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A MATHEMATICAL MODEL FOR TUBERCULOSIS INFECTION TRANSMISSION DYNAMICS IN THE PRESENCE OF TESTING AND THERAPY, ISOLATION AND TREATMENT

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ABSTRACT

In this study, a mathematical model for Tuberculosis infection transmission dynamics is developed by incorporating testing and therapy of latent individuals, the isolation of infectious individuals and the treatment of the isolated individuals. The basic reproduction number was computed using the next generation matrix method. Analysis of the model at the disease-free equilibrium state and the endemic equilibrium states shows that it is locally and globally asymptomatically stable whenever the basic reproduction number is less than unity at the disease -free equilibrium state and locally and globally asymptotically stable whenever the basic reproduction number is greater than unity. The result from the sensitivity index of R_0 show that the infection transmission parameter and other control parameters such as early detection and therapy, the isolation of infected individuals and treatment are crucial parameters to tuberculosis management. It is shown from numerical simulations that the early detection and therapy, isolation and treatment of infected individuals will reduce the infection transmission. Further numerical results show that the combination of early detection and therapy, isolation and treatment of infectious individuals will decrease the infection transmission and its eventual eradication from the human population.

Keywords: Tuberculosis, Basic reproduction number, local stability, global stability, sensitivity

INTRODUCTION

Tuberculosis (TB) is a contagious disease that continue to be a major cause of morbidity and mortality in many countries worldwide. Until the coronavirus (COVID-19) pandemic, TB according to World Health Organisation (WHO, 2020) report, was the leading cause of death from single infectious agent, ranking above HIV/AIDS. It is the second leading cause of deaths related to infectious pathology, affecting many countries, especially in the low resource region of Africa and Asia (Kasznia-Brown, 2023).

Tuberculosis (TB) is caused by a bacterium called *mycobacterium tuberculosis*. The disease typically affects the lungs (Pulmonary TB) but TB bacteria can attack other part of the body such as the kidney, spine, and brain (Sakula, 1982; Hershkovitz et al., 2015).

TB bacteria spread when a person with TB disease of the lungs or throat expel bacteria into the air (e.g. by coughing, speaking or singing). People nearby may breathe in these bacteria and become infected (WHO, 2023; Hershkovitz et al., 2015). TB in other parts of the body, such as the kidney or spine, is usually not infectious (WHO, 2023).

In 2022, approximately 10.6 million people developed active TB disease, up from best estimates of 10.3 million in 2021 and 10.0 million in 2020. Also, TB caused an estimated 1.30 million deaths globally in 2022 (WHO, 2023). Of concern, is the fact that a person with TB disease can infect 10 to 15 persons he or she comes into contact with (Houben & Dodd, 2016). Nigeria is among the thirty countries with the highest TB, Tuberculosis/ Human Immunodeficiency Virus (TB /HIV) and Multi-Drug Resistant TB (MDR-TB) burden (WHO 2023).

The probability of developing TB disease is much higher among people living with HIV, and among people affected by risk factors such as undernutrition, diabetes, smoking and alcohol consumption (WHO, 2023). Once infected, a person stays infected for many years, possibly latently-infected for life. The clinical observation of this disease reveals that the patient suffers from a latent fever that begins towards the evening and vanishes again at the break of day. It is accompanied by violent coughing, which expel thin purulent sputum. The patient speak with hoarse voice, breathes with difficulty and has flushed cheeks (Lienhardt et al., 2012).

Tuberculosis is not only a health problem but also an economic problem of mankind as out breaks usually lead to enormous expenditure on health care. Economic and financial barriers can affect access to health care for TB diagnosis and completion of TB treatment; about half of TB patients and their households face catastrophic total costs due to TB disease (Houben & Dodd, 2016).

A number of mathematical modelling studies have been carried out in recent time to quantify Tuberculosis burden. A global modelling study published in 2016 estimated that about a quarter of the world's population had been infected with M. tuberculosis (Houben & Dodd, 2016).

Zhao, et al., (2017) proposed a susceptible-exposed-infectious-recovered (SEIR) epidemic model with age groupings, involving three categories: children, the middle – aged and senior to investigate the role of age on the transmission of tuberculosis in Mainland China from 2015 to 2016. They estimated the basic reproduction number, $R_0 = 1.7858$ and further demonstrated that diverse age groups have different effects on TB and that increase in the recovery rate and reduction in the infection rate of senior aged group would help reach the goals of the WHO End TB strategy.

Jerubet et al., (2019) developed a mathematical model that explains the transmission of Tuberculosis consisting of four compartments: the susceptible humans, infectious humans, latently infected humans and the recovered humans. Results from the sensitivity analysis shows that the recruitment and contact rate are the most sensitive parameter that contributes to the basic reproduction number. Further findings showed that as more people come into contact with infectious individuals, the spread of TB would increase. However, the recovery rate of infectious individuals showed that the spread of the disease will reduce with time which could help curb TB transmission.

Nayeem and Sultana (2019) developed a dynamical model to understand the underlying dynamics of Tuberculosis infection at the population level by incorporating treatment of individuals, the infection of latent and recovery individuals. Their analysis revealed that the model exhibits a backward bifurcation when TB treatment remains in the infected class.

Omale et al., (2019) formulated a mathematical model for the transmission dynamics of tuberculosis, a case study of Ika Christian hospital, Ankpa LGA, Kogi State, Nigeria by incorporating treatment and vaccination as control strategies. Their numerical results shows that the disease will be eradicated from the population with time by using vaccination and treatment as intervention strategies.

Mettle et al., (2020) developed both deterministic and statistical model for tuberculosis (TB) dynamics among high-burden districts in the Ashanti Region of Ghana by employing SEIR model with demography. Their findings on the effect of treatment at the incubation stage of TB transmission shows that treatment decreased the spread of TB.

Andrawus et al., (2020) presented a mathematical model of tuberculosis transmission dynamics by incorporating first and second line treatment. Their analytical results shows that the disease-free equilibrium and endemic equilibrium states exist and is locally asymptotically stable. Further results shows that the numerical results are consistent with the analytical results.

Liu et al., (2020) investigated the impact of control strategy (i.e., new vaccine and improving treatment) on the transmission of tuberculosis in China by dynamic model. Their theoretical analysis based on the data reported by National Bureau of Statistics of China (NBSC), shows that the basic reproduction number R_0, of each stage is estimated as 1.7885 and 1.0740 respectively. The diagnosis and treatment of TB according to their findings have promoted a lot and the basic reproduction number R_0, is reduced by full coverage of DOTs strategy, however the R_0 in China is still greater than one.

Sulayman et al., (2021) extended a deterministic mathematical model for the dynamics of tuberculosis transmission to examine the impact of an imperfect vaccine and other exogenous factor, such as re-infection. Their findings revealed that imperfect tuberculosis vaccine is effective at reducing the spread of infectious diseases within the population. Specifically, being vaccinated at steady-state and vaccine efficacy assume an equivalent role in decreasing disease burden. Further numerical results showed that using an imperfect vaccine led to effective control of tuberculosis in a population, provided that the efficacy of the vaccine and its coverage are reasonably high.

Kuddus et al., (2022) developed a mathematical model of a two-strain (drug-susceptible (DS) and drug-resistant (DR)) tuberculosis infection in Bangladesh. Both their analytical and numerical results showed that the presence of drug-resistant infection increases with increasing drug use through amplification. Sensitivity analysis of the model parameters found that the transmission rate of both strains had the greatest influence on DS and DRTB prevalence, indicated that inadequate or in appropriate treatment makes co-existence of DRTB infection.

Dauda et al., (2020) formulated a mathematical model for the transmission dynamics of tuberculosis in Kaduna Metropolis. Using secondary data, they obtained a basic reproduction number $R_0 = 1.0623$. This finding revealed that tuberculosis infection will remain endemic in Kaduna Metropolis. However, their model did not capture any control strategy in mitigating the transmission of tuberculosis disease in Kaduna Metropolis.

