta SI - (\mu + \varepsilon)E \\ \dfrac{dI}{dt} = \varepsilon SI - (\mu + \alpha + \gamma)I \\ \dfrac{dE}{dt} = (1-k)\gamma I - (\mu + \alpha_1 + \delta)R_{ES} \end{cases} \tag{20}$$

Let $X = (E, I, R_{ES})$ then the above system can be represented in matrix form as shown below where F is the Jacobian of the matrix of infection rates and V is the Jacobian of transition rates at $\left(\frac{\Theta}{\mu}, 0, 0, 0, 0\right)$.

$$\frac{dX}{dt} = F(X) - V(X) \text{ where } F(X) = \begin{bmatrix} \beta SI \\ 0 \\ 0 \end{bmatrix} \text{ where } V(X) = \begin{bmatrix} (\mu + \varepsilon)E \\ -\varepsilon E + (\mu + \alpha + \gamma)I \\ -(1-k)\gamma I + (\mu + \alpha_1 + \delta)R_{ES} \end{bmatrix}$$

Jacobian matrix of $F(X)$ and $V(X)$ at DFE, X_0:

$$\text{DF}(X_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \; V(X) = \begin{pmatrix} V & 0 \\ 0 & 0 \end{pmatrix}$$

respectively where

$$F = \begin{bmatrix} 0 & \beta\frac{\Theta}{\mu} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \; V = \begin{bmatrix} \mu + \varepsilon & 0 & 0 \\ -\varepsilon & \mu + \alpha + \gamma & 0 \\ 0 & -(1-k)\gamma & (\mu + \alpha_1 + \delta) \end{bmatrix} \tag{21}$$

The spectral radius FV^{-1}, ρ, defined as the largest eigenvalue of FV^{-1}. Where;

$$FV^{-1} = \begin{bmatrix} 0 & \beta\frac{\Theta}{\mu} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{\mu+\varepsilon} & 0 & 0 \\ \frac{\varepsilon}{(\mu+\alpha+\gamma)(\mu+\varepsilon)} & \frac{1}{\mu+\alpha+\gamma} & 0 \\ \frac{(1-k)\varepsilon\gamma}{(\mu+\alpha+\gamma))(\mu+\varepsilon)(\mu+\gamma)} & \frac{-\gamma(1-k)}{(\mu+\alpha+\gamma)(\mu+\alpha_1+\gamma)} & \frac{1}{(\mu+\alpha_1+\delta)} \end{bmatrix} \tag{22}$$

Computing eigenvalue of matrix (22) to $\mathscr{R}_0$ defined as spectral radius (dominant eigenvalue) of the matrix.

This is computed by $|A - I\lambda| = 0$ where A is matrix (22) and I is a 3×3 identity matrix. Hence, matrix (22);

$$\begin{bmatrix} \frac{\beta\Theta\varepsilon}{\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)} - \lambda & \frac{\beta\Theta}{\mu(\mu+\alpha+\gamma)} & 0 \\ 0 & 0-\lambda & 0 \\ 0 & 0 & 0-\lambda \end{bmatrix} = 0 \tag{23}$$

From matrix (23), eigenvalues are given by;

$$\lambda = \frac{\beta\Theta\varepsilon}{\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)} \quad \text{or} \quad \lambda = 0 \tag{24}$$

The eigenvalue FV^{-1} are;
$\left\{\frac{\beta\Theta\varepsilon}{\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)}, 0\right\}$. Clearly,
$\lambda = \frac{\beta\Theta\varepsilon}{\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)}$ is the dominant eigenvalue and hence;

$$\mathscr{R}_0 = \frac{\beta\Theta\varepsilon}{\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)} \tag{25}$$

2.3. Stability Analysis of Disease-Free Equilibrium.

2.3.1. *Local Stability of DFE.* We analyse the stability of the DFE points. By linearising the system of differential equation (2) by obtaining its Jacobian at the disease free equilibrium $\left(\frac{\Theta}{\mu}, 0, 0, 0, 0\right)$

Theorem 2.3. *The disease-free equilibrium* $\left(\frac{\Theta}{\mu}, 0, 0, 0, 0\right)$ *is locally asymptotically stable if* $\mathscr{R}_0$

Proof. The Jacobin matrix of (2) is

$$j = \begin{bmatrix} -\beta I - \mu & 0 & -\beta S & 0 & \rho \\ \beta I & -(\mu+\varepsilon) & \beta S & 0 & 0 \\ 0 & \varepsilon & -(\mu+\alpha+\gamma) & 0 & 0 \\ 0 & 0 & (1-k)\gamma & -(\mu+\alpha_1+\delta) & 0 \\ 0 & 0 & k\gamma & \delta & -(\mu+\rho) \end{bmatrix} \tag{26}$$

$$J_{\mathrm{DFE}} = \begin{bmatrix} -\mu & 0 & -\beta\frac{\Theta}{\mu} & 0 & \rho \\ 0 & -(\mu+\varepsilon) & \beta\frac{\Theta}{\mu} & 0 & 0 \\ 0 & \varepsilon & -(\mu+\alpha+\gamma) & 0 & 0 \\ 0 & 0 & (1-k)\gamma & -(\mu+\alpha_1+\delta) & 0 \\ 0 & 0 & k\gamma & \delta & -(\mu+\rho) \end{bmatrix} \tag{27}$$

