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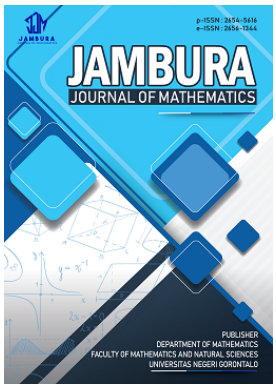

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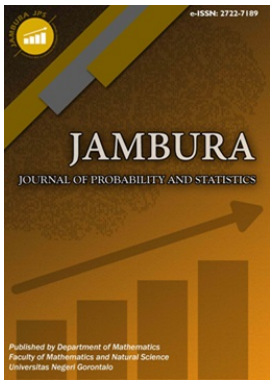

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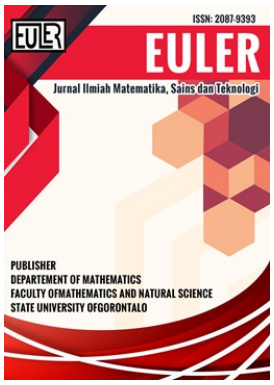

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Research Article

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Mathematical Analysis of Tuberculosis Transmission Model with Multidrug and Extensively Drug-resistance Incorporating Chemoprophylaxis Treatment

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ABSTRACT. *Tuberculosis has remained the principal cause of mortality worldwide, and one of the major sources of concern is drug-resistant TB. The increasing emergence of extensively drug-resistant and multidrug-resistant TB has further increased the TB epidemic. In this current work, we suggest a model to study the transmission of TB with extensively drug-resistant and multidrug-resistant compartments, incorporating chemoprophylaxis treatment. In the theoretical analysis, the concept of the next-generation matrix and the Jacobian method are applied to obtain a formula that states the reproductive number. The existence of endemic and disease-free equilibrium points was checked, and their stability has been analyzed using the Lyapunov method. The qualitative-based analysis indicated the local asymptotic stability of the disease-free-state for* $R_0 < 1$*, whereas the endemic state is globally asymptotically stable if* $R_0 > 1$*. Moreover, sensitivity analysis was carefully done using normalized forward sensitivity, and numerical simulation was carried out. Based on the results of numerical simulation and sensitivity analysis, chemoprophylaxis treatment was found to drastically minimize the progression of exposed individuals to infectious classes and also reduce the progression to extensively drug-resistant and multidrug-resistant classes, which decreases disease transmission.*

1. Introduction

Tuberculosis is considered to be responsible for more deaths worldwide when compared to other infectious diseases. It is a curable disease given that an early diagnosis is made and one properly follows an appropriate treatment regimen, which would last six months up to two years for the active TB to clear [1]. Tuberculosis has remained the main cause of mortality worldwide, and one of the major sources of concern is drug-resistant TB, such as extensively drug-resistant and multidrug-resistant TB, as reported by [2].

Mathematical formulation in disease models has been awfully flourishing to understand epidemiological models of diseases [3]. Mathematical modeling is practiced in the prediction of the disease spread, number of active cases, and duration of the pandemic [4]. The first model for studying the transmission of TB was proposed and analyzed by Waaler and Anderson [5]. An analysis of a model for tuberculosis with a diagnosis was proposed by Egonmwan [6]. A deterministic model for tuberculosis transmission with treatment and vaccination for both high-risk latent and active TB-infected classes was studied in [7]. In their study, the reproductive number was computed and the equilibrium points were described. Furthermore, it was shown that an increase in treatment and vaccination coverage minimizes the number of individuals infected by TB. In [8] a model is developed to investigate the transmission of tuberculosis disease by considering recurrent infection and vaccination. They obtained an equilibrium point that is disease-free and demonstrated its stability.

The authors of [9] formulated the SIR type of TB epidemic model and carried out its simulation using the Runge-Kutta method of the fourth order. The result of their study pointed out that the spread of TB can be prevented from becoming an epidemic by reducing the transmission rate and increasing the recovery rate. Their study showed that a means for decreasing the rate of transmission is to keep the TB-infected individual away from the susceptible group, whereas it needs to maximize treatment so as to amplify the rate of recovery. A non-linear model that incorporated treatment and case detection of tuberculosis was analyzed by Athithan and Ghosh [10]. In this work, they divided the whole population under consideration into four categories, such as susceptible, exposed, infected, and recovered groups, to study the transmission of tuberculosis.

According to [8, 11], the transmission rate of TB can be controlled through preventative therapy, known as chemoprophylaxis. If preventative therapy is given for the latently infected groups, then their progression to the infected group becomes delayed, resulting in a decline in the rate of transmission of TB. Chemoprophylaxis treatment (preventive therapy) is the use of isoniazid intended to minimize the risk of an initial episode of tuberculosis, which may arise in people exposed to this disease or have a latent infection, and a recurrent episode of TB [12].

The increasing emergence of extensively drug-resistant and multi-drug-resistant TB has further increased the TB epidemic.

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Thus, diagnosis of latent TB infections (LTBI) and timely treatment for active cases of TB remain important constituents for the effective control of TB [13]. In [14], vaccination and treatment are incorporated to mathematically model the outbreak of TB in the East African country.

A deterministic epidemic model of tuberculosis in a vaccinated population was proposed and studied by employing the SEIR model [15]. In their model, the entire population was categorized as susceptible, exposed, infected, and recovered. Moreover, the susceptible group was categorized into two classes: the vaccinated and unvaccinated groups. The epidemic property was investigated by analyzing the equilibrium of the model. According to their analysis, the equilibrium point of the disease-free state is asymptotically stable, which means that at some point the TB disease will vanish from the population. The vaccination rate greatly affects the propagation of the TB disease; the higher the vaccination rate, the lower the spread of the TB epidemic.

A study conducted by Egbetade et al. [16] suggested a mathematical model for TB treatment in a population. They established a proof for the uniqueness and existence of a solution for their proposed mathematical model. Moreover, it was demonstrated that if the reproductive ratio is less than one, then the disease will be cleared from the population. Fredlina et al. [17] proposed a model to analyze the transmission of MDR TB, and then they simulated the results by using the 4^{th}-order Runge-Kutta method. The results of their study show that the spread of TB disease can be controlled by lowering the rate of epidemic transmission and increasing the rate of recovery. According to them, another way of reducing the rate of infection is to keep TB-infected individuals from susceptible populations, whereas to boost the healing rate, the provision of treatment to a maximum standard is required.