The various studies from available literatures focuses on vaccination of susceptible population, testing and treatment for TB disease when they become symptomatic. However, screening individuals in any community especially the latent population has not really been in place. Thus, it is needful to carry out a study that focuses on testing and therapy of exposed individuals, isolation and treatment of an infected individuals. The present study extends the Dauda et al., (2020) study by incorporating screening (detection) and therapy at the latent population, isolation and treatment of individuals with tuberculosis disease.

The remaining part of this paper is organized as follows. The mathematical model is formulated in Section 2. The basic reproduction number, local and global analysis of the disease-free equilibrium and endemic equilibrium states and sensitivity analysis of the basic reproduction number with respect to the model parameters are presented in Section 3. Numerical simulations and discussion of results are carried out in Section 4. The conclusive remarks are passed in section 5.

Model Formulation

We begin our model formulation by introducing the model by Dauda et al., (2020).

Model Assumption and definition of Variables and Parameter by Dauda et al, (2020):

The following are the assumptions of the model by Dauda et al (2020)

i. The birth and deaths occur at equal rates.
ii. An infected individual has a latency period before becoming infectious.
iii. Those that recovered from the disease become immune.

The variables and parameter used in the existing model are defined in Table 1.

Table 1: Description of Variables and Parameter used by Dauda et al (2020).

Variable/Parameter	Description
$S(t)$	The number of Susceptible individuals at time t
$E(t)$	The number of Exposed individuals at time t
$I(t)$	The number of Infectious individuals at time t
$R(t)$	The number of Recovered individuals at time t
β	Infection transmission rate
τ	Loss of latency rate
ρ	Recovery rate
μ	Recruitment/Natural death rate

The Equations of the Existing Model

Using the above assumptions, variables and parameters, Dauda et al (2020) derived the following model equations

$$\frac{dS}{dt} = \mu N - \beta \frac{IS}{N} - \mu S \quad (1)$$

$$\frac{dE}{dt} = \beta \frac{IS}{N} - (\tau + \mu)E \quad (2)$$

$$\frac{dI}{dt} = \tau E - (\rho + \mu)I \quad (3)$$

$$\frac{dR}{dt} = \rho I - \mu R \quad (4)$$

The system (1) – (4) expressed in proportion is given as

$$\frac{ds}{dt} = \mu - \beta is - \mu s \quad (5)$$

$$\frac{de}{dt} = \beta is - (\tau + \mu)e \quad (6)$$

$$\frac{di}{dt} = \tau e - (\rho + \mu)i \quad (7)$$

$$\frac{dr}{dt} = \rho i - \mu r \quad (8)$$

Basic Assumptions and Description of Variables and Parameters of the Modified Model

Here, we modify the Tuberculosis disease model proposed by Dauda et al (2020) by incorporating

i. The role of testing and therapy at the rate k in our model.
ii. A proportion of the infectious individuals are isolated at the rate α.
iii. Recruitment into the susceptible population at the rate Π and natural death rate μ.
iv. Disease induced death rate σ.

The total population at time t, denoted by $N(t)$ is sub-divided into five mutually-exclusive compartments namely susceptible individuals $S(t)$, individuals who are exposed to the tuberculosis infection but not infectious $E(t)$, infectious individuals $I(t)$, isolated individuals $Q(t)$ and recovered individuals $R(t)$. So that, $N(t) = S(t) + E(t) + I(t) + Q(t) + R(t)$

Table 2: Description of Variables and Parameters of the Extended Model.

Variable/Parameter	Description
$S(t)$	The total number of Susceptible individuals at time t
$E(t)$	The total number of Exposed individuals at time t
$I(t)$	The total number of Infectious individuals at time t
$Q(t)$	The total number of Isolated individuals at time t
$R(t)$	The total number of Recovered individuals at time t
β	Infection transmission rate
z	Progression rate from exposed class to infectious class
ρ	Recovery rate
Π	Recruitment rate
μ	Natural death rate
δ	Disease-induced death rate
α	Isolation rate
k	Tuberculosis testing and therapy rate

From the above assumptions, description of variables and parameters, the interactions and flow in the different compartments are as depicted in the schematic diagram below:

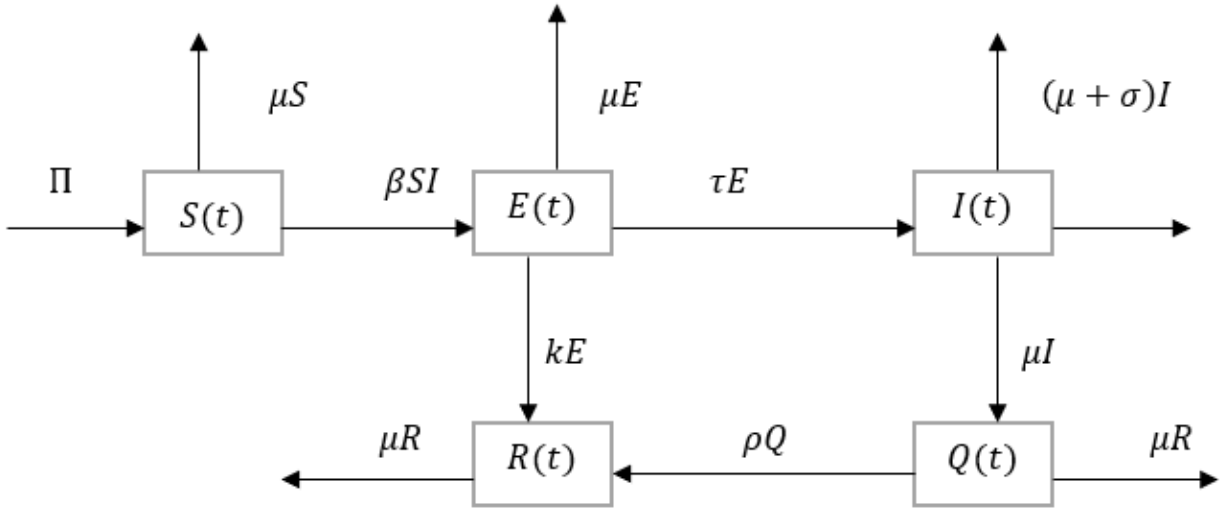

Figure 1: Schematic description of the tuberculosis disease model.

Description of the Model Equations

The population of Susceptible individuals $S(t)$ are recruited at the rate Π. It is reduced by infection, following contact with infectious individuals at a rate β and further reduced by natural death at the rate μ. Putting all these definitions together leads to the following expression for the rate of change of the susceptible population.

$$\frac{dS}{dt} = \Pi - \beta SI - \mu S$$

The population of Exposed individuals $E(t)$ is generated following infection at the rate β. They are decreased as a result of progression to infectious compartment at the rate τ, tuberculosis testing and therapy at the rate k, and natural death rate μ, so that

$\frac{dE}{dt} = \beta SI - (\tau + k + \mu)E$

Infectious individuals $I(t)$ are generated as a result of progression into the infectious class from the exposed class at the rate τ. It is diminished by isolation at the rate α, disease-induced death at the rate δ, and natural death at the rate μ, so that

$\frac{dI}{dt} = \tau E - (\alpha + \delta + \mu)I$

The population of isolated individuals $Q(t)$, are generated following isolation of infectious individuals at the rate α. It is diminished by recovery as a result of treatment at the rate ρ and natural death rate μ, so that

$\frac{dQ}{dt} = \alpha I - (\rho + \mu)Q$

The population of the recovered individuals R, are generated following tuberculosis testing and therapy at the rate k, and recovery from the tuberculosis infection at the rate ρ. It is reduced by natural death at the rate μ, so that

$\frac{dR}{dt} = kE + \rho Q - \mu R$

Model Equations

The above assumptions and formulations lead to the following system of ordinary differential equation:

$\frac{dS}{dt} = \Pi - \beta SI - \mu S$ (9)

$\frac{dE}{dt} = \beta SI - (\tau + k + \mu)E$ (10)

$\frac{dI}{dt} = \tau E - (\alpha + \delta + \mu)I$ (11)

$\frac{dQ}{dt} = \alpha I - (\rho + \mu)Q$ (12)

$\frac{dR}{dt} = kE + \rho Q - \mu R$ (13)

with the non-negative initial conditions

$S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, Q(0) \geq 0, R(0) \geq 0$ (14)

Invariant Region

Consider the biological feasible region

$\Omega = \{(S, E, I, Q, R) \in \mathbb{R}^5 : N \leq \frac{\pi}{\mu}\}$

Lemma 1: The closed set Ω is positively and attracting with respect to the system equations (9) – (13).