Let;

$k_1 = -(\mu+\varepsilon)$, $k_2 = -(\mu+\alpha+\gamma)$, $k_3 = -(\mu+\alpha_1+\delta)$, $k_4 = -(\mu+\rho)$. Then

$$(-\mu-\lambda)\begin{vmatrix} k_1-\lambda & \beta\frac{\Theta}{\mu} & 0 & 0 \\ \varepsilon & k_2-\lambda & 0 & 0 \\ 0 & (1-k)\gamma & k_3-\lambda & 0 \\ 0 & k\gamma & \delta & k_4-\lambda \end{vmatrix} = 0 \implies \lambda = -\mu < 0 \tag{28}$$

and

$$\begin{vmatrix} k_1-\lambda & \beta\frac{\Theta}{\mu} & 0 & 0 \\ \varepsilon & k_2-\lambda & 0 & 0 \\ 0 & (1-k)\gamma & k_3-\lambda & 0 \\ 0 & k\gamma & \delta & k_4-\lambda \end{vmatrix} = 0 \implies \tag{29}$$

$$(k_4-\lambda)\begin{vmatrix} k_1-\lambda & \beta\frac{\Theta}{\mu} & 0 \\ \varepsilon & k_2-\lambda & 0 \\ 0 & (1-k)\gamma & k_3-\lambda \end{vmatrix} = 0 \implies \lambda = k_4 = -(\mu+\rho) < 0 \tag{30}$$

$$\text{and} \begin{vmatrix} k_1-\lambda & \beta\frac{\Theta}{\mu} & 0 \\ \varepsilon & k_2-\lambda & 0 \\ 0 & (1-k)\gamma & k_3-\lambda \end{vmatrix} = 0 \tag{31}$$

$$(k_3-\lambda)\begin{vmatrix} k_1-\lambda & \beta\frac{\Theta}{\mu} \\ \varepsilon & k_2-\lambda \end{vmatrix} = 0 \quad \text{then} \tag{32}$$

$$(k_3-\lambda)=0 \quad \text{and} \begin{vmatrix} k_1-\lambda & \beta\frac{\Theta}{\mu} \\ \varepsilon & k_2-\lambda \end{vmatrix} = 0 \tag{33}$$

$$\lambda = k_3 = -(\mu+\alpha_1+\delta) < 0 \tag{34}$$

$$\text{and} \begin{vmatrix} k_1-\lambda & \beta\frac{\Theta}{\mu} \\ \varepsilon & k_2-\lambda \end{vmatrix} = 0 \tag{35}$$

$$(k_1-\lambda)(k_2-\lambda)-\frac{\varepsilon\beta\Theta}{\mu} = 0 \tag{36}$$

By Routh-Hurwitz Criteria;

$\lambda^2-\lambda(k_1+k_2)+k_1k_2-\frac{\varepsilon\beta\Theta}{\mu}>0$

By ultiplying both sides by negative;

$$\begin{aligned} -\lambda^2-\lambda(k_1+k_2)+k_1k_2-\frac{\varepsilon\beta\Theta}{\mu} &> 0 \\ -\lambda^2-\lambda(2\mu+\varepsilon+\alpha+\gamma)+\frac{\varepsilon\beta\Theta}{\mu}-(\mu+\varepsilon)(\mu+\alpha+\gamma) &< 0 \\ -\lambda^2-\lambda(2\mu+\varepsilon+\alpha+\gamma)+(\mu+\varepsilon)(\mu+\alpha+\gamma)\left(\frac{\varepsilon\beta\Theta}{\mu(\mu+\varepsilon)(\mu+\alpha+\gamma)}\right) &< 0 \\ -\lambda^2-\lambda(2\mu+\varepsilon+\alpha+\gamma)+(\mu+\varepsilon)(\mu+\alpha+\gamma)(\mathscr{R}_0-1) &< 0 \end{aligned}$$

If $\mathscr{R}_0-1<0$ then $\mathscr{R}_0<-1$. Therefore the disease free equilibrium is locally asymptotically stable. □

2.3.2. *Global Stability of the disease free Equilibrium.*

Theorem 2.4. *If $\mathscr{R}_0 \leq 1$, then the disease-free equilibrium $(E,I,R_{ES})=(0,0,0)$ of the system is globally asymptotically stable on Ω.*

Proof. Constructing the following Lasalle-Lyapunov function $V(E,I,R_{ES})$ on the positively invariant compact set Ω.