Shah et al. [18] used an ordinary differential equation to construct and analyze a model of tuberculosis that resembles the SEIR epidemic model. The authors of [19] proposed a model for pulmonary and multidrug-resistant tuberculosis with vaccination class to describe the dynamics of TB propagation with regard to time in humans. The results of the work presented by Mustapha et al. [20] showed the importance of campaign awareness, treatment, and other possible measures in controlling MTB infection.

Suddin et al. [21] developed a model for MDR-TB in order to estimate the vaccination impact on future epidemiology. Besides determining equilibrium and performing stability analysis on their model, they also carried out numerical simulations using MATLAB software. Yu et al. [22] also analyzed the epidemic model of MDR-TB and recommended that the main goal to reduce the spread of TB is to increase TB detection and then carry out appropriate active TB treatment so that it does not open an opportunity to develop into MDR-TB.

A study in [2] suggested a mathematical model to study the spread of TB with drug resistance to the first and second lines of treatment. In their work, the reproduction number related to their model was obtained by using the next-generation method. They investigated the equilibrium state of their model and also analyzed the global stability of the endemic and disease-free equilibriums. Their study showed the effect of the resistance rate of the first and second lines of treatment on the infected and resistant populations. They formulated their model, considering only one progression rate from the exposed class to the infected class after infection but without including chemoprophylaxis treatment. The majority of the features in [2] have been adopted into our SEIRS mathematical model with some modifications. Particularly, this study presents a mathematical model that incorporates chemoprophylaxis treatment of latently infected individuals with multidrug and extensively drug-resistant classes. So, it provides additional information for looking at the effect of chemoprophylaxis treatment on the dynamics of the spread of TB in MDR and XDR classes.

2. Model

This study tries to extend the standard SEIRS mathematical model for the dynamics of tuberculosis with the aim of demonstrating the transmission of Mycobacterium tuberculosis (MTB) in human hosts, taking into account extensively drug-resistant (XDR) and multidrug-resistant (MDR) tuberculosis. We have attempted to propose a model that can easily be analyzed so as to properly understand the dynamics of TB disease. Individuals usually contract MTB when they get in touch with individuals having active TB; thereafter, they join the exposed compartment, where a proportion of this class moves into an infectious class by developing active TB. If timely treatment is given, individuals who are recovering from the disease progress to the recovered class, whereas those who interrupt treatment develop MDR TB and progress to the resistant class. Individuals recovering from MDR TB go to the recovered class, but those who do not recover from MDR-TB develop XDR-TB. As there is no everlasting immunity to TB, recovered individuals can become susceptible to TB by losing their immunity. The flow of the individuals into different compartments is represented by the diagram below, and it has been constructed with these assumptions: recruitment is by birth only; a variable population; a constant mortality rate; immunity to TB is not permanent; no immediate infectivity.

The overall human population was grouped into six compartments. These are susceptible to TB (S), exposed to TB (E), infected with active TB (I), multidrug-resistant (D), extensively drug-resistant (X), and recovered (R). Thus, the entire human population was expressed by

$$N = S + E + I + D + X + R.$$

The recruitment of individuals into the susceptible class takes place by birth which is represented by A. The susceptible group is also increased by partially immune individuals losing their immunity at a rate denoted by d, but it is decreased by the natural death rate represented by c and exposure to TB at a rate of a. Thus, the ODE that demonstrates the dynamics corresponding to the susceptible population becomes

$$\frac{dS}{dt} = A - aSI - cS + dR.$$

The exposed class (E) is increased by the susceptible individuals exposed to TB at a rate denoted by a. However it is decreased by the natural death rate represented by c, chemoprophylaxis treatment rate denoted by e, and the proportion of the population moving to the infected class I by developing active tuberculosis at a rate denoted by b. Therefore, we obtain

$$\frac{dE}{dt} = aSI - (c + b + e)\, E.$$

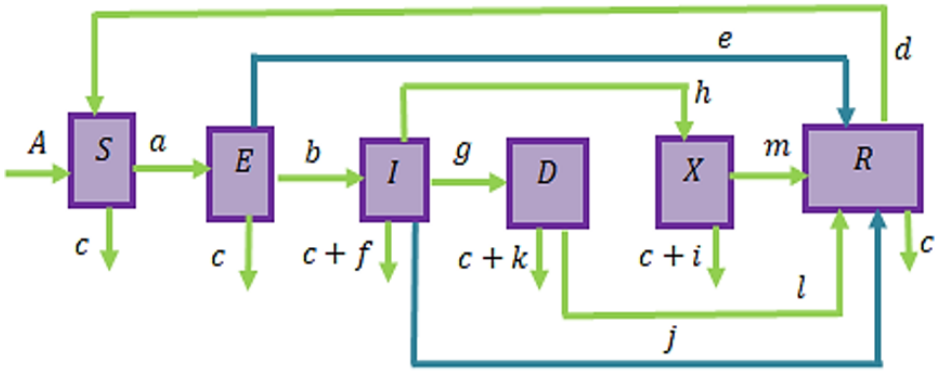

Figure 1. Flow diagram of the model

The infected class (I) is increased as a result of progression from the exposed class to the infected class after developing active TB at a rate denoted by b. But it decreases due to natural deaths at a rate of c; disease-induced death rate denoted by f; recovery at a rate of j; and also those who become resistant to the first and second lines of treatment at rates of g and h, respectively. Consequently, we obtained

$$\frac{dI}{dt} = bE - (h + c + f + g + j)\, I.$$

The multidrug-resistant group (D) increases due to resistance to the first line of treatment at a rate of g. However, it decreases as a consequence of recovery at a rate of l; disease-induced death denoted by k, and natural deaths at a rate denoted by c. Hence,

$$\frac{dD}{dt} = gI - (c + k + l)\, D.$$

The extensively drug-resistant class (X) increases due to resistance to the second line of treatment at a rate represented by h. However, it decreases as a result of recovery at a rate of m, disease-induced death rate denoted by i, and natural death at a rate denoted by c. Consequently,

$$\frac{dX}{dt} = hI - (c + i + m)\, X.$$

The recovered class (R) is increased by the individuals leaving the infected, multidrug-resistant, and extensively drug-resistant classes due to recovery at the rates denoted by j, l, and m, respectively. Moreover, it is increased by individuals moving from an exposed class at a rate designated by e. This class decreases as a result of the natural death rate represented by c, and loss of the partial immunity at a rate denoted by d. Thus,

$$\frac{dR}{dt} = mX + jI + lD + eE - (c + d)\, R.$$

Therefore, the system consisting of six differential equations is derived from the flow diagram of the model:

$$\begin{aligned}
\frac{dS}{dt} &= A - aSI - cS + dR \\
\frac{dE}{dt} &= aSI - (c + b + e)\, E \\
\frac{dI}{dt} &= bE - (h + c + f + g + j)\, I \\
\frac{dD}{dt} &= gI - (c + k + l)\, D \\
\frac{dX}{dt} &= hI - (c + i + m)\, X \\
\frac{dR}{dt} &= mX + jI + lD + eE - (c + d)\, R
\end{aligned} \tag{1}$$

with these initial conditions $S_0 > 0$, $E_0 \geq 0$, $I_0 \geq 0$, $D_0 \geq 0$, $X_0 \geq 0$, and $R_0 \geq 0$.

