

MATHEMATICAL MODELING AND ANALYSIS OF MYCOBACTERIUM TUBERCULOSIS TRANSMISSION IN HUMANS WITH HOSPITALIZATION AND REINFECTION

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Abstract. Tuberculosis (TB), a serious public health infection that mainly affects the lungs, is caused by bacteria (*Mycobacterium tuberculosis*, TB). This research is designed and analyzed using a compartmental modelling approach to study the transmission dynamics of TB with different stages of infection. Qualitative analysis of the proposed model reveals that the model exhibits two equilibrium points: the disease-free equilibrium point (DFE) and the endemic equilibrium (EE). The basic reproduction number (R_0) is determined using the next-generation matrix technique, and stability analysis is carried out to show whether the disease can persist or die out in population. Further analysis of the model shows that the EE is globally asymptotically stable (GAS) when $R_0 > 1$. With the aid of the forward sensitivity index method, we determine the most sensitive parameters of the model to control the spread of TB infection effectively. Our analysis shows that treatment (medication) and campaign awareness coupled with other key control measures, could help maintain the spread of MTB infection in human geographical boundaries.

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1. Background of the research work

Mycobacterium tuberculosis (MTB) is a disease caused by tubercle bacillus or *M. tuberculosis* which belongs to the genus *Mycobacterium* under the family of *Mycobacteriaceae* that affect a variety of hosts, including humans, livestock animals (horse, camel, pig) and wild animals (tiger, lion, gorilla), which serve as a reservoir or

spillover [1]. The disease ranks second to HIV among the leading causes of death worldwide, killing about two million people every year, especially in developing countries, such as India, China, Indonesia, Nigeria, South Africa and so on [1]. In the year 2017 alone, there were about 12.2 million new cases of TB infection globally, including about 1.93 million deaths (and about 0.4 million are people living with HIV) [2]. Previous studies show, that about six countries are considered to have about 60% of the total MTB cases globally, of which four are countries within Asia, and the rest are African countries [2].

The MTB infection is an air-borne disease which is transmitted from human to human via air [2]. When a human with lung MTB infection coughs, he/she drops the pathogen in the air; an individual is required to inhale a few among the pathogen to get infected with the disease. MTB is classified as pulmonary TB when it affects the lungs, while it is considered extra-pulmonary TB when it affects other parts of the body [1, 2]. The most common signs and symptoms of MTB disease are dry coughing, feverish condition, chest pain and most a times loss of weight. MTB appears in the host's body roughly fourteen to eighty-four days (i.e., two to twelve weeks) [1]. The MTB disease can be cured and treated when it has been noticed during the early phase [2]. Active MTB disease can be treated within one hundred and eighty days with non-stop taking of medication (drugs) under the supervision of certified medical personnel trained on handling TB patients. At least 50 million lives were saved during 15 years of TB infection, some of which through treatment, and some via special diagnosis [1, 2].

A lot of epidemiological models have been designed and used to assess the transmission dynamics of MTB infection in humans based on geographical disparities (see, for instance, [1, 3–6] and the references therein). Some previous studies of epidemic models examined the transmission dynamics of MTB in humans in a confined area/environment, such as transmission of TB infection among prison inmates, and the effect of home and hospital treatment on the overall dynamics of TB infection [7–9]. The aim of the current research work is to design a dynamic model (based on extending some of the research mentioned above) for MTB transmission dynamics to gain more qualitative insight on TB control.

The paper is organised as follows: the model description is contained in section 2, and section 3 consists of a basic analysis of the model while the sensitivity analysis was carried out in section 4. Finally, the numerical scenario and conclusion are contained in section 5 and 6 respectively.