Thus on Ω, $V(E,I,R_{ES})$ is continuous and non negative. We define $V(E,I,R_{ES}) = \varepsilon E + (\mu + \varepsilon)I$. The system of ordinary differential equations given by Equation (21) can be written as;

$$\begin{bmatrix} E \\ I \\ R_{ES} \end{bmatrix} = \begin{bmatrix} -(\mu+\varepsilon) & \frac{\beta\Theta}{\mu} & 0 \\ \varepsilon & -(\mu+\alpha+\gamma) & 0 \\ 0 & (1-k)\gamma & -(\mu+\alpha_1+\delta) \end{bmatrix} \begin{bmatrix} E \\ I \\ R_{ES} \end{bmatrix} \tag{37}$$

This can also be written as;

$$I = A(I) \text{ where } A = \begin{bmatrix} -(\mu+\varepsilon) & \frac{\beta\Theta}{\mu} & 0 \\ \varepsilon & -(\mu+\alpha+\gamma) & 0 \\ 0 & (1-k)\gamma & -(\mu+\alpha_1+\delta) \end{bmatrix} \text{ and } I = \begin{bmatrix} E \\ I \\ R_{ES} \end{bmatrix} \tag{38}$$

Let,

$V' = [\varepsilon, \mu+\varepsilon, 0]$

It's derivative along the trajectories is given by $V' = V'A(I)$ as;

$$|V'A(I) = [\varepsilon, \mu+\varepsilon, 0] \begin{bmatrix} -(\mu+\varepsilon) & \frac{\beta\Theta}{\mu} & 0 \\ \varepsilon & -(\mu+\alpha+\gamma) & 0 \\ 0 & (1-k)\gamma & -(\mu+\alpha_1+\delta) \end{bmatrix} \tag{39}$$

$$= \begin{bmatrix} 0 & \frac{\beta\Theta\varepsilon}{\mu} - (\mu+\varepsilon)(\mu+\alpha+\gamma) & 0) \end{bmatrix} \tag{40}$$

$$= \begin{bmatrix} 0 & (\mu+\varepsilon)(\mu+\alpha+\gamma)\left(\frac{\beta\Theta\varepsilon}{\mu(\mu+\varepsilon)(\mu+\alpha+\gamma)} - 1\right) & 0) \end{bmatrix} \tag{41}$$

$$= \begin{bmatrix} 0 & (\mu+\varepsilon)(\mu+\alpha+\gamma)(\mathscr{R}_0 - 1) & 0 \end{bmatrix} \tag{42}$$

This is strictly decreasing when $\mathscr{R}_0$ thus $V'le(\mu+\varepsilon)(\mu+\alpha+\gamma)(\mathscr{R}_0-1)$.

Define the set $EE = (E,I,R_{ES}) \in \Omega | V(E,I,R_{ES}) = 0)$. The largest invariant set is contained in the set E for which $E = 0$ or $I = 0$ or $R_{ES} = 0$. Thus $V < 0$ when $\mathscr{R}_0$. If $I = 0$ or $\mathscr{R}_0 = 1$, then $V = 0$. Thus by LaSalle's invariance principle the disease free equilibrium is globally asymptotically stable Ω [23, 24] □

2.4. Endemic Equilibrium.

Definition 2.1. *The endemic equilibrium is denoted by a* Φ *defined as steady-state solutions for the model (2).This can occur when there is a persistence of the disease. It can be obtained by equating the system of Equation (2) to zero.*

Considering the second and third equations of model (2) and combining;

$$S^* = \frac{(\mu+\varepsilon)(\mu+\alpha+\gamma)}{\beta E} \tag{43}$$

Equating equation 2 of model (2) to zero;

$$E^* = \frac{\beta S^* I^*}{(\mu+\varepsilon)} \tag{44}$$

Equating equation 4 of model (2) to zero;

$$I^* = \frac{(\mu+\alpha_1+\delta)}{(1-k)(\mu+\rho)} R^*_{ES} \tag{45}$$

Substituting (45) in equation 5 of model (2);

$$R^* = \frac{(\mu+\alpha_1+\delta)+(1-k)\gamma}{(1-k)(\mu+\rho)} R^*_{ES} \tag{46}$$

Substituting (44), (45) and (46), in equation 1 of model (2);

$$\begin{aligned}
\Theta-\beta\left(\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma)}{\beta\varepsilon}\right)\left(\frac{(\mu+\alpha_1+\delta)}{(1-k)\gamma}R^*_{ES}\right)-\mu\left(\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma)}{\beta\varepsilon}\right)+\rho\left(\frac{(\mu+\alpha_1+\delta)(1-k)\gamma}{(1-k)(\mu+\rho)}R^*_{ES}\right) &= 0\\
\rho\left(\frac{(\mu+\alpha_1+\delta)(1-k)\gamma}{(1-k)(\mu+\rho)}R^*_{ES}\right)-\beta\left(\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma)}{\beta\varepsilon}\right)\left(\frac{(\mu+\alpha_1+\delta)}{(1-k)\gamma}R^*_{ES}\right)=\mu\left(\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma)}{\beta\varepsilon}\right) &- \Theta\\
R^*_{ES}\left[\rho\left(\frac{(\mu+\alpha_1+\delta)(1-k)\gamma}{(1-k)(\mu+\rho)}\right)-\beta\left(\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma)}{\beta\varepsilon}\right)\left(\frac{(\mu+\alpha_1+\delta)}{(1-k)\gamma}\right)\right]=\mu\left(\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma)}{\beta\varepsilon}\right) &- \Theta\\
\frac{\mu\left(\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma)}{\beta\varepsilon}\right)-\Theta}{\left[\rho\left(\frac{(\mu+\alpha_1+\delta)(1-k)\gamma}{(1-k)(\mu+\rho)}\right)-\beta\left(\frac{(\mu+\varepsilon)(\mu+\alpha+\gamma)}{\beta\varepsilon}\right)\left(\frac{(\mu+\alpha_1+\delta)}{(1-k)\gamma}\right)\right]} &= R^*_{ES}\\
\frac{\Theta-\mu x}{\beta Q-\rho P} &= R^*_{ES}
\end{aligned}$$