Proof:

Adding equation (9) – (13) gives the rate of change of the total population

$\frac{dN}{dt} = \Pi - \mu N - \delta I$ (15)

It is clear from the equation (15) that

$\frac{dN}{dt} \leq \Pi - \mu N$

it follows that

$\frac{dN}{dt} \leq 0, \quad \text{if } N(t) \geq \frac{\Pi}{\mu}$

Thus, by a standard comparison theorem (Lakstimikantham et al., 1989) can be used to show that

$N(t) = N(0)e^{-\mu t} \leq \frac{\Pi}{\mu}(1 - e^{-\mu t})$ (16)

In particular,

$N(t) \leq \frac{\Pi}{\mu}$ if $N(0) \leq \frac{\Pi}{\mu}$

Thus, the region $\Omega = \{(S, E, I, Q, R) \in \mathbb{R}^5 : N \leq \frac{\pi}{\mu}\}$ is positively invariant. However, if $N(t) \leq \frac{\Pi}{\mu}$, then either the solution enters Ω in a finite time, or $N(t)$ approaches $\frac{\Pi}{\mu}$ asymptotically. Hence, the region Ω attracts all solutions in $\mathbb{R}^5$.

Therefore, it is sufficient to consider the dynamics of the flow generated by equations (9) – (13) in Ω where the usual existence, uniqueness, continuation results hold for the system (9) – (13), that is, the system is mathematically and epidemiologically well-posed in Ω.

Model Analysis

Disease-Free Equilibrium (DFE) and Endemic Equilibrium (EE) States

Since the equation (9) – (13) are independent of the variable, $R(t)$, it suffices to consider the first four equations of the system (9) – (12), as our new system.

Setting the right-hand sides of the equations (9) – (12) to zero, we have

$\Pi - \beta SI - \mu S = 0$ (17)

$\beta SI - (\tau + k + \mu)E = 0$ (18)

$\tau E - (\alpha + \delta + \mu)I = 0$ (19)

$\alpha I - (\rho + \mu)Q = 0$ (20)

From equation (19)

$I = \frac{\tau E}{(\alpha + \delta + \mu)}$ (21)

From equation (20)

$Q = \frac{\alpha I}{(\rho + \mu)}$ (22)

substitute equation (21) into equation (18) to have

$$\frac{\tau\beta SE}{(\alpha + \delta + \mu)} - (\tau + k + \mu)E = 0$$

i.e.

$$E\left[\frac{\tau\beta S - (\tau + k + \mu)(\alpha + \delta + \mu)}{(\alpha + \delta + \mu)}\right] = 0$$

Either $E = 0$ or $S = \frac{(\tau + k + \mu)(\alpha + \delta + \mu)}{\tau\beta}$ (23)

CASE I:

For $E^* = 0$ (24)

Substitute $E = 0$ into equation (21) to obtain

$I^* = 0$ (25)

and substitute $I = 0$ into equation (22) and equation (17) to obtain

$Q^* = 0$ (26)

and

$S^* = \frac{\Pi}{\mu}$ (27)

From equation (24), (25), (26) and (27), we obtain the Disease-Free Equilibrium (DFE) state $\Omega_0 = (S^*, E^*, I^*, Q^*)$ as

$\Omega_0 = \left(\frac{\Pi}{\mu}, 0, 0, 0\right)$ (28)

CASE II: When $E \neq 0$

Then from equation (23)

$S^{**} = \frac{(\tau + k + \mu)(\alpha + \delta + \mu)}{\tau\beta}$ (29)

substituting equation (29) into equation (17) will give

$\Pi - \frac{(\tau+k+\mu)(\alpha+\delta+\mu)}{\tau} - \frac{\mu(\tau+k+\mu)(\alpha+\delta+\mu)}{\tau\beta} = 0$

solving for I^{**} gives

$I^{**} = \frac{\mu}{\beta}\left[\frac{\tau\beta\Pi}{\mu(\tau+k+\mu)(\alpha+\delta+\mu)} - 1\right]$ (30)

substituting equation (30) into equation (20) and solving for E^{**} to obtain

$E^{**} = \frac{\mu(\alpha+\delta+\mu)}{\alpha\beta}\left[\frac{\tau\beta\Pi}{\mu(\tau+k+\mu)(\alpha+\delta+\mu)} - 1\right]$ (31)

And substituting equation (21) into (22) to have

$Q^{**} = \frac{\alpha\mu}{\beta(\rho+\mu)}\left[\frac{\tau\beta\Pi}{\mu(\tau+k+\mu)(\alpha+\delta+\mu)} - 1\right]$ (32)

Therefore, from equation (28), (30), (31) and (32), it follows that the Endemic Equilibrium (EE) state,

$\Omega_1 = (S^{**}, E^{**}, I^{**}, Q^{**})$ is given as

$\Omega_1\left(\frac{(\tau+k+\mu)(\alpha+\delta+\mu)}{\tau\beta}, \frac{\mu(\alpha+\delta+\mu)}{\alpha\beta}\left[\frac{\tau\beta\Pi}{\mu(\tau+k+\mu)(\alpha+\delta+\mu)}1\right],\right.$

$\left.\frac{\mu}{\beta}\left[\frac{\tau\beta\Pi}{\mu(\tau+k+\mu)(\alpha+\delta+\mu)} - 1\right], \frac{\alpha\mu}{\beta(\rho+\mu)}\left[\frac{\tau\beta\Pi}{\mu(\tau+k+\mu)(\alpha+\delta+\mu)} - 1\right]\right)$ (33)

Basic Reproduction Number (R_0)

The basic reproduction number of an infectious disease is the average of secondary infections when one infected individual is introduced into a host population where everyone is susceptible (Diekmann et al., 1990, Diekmann et al., 2010). We use the next generation matrix approach to compute the basic reproduction number R_0. The basic reproduction number R_0 is the spectral radius pf the product matrix FV^{-1}. That is,

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

where σ denotes the spectral radius.

The associated non-negative matrix F, for the new infective terms and the non-singular M-matrix, V, for the remaining transfer terms at the DFE are respectively given by

$F = \begin{pmatrix} 0 & \beta S \\ 0 & 0 \end{pmatrix} = \begin{pmatrix} 0 & \frac{\beta\Pi}{\mu} \\ 0 & 0 \end{pmatrix}$

and $V = \begin{pmatrix} (\tau+k+\mu) & 0 \\ -\tau & (\alpha+\delta+\mu) \end{pmatrix}$

$V^{-1} = \begin{pmatrix} \frac{1}{(\tau+k+\mu)} & 0 \\ \frac{\tau}{(\tau+k+\mu)(\alpha+\delta+\mu)} & \frac{1}{(\alpha+\delta+\mu)} \end{pmatrix}$

so that

$FV^{-1} = \begin{pmatrix} \frac{\beta\Pi\tau}{\mu(\tau+k+\mu)(\alpha+\delta+\mu)} & \frac{\beta\Pi}{\mu(\alpha+\delta+\mu)} \\ 0 & 0 \end{pmatrix}$

It follows that the basic reproduction number, denoted by R_0, given by $\sigma(FV^{-1})$

where σ denotes the spectral radius is

$R_0 = \frac{\beta\Pi\tau}{\mu(\tau+k+\mu)(\alpha+\delta+\mu)}$ (34)

Local Stability of Disease-Free Equilibrium (DFE) State

We investigate the local stability of the disease-free equilibrium (DFE) state by evaluating the associated Jacobian of equations (9) – (12) at the DFE state. The Jacobian matrix J for the system (9) – (12) evaluated at the disease-free equilibrium, Ω_0 is given by

$$J(\Omega_0) = \begin{pmatrix} -\mu & 0 & \frac{-\beta\Pi}{\mu} & 0 \\ 0 & -(\tau+k+\mu) & \frac{\beta\Pi}{\mu} & 0 \\ 0 & \tau & -(\alpha+\delta+\mu) & 0 \\ 0 & 0 & \alpha & -(\rho+\mu) \end{pmatrix}$$

Theorem 2: The DFEs of the model (9) – (12), given by Ω_0, is locally asymptotically stable (LAS) if $R_0 < 1$ and Ω_0 is unstable if $R_0 > 1$.