3. Results and Discussion

This section is dedicated to analyzing the invariant region, positivity of the solution, reproductive number, stability, and sensitivity analysis.

3.1. Invariant Region

In this subsection, we discuss a region where the feasible point corresponding to the governing equation of the model is bounded.

Since the entire population is $N = S + E + I + D + X + R$ at any time t, the differentiation of both sides with regard to t provides

$$\begin{aligned}
\frac{dN}{dt} &= \frac{d\,(S + E + I + D + X + R)}{dt} \\
&= \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dD}{dt} + \frac{dX}{dt} + \frac{dR}{dt}.
\end{aligned}$$

So, it is found that

$$\begin{aligned}
\frac{dN}{dt} &= B - c\,(S + E + I + D + X + R) - f\mathrm{I} - kD - iX \\
&= B - c\mathrm{N} - f\mathrm{I} - kD - iX.
\end{aligned}$$

Due to the fact that f, i, and k are non-negative, from $\frac{dN}{dt} =$

$A - c\mathrm{N} - f\mathrm{I} - hD$, we obtain that

$$\begin{aligned}\frac{dN}{dt} \leq A - c\mathrm{N} \Leftrightarrow\ & dN \leq (A - cN)\, dt \\ \Leftrightarrow\ & \frac{dN}{(A - cN)} \leq dt \\ \Leftrightarrow\ & \int \frac{dN}{(A - cN)} \leq \int dt \\ \Leftrightarrow\ & A - cN \geq Ke^{-ct},\ K = e^{-cM} \text{ is a constant.}\end{aligned}$$

Under $N(0) = N_0$, we get $K = A - cN_0$. Thus, $A - cN \geq (A - cN_0)\, e^{-ct}$, obtain

$$N \leq \frac{A}{c} - \frac{(A - cN_0)\, e^{-ct}}{c}.$$

From this, one can observe that as $t \to \infty$, the population size $N \to \frac{A}{c}$ implying that, $0 \leq N \leq \frac{A}{c}$. Hence, the feasible point can be given by

$$\Omega = \left\{(S, E, I, D, X,\ R) \in \mathbb{R}^6{}_+ :\ N \leq \frac{A}{c}\right\}.$$

This shows the basic model is epidemiologically meaningful and mathematically well posed, and thus it is enough to study the dynamics of the basic model in the region Ω.

3.2. Positivity of the Solutions

This section is aimed at finding non-negative solutions when dealing with human populations. It is crucial to verify that all solutions of the system remain positive for all time $t \geq 0$ provided that the initial data is positive. That is, for system (1) to be meaningful and well-posed, all variables are required to be non-negative for $t \geq 0$.

Theorem 1. *If $S(0)$, $E(0)$, $I(0)$, $D(0)$, $X(0)$ and $R(0)$ are all non-negative, then the solutions $S(t)$, $E(t)$, $I(t)$, $D(t)$, $X(t)$ and $R(t)$ are all positive for $t \geq 0$.*

Proof. To verify the positivity of $S(t)$, the first equation of the system of ordinary differential equation in (1) can be taken as follows:

$$\frac{dS}{dt} = A - aSI - cS + dR.$$

We can eliminate the positive terms in this equation so as to get an inequality:

$$\frac{dS}{dt} \geq -aSI - cS = -(c + aI)S.$$

Aided by the separation method, the solution to the differential inequality can be obtained as follows:

$$\begin{aligned}\frac{dS}{S} \geq -(c + aI)\, dt \ \Rightarrow\ & \int \frac{dS}{S} \geq -\int (c + aI)dt \\ \Rightarrow\ & s(t) \geq S_0 e^{-[ct + a\int I dt]}.\end{aligned}$$

The function $e^{-[ct + a\int I dt]}$ is a non-negative term. Hence, we may possibly observe that $S(t) \geq 0$.

In a similar fashion, we can verify that all the remaining state variables are positive. Consequently, the state variables $S(t)$, $E(t)$, $I(t)$, $D(t)$, $X(t)$, and $R(t)$ are positive quantities, and they remain in $\mathbb{R}^6{}_+$ for all time t. □

3.3. Disease-Free Equilibrium (DFE)

This section centers on obtaining a steady-state solution called a disease-free equilibrium point of the model. This point is a place where the disease vanishes from the population. That is, all infected groups are set to zero, and the total population becomes merely susceptible individuals. It is usually obtained by setting the left side of equation (1) equal to zero and letting $E = 0, I = 0, D = 0, X = 0$, and $R = 0$.

$$\begin{aligned} A - aSI - cS + dR &= 0 \\ aSI - (c + b + e)\, E &= 0 \\ bE - (h + c + f + g + j)\, I &= 0 \\ gI - (c + k + l)\, D &= 0 \\ hI - (c + i + m)\, X &= 0 \\ mX + jI + lD + eE - (c + d)\, R &= 0 \end{aligned} \tag{2}$$

By solving the homogeneous system of differential equations in (2), the disease-free equilibrium point is given by $(S_0,\ E_0,\ I_0,\ D_0,\ X_0,\ R_0) = \left(\frac{A}{c}, 0, 0, 0, 0, 0\right)$.

3.4. Basic Reproduction Number

The reproductive number R_0 is used for the prediction of whether the disease spreads or dies out. According to [23], FV^{-1} is the next generation matrix, and the reproductive number is

$$R_0 = \rho(FV^{-1})$$

where $F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right]$ and $V = \left[\frac{\partial V_i(x_0)}{\partial x_j}\right]$, $i \geq 1$ for the number of compartments, $1 \leq j \leq m$ for the infected compartments only. The spectral radius of a matrix FV^{-1} is represented by $\rho(FV^{-1})$. The matrices F and V are $m \times m$ matrices, where m is the number of infected compartments.