By backward substitution;

$$R^* = \frac{\rho\Theta-\mu x}{\beta Q-\rho P},\ E^* = \frac{\beta x Q(\Theta-\mu x)}{(\mu+\varepsilon)(\beta Q-\rho P)}.\ I^* = \frac{\mu+\alpha_1+\delta}{(1-k)\gamma}\frac{\Theta-\mu x}{\beta Q-\rho P}$$

where

$$x = S^*,\ Q = \frac{\mu+\alpha_1+\delta}{(1-k)\gamma},\ P = \frac{(\mu+\alpha_1+\delta)(1-k)}{(1-k)(\mu+\rho)}$$

2.4.1. *Stability Analysis of Endemic Equilibrium.*

2.4.2. *Global stability of the endemic equilibrium.*

Theorem 2.5. *If $\mathscr{R}_0 > 1$, the endemic equilibrium Φ of model (2) is globally asymptotically stable.*

Proof. Using the Lyapunov function approach;
Define;
$L(S^*,E^*,I^*,R^*_{ES},R^*) = (S-S^*-S^*\ln\frac{S}{S^*})+(E-E^*-E^*\ln\frac{E}{E^*})+(I-I^*-I^*-\ln\frac{I}{I^*})+(R_{ES}-R^*_{ES}-R^*_{ES}\ln\frac{R_{ES}}{R^*_{ES}})+(R-R^*-R^*\ln\frac{R}{R^*})$
Computing the derivative of L along the solution of (2);

$$\begin{aligned}
\frac{dL}{dt} &= \left(\frac{S-S^*}{S}\right)\frac{dS}{dt}+\left(\frac{E-E^*}{E}\right)\frac{dE}{dt}+\left(\frac{I-I^*}{I}\right)\frac{dI}{dt}+\left(\frac{R_{ES}-R^*_{ES}}{R_{ES}}\right)\frac{dR^*_{ES}}{dt}+\left(\frac{R-R^*}{R}\right)\frac{dR}{dt}\\
\frac{dL}{dt} &= \left(\frac{S-S^*}{S}\right)(\Theta-\beta SI-\mu S+\rho R)+\left(\frac{E-E^*}{E}\right)(\beta SI-(\mu+\varepsilon)E)+\left(\frac{I-I^*}{I}\right)(\varepsilon E-(\mu+\alpha+\gamma)I)\\
&\quad+\left(\frac{R_{ES}-R^*_{ES}}{R_{ES}}\right)[(1-k)\gamma I-(\mu+\alpha_1+\delta)R_{ES})]+\left(\frac{R-R^*}{R}\right)[\gamma I-(\mu+\rho)R+\delta R_{ES}]\\
\frac{dL}{dt} &= \left(1-\frac{S^*}{S}\right)(\Theta-\beta SI-\mu S+\rho R)+\left(1-\frac{E^*}{E}\right)(\beta SI-(\mu+\varepsilon)E)+\left(1-\frac{I^*}{I}\right)(\varepsilon E-(\mu+\alpha+\gamma)I)\\
&\quad+\left(1-\frac{R^*_{ES}}{R_{ES}}\right)[(1-k)\gamma I-(\mu+\alpha_1+\delta)R_{ES})]+\left(1-\frac{R^*}{R}\right)[\gamma I-(\mu+\rho)R+\delta R_{ES}]\\
\frac{dL}{dt} &= \Theta-\beta SI-\mu S+\rho R+-\Theta\frac{S^*}{S}+\beta S^*I+\mu S^*-\rho R\frac{S^*}{S}+\beta SI-(\mu+\varepsilon)E-\beta SI\frac{E^*}{E}+\mu E^*\\
&\quad+\varepsilon E-(\beta SI-(\mu+\varepsilon)E)+\left(1-\frac{I^*}{I}\right)(\varepsilon E-(\mu+\alpha+\gamma)I)+\left(1-\frac{R^*_{ES}}{R_{ES}}\right)[(1-k)\gamma I\\
&\quad-(\mu+\alpha_1+\delta)R_{ES})]+\left(1-\frac{R^*}{R}\right)[\gamma I-(\mu+\rho)R+\delta R_{ES}]
\end{aligned}$$