2. Description of the model

The total number of population at time t , represented by $N(t)$, is categorised into six (6) compartments as follows: susceptible human, who are at risk of being infected with MTB disease ($S(t)$), Exposed individuals or latent stage ($E(t)$), asymptomatic MTB infected individuals with no clinical symptoms of MTB infection ($A(t)$), symp-

tomatic MTB infected individuals with clinical symptoms ($I(t)$), hospitalized individuals, who are under treatment of MTB infection ($H(t)$), individuals who recovered from MTB infection ($R(t)$), so that:

$$N(t) = S(t) + E(t) + A(t) + I(t) + H(t) + R(t).$$

The model flow chart (Fig. 1) and the equations for the MTB dynamics are given below.

$$\begin{aligned} \frac{dS}{dt} &= \Pi - \lambda S + \theta R - \mu S, \\ \frac{dE}{dt} &= \lambda S - (\sigma + \mu)E, \\ \frac{dA}{dt} &= \alpha\sigma E - (\gamma_1 + \tau_1 + \delta_1 + \mu)A, \\ \frac{dI}{dt} &= (1 - \alpha)\sigma E - (\gamma_2 + \tau_2 + \delta_2 + \mu)I, \\ \frac{dH}{dt} &= \gamma_1 A + \gamma_2 I - (\delta_3 + \tau_3 + \mu)H, \\ \frac{dR}{dt} &= \tau_1 A + \tau_2 I + \tau_3 H - (\theta + \mu)R, \end{aligned} \tag{1}$$

where

$$\lambda = \frac{\beta(\eta_1 E + \eta_2 H + \eta_3 A + I)}{N}, \tag{2}$$

β is the effective contact rate, and η_1 , η_2 and η_3 are modification for for the decrease/increase of MTB infection.

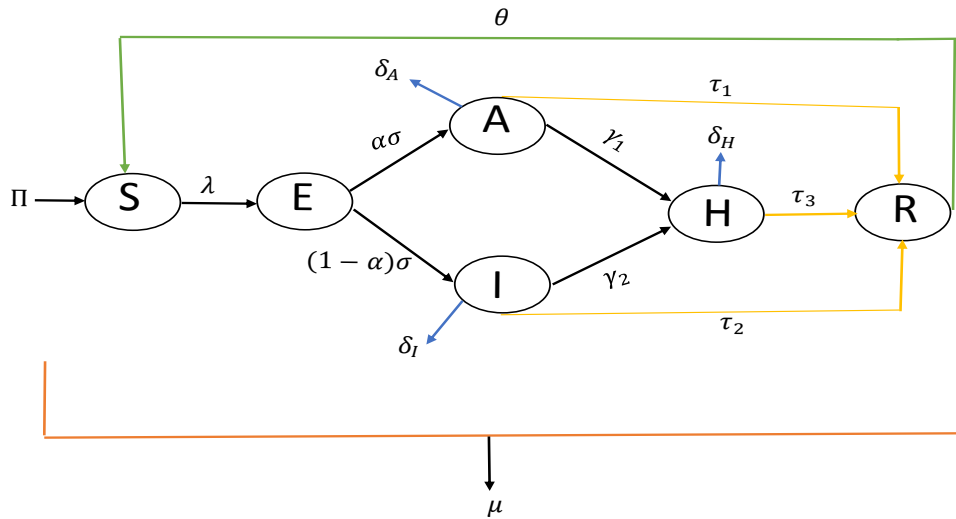


Fig. 1. Flow chart of the MTB infection model

Table 1. Description of the state variables and parameters apply in the system (1)

Variables	Demonstration
N	Total humans population
S	Susceptible individuals
E	Latent individuals
A	Asymptomatically infected individuals with no clinical symptoms of MTB infection
I	Symptomatically infected individuals with clinical symptoms of MTB infection
H	Hospitalized individuals
R	Recovered individuals
Parameters	
Π	Recruitment rate of humans
μ	Natural death rate
β	Transmission probability for the MTB infection
σ	Progression of individuals from latent state of MTB infection
α	Proportion of infected individuals who developed symptoms
$\tau_i (i = 1, 2, 3)$	Recovery rates of individuals
θ	Loss of immunity
$\delta_j (j = 1, 2, 3)$	Death caused by the disease
$\gamma_k (k = 1, 2)$	Hospitalization rate of individuals

3. Basic analysis of the model

3.1. Positivity of the solution and invariant region

Theorem 1 *The solutions of the system (1) remain positive at initial condition $\forall t > 0$.*