Rewriting the model equations in (1) corresponding to infected classes yields

$$\begin{aligned} \frac{dE}{dt} &= aSI - (c + b + e)\, E \\ \frac{dI}{dt} &= bE - (h + c + f + g + j)\, I \\ \frac{dD}{dt} &= gI - (c + k + l)\, D \\ \frac{dX}{dt} &= hI - (c + i + m)\, X \end{aligned} \tag{3}$$

The principle of next-generation matrix is applied to get f and v as follows:

$$f = \begin{bmatrix} aSI \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

and

$$v = \begin{bmatrix} (c+b+e)\,E \\ (h+c+f+g+j)\,I - bE \\ (c+k+l)\,D - gI \\ (c+i+m)\,X - hI \end{bmatrix}.$$

The Jacobian matrices of $f$and v, evaluated at DFE, are given by F and V as follows:

$$F = \begin{bmatrix} 0 & \frac{A}{c} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

and

$$V = \begin{bmatrix} c+b+e & 0 & 0 & 0 \\ -b & h+c+f+g+j & 0 & 0 \\ 0 & -g & c+k+l & 0 \\ 0 & -h & 0 & c+i+m \end{bmatrix}.$$

Next, FV^{-1} is worked out, and it is obtained to be

$$FV^{-1} = \begin{bmatrix} \frac{abA}{c(c+b+e)(h+c+f+g+j)} & \frac{aA}{c(h+c+f+g+j)} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}.$$

Finally, the eigenvalues of FV^{-1} are determined by solving $\left|FV^{-1} - \lambda I_4\right| = 0$. That is

$$\begin{vmatrix} \frac{abA}{c(c+b+e)(h+c+f+g+j)} - \lambda & \frac{aA}{c(h+c+f+g+j)} & 0 & 0 \\ 0 & -\lambda & 0 & 0 \\ 0 & 0 & -\lambda & 0 \\ 0 & 0 & 0 & -\lambda \end{vmatrix} = 0$$

This yields us

$$\left(\frac{abA}{c\,(c+b+e)\,(h+c+f+g+j)} - \lambda\right)(-\lambda)\,(-\lambda)\,(-\lambda) = 0$$

As a result, the eigenvalues of the next generation matrix FV^{-1} are

$$\lambda_1 = 0,\ \lambda_2 = 0,\ \lambda_3 = 0, \text{ and}$$
$$\lambda_4 = \frac{abA}{c\,(c+b+e)\,(h+c+f+g+j)},$$

with the dominant eigenvalue being λ_4. Hence, the corresponding basic reproductive number becomes

$$R_0 = \rho\left(FV^{-1}\right) = \frac{abA}{c\,(c+b+e)\,(h+c+f+g+j)}. \quad (4)$$

3.5. *Local Stability of DFE*

The local stability for the DFE point is established by linearizing the system of differential equations given in (1) and finding its Jacobian at the point $\left(\frac{A}{c},\ 0,\ 0,\ 0,\ 0,\ 0\right)$.

Theorem 2. *The disease-free equilibrium* $\left(\frac{A}{c},\ 0,\ 0,\ 0,\ 0,\ 0\right)$ *exhibits local asymptotic stability if* $R_0 < 1$.

Proof. The Jacobian of the system of differential equations in (1) evaluated at the disease-free equilibrium is

$$J = \begin{bmatrix} J_{11} & 0 & J_{13} & 0 & 0 & J_{16} \\ 0 & J_{22} & J_{23} & 0 & 0 & 0 \\ 0 & J_{32} & J_{33} & 0 & 0 & 0 \\ 0 & 0 & J_{43} & J_{44} & 0 & 0 \\ 0 & 0 & j_{53} & 0 & J_{55} & 0 \\ 0 & J_{62} & J_{63} & J_{64} & J_{65} & J_{66} \end{bmatrix}$$

where

$$J_{11} = -c;\ J_{13} = -\frac{aA}{c};\ J_{16} = d;\ J_{22} = -(c+b+e);$$
$$J_{23} = \frac{aA}{c};\ J_{32} = b;\ J_{33} = -(h+c+f+g+j);$$
$$J_{43} = g;\ J_{44} = -(c+k+l);\ J_{53} = h;\ J_{55} = -(c+i+m);$$
$$J_{62} = e;\ J_{63} = j;\ J_{64} = l;\ J_{65} = m;\ J_{66} = -(c+d).$$

Hence, the eigenvalues corresponding to this linearized system are obtained by solving the equation $|J - \lambda I_6| = 0$. That is,

$$\begin{vmatrix} J_{11} & 0 & J_{13} & 0 & 0 & d \\ 0 & J_{22} & J_{23} & 0 & 0 & 0 \\ 0 & b & J_{33} & 0 & 0 & 0 \\ 0 & 0 & g & J_{44} & 0 & 0 \\ 0 & 0 & h & 0 & J_{55} & 0 \\ 0 & e & j & l & m & J_{66} \end{vmatrix} = 0.$$

where

$$J_{11} = -c - \lambda;\ J_{13} = -\frac{aA}{c};\ J_{22} = d - (c+b+e) - \lambda;$$
$$J_{23} = \frac{aA}{c};\ J_{33} = -(h+c+f+g+j) - \lambda;$$
$$J_{44} = -(c+k+l) - \lambda;\ J_{55} = -(c+i+m) - \lambda;$$
$$J_{66} = -(c+d) - \lambda.$$

Thus, we have characteristic equation:

$$[-c-\lambda]\,[-(c+d)-\lambda]\,[-(c+i+m)-\lambda]\,[-(c+k+l)-\lambda]$$
$$\left[-(c+b+e)-\lambda\right]\left[-(h+c+f+g+j)-\lambda\right] - \frac{abA}{c}\Bigg] = 0.$$

From this equation, we get eigenvalues:

$$\lambda_1 = -c,\ \lambda_2 = -(c+d),\ \lambda_3 = -(c+i+m),$$
$$\lambda_4 = -(c+k+l),$$

and two other eigenvalues of the quadratic equation

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

where

$$a_1 = [c+b+e] + [h+c+f+g+j],$$
$$a_2 = c\,[c+b+e]\,[h+c+f+g+j] - \frac{abA}{c}.$$

From this result, it is observed that the first four eigenvalues $\lambda_1,\ \lambda_2,\ \lambda_3$ and λ_4 are entirely negative quantities, as all parameters are positive. This satisfies that $\lambda_1,\ \lambda_2,\ \lambda_3$ and λ_4 are stable.