Considering positive terms and negative terms separately from above leads to;

$$\frac{dL}{dt} = M-T$$

where

$$\begin{aligned} M &= \Theta+\beta S^*I+\mu S^*+\mu E^*+\varepsilon E^*+\mu I^*+\alpha I^*+\gamma I^*+\frac{R^*_{ES}k\gamma I}{R_{ES}}+\mu R^*_{ES} \\ &\quad +\alpha_1 R^*_{ES}+\delta R^*_{ES}+\mu R^*+\rho R^* \text{ and} \\ T &= \mu S+\frac{\Theta S^*}{S}+\frac{\rho R S^*}{S}+\mu E+\frac{E^*\beta SI}{E}+\mu I+\alpha I+\frac{\varepsilon I^*E}{t}I+k\gamma+\mu R_{ES} \\ &\quad +\alpha_1 R_{ES}+\frac{R^*_{ES}\gamma I}{R_{ES}}+\mu R+\frac{R^*\gamma I}{R}+\frac{R^*\delta R_{ES}}{R} \end{aligned}$$

Thus if

$M < T$, then $\frac{dL}{dt} < 0$;

Noting that $\frac{dL}{dt} = 0$ if and only if

$S = S^*, E = E^*, I = I^*, R_{ES} = R^*_{ES}, R = R^*$

largest compact invariant set is the singleton set Φ which is the EE. By LaSalle Invariance principle Φ is globally asymptotically stable if $M < T$ [25]

□

2.5. Sensitivity Analysis of Model parameter. In determining how best to reduce human mortality and morbidity due to TB, we compute the sensitivity indices of paramters in $\mathscr{R}_0$ using approach [7, 26, 21, 27].

Sensitivity index of $\mathscr{R}_0$ with respect to some parameter, say ρ is given by:

$$\begin{aligned} \Lambda^{\mathscr{R}_0}_{\rho} &= \frac{\partial \mathscr{R}_0}{\partial \rho}\frac{\rho}{\mathscr{R}_0}, \quad P\beta = \frac{\partial \mathscr{R}_0}{\partial \beta}\frac{\beta}{\mathscr{R}_0}, \quad \frac{\partial \mathscr{R}_0}{\partial \beta} = \frac{\Theta\varepsilon}{(\mu+\alpha+\gamma)(\mu+\varepsilon)} \\ P_\beta &= \frac{\Theta\varepsilon}{\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)}\frac{\beta\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)}{\beta\Theta\varepsilon} = 1 > 0 \\ P_\Theta &= \frac{\partial \mathscr{R}_0}{\partial \Theta}\frac{\Theta}{\mathscr{R}_0}, \quad \frac{\partial \mathscr{R}_0}{\partial \Theta} = \frac{\beta\varepsilon}{\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)} \\ P\varepsilon &= \frac{\partial \mathscr{R}_0}{\partial \varepsilon}\frac{\varepsilon}{\mathscr{R}_0} and \frac{\partial \mathscr{R}_0}{\partial \varepsilon}\frac{\beta\Theta}{m(\mu+\alpha+\gamma)(\mu+\varepsilon)^2} \\ P_\Theta &= \frac{\beta\varepsilon}{\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)}\frac{\Theta\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)}{\beta\Theta\varepsilon} = 1 > 0 \\ P_\Theta &= \frac{\beta\Theta}{\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)}\frac{\Theta\mu(\mu+\alpha+\gamma)(\mu+\varepsilon)}{\beta\Theta\varepsilon} = 1 > 0 \end{aligned}$$

Hence the sensitive indices for all parameters;

TABLE 2. parameter and sensitivity indices.

Parameters	Expressions	Sensitivity Value
θ	Recruitement rate	+
β	Transmission rate	+
ε	Infection rate	+
α	Induced death rate	-
μ	Natural death rate	-
γ	Recovery rate due to prompt treatment	-

From Table (2), the parameters θ, β and ε have positive sensitivity indices. They have a high impact on the transmission dynamics and prevalence of TB.
However, the parameters α, μ and γ have negative sensitivity indices. Hence, they have high influence on controlling and eradicating TB infections from the community.

2.6. Parameter Estimation. We estimated the model parameters with respect to the incidence data of Tuberculosis as follows;

- Mortality rate: Estimated by the inverse of life expectancy at birth, $\mu(t) = 1/\tau(t)$ [5]. The WHO data published in 2018, Ethiopia's life expectancy was 63.7 for male, 67.3 for female and total life expectancy was 65.5.
  Hence $\mu = \frac{1}{65.5} = 0.015$
- The recruitment rate, θ : Taking into account the population of North Shoa Zone. Population Projection of Oromiya Region by Zone from 2007 to 2018, the average recruitment in population during the last twelve year is $\theta = 35055$ per year.
- TB-induced mortality rate, α: This varies from country to country. It is 0.193 per year in developed countries, but could be as high as 0.45 per year in some African countries. An intermediate value of 0.193 per year can be applied to most developed and developing countries [5].

- Transmission rate, β: Estimated as $\beta = \frac{\text{effective contact}}{\text{total contact}} = \frac{\text{Number of smear posetive}}{\text{Total case}}$ $\beta = \frac{35\%}{100\%} =$ 0.35 or $\beta = \frac{102}{290} = 0.35$ [5]
- Recovery rate due to prompt treatment, γ: Estimated by $\gamma = \frac{\text{minimum recovery time + maximum recovery time}}{2} = \frac{0.5+1}{2} = 0.75\text{yr}$

For numerical simulation purposes, some data values were collected for the parameters from TB cases in North Shoa Zone, Oromiya Regional State. These parameters were used for simulation purposes as listed in Table (3).