Moreover $\limsup_{t \rightarrow \infty} N(t) \leq \frac{\Pi}{\mu}$. □

PROOF Let us consider, the first equation of the system (1) so,

$$\frac{dS}{dt} = \Pi + \theta R - \lambda S - \mu S \geq -(\lambda + \mu)S. \quad (3)$$

So that

$$S(t) \geq S(0) \exp^{-\int_0^t (\lambda + \mu) dt} > 0. \quad (4)$$

Similarly, one can see that all the remaining variables of the system are positive $\forall t > 0$. ■

Lemma 1 *Let the feasible biological region of the system be (1)*

$$D = \left\{ (S, E, A, I, H, R) \in \mathfrak{R}_+^6 : N \leq \frac{\Pi}{\mu} \right\}$$

are positively, invariant region and also attracting. □

PROOF It is from the fact that $\frac{dN(t)}{dt} = \Pi - \mu N - (\delta_A A + \delta_I I + \delta_H H) \leq \Pi - \mu N$, so that, $\frac{dN(t)}{dt} < 0$, if $N(t) > \frac{\Pi}{\mu}$. Hence, standard comparison theorem [10] are used to prove that $N(t) \leq N(0) \exp^{-\mu t} + \frac{\Pi}{\mu} (1 - \exp^{-\mu t})$. Specifically, $N(t) \leq \frac{\Pi}{\mu}$ if $N(0) \leq \frac{\Pi}{\mu}$. So, D is positive invariant region. Moreover, if $N(t) > \frac{\Pi}{\mu}$ the solution move into D infinitely many time, or $N(t)$ moves closer to $\frac{\Pi}{\mu}$ then variables that are infected move closer to zero. So D is attracting (The solutions are all in \mathfrak{R}_+^6 and finally, D stays or approaches the region).

Consequently, the system (1) is mathematically well-posed and epidemiologically reasonable because the variables are positive for all $t \geq 0$. Thus, it is enough to consider the changes in the system (1) in D [11]. ■

3.2. Disease-free equilibrium and basic reproduction number

In the absence of the disease, this means that $(E^* = 0, A^* = 0, I^* = 0, H^* = 0)$, therefore the system above becomes

$$G^\circ = (S^*, E^*, A^*, I^*, H^*, R^*) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0\right). \tag{5}$$

The stability state of ϵ_0 will be investigated by applying the method of next generation matrix on the system (1) [12]. The matrices F (is the rate of appearance of new infection) and V (is the matrix containing the rest of the terms)

$$F = \begin{bmatrix} \beta \eta_1 & \beta \eta_3 & \beta & \beta \eta_2 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, V = \begin{bmatrix} K_1 & 0 & 0 & 0 \\ -\alpha \sigma & K_2 & 0 & 0 \\ -\sigma K_5 & 0 & K_3 & 0 \\ 0 & -\gamma_1 & -\gamma_2 & K_4 \end{bmatrix} \tag{6}$$

then V^{-1} is obtained as

$$V^{-1} = \begin{bmatrix} \frac{1}{K_1} & 0 & 0 & 0 \\ \frac{\alpha \sigma}{K_1 K_2} & \frac{1}{K_2} & 0 & 0 \\ \frac{\sigma K_5}{K_1 K_3} & 0 & \frac{1}{K_3} & 0 \\ \frac{\sigma(\alpha K_3 \gamma_1 + K_2 K_5 \gamma_2)}{K_2 K_1 K_3 K_4} & \frac{\gamma_1}{K_2 K_4} & \frac{\gamma_2}{K_3 K_4} & \frac{1}{K_4} \end{bmatrix}, \tag{7}$$

and

$$FV^{-1} = \begin{bmatrix} K_7 & \frac{\beta \eta_3}{K_2} + \frac{\beta \eta_2 \gamma_1}{K_2 K_4} & \frac{\beta}{K_3} + \frac{\beta \eta_2 \gamma_2}{K_3 K_4} & \frac{\beta \eta_2}{K_4} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad (8)$$

where,

$$K_1 = \sigma + \mu, K_2 = \gamma_1 + \tau_1 + \delta_A + \mu, K_3 = \gamma_2 + \tau_2 + \delta_I + \mu, K_4 = \delta_H + \tau_3 + \mu, K_5 = 1 - \alpha \text{ and } K_6 = \theta + \mu, K_7 = \frac{\beta \eta_1}{K_1} + \frac{\beta \eta_3 \alpha \sigma}{K_1 K_2} + \frac{\beta \sigma K_5}{K_1 K_3} + \frac{\beta \eta_2 \sigma (\alpha K_3 \gamma_1 + K_2 K_5 \gamma_2)}{K_1 K_2 K_3 K_4}.$$