Now consider the remaining part of the characteristic equation given by $\lambda^2 + a_1\lambda + a_2 = 0$. Then, by using the Routh-Hurwith criteria, all the eigenvalues of $\lambda^2 + a_1\lambda + a_2 = 0$ have negative real parts if $a_1 > 0$ and $a_2 > 0$. It can be seen that a_1 is positive as all parameters are positive and their sum is also positive. However, for a_2 to be positive, $c\,[c+b+e]\,[h+c+f+g+j] - \frac{abA}{c}$ has to be positive. That is, $a_2 > 0$ if $[c+b+e]\,[h+c+f+g+j] > \frac{abA}{c}$, and then division of both sides by $[c+b+e]\,[h+c+f+g+j]$ gives $1 > \frac{abA}{c[c+b+e][h+c+f+g+j]}$, revealing that $1 > R_0$. This implies that $a_2 > 0$ for $R_0 < 1$, and hence this leads to the conclusion that the disease-free-equilibrium point of the system (1) is locally asymptotically stable if $R_0 < 1$. □

3.6. Global Stability of DFE

Theorem 3. *If $R_0 < 1$, the DFE point of the system in (1) becomes globally asymptotically stable.*

Proof. Consider the Lyapunov function defined on the positively invariant compact set Ω by

$$\mathrm{V} = \frac{b}{(c+b+e)\,(h+c+f+g+j)}E + \frac{1}{(h+c+f+g+j)}I.$$

Here, V is non-negative and continuously differentiable on Ω. Thus, we get

$$\begin{aligned}\frac{dV}{dt} &= \frac{b}{(c+b+e)\,(h+c+f+g+j)}\frac{dE}{dt} \\ &\quad + \frac{1}{(h+c+f+g+j)}\frac{dI}{dt} \\ &= \frac{b}{(c+b+e)\,(h+c+f+g+j)}\left[\frac{aA}{c}I - (c+b+e)\,E\right] \\ &\quad + \frac{1}{(h+c+f+g+j)}\left[bE - (h+c+f+g+j)\,I\,\right] \\ &= \frac{abA}{c\,(c+b+e)\,(h+c+f+g+j)}I - I \\ &= \left(\frac{abA}{c\,(c+b+e)\,(h+c+f+g+j)} - 1\right)I.\end{aligned}$$

This implies that

$$\frac{dV}{dt} = (R_0 - 1)\,I.$$

To have $\frac{dV}{dt} \le 0$, we must have $R_0 - 1 \le 0$. Therefore, $\frac{dV}{dt} < 0$ if $R_0 < 1$, and $\frac{dV}{dt} = 0$ if and only if $I = 0$. Hence, the singleton set $E_0 = \left(\frac{A}{c},\ 0,\ 0,\ 0,\ 0,\ 0\right)$ is the largest compact invariant set in Ω. So, every solution of the model in equation (1) with initial conditions in Ω approaches the disease-free equilibrium point as time t closes to infinity whenever $R_0 < 1$, according to LaSalle's invariant principle. This shows that the equilibrium point of a disease-free state is globally asymptotically stable if $R_0 < 1$ in Ω. □

3.7. Stability Analysis of Endemic Equilibrium (EE)

An endemic equilibrium point, denoted by $(S^*,\ E^*,\ I^*,\ D^*,\ X^*,\ R^*)$, is a steady-state solution that occurs whenever the disease exists in the population. To find the endemic equilibrium point, the model equations in (1) are set equal to zero, and then they are solved to get

$$\begin{aligned}S^* &= \frac{(c+b+e)\,(c+h+f+g+j)}{ab} \\ E^* &= \frac{(c+h+f+g+j)}{b}I^* \\ I^* &= \frac{A - cS^*}{aS^* - \frac{d}{c+d}\left[j + \frac{hm}{c+i+m} + \frac{lg}{c+k+l} + \frac{e(c+h+f+g+j)}{b}\right]} \\ D^* &= \frac{g}{(c+k+l)}I^* \\ X^* &= \frac{h}{(c+i+m)}I^* \\ R^* &= \frac{1}{c+d}\left[\frac{hm}{c+i+m} + j + \frac{g}{c+k+l} + \frac{e\,(c+h+f+g+j)}{b}\right]I^*\end{aligned}$$

Since $aS^* - \frac{d}{c+d}\left[j + \frac{hm}{c+i+m} + \frac{lg}{c+k+l} + \frac{e(c+h+f+g+j)}{b}\right] > 0$, an endemic equilibrium point exists if

$$\begin{aligned}A - cS^* > 0 &\Leftrightarrow A - \frac{c\,(c+b+e)\,[h+c+f+g+j]}{ab} > 0 \\ &\Leftrightarrow A > \frac{c\,(c+b+e)\,[h+c+f+g+j]}{ab} \\ &\Leftrightarrow \frac{abA}{c\,[c+b+e]\,[h+c+f+g+j]} > 1 \\ &\Leftrightarrow R_0 > 1.\end{aligned}$$

Thus, this model possesses an endemic equilibrium that is unique if $R_0 > 1$.

Theorem 4. *If $R_0 > 1$, the EE point of the system in (1) becomes globally asymptotically stable.*

Proof. Choose the Lyapunov function defined by

$$\begin{aligned}\mathrm{V} =& \frac{1}{2}((S - S^*) + (E - E^*) + (I - I^*) + (D - D^*) + (X - X^*) \\ &+ (R - R^*))^2.\end{aligned}$$

The derivative of V with regard to time (t) corresponding to system (1) is given by

$$\begin{aligned}\frac{dV}{dt} =& ((S - S^*) + (E - E^*) + (I - I^*) + (D - D^*) \\ &+ (X - X^*) + (R - R^*))\frac{dN}{dt}.\end{aligned}$$

Since $\frac{dN}{dt} = A - cN$, we must have

$$\frac{dV}{dt} = \left(N - \frac{A}{c}\right)(A - cN).$$

After rearrangement and simplification of the equation, we get

$$\frac{dV}{dt} \leq -\frac{1}{c}(A - cN)^2.$$

Thus, $\frac{dV}{dt} = 0$, and $\frac{dV}{dt} = 0$ if and only if $S = S^*$, $E = E^*$, $I = I^*$, $D = D^*$, $X = X^*$, and $R = R^*$. Hence, the singleton set $E_* = (S^*, E^*, I^*, D^*, X^*, R^*)$ is the largest positive invariant set in $(S^*, E^*, I^*, D^*, X^*, R^*) \in \Omega$: $\frac{dV}{dt} = 0$. This indicates that E_* is globally asymptotically stable if $R_0 > 1$ in Ω as a result of LaSalle's invariant principle. □

3.8. *Sensitivity Analysis of Model Parameters*

Sensitivity analysis enables us to identify those parameters that highly influence the basic reproduction number and thus must be targeted by intervention strategies. It is performed by calculating the sensitivity indices of the basic reproduction number R_0 in order to determine whether the disease can spread or not.