TABLE 3. parameter values.

Parameters	Expressions	value	Source
θ	Recruitment rae	35055/yr	Estimated
β	Transmission rate	0.35	Estimated
ε	Infection rate	0.2	Assumed
α	Induced death rate	0.19	[5]
μ	Natural death rate	0.015	Estimaed
ρ	Rate of lose of Immunity	0.008	[28]
γ	Recovery rate due to prompt treamtent	0.75	Estimated
α_1	Disease induced deaths	0.004	Assumed
δ	Recovery rate after second line treatment	0.012	Assumed

3. NUMERICAL SIMULATION

In this section, we explore the behaviour of TB infections quantitatively by applying the numerical approach. We lay emphasis on infected and resistant classes by checking their behaviour when their related parameters changes with time.

Our model uses a yearly time step and was solved by a Maple 18 software. Our simulation runs between intervals of 6 years to obtaining solution for the system. We start by defining the values of the parameters in Table (3).

Taking parameters of the system as: $\theta = 1, \beta = 0.35, \varepsilon = 0.2, \alpha = 0.19, \mu = 0.015, \rho = 0.008, \alpha_1 = 0.004, \delta = 0.012, \eta = 0.75, k = 0.7$.

Then $\Theta(S^*, E^*, I^*, R_{ES}^*, R^*) = (1.56, 5.77, 53.68, 10.56, 4.23)$ and $R_0 = 23.8 > 1$. If the initial values of susceptible, exposed, infected, resistant of first line treatment and recovered population are 1, 2, 1, 1 and 1 respectively therefore by theorem(2.5), the endemic equilibrium is global asymptotically stable as shown in Figure (3).

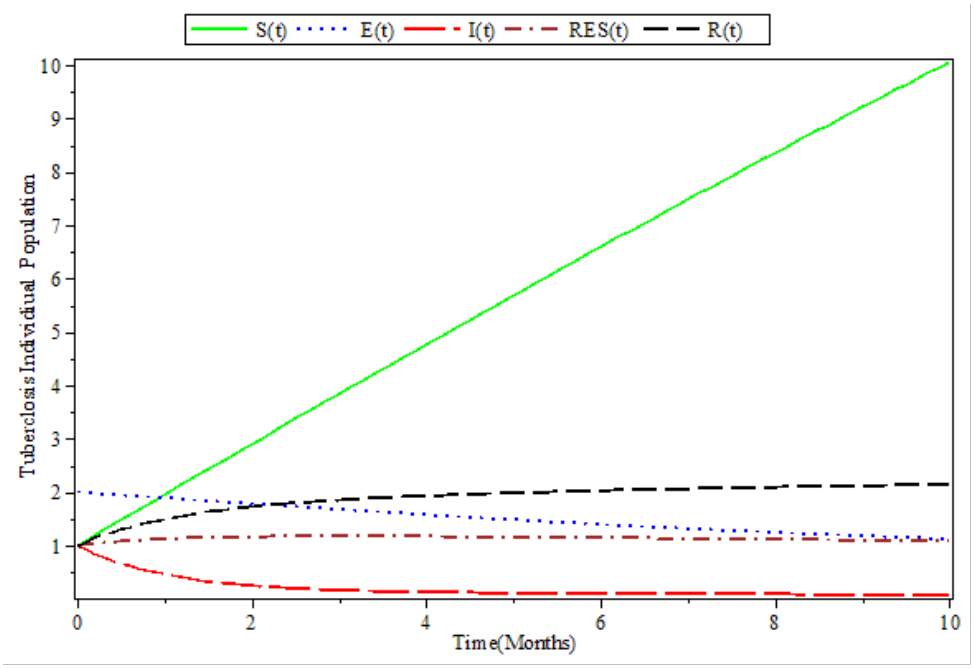

FIGURE 3. $\mathscr{R}_0 = 0.071 < 1$

Taking parameters of the system as: $\theta = 1, \beta = 0.35, \varepsilon = 0.2, \alpha = 0.19, \mu = 0.015, \rho = 0.008, \alpha_1 = 0.004, \delta = 0.012, \eta = 0.75, k = 0.7$.

Then $\Theta(S^*, E^*, I^*, R_{ES}^*, R^*) = (1.56, 5.77, 53.68, 10.56, 4.23)$ and $R_0 = 23.8 > 1$. If the initial values of susceptible, exposed, infected, resistant of first line treatment and recovered population are 1, 2, 1, 1 and 1 respectively therefore by theorem(2.5), the endemic equilibrium is global asymptotically stable as shown in Figure (4).