It follows that the associated basic reproduction number of the model (1), represented by R_0 , is known as:

$$R_0 = \frac{\beta (\alpha \sigma K_3 K_4 \eta_3 + \alpha \sigma K_3 \eta_2 \gamma_1 + \sigma K_2 K_5 \eta_2 \gamma_2 + \sigma K_2 K_4 K_5 + K_2 K_3 K_4 \eta_1)}{K_1 K_2 K_3 K_4} \quad (9)$$

where ρ represents the spectral radius of FV^{-1} . The threshold quantity, R_0 , is the basic reproduction number for MTB infection, which determines whether the disease persists or is eliminated in time [11, 13–15].

Using theorem 2 of [12], with reproduction number, $R_0 < 1$, the disease free-equilibrium (DFE) point is locally asymptotically stable, indicating that the population can not be invaded by the disease. Hence, the proof of the following theorem holds as follows.

Theorem 2 *The DFE (ε_0), of the MTB model (1) is locally asymptotically stable (LAS) if $R_0 < 1$, and unstable if $R_0 > 1$. \square*

3.3. Endemic equilibrium analysis

Here, the non-continuation of the endemic equilibrium (EE) point of system (1) will be dealt with whenever the R_0 is less than one. We can say that, the EE point of system (1) is in a stable state, that is, the infection might be wiped out. For $R_0 > 1$, we can say the disease continues to remain in the human population, hence at least one compartment among the compartments of the system (1) is not null. Let $\varepsilon_1 = (S^*, E^*, A^*, I^*, H^*, R^*)$ be an endemic equilibrium solution of model (1). Solving the equations of the system (1) with respect to λ , gives:

$$\begin{aligned}
 S^* &= \frac{K_1 K_4 K_2 K_3 K_6 \Pi_H}{(K_4 K_6 (\lambda + \mu) K_3 - \sigma \theta \lambda K_5 (K_4 \tau_2 + \gamma_2 \tau_3)) K_2 - \alpha \sigma \theta \lambda K_3 (K_4 \tau_1 + \tau_3 \gamma_1)}, \\
 E^* &= \frac{K_4 K_2 K_3 K_6 \lambda \Pi_H}{((K_4 K_3 K_6 K_1 - \sigma \theta K_5 (K_4 \tau_2 + \gamma_2 \tau_3)) K_2 - \alpha \sigma \theta K_3 (K_4 \tau_1 + \tau_3 \gamma_1)) \lambda + K_4 K_2 K_3 K_6 K_1 \mu}, \\
 A^* &= \frac{\alpha \sigma K_4 K_3 K_6 \lambda \Pi_H}{((K_3 K_6 K_1 - \sigma \theta K_5 (K_4 \tau_2 + \gamma_2 \tau_3)) K_2 - \alpha \sigma \theta K_3 (K_4 \tau_1 + \tau_3 \gamma_1)) \lambda + K_4 K_2 K_3 K_6 K_1 \mu}, \\
 I^* &= \frac{K_5 \sigma K_4 K_2 K_6 \lambda \Pi_H}{((K_4 K_3 K_6 K_1 - \sigma \theta K_5 (K_4 \tau_2 + \gamma_2 \tau_3)) K_2 - \alpha \sigma \theta K_3 (K_4 \tau_1 + \tau_3 \gamma_1)) \lambda + K_4 K_2 K_3 K_6 K_1 \mu}, \\
 H^* &= \frac{\sigma (K_2 \gamma_2 K_5 + K_3 \gamma_1 \alpha) K_6 \lambda \Pi_H}{((K_4 K_3 K_6 K_1 - \sigma \theta K_5 (K_4 \tau_2 + \gamma_2 \tau_3)) K_2 - \alpha \sigma \theta K_3 (K_4 \tau_1 + \tau_3 \gamma_1)) \lambda + K_4 K_2 K_3 K_6 K_1 \mu}, \\
 R^* &= \frac{\Pi_H (K_5 (K_4 \tau_2 + \gamma_2 \tau_3) K_2 + \alpha K_3 (K_4 \tau_1 + \tau_3 \gamma_1)) \lambda \sigma}{(K_4 K_6 K_1 (\lambda + \mu) K_3 - \sigma \theta \lambda K_5 (K_4 \tau_2 + \gamma_2 \tau_3)) K_2 - \alpha \sigma \theta \lambda K_3 (K_4 \tau_1 + \tau_3 \gamma_1)}.
 \end{aligned} \tag{10}$$