Proof:

It suffices to show that all the eigenvalues of the characteristic equation of the Jacobian matrix $J(\Omega_0)$ have negative real parts. The characteristic equation of the Jacobian matrix is given by

$(-\mu-\lambda)(-(\rho+\mu)-\lambda)[-(\tau+k+\mu)-\lambda][-(\alpha+\delta+\mu)-\lambda] - \frac{\beta\Pi\tau}{\mu}] = 0$

that is,

$(-\mu-\lambda)(-(\rho+\mu)-\lambda)\left[(\tau+k+\mu)(\alpha+\delta+\mu) + (\tau+k+\mu)\lambda + (\alpha+\delta+\mu)\lambda + \lambda^2 - \frac{\beta\Pi\tau}{\mu}\right] = 0$

that is,

$(-\mu-\lambda)(-(\rho+\mu)-\lambda)\left[\lambda^2 + [(\tau+k+\mu)(\alpha+\delta+\mu)]\lambda + (\tau+k+\mu)(\alpha+\delta+\mu) - \frac{\beta\Pi\tau}{\mu}\right] = 0$

The eigenvalues of the characteristic equation are

$\lambda = -\mu, -(\rho+\mu)$ and the root of the polynomial $q(\lambda) = \lambda^2 + A\lambda + B$ (35)

where

$A = (\tau+k+\mu) + (\alpha+\delta+\mu)$ (36)

and

$B = (\tau+k+\mu)(\alpha+\delta+\mu) - \frac{\beta\Pi\tau}{\mu}$

$B = (\tau+k+\mu)(\alpha+\delta+\mu)\left[1 - \frac{\beta\Pi\tau}{\mu(\tau+k+\mu)(\alpha+\delta+\mu)}\right]$

$B = (\tau+k+\mu)(\alpha+\delta+\mu)[1-R_0]$ (37)

For $R_0 < 1$, we have $A > 0$ and $B > 0$, and thus following Routh-Hurwitz stability criterion (Hurwitz, 1964) for the polynomial $q(\lambda)$, the state Ω_0 is locally asymptotically stable whenever $R_0 < 1$.

Global Asymptotic Stability (GAS) of the Disease-Free Equilibrium (DFE) State

To ensure that the tuberculosis infection eradication is independent of initial sizes of the population of the model, it is imperative to show that the DFE of the model (9) – (12), given Ω_0 is globally asymptotically stable (GAS). This is done now.

Theorem 3: The DFE of model (9) – (12) given by Ω_0 is GAS whenever $R_0 \leq 1$.

Proof:

Consider the Lyapunov function

$F = \tau E + (\tau + k + \mu)I$

with Lyapunov derivative (where a prime represent differentiation w.r.t. t)

$F' = \tau[\beta SI - (\tau + k + \mu)E] + [(\tau + k + \mu)(\tau E - (\alpha + \delta + \mu))]$

$F' = \tau\beta SI - [(\tau + k + \mu)(\alpha + \delta + \mu)]I$

$F' = [\tau\beta S - [(\tau + k + \mu)(\alpha + \delta + \mu)]I$

$$F' = (\tau + k + \mu)(\alpha + \delta + \mu)\left[\frac{\tau\beta S^*}{(\tau + k + \mu)(\alpha + \delta + \mu)} - 1\right]I$$

$$F' = (\tau + k + \mu)(\alpha + \delta + \mu)\left[\frac{\tau\beta\Pi}{\mu(\tau + k + \mu)(\alpha + \delta + \mu)} - 1\right]I$$

$F' = (\tau + k + \mu)(\alpha + \delta + \mu)I[R_0 - 1] \leq 0 \quad$ for $R_0 \leq 1$ (38)

It follows from the Lassale invariance principle (Lasalle, 1976) that every solution to the equations (9) – (12) with initial condition in $\mathbb{R}^4$, approaches Ω_0 as $t \to \infty$ for $R_0 \leq 1$.

Local Stability of Endemic Equilibrium (EE) State

Substituting the expression of R_0 in equation (29) into equation (32), the endemic equilibrium (EE) state can be expressed as

$$\Omega_1 = \left(\frac{(\tau + k + \mu)(\alpha + \delta + \mu)}{\tau\beta}, \frac{\mu(\alpha + \delta + \mu)}{\alpha\beta}[R_0 - 1], \frac{\mu}{\beta}[R_0 - 1], \frac{\alpha\mu}{\beta(\rho + \mu)}[R_0 - 1]\right) \quad (39)$$

Theorem 3: The unique endemic equilibrium of the model (9) – (12) given by Ω_1 is locally asymptotically stable (LAS) whenever $R_0 > 1$.

Proof:

To investigate the local stability of the endemic equilibrium, the associated Jacobian matrix of the system (9) – (12) is evaluated at the endemic equilibrium state. Thus, the Jacobian matrix Ω_1 is given by

$$J(\Omega_1) = \begin{pmatrix} -(\mu(R_0 - 1) + \mu) & 0 & \frac{-(\alpha + \delta + \mu)(\tau + k + \mu)}{\tau} & 0 \\ \mu(R_0 - 1) & -(\tau + k + \mu) & \frac{(\alpha + \delta + \mu)(\tau + k + \mu)}{\tau} & 0 \\ 0 & \tau & -(\alpha + \delta + \mu) & 0 \\ 0 & 0 & \alpha & -(\rho + \mu) \end{pmatrix}$$

The characteristic equations of the Jacobian matrix $J(\Omega_1)$ is given by

$$[-(\rho + \mu) - \lambda][-[\mu(R_0 - 1) + \mu] - \lambda]\big[[(\tau + k + \mu) + \lambda][(\alpha + \delta + \mu) + \lambda] - (\tau + k + \mu)(\alpha + \delta + \mu)\big] - \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu)] = 0$$

that is,

$$[-(\rho + \mu) - \lambda][-[\mu(R_0 - 1) + \mu] - \lambda][\lambda^2 + [(\tau + k + \mu)(\alpha + \delta + \mu)]\lambda + (\tau + k + \mu)(\alpha + \delta + \mu) - ab] - \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu)] = 0$$

that is,

$$[-(\rho + \mu) - \lambda][\lambda^3 + [(\mu(R_0 - 1) + \mu) + (\tau + k + \mu) + (\alpha + \delta + \mu)]\lambda^2 + [(\tau + k + \mu)(\alpha + \delta + \mu)(\mu(R_0 - 1) + \mu) + 2(\tau + k + \mu)(\alpha + \delta + \mu)]\lambda + (\mu(R_0 - 1) + \mu)(\tau + k + \mu)(\alpha + \delta + \mu) - [\mu(R_0 - 1) + \mu](\tau + k + \mu)(\alpha + \delta + \mu) + \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu)] = 0 \quad (40)$$

The eigenvalues of the characteristic equation (44) are

$\lambda = -(\rho + \mu)$ and the root of the polynomial $g(\lambda) = \lambda^3 + A\lambda^2 + B\lambda + C$

where

$A = (\mu(R_0 - 1) + \mu) + (\tau + k + \mu) + (\alpha + \delta + \mu)$

$B = (\mu(R_0 - 1) + \mu)(\tau + k + \mu)(\alpha + \delta + \mu) + 2(\tau + k + \mu)(\alpha + \delta + \mu)$

$C = (\mu(R_0 - 1) + \mu)(\tau + k + \mu)(\alpha + \delta + \mu) - [\mu(R_0 - 1) + \mu](\tau + k + \mu)(\alpha + \delta + \mu) + \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu)$

$C = \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu) + \mu(\tau + k + \mu)(\alpha + \delta + \mu) - \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu) + \mu(\tau + k + \mu)(\alpha + \delta + \mu) + \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu)$

$C = \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu)$

Following Routh-Hurwitz stability criterion (Hurwitz, 1964), all the roots of the polynomial $g(\lambda)$ have negative real parts if $A > 0, B > 0, C > 0$ and $AB - C > 0$.