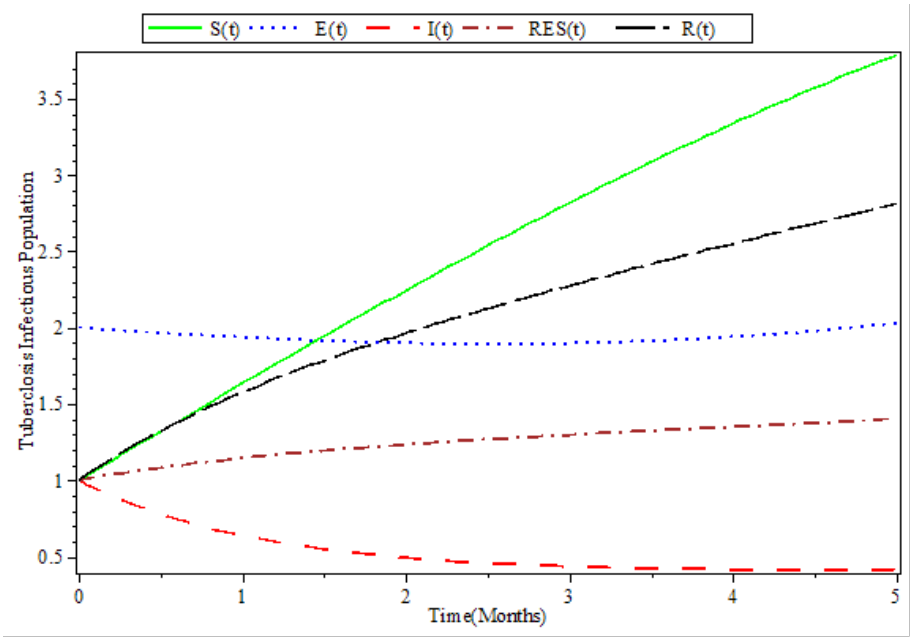

FIGURE 4. $\mathscr{R}_0 = 23.8 > 1$

3.1. Effects of Contact Rate, β on TB Exposed Population. From the diagram in Figure (5), it can be observed that an increase in contact rate, β increases the population of exposed individuals to TB infections.

The epidemiological implication is that, contact rate, β is a determiner of TB infections and hence should be kept on checks.

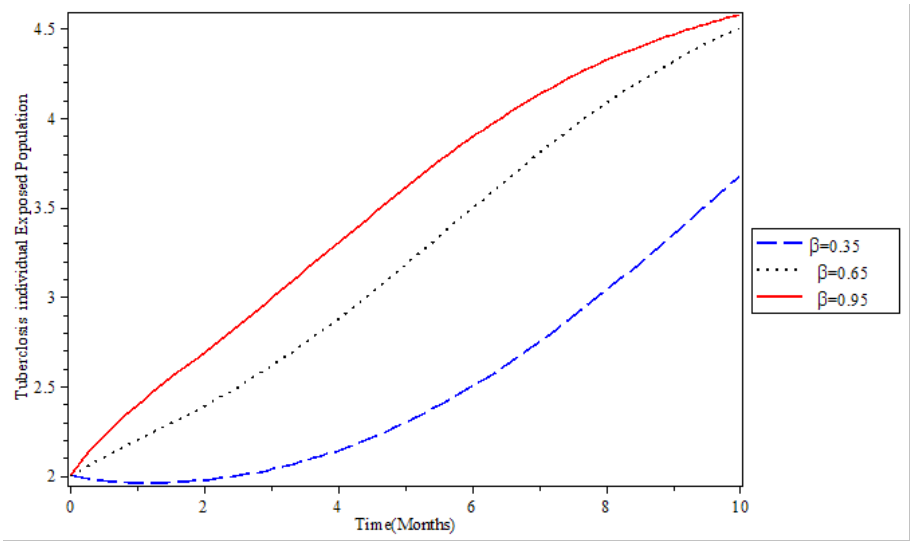

FIGURE 5. individuals of TB Exposed population with different contact rate β

3.2. Effect of Contact rate, ε on TB Infected Population. An increase in value of the contact rate, ε increases the number of infected population as shown in Figure (6).
Biologically, it implies that the contact rate, ε should be kept under control as it determines the population dynamics of TB infections.

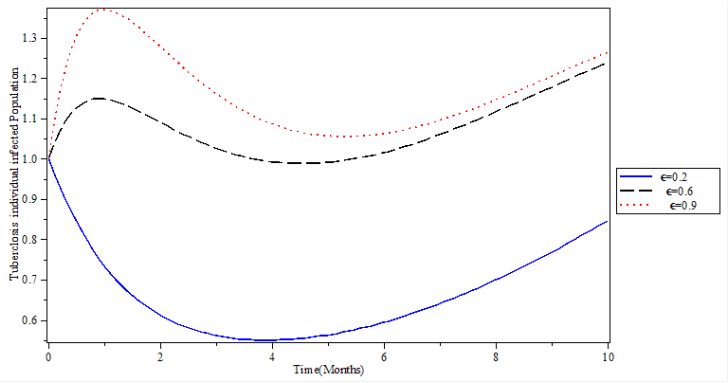

FIGURE 6. Individuals of TB infectious population with different infection rate ε

3.3. Effects of Resistance of 1st line treatment on TB Resistance Population. Considering all parameters fixed except for resistance rate of first line of treatments, population increases as resistance rate of first line of treatment increases as shown in Figure (7).
Epidemiologically, infected population moves to resistant population of the first line of treatment as resistant rate increases.