Definition 1. A normalized forward sensitivity index for a variable with regard to the given parameter is defined as a ratio of the respective variation in the variables to the respective variation in the corresponding parameters. Given that a variable is a differentiable function of the parameter, partial derivatives can alternatively be used to define the sensitivity index as $\frac{\partial R_0}{\partial m} \times \frac{m}{R_0}$.

The differentiation of R_0 relative to each of the parameters is done as follows:

$$\frac{\partial R_0}{\partial a} \times \frac{a}{R_0} = 1; \quad \frac{\partial R_0}{\partial b} \times \frac{b}{R_0} = \frac{c+e}{c+b+e}$$

$$\frac{\partial R_0}{\partial c} \times \frac{c}{R_0} = -\frac{c^\star}{(c+b+e)(h+c+f+j+g)}$$

$$c^\star = b(2c+f+j+g+h) + 3c^2 + 2c(f+g+h+j+e) + e(f+g+h+j)$$

$$\frac{\partial R_0}{\partial e} \times \frac{e}{R_0} = -\frac{e}{c+b+e}; \quad \frac{\partial R_0}{\partial f} \times \frac{f}{R_0} = -\frac{f}{c+f+g+h+j}$$

$$\frac{\partial R_0}{\partial g} \times \frac{g}{R_0} = -\frac{g}{c+f+g+h+j};$$

$$\frac{\partial R_0}{\partial h} \times \frac{h}{R_0} = -\frac{h}{c+f+g+h+j}$$

$$\frac{\partial R_0}{\partial j} \times \frac{j}{R_0} = -\frac{j}{c+f+g+h+j}$$

The sensitivity indices of R_0 to the parameters used in the model are shown in Table 1.

In the table 1 shown above, it is easily noticed that the force of infection parameter a and the progression rate to active tuberculosis parameter b have positive indices, and hence they are the most sensitive parameters for propagating this disease. This is due to the fact that the basic reproductive number increases as their values increase, implying that the average number of secondary cases of infection increases in the population. For instance, $\frac{\partial R_0}{\partial a} \times \frac{a}{R_0} = +1$ means that if the parameter a is increased (or decreased) by 10%, then the reproductive number R_0 will be increased (or decreased) by 10%. Similarly, $\frac{\partial R_0}{\partial b} \times \frac{b}{R_0} = +0.7537$ means that when the parameter b is increased (or decreased) by 10%, the reproductive number R_0 will be increased (or decreased) by 7.537%. On the other hand, the parameters c, e, f, g and j have negative indices, and hence they have the influence of minimizing the burden of the disease. For instance, it can be observed from $\frac{\partial R_0}{\partial e} \times \frac{e}{R_0} = -0.7389$ that a 10% increase (or decrease) in the parameter e leads to a 7.389% decrease (or increase) in the reproductive number R_0. Thus, it is important to notice that increasing their values while keeping the other parameters constant decreases the basic reproductive number, which leads to a reduction in the endemicity of the disease. This shows that screening and treatment for latently infected people reduces the progression rate to the infectious stage, and treatment of infectious people will stop them from transmitting the disease, thereby leading to a reduction in disease transmission.

Table 1. Sensitivity indices for R_0 relative to parameters

Parameters	Values	Sources	Sensitivity
a	0.0015	[11]	$+1$
b	0.25	[24]	$+0.7537$
c	0.015	[11]	-0.6291
e	0.75	*Assumed*	-0.7389
f	0.25	*Assumed*	-0.1608
g	0.4	[2]	-0.3215
h	0.275	*Assumed*	-0.1768
j	0.5	[24]	-0.3312

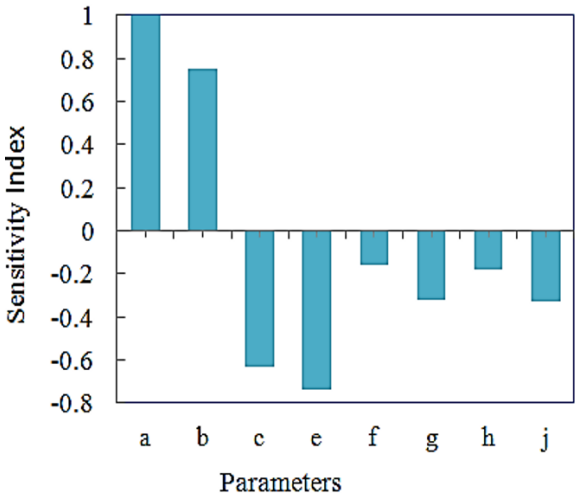

Figure 2. The sensitivity of R_0

3.9. *Numerical Simulation and Result Discussion*

In this section, the illustration of analytical results is provided by working on the numerical simulation of the model by means of the MATLAB ode45 solver.