Obviously,

$A = \mu(R_0 - 1) + \mu + (\tau + k + \mu) + (\alpha + \delta + \mu) > 0$ if $R_0 > 1$

$B = (\mu(R_0 - 1) + \mu)(\tau + k + \mu)(\alpha + \delta + \mu) + 2(\tau + k + \mu)(\alpha + \delta + \mu) > 0$ if $R_0 > 1$

$C = \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu) > 0$ if $R_0 > 1$
and
$AB - C = [(\mu(R_0 - 1) + \mu) + (\tau + k + \mu) + (\alpha + \delta + \mu)][(\mu(R_0 - 1) + \mu)(\tau + k + \mu)(\alpha + \delta + \mu) + 2(\tau + k + \mu)(\alpha + \delta + \mu)] - \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu)$
$= (\mu(R_0 - 1) + \mu)(\mu(R_0 - 1) + \mu)(\tau + k + \mu)(\alpha + \delta + \mu) + 2(\mu(R_0 - 1) + \mu)(\tau + k + \mu)(\alpha + \delta + \mu) + (\mu(R_0 - 1) + \mu)(\tau + k + \mu)(\alpha + \delta + \mu) + 2[(\tau + k + \mu)(\alpha + \delta + \mu)]^2 - \mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu)$
$= \mu(R_0 - 1)^2(\tau + k + \mu)(\alpha + \delta + \mu) + 2\mu^2(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu) + \mu^2(\tau + k + \mu)(\alpha + \delta + \mu) + 2\mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu) + 2\mu(\tau + k + \mu)(\alpha + \delta + \mu) + (\tau + k + \mu)(\alpha + \delta + \mu)\mu(R_0 - 1) + \mu(\tau + k + \mu)(\alpha + \delta + \mu) + 2[(\tau + k + \mu)(\alpha + \delta + \mu)]^2 - (\tau + k + \mu)(\alpha + \delta + \mu)\mu(R_0 - 1)$
$= \mu(R_0 - 1)^2(\tau + k + \mu)(\alpha + \delta + \mu) + 2\mu^2(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu) + \mu^2(\tau + k + \mu)(\alpha + \delta + \mu) + 2\mu(R_0 - 1)(\tau + k + \mu)(\alpha + \delta + \mu) + 2\mu(\tau + k + \mu)(\alpha + \delta + \mu) + \mu(\tau + k + \mu)(\alpha + \delta + \mu) + 2[(\tau + k + \mu)(\alpha + \delta + \mu)]^2 > 0$ if $R_0 > 1$ (41)

Global Stability of Endemic Equilibrium (EE) State
The global stability of the system (9) – (12) of the unique endemic equilibrium state Ω_1 is now employed.

Theorem 4: The endemic equilibrium of the model (9) – (12) is globally asymptotically stable (GAS) whenever $R_0 > 1$.

Proof:
Since Q and R do not feature in any of the other equations in equation (9) – (13), the equation for $\frac{dQ}{dt}$ and $\frac{dR}{dt}$ can be removed from the analysis. The global stability of the endemic equilibrium of the model (9) – (13) will be based on the following equations:

$$\frac{dS}{dt} = \Pi - \beta SI - \mu S \quad (42)$$
$$\frac{dE}{dt} = \beta SI - (\tau + k + \mu)E \quad (43)$$
$$\frac{dI}{dt} = \tau E - (\alpha + \delta + \mu)I \quad (44)$$

The endemic equilibrium satisfies the following relation
$\Pi = \beta S^* I^* + \mu S^*$ (45)
$\beta S^* I^* = (\tau + k + \mu)E^*$ (46)
$\tau E^* = (\alpha + \delta + \mu)I^*$ (47)
Let us consider a possible non-linear Lyapunov function (non-linear function of this type have been used in Korobeinikov and Maini, 2004, Korobeinikov, 2006, Fall et al., 2007).

$V = (S - S^* \ln S) + (E - E^* \ln E) + (I - I^* \ln I)$
It derivatives along the trajectories of (9) – (11) is
$V' = \left(1 - \frac{S^*}{S}\right)S' + \left(1 - \frac{E^*}{E}\right)E' + \left(1 - \frac{I^*}{I}\right)I'$
It follows from equation (42) – (44) that
$V' = \Pi - \beta SI - \mu S - \frac{S^*}{S}[\Pi - \beta SI - \mu S] + \beta SI - (\tau + k + \mu)E - \frac{E^*}{E}[\beta SI - (\tau + k + \mu)E] + \tau E - (\alpha + \delta + \mu)I - \frac{I^*}{I}[\tau E - (\alpha + \delta + \mu)I]$
By using the endemic relations in the system (45) – (47)
$V' = \beta S^* I^* + \mu S^* - \beta SI - \mu S - \frac{S^*}{S}[\beta S^* I^* + \mu S^* - \beta SI - \mu S] + (\tau + k + \mu)E^* - (\tau + k + \mu)E - \frac{E^*}{E}[(\tau + k + \mu)E^* - (\tau + k + \mu)E] + (\alpha + \delta + \mu)I^* - (\alpha + \delta + \mu)I - \frac{I^*}{I}[(\alpha + \delta + \mu)I^* - (\alpha + \delta + \mu)I]$
By using the endemic relations in the system (45) – (47)
$V' = \beta S^* I^* + \beta SI - \frac{\beta I^* (S^*)^2}{S} + \beta S^* I^* + \mu S^* - \mu S - \frac{\mu (S^*)^2}{S} + \mu S^* + kE^*\left[1 - \frac{E}{E^*} - \frac{E^*}{E} - 1\right] + \tau E^*\left[1 - \frac{E}{E^*} - \frac{E^*}{E} - 1\right] + \mu E^*\left[1 - \frac{E}{E^*} - \frac{E^*}{E} - 1\right] + \alpha I^*\left[1 - \frac{I}{I^*} - \frac{I^*}{I} - 1\right] + \delta I^*\left[1 - \frac{I}{I^*} - \frac{I^*}{I} - 1\right] + \mu I^*\left[1 - \frac{I}{I^*} - \frac{I^*}{I} - 1\right]$
$V' = \beta S^* I^*\left[1 - \frac{SI}{S^* I^*} - \frac{S^*}{S} + \frac{I}{I^*}\right] + \mu S^*\left[1 - \frac{S}{S^*} - \frac{S^*}{S} + 1\right] + kE^*\left[2 - \frac{E}{E^*} - \frac{E^*}{E}\right] + \tau E^*\left[2 - \frac{E}{E^*} - \frac{E^*}{E}\right] + \mu E^*\left[2 - \frac{E}{E^*} - \frac{E^*}{E}\right] + \alpha I^*\left[2 - \frac{I}{I^*} - \frac{I^*}{I}\right] + \delta I^*\left[2 - \frac{I}{I^*} - \frac{I^*}{I}\right] + \mu I^*\left[2 - \frac{I}{I^*} - \frac{I^*}{I}\right]$
$V' = \beta S^* I^*\left[1 - \frac{SI}{S^* I^*} - \frac{S^*}{S} + \frac{I}{I^*}\right] + \mu S^*\left[2 - \frac{S}{S^*} - \frac{S^*}{S}\right] + (\tau + k + \mu)E^*\left[2 - \frac{E}{E^*} - \frac{E^*}{E}\right] + (\alpha + \delta + \mu)I^*\left[2 - \frac{I}{I^*} - \frac{I^*}{I}\right]$
using the comparison between the arithmetic and geometric means (Fall et al, 2007).
(That is, $a_1 + a_2 + \cdots + a_n \geq n\sqrt[n]{a_1, a_2, \ldots, a_n}$ for $a_i \geq 0$, $i = 1,2, \ldots, n$).
Then,

$$1-\frac{SI}{S^*I^*}-\frac{S^*}{S}+\frac{I}{I^*}\leq 0$$
$$2-\frac{S}{S^*}-\frac{S^*}{S}\leq 0$$
$$2-\frac{E}{E^*}-\frac{E^*}{E}\leq 0$$
$$2-\frac{I}{I^*}-\frac{I^*}{I}\leq 0$$
so that,
$$V'\leq 0$$
Thus, it follows by Lyapunov functions V and Laselle invariance principle (Lasalle, 1976) that all solution with initial condition in $\Omega\backslash\Omega_0$ will converge to Ω.