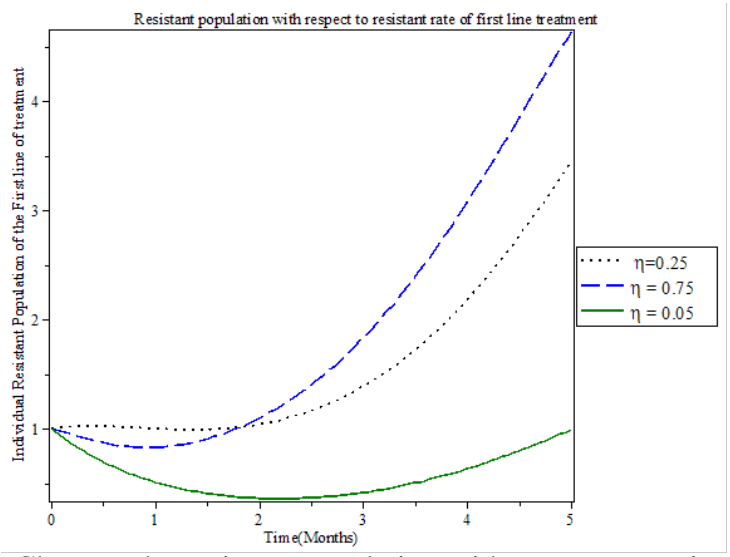

FIGURE 7. Changes the resistant population with respect to resistance rate of the first line of treatment, keeping all the other parameters fixed

3.4. Effects of Recovery Rates, δ and η on TB Recovered Population. By the assumption that all parameters are fixed except for recovery rates δ and η the infected population decreases as the recovery rates δ and η increases as shown in Figure (8).

As a result of these phenomenon, infected population and resistant population move to recovered population respectively.

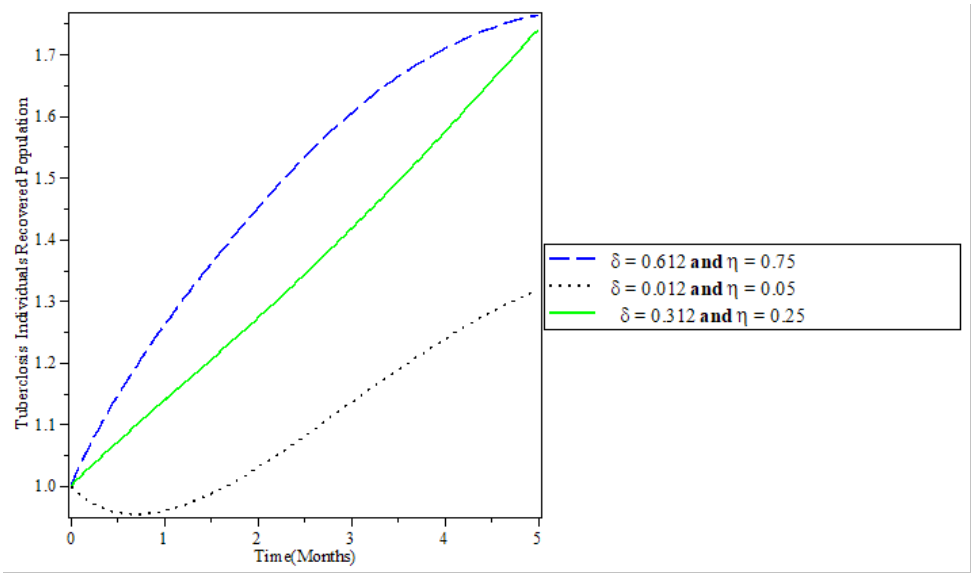

FIGURE 8. Changes the recovered population with respect to recovery rate of δ and η, keeping all other parameters is fixed.

4. CONCLUSION

We formulated and analysed a Tuberculosis model qualitatively and quantitatively using a data from the Health office in North Shoa Zone Oromiya region, Ethiopia.

The qualitative analysis of the TB model revealed that the disease free and disease endemic equilibrium points were found to be locally and globally asymptotically stable whenever the basic reproduction number was less than unity, $\mathscr{R}_0 < 1$ and unstable whenever $\mathscr{R}_0 > 1$.

Sensitivity analysis was conducted to determine the contribution of each parameter to the basic reproduction number. The results showed that the parameters θ, β and ε have positive sensitivity indices. This imply a high impact on TB transmission. However, the parameters α, μ and γ have negative sensitivity indices. Hence, they have high influence on TB control and eradication.

An analysis of the TB model was conducted quantitatively using a maple 18 software by plotting the graphs numerically. These revealed the following;

- An increase in contact rate, β increases the population of exposed individuals to TB infections.
- An increase in value of the contact rate, ε increases the number of infected population.
- The infected population decreases as the recovery rates δ and η increases

TB infected population may be large and treatment of such a number might pose a challenge economically for developing countries. Hence treatment of such a great number may led to an increase in number of TB drugs. Therefore, focus should be on education, sensitisation and awareness creation programs that will reduce transmission of TB bacteria from infected to susceptible population.

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DATA AVAILABILITY STATEMENT

The data supporting this Tuberculosis model analysis is from the Ethiopia National Institute of Health, a division of the National Health. Some of the parameter values are assumed and others are taken from published articles and are cited in this paper. These published articles are also cited at relevant places within the text as references.

CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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