By taking values of parameter $A = 84$; $a = 0.0015$; $b = 0.25$; $c = 0.015$; $d = 0.015$; $e = 0.75$; $f = 0.25$; $g = 0.4$; $h = 0.275$; $i = 0.175$; $j = 0.515$; $k = 0.15$; $l = 0.25$; and $m = 0.215$ we obtain $R_0 = 0.88 < 1$. Thus, by using the initial conditions $S(0) = 7500$, $E(0) = 2500$, $I(0) = 500$, $D(0) = 250$, $X(0) = 100$, $R(0) = 400$ and the above values of parameters, the graph shown in figure 4 below is obtained. From

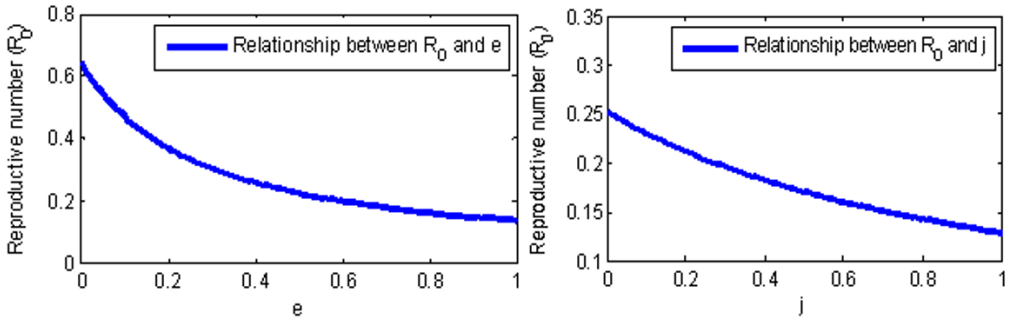

Figure 3. The relationship between e, j, and R_0

Figure 4, it is possible to notice that the individuals from susceptible and recovered classes progress to their state values while the individuals from exposed, infectious, drug-resistant, and multi-drug-resistant classes get nearer and nearer to zero as time goes on. Thus, it is evident to observe that the disease gets out of the population, which is in line with the analytical results of the model.

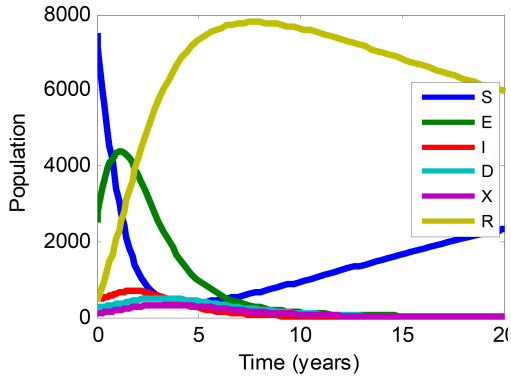

Figure 4. The population dynamics when $R_0 = 0.88 < 1$

By using a set of values for parameters $B = 84$; $a = 0.0015$; $b = 0.15$; $c = 0.015$; $d = 0.015$; $e = 0.0075$; $f = 0.075$; $g = 0.165$; $h = 0.125$; $i = 0.175$; $j = 0.315$; $k = 0.15$; $l = 0.075$; and $m = 0.0725$, we get $R_0 = 7.39 > 1$. For the initial conditions $S(0) = 7500$, $E(0) = 2500$, $I(0) = 500$, $D(0) = 250$, $X(0) = 100$, $R(0) = 400$, and the above parameter values, we get the graph shown in Figure 5 below. From figure 5, it can be noted that the infectious, drug-resistant, and recovered classes go to their steady-state values, while the susceptible and exposed classes decline with time. Thus, we see that the disease persists in this case, which also agrees with the analytical results of the model.

The mathematical model proposed by Gupta et al. [2] did not take the chemoprophylaxis for latently infected and treatment for active TB individuals into consideration. Therefore, this work has tried to modify their model by incorporating the chemoprophylaxis treatment for latently infected individuals and the treatment for active TB individuals.

In order to see the effect of chemoprophylaxis treatment on the transmission dynamics of tuberculosis and compare their model with the new model, a simulation study of the new model was carried out with chemoprophylaxis treatment parameter $(e > 0)$ and without chemoprophylaxis treatment parameter $(e = 0)$. The numerical simulations were performed

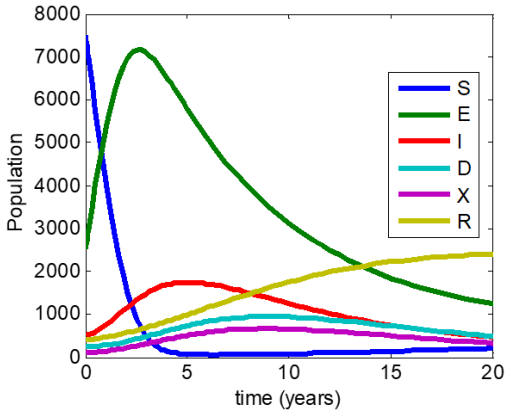

Figure 5. The population dynamics when $R_0 = 7.39 > 1$

to see its effects on the infected class, the multi-drug-resistant class, and the extensively drug-resistant class for three different values of the chemoprophylaxis treatment parameter e while holding the other parameters constant, as shown below in Figures 6, 7, 8, and 9, respectively.

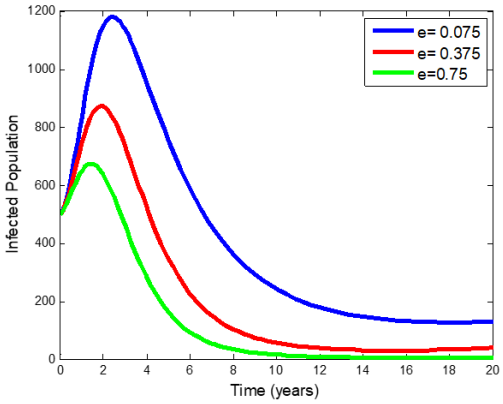

Figure 6. Effect of chemoprophylaxis treatment on the infected class

From Figure 6, it can be observed that the number of individuals in the infected compartment without chemoprophylaxis treatment is larger than the number with chemoprophylaxis treatment of latently infected individuals. Furthermore, the infected class drops whenever the chemoprophylaxis treatment parameter is enlarged. This confirms that chemoprophylaxis treatment of latently infected individuals plays a significant role in reducing the transmission of tuberculosis.

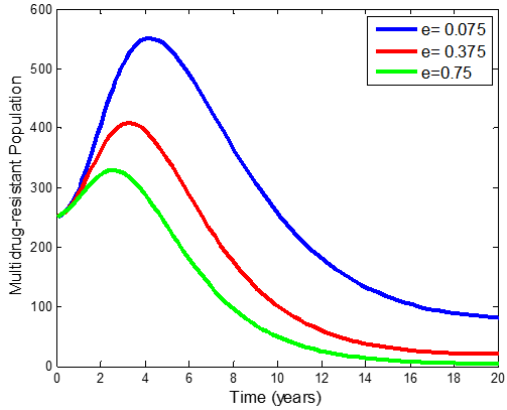

Figure 7. Effect of chemoprophylaxis treatment on a multidrug-resistant class

By observing Figure 7, one can notice that the number of individuals in the multidrug-resistant class without chemoprophylaxis treatment is larger than the number with chemoprophylaxis treatment for latently infected groups. Moreover, the multidrug-resistant group decreases as the chemoprophylaxis treatment parameter is increased. This verifies that chemoprophylaxis treatment of latently infected individuals plays a decisive role in reducing the transmission of tuberculosis.