Sensitivity Analysis of R_0

We carried out sensitivity analysis on the basis of the model parameter (Table 1) by the normalized forward sensitivity indices (Chitnis et al., 2006; Wu et al., 2013) using the following formula

$$\Lambda_{\mathrm{Q}}^{R_0}=\frac{\partial R_0}{\partial Q}\left(\frac{Q}{R_0}\right) \qquad (48)$$

where Q denotes the model parameter.

The sensitivity index of R_0 with respect to each parameter is given in Table 2.

Table 3: Sensitivity indices of R_0

Parameter	Description	Sensitivity Indices
β	Infection transmission rate	1
τ	Progression rate from exposed class to infectious class	0.8886
Π	Recruitment rate	1
k	Tuberculosis testing and therapy rate	-0.6120
μ	Natural death rate	-0.7891
α	Isolation rate	-0.5638
δ	Disease-induced death rate	0.0526

It is shown from Table 3, that the threshold R_0 is sensitive proportionally to the changes in the parameter values of $\beta, \Pi, \text{and } \tau$. It implies that an increase (or decrease) in the value of each of the parameter in this case will lead to increase (or decrease) in R_0 of the model (9) – (12). On the contrary, the threshold R_0, is sensitive inversely proportional to the variation the values of $\mu, k, \alpha, \text{and } \delta$. In other words, an increase (or decrease) in the value of each of the parameter in this case leads to a corresponding decrease (or increase) in R_0.

Numerical Simulations

Numerical simulations for the model (9) – (12) are carried out using the parameters in Table 3 unless otherwise stated to illustrate some of the analytical results established in this study. The numerical simulations were conducted using the Runge-Kutta fourth order method (RK4) embedded in MATLAB.

Baseline Parameter Values

We show a baseline table for the parameters used in this model. The sources are also stated.

Table 3: Baseline parameter values for equations (9) – (12).

Parameters	Baseline value	Reference
π	0.984	Omale et al., (2019)
β	0.5853	Dauda et al., (2020)
τ	0.048	WHO (2020)
ρ	0.1	Assumed
μ	0.02041	Egonmwan & Okuonghue (2009)
δ	0.0028	Omale et al., (2019)
α	0.030	Assumed
k	0.1	Assumed

The numerical results are shown in Figure 2 – Figure 8.

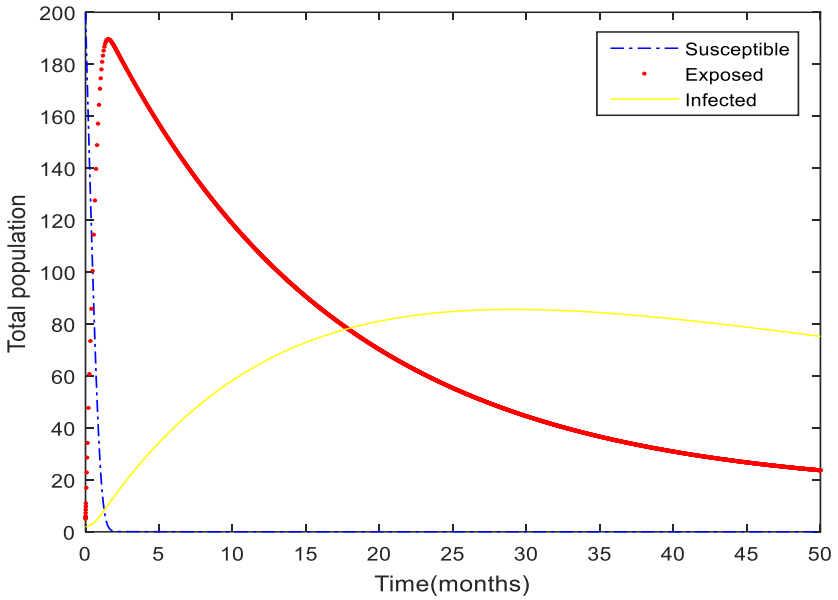

Figure 2: Graph of Susceptible, Exposed and Infected individual with no control ($\alpha = 0; k = 0;\ \rho = 0$).

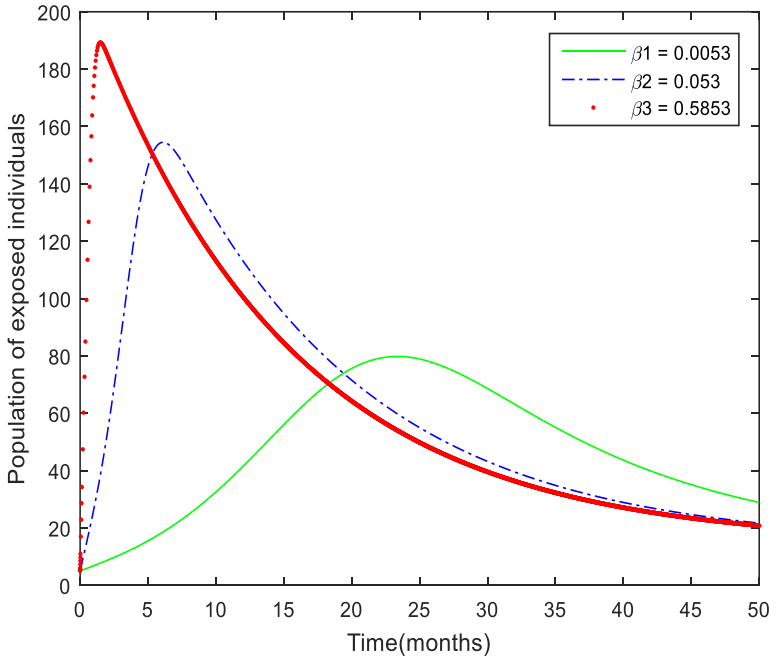

Figure 3: Graph of Exposed individuals with no control ($\alpha = 0; k = 0;\ \rho = 0$) varying the infection transmission ($\beta = 0.0053;\ \beta = 0.053;\ \beta = 0.5853$).

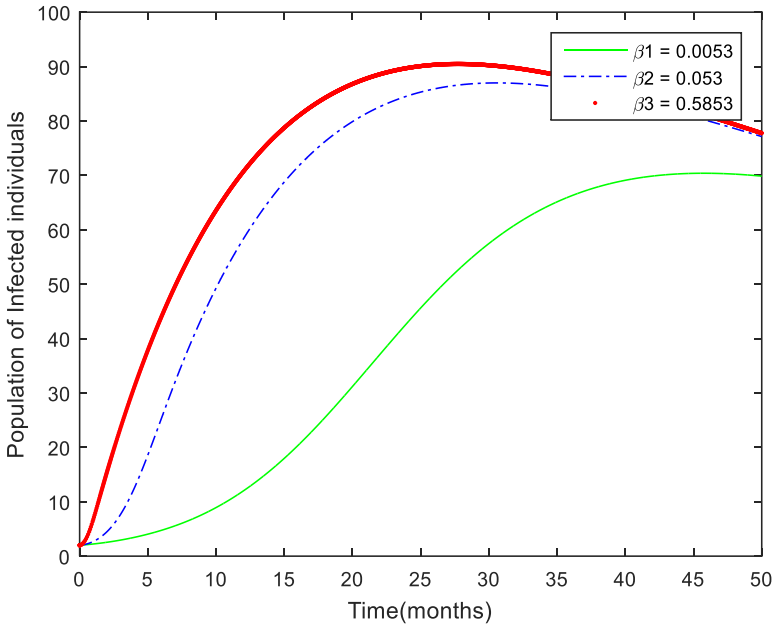

Figure 4: Graph of infectious individual with respect to time with no control ($\alpha = 0; k = 0;\ \rho = 0$) varying the infection transmission ($\beta = 0.0053;\ \beta = 0.053;\ \beta = 0.5853$).