3.4. Global stability of equilibrium point

To prove the global stability of the EE points, the following theorem is claimed.

Theorem 3 *The EE points, ε_1 , of the model (1) is globally asymptotically stable (GAS) if $R_0 > 1$ and unstable if $R_0 < 1$. \square*

PROOF Suppose the Lyapunov function given by $f = g_1 E + g_2 A + g_3 I + g_4 H$. Where,

$$g_1 = R_0, g_2 = \frac{\beta(K_4 + \eta_2 \gamma_2)}{K_3 K_4}, g_3 = \frac{\beta(K_4 + \eta_2 \gamma_1)}{K_2 K_4}, g_4 = \frac{\beta \eta_2}{K_4}.$$

The Lyapunov derivative is known as (dot stand for differentiation with respect to time, t)

$$\begin{aligned}
 \dot{f} &= g_1 \dot{E} + g_2 \dot{A} + g_3 \dot{I} + g_4 \dot{H}, \\
 &= g_1 [\beta(\eta_1 E + A + I + \eta_2 H) - K_1 E] + g_2 (\alpha \sigma E - K_2 A) + g_3 (\sigma K_5 E - Q_3 I) + g_4 (\gamma_1 A + \gamma_2 I - K_4 A) \\
 &= (g_1 \beta \eta_1 - g_1 K_1 + g_2 \alpha \sigma + g_3 \sigma G_5) E + (g_1 \beta - g_2 K_2 + g_4 \gamma_1) A + (g_1 \beta - g_3 K_3 + g_4 \gamma_2) I + (g_1 \beta \eta_2 - g_4 K_4) H,
 \end{aligned}$$

$\leq (R_0 - 1)(\eta_1 E + A + I + \eta_2 H) \leq 0$ if $R_0 \leq 1$, since $S \leq N = \frac{\Pi}{\mu}$ for all $t \in D$. Thus,

$\dot{f} \leq 0$ if $R_0 \leq 1$ with $\dot{f} = 0$ if and only if $E = A = I = H = 0$. Moreover, the biggest compact invariant region in $D = \left\{ (S, E, A, I, H, R) \in D : \dot{f} = 0 \right\}$ is the singleton E_0 . It shows from the LaSalle's Invariance Principle [16] that each solution of equations (1) with a starting point in D converges to DFE E_0 as $t \rightarrow \infty$. Substituting $E = A = I = H = 0$ into the equation of the model (1), gives $S(t) \rightarrow \frac{\Pi}{\mu}$ as $t \rightarrow \infty$.

Therefore, $(S, E, A, I, H, R) \rightarrow (\frac{\Pi}{\mu}, 0, 0, 0, 0, 0)$ as $t \rightarrow \infty$ for $R_0 \leq 1$, so that E_0 is GAS in D if $R_0 \leq 1$. ■