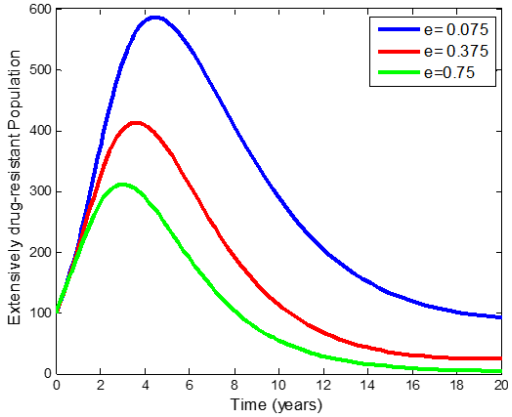

Figure 8. Effect of chemoprophylaxis treatment on an extensively drug-resistant class

From Figure 8, it is clearly seen that the number of individuals in the extensively drug-resistant compartment with no chemoprophylaxis treatment is higher than the one in which chemoprophylaxis treatment of latently infected individuals is incorporated. Additionally, the extensively drug-resistant group decreases as the chemoprophylaxis treatment parameter is increased. This leads to the conclusion that chemoprophylaxis treatment of latently infected individuals plays a crucial role in reducing the transmission of tuberculosis. Similarly, Figure 9 displays the impact of chemoprophylaxis treatment on susceptible, exposed, and recovered classes.

Furthermore, Figure 10 exemplifies the effect of active TB treatment on infected, multidrug-resistant, and extensively drug-resistant classes. The figures indicate that the increase in the treatment rate of active TB reduces the infected, multidrug-resistant, and extensively drug-resistant classes.

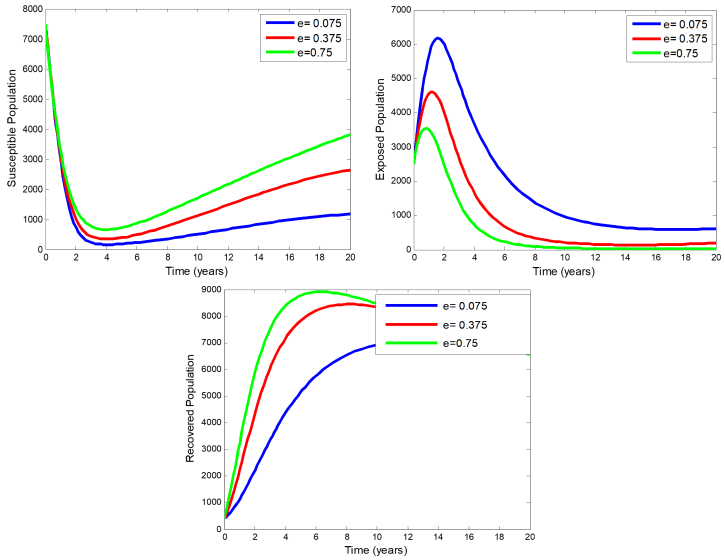

Figure 9. Effect of chemoprophylaxis treatment on susceptible, exposed, and recovered classes

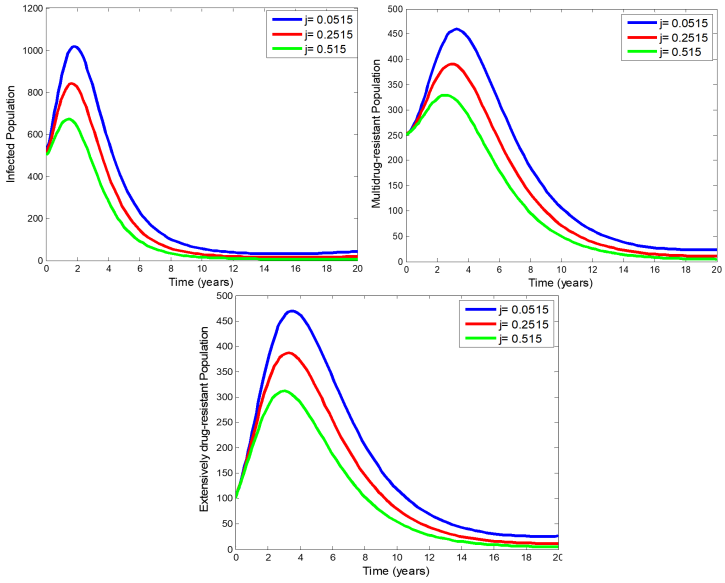

Figure 10. Effect of treatment on infected, multidrug-resistant, and extensively drug-resistant classes

Generally, the numerical simulations evidently substantiate that the model consisting of chemoprophylaxis treatment and treatment for active TB has a better result in reducing the transmission of tuberculosis with multi-drug-resistant and extensively drug-resistant compartments as compared to the model without chemoprophylaxis treatment for latently infected individuals and treatment for active TB.

4. Conclusion

In this study, the transmission of tuberculosis with multidrug and extensively drug-resistant compartments was mathematically formulated and analyzed by incorporating chemoprophylaxis treatment for latent groups. For qualitative analysis of the model, a formula that depicts the basic reproductive number R_0 is computed by applying the principle of the next-generation matrix. The existence of a disease-free state as well as an en-

demic equilibrium point was investigated, and their stability was also analyzed. The results of the analysis verified that the local asymptotic stability of disease-free equilibrium takes place whenever $R_0 < 1$, and the global asymptotic stability of endemic equilibrium occurs if $R_0 > 1$. Moreover, sensitivity analysis was carried out with the help of a normalized forward sensitivity index, and the numerical simulation was also done using MATLAB ode45. It was verified that the result of the numerical simulation was in harmony with the analytical results. From sensitivity analysis and numerical simulation, it was observed that increasing the effort on chemoprophylaxis treatment of latently infected individuals reduces the progression to multidrug-resistant, infectious, and extensively drug-resistant compartments. Additionally, treatment of infectious people will stop them from transmitting the disease to healthy individuals and therefore contribute to the reduction in disease transmission.

Conflict of interest. The authors declare no conflict of interest.

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