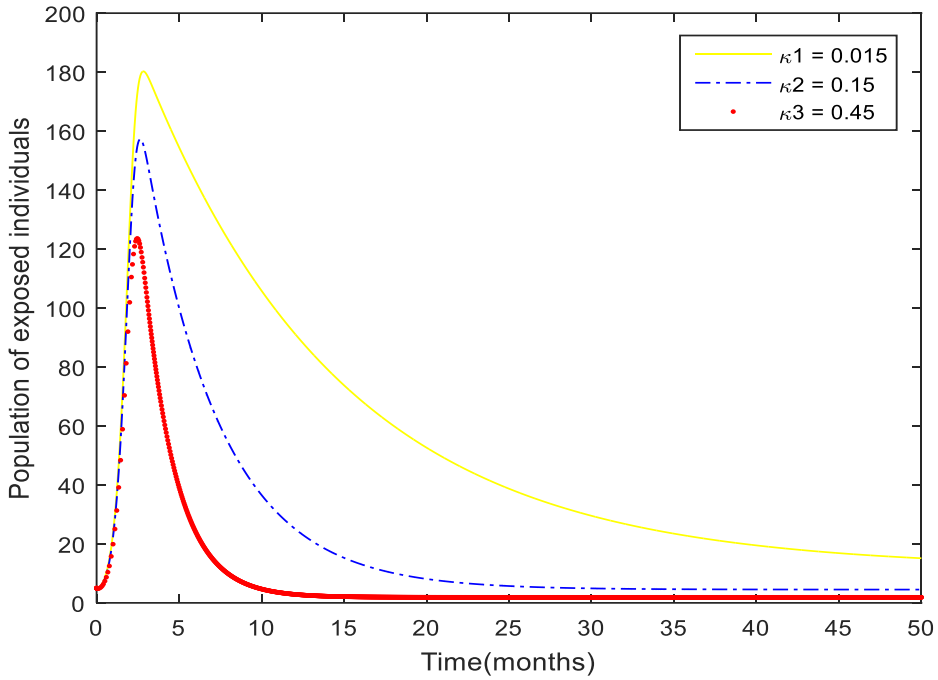

Figure 5: Effect of early detection and therapy ($k_1 = 0.015;\ k_2 = 0.15;\ k_3 = 0.45$)) of Exposed individuals without isolation ($\alpha = 0;\ \rho = 0$).

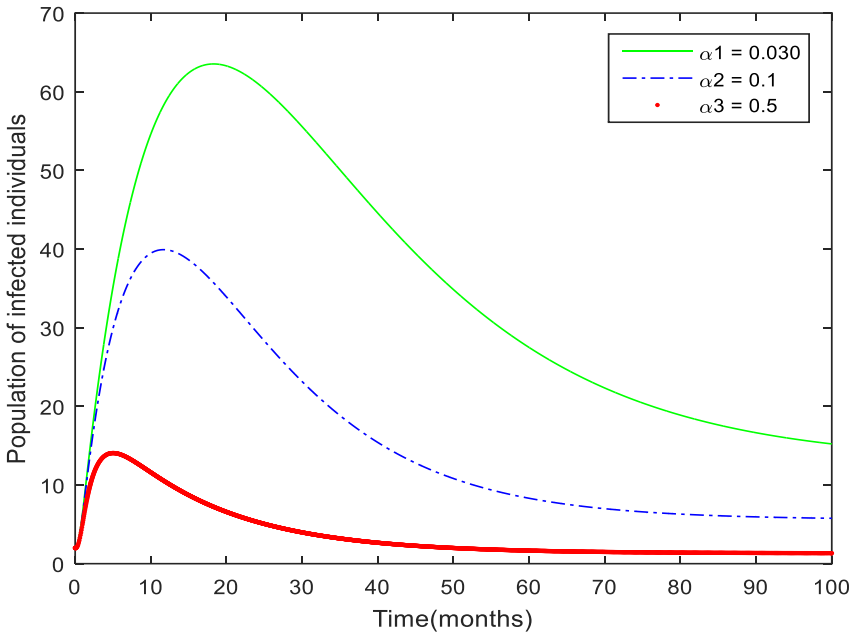

Figure 6: Effect of isolation and treatment ($\alpha_1 = 0.030,\ \rho = 0.1;\ \alpha_2 = 0.1,\ \rho = 0.1;\ \alpha_3 = 0.5, \rho = 0.1$)without early detection and therapy of infected individuals ($k = 0$).

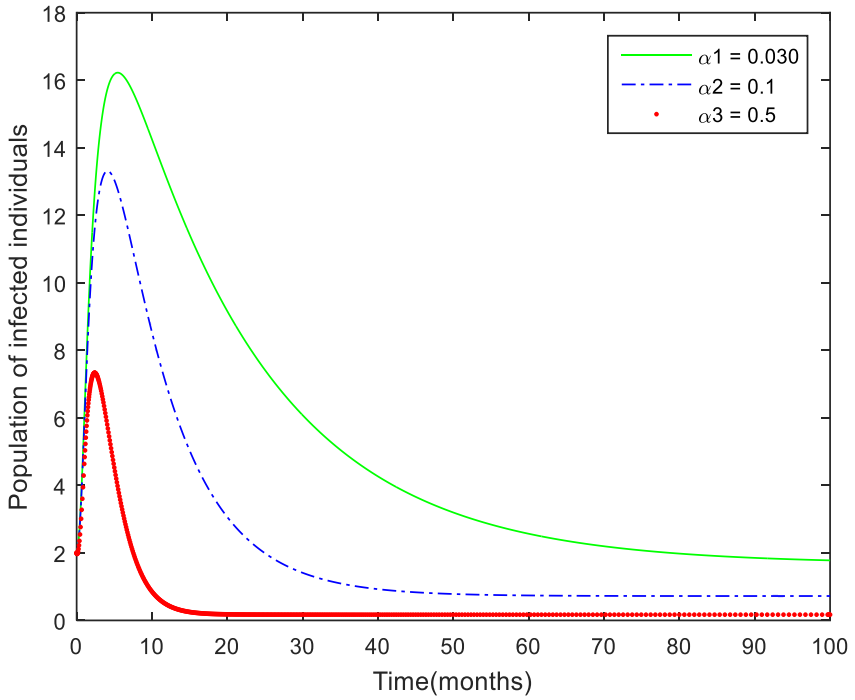

Figure 7: Effect of early detection and isolation of infected individuals with respect to time.($k = 0.45;\ \rho = 0.1;\ \alpha_1 = 0.030;\ \ \alpha_2 = 0.1;\ \alpha_3 = 0.5$).