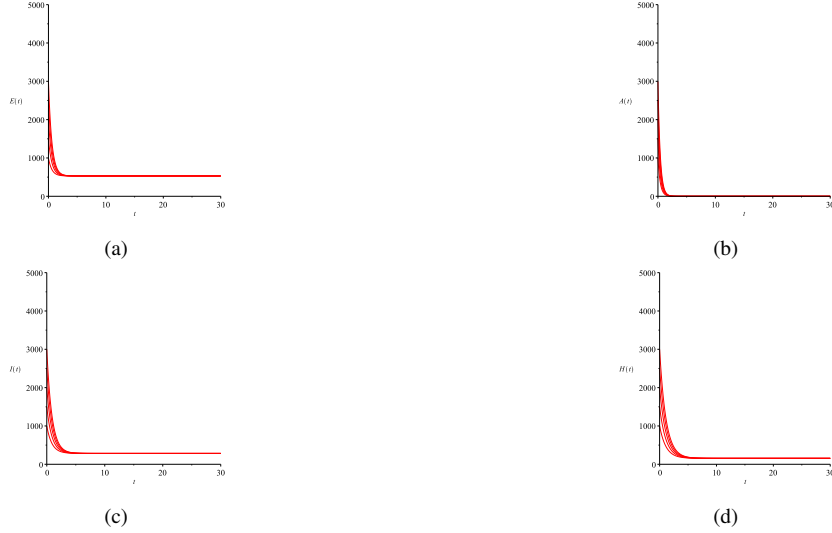


Fig. 2. Time series plot of the model (1) considering initial condition, using the estimated values (1) with $R_0 < 1$

4. Sensitivity analysis

In this section, local sensitivity indexes were evaluated in relation to the reproduction number, R_0 , for the biological parameters of the MTB infection. The model is analyzed by applying the method of forward sensitivity index. The optimization of the projected result is obtained by investigating the impacts and status of key control parameters and their relative effects on the control of the infection [17–19].

It is indicated by $\Gamma_{\beta}^{R_0}$ the normalized sensitivity index of the output R_0 with respect to a parameter (θ) , and is defined as

$$\chi_{\theta} = \Gamma_{\theta}^{R_0} = \frac{\theta}{R_0} \times \frac{\partial R_0}{\partial \theta}. \quad (11)$$

Using the parameter values defined above $\Pi = 53$, $\mu = 0.0047$, $\beta = 0.000535$, $\sigma = 0.001$, $\alpha = 0.00071$, $\tau_1 = 0.000453$, $\tau_2 = 0.000543$, $\tau_3 = 0.000234$, $\gamma_1 = 0.2849$, $\gamma_2 = 0.22806$, $\delta_1 = 0.0002$, $\delta_2 = 0.0003$, $\theta = 0.00271$, $\delta_3 = 0.0004$, the elasticity index values have been calculated (see Table 2 and Fig. 3).

From the elasticity investigation conducted above, one can see that if θ increases let say by 5% with the remaining parameters fixed, it attracts another 5% in R_0 . Similarly, an increase or decrease of any biological parameter of the model (1) will cause the increase or decrease in the reproduction number.

Table 2. Forward Normalized Sensitivity Indices

Parameter	Elasticity Indices	Elasticity index values
β	χ_{β}	0.470
Π	χ_{Π}	0.023
μ	χ_{μ}	0.500
θ	χ_{θ}	0.320
σ	χ_{σ}	0.011
α	χ_{α}	0.015
γ_1	χ_{γ_1}	0.543
γ_2	χ_{γ_2}	0.900
γ_3	χ_{γ_3}	-0.600
τ_1	χ_{τ_1}	-0.500
τ_2	χ_{τ_2}	-0.340
τ_3	χ_{τ_3}	-0.150

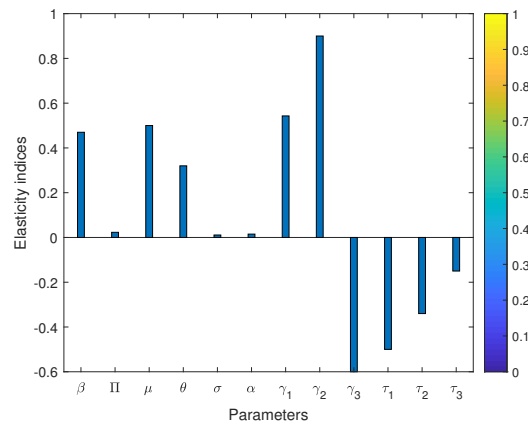


Fig. 3. Elasticity indices with respect to parameters presented in Table 2

5. Numerical simulations

Here, we performed numerical simulation for the MTB infection using the model (1). The parameters used are given in Table 1, and the results are demonstrated with control measures. From Figure 4, the susceptible individuals $S(t)$ increase, while exposed individuals decrease $E(t)$, which is plausibly due to the effect of awareness programs. In Figure 5, shows that asymptomatic individuals $A(t)$ and symptomatic individuals $I(t)$ decrease due to medication, campaign awareness and other control measures; a hospitalized compartment, $H(t)$, those who are hospitalized due to infection, decrease due to treatment, and the recovery compartment $R(t)$ increases.

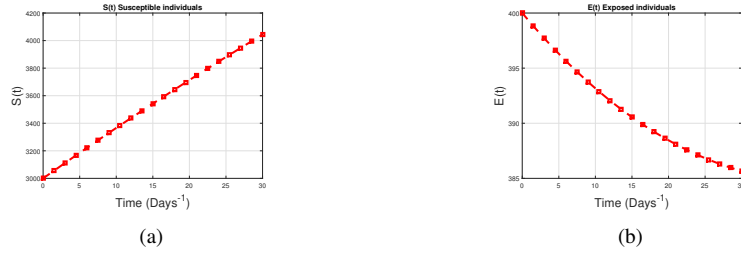
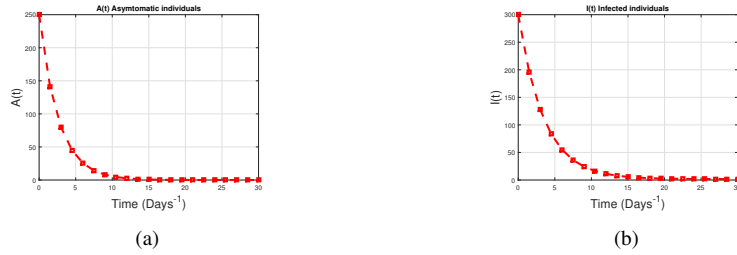
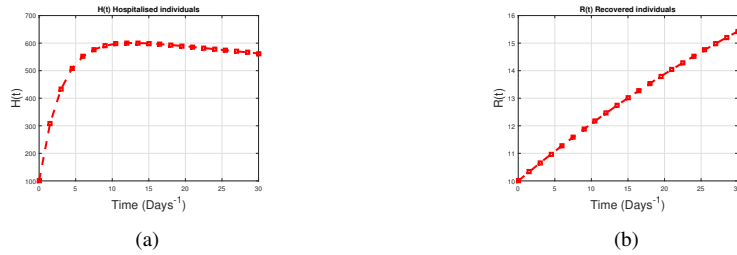
Fig. 4. Dynamical behaviour of Vulnerable humans $S(t)$ and that of Latent humans $E(t)$ with controlFig. 5. Dynamical behaviour of asymptomatic individuals $A(t)$ and that of infected individuals $I(t)$ with controlFig. 6. Dynamical behaviour of hospitalised individuals $H(t)$ and that of recovered individuals $R(t)$ with control

Table 3. Parameter values for Numerical Simulations

Parameter	Values	Units	Source
Π	53	Day ⁻¹	Assumed
μ	0.0047	Day ⁻¹	[1]
β	0.000535	Day ⁻¹	[1]
η_1	[0, 1]	Dimensionless	Assumed
η_2	[0, 1]	Dimensionless	Assumed
θ	0.00271	Day ⁻¹	Est. Using [1]
$\tau_i (i = 1, 2, 3)$	(0.000453, 0.000543, 0.000234)	Day ⁻¹	[1]
σ	(0.001)	Day ⁻¹	[20, 21]
$\delta_j (j = 1, 2)$	(0.0002, 0.0003)	Day ⁻¹	[1]

6. Conclusions

This research work presented an epidemic modelling study for the transmission dynamics of MTB infection in the human population. The model was qualitatively

analysed to examine the transmission dynamics of MTB disease and was used in curbing the transmission with consideration of different stages of the infection. The system exhibits two equilibrium points: the disease-free equilibrium point (DFE), which is locally asymptotically stable whenever the $R_0 < 1$, otherwise is unstable, and the endemic equilibrium. Numerical results also showed that the treatment, campaign awareness, and other possible measures are vital to control MTB infection in human geographical boundaries.

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