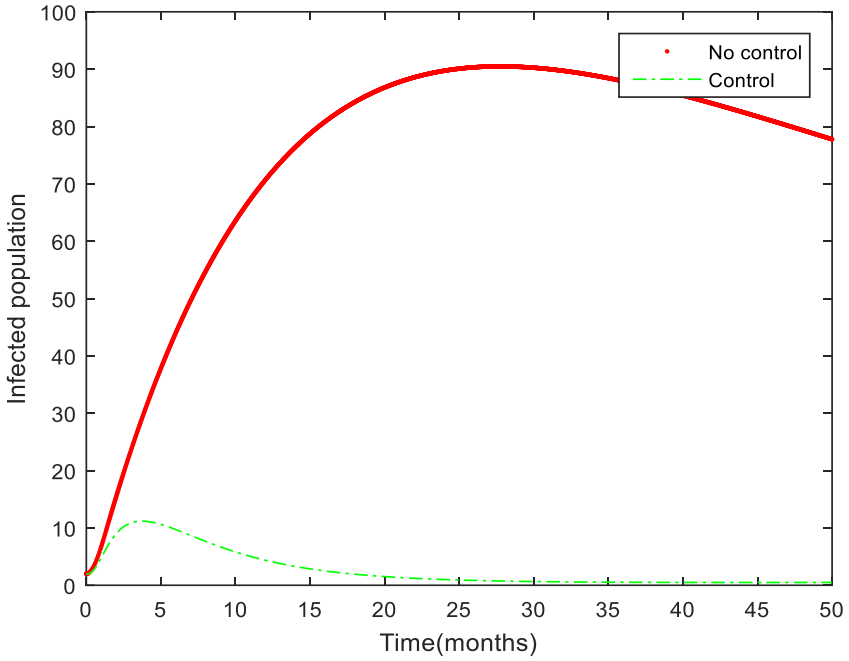

Figure 8: Graph of infected human with no control $k = \alpha = \rho = 0$) and with control ($k = 0.1;\ \alpha = 0.5;\ \rho = 0.1$).

Discussion of Results

In this study we extended and analyzed a mathematical model for the transmission dynamics of tuberculosis infection by incorporating two types of intervention strategies based on early detection and therapy and isolation of infected individuals.

The analytical result of the model shows that the solution of the model is bounded, positively and attracting with respect to the system equations (9) – (12) where the usual existence, uniqueness, continuation results hold. The theoretical analysis showed that in closed region the model is epidemiological meaningful and mathematical well posed

The basic reproduction number, R_0 is an important threshold parameter used to determine the threshold between disease eradication and outbreak and thus R_0 was shown to be crucial to the stability analysis of the model. We computed the basic reproduction number, R_0 using the next generation method and is given by

$$R_0 = \frac{\beta\pi\tau}{\mu(\tau + k + \mu)(\alpha + \delta + \mu)}$$

The basic reproduction number, R_0 is given by the product of the infection transmission rate of the susceptible individuals by infectious individuals near the disease-free equilibrium states (DFEs) $\frac{\beta\pi}{\mu}$, the rate of exposed individuals that moves to the infectious class τ, the average duration of the exposed class and the infectious class $\frac{1}{(\tau+k+\mu)(\alpha+\delta+\mu)}$.

The result from the stability analysis of the disease-free equilibrium (DFE) state is shown to be locally and globally asymptotically stable if the basic reproduction number is less than unity, as shown in Theorem 2 and Theorem 4 respectively. The epidemiological implication of Theorem 2 and Theorem 3 is that the small influx of tuberculosis infection cases will not generate a tuberculosis outbreak if the basic reproduction number, R_0 of the model (9) – (12) is less than unity. Results found in Theorem 4 and Theorem 5 shows that the endemic equilibrium (EE) state is locally as well as globally asymptotically stable if the basic reproduction number is greater than unity ($R_0 > 1$). The implication is that, tuberculosis infection will persist in the population if the initial sizes of the population of the model are in the basin of attraction of the endemic equilibrium states (EEs).

The sensitivity analysis of R_0 with respect to the model parameters was carried out using the normalized forward sensitivity indices. The results of the sensitivity index of R_0 is given in Table 3 and it shows that the more sensitive parameter is the infection transmission rate β. It is followed by the recruitment rate Π and progression rate from exposed class to infectious class τ. The parameter β as positive index 1 as shown in Table 3 reveals that by decreasing or increasing infection transmission parameter will decrease or increase the basic reproduction number, R_0. Thus, preventive effort should be geared towards decreasing the infection transmission to ensure tuberculosis disease elimination. The parameters with the negative sensitivity indices, $-0.0936;\ -2.2356;-0.0315;\ -0.0029$ that correspond to tuberculosis testing and therapy k, natural death rate μ, isolation rate α and disease-induced death rate δ, respectively (as shown in Table 3) have influence of reducing the disease burden in the population as their values increases.

The numerical results are based on the numerical simulations presented in Figure 2 to Figure 8. The simulations in Figure 2 shows the dynamical behavior of the population of susceptible, exposed, and infectious individuals for fixed value of infection rate ($\beta = 0.01328$) with no control measure ($k = 0;\ \alpha = 0$). It shows prevalence of tuberculosis infection in the population. Thus, with no control measures put in place tuberculosis infection will persist in the population.

Figure 3 and Figure 4 shows increasing prevalence of tuberculosis with increasing infection transmission rates ($\beta = 0.0053;\ 0.053;\ 0.5853$)in the absence of any intervention ($k = 0;\ \alpha = 0$). With the basic reproduction number, $R_0 > 1$ in each case, shows convergence of the solution profile to the endemic equilibrium (EE) state. This is consistent with Theorem 4 and Theorem 5 respectively. The implication of

this result is that, for an effective preventive strategy, effort should be geared at reducing the infection transmission rate.
Figure 5 shows effect of early detection and therapy ($k_1 = 0.015;\ k_2 = 0.15;\ k_3 = 0.45$)) of
exposed individuals without isolation ($\alpha = 0;\ \rho = 0$). The figure shows a significant decrease of tuberculosis infection with increasing testing and therapy of latent individuals in a population.
Figure 6 shows effect of isolation and treatment ($\alpha_1 = 0.030,\ \rho = 0.1;\ \alpha_2 = 0.1,\ \rho = 0.1;\ \alpha_3 = 0.5, \rho = 0.1$) without early detection and therapy of infected individuals ($k = 0$). The figure revealed a decreasing number of infected individuals by increasing isolation and treatment of infected individuals.
Figure 7 depicts the impact of combining early detection of latent individuals and isolation of infected individuals. It shows a decreasing tuberculosis disease in the population with effective combination of the two control measures. It further reveals a rapid convergence of the solution profile to the disease-free equilibrium (DFE) with the basic reproduction number $R_0 < 1$ (that is $R_0 = 0.0325, 0.0303, 0.0218$). Thus, we can deduce that a combination of early detection and therapy of latent individuals, with effective isolation and treatment of infected individuals, tuberculosis disease can be eliminated from the population.
Figure 8 shows the difference between applying different intervention strategy with no control on tuberculosis disease transmission. Without any control measure, the tuberculosis infection will persist within the community. It further shows that the infection will die out with a combination of early detection and effective isolation and treatment of infected individuals in the population.

CONCLUSION

A deterministic model of tuberculosis disease was presented. This model extended the model by Dauda et al. (2020) by incorporating testing and therapy in the latent population, isolation and treatment in the infectious class. The analysis of the model shows that there exists a unique solution that is bounded and positively invariant. The disease-free equilibrium (DFE) state and the endemic equilibrium (EE) state of the model was obtained and the basic reproduction number R_0, which is a threshold in the study of tuberculosis infection both to predict its outbreak and for assessing its control strategies was computed using the next generation matrix operator. Analytical results shows that the DFEs is locally as well as globally asymptotically stable whenever $R_0 < 1$ and further stability analysis shows that the EEs is locally as well as globally asymptotically stable if $R_0 > 1$. Sensitivity analysis of R_0 with respect to the model parameters was carried out and the results shows that the more sensitive parameter is the infection transmission rate β. It is followed by the recruitment rate Π and progression rate from exposed class to infectious class τ. The parameter β as positive index 1 as shown in Table 3 reveals that by decreasing or increasing infection transmission parameter will directly decrease or increase the basic reproduction number, R_0. Numerical results shows that tuberculosis infection will persist in a population if control measures are put in place. Further numerical results shows that the infection will die out with a combination of early detection and effective isolation and treatment of infected individuals in the population.

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