

ANALYSIS OF THE EFFECTS OF
MALNUTRITION ON THE SPREAD OF TUBERCULOSIS

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Abstract: We present a deterministic model for TB (Malnutrition impairs tuberculosis (TB) immunity) in a community in order to determine the effects of malnutrition in the spread of this disease. The important mathematical features of the tuberculosis model are thoroughly investigated. The epidemic threshold known as the basic reproduction number and the equilibria for the model are determined and their stabilities are analyzed. We perform sensitivity analysis on the key parameters that drive the disease dynamics in order to determine their relative importance to disease transmission and prevalence. The model is numerically analyzed to assess the effects of malnutrition on the transmission dynamics of tuberculosis. Numerical simulations suggest that an increase in susceptibility to TB due to malnutrition

results in an increase in the number of infectious individuals in a community. The results suggest that nutritional issues should be addressed in impoverished communities affected by tuberculosis in order to reduce the burden of the disease.

Key Words: tuberculosis model, malnutrition, susceptibility, reproduction number, equilibria, stability

1. Introduction

Tuberculosis is an old disease whose world-wide prevalence had been diminishing even before vaccination and prophylaxis strategies were firstly accomplished [1-3]. Its recent return in developing countries, mainly in Southeast Asia, have attracted renewed interest in it. The current world estimate of prevalence is about 33%, while the number of deaths per year that it is causing reaches more than 3 million people [4]. More than 36 million patients have been successfully treated via the World Health Organization (WHO) strategy for tuberculosis control since 1995 [5]. Despite predictions of a decline in global incidence, the number of new cases continues to grow, approaching 10 million in 2010 [4]. This rise has been attributed to the spread of HIV, the collapse of public health programs as well as the emergence of drug-resistant strains of *Mycobacterium tuberculosis* (Mtb). Depending on the kind and the intensity of immune response that the host immune system performs after initial infection with *M. tuberculosis* bacillus, the individual can suffer latent infection, in which the bacteria are under a growth-arrest regime and the individual neither suffer any clinical symptoms nor becomes infectious or active infection, where the host suffers clinical symptoms and can transmit the pathogen by air [6,7]. Latently infected individuals can, generally after an immune-depression episode, reach the active phase. Estimating the probability of developing direct active infection after a contact, or alternatively, the lifetime's risk for a latent infected individual to evolve into the active phase, are not easy tasks. However, it is generally accepted that only 5–10% of the infections directly produce active TB [6,7], while the ranges concerning the estimation of typical “half-life” of latent state rounds about 500 years [8].

Infectious diseases and malnutrition represent major burdens afflicting millions of people in developing countries. Both conditions affect individuals in industrialized nations, particularly the aged, the HIV-infected, and people with chronic diseases. The number of overweight or obese people is increasing worldwide, but so is the number who are underweight. The number nourished people has grown by an estimated 9% since 1990, exceeding a billion in 2009 [9]. Although, there are various factors which play a significant role on the spread of TB in the community such as HIV/AIDS, exogenous reinfections, alcohol, tobacco, diabetes, etc., it has long been known that there is an association between TB and malnutrition. Malnutrition enhances the development of active TB, and active TB makes malnutrition

worse [10-12]. Malnutrition profoundly affects cell-mediated immunity (CMI), and CMI is the principle host defense against TB. More than 500, 000 TB patients die annually in Africa where malnutrition is common. This disease is commonly associated with poverty and is prevalent in undernourished individuals. The prevalence of widespread malnutrition in the population may be expected to pose some special problems with regard to the control of TB in the developing countries from the larger point of view of prevention and therapeutic management of individual cases, from the narrower clinical point of view.

A vicious cycle is known to exist between TB, HIV and malnutrition such that one is promoting the other(s). Some of the key signs and symptoms of TB, e.g., anaemia, loss of lean and fat mass, are also signs of malnutrition. Tuberculosis results in anorexia, cachexia and generalized weakness. Nutritional deficiencies are generally associated with increased risk for and severity of tuberculosis by adversely affecting precisely those immunological mechanisms that are crucial for the successful control of mycobacterium, namely the functions of T-lymphocytes and a variety of phagocytic cells. There are several ways in which nutritional deficiencies could influence the prevention and management of TB. A central way in which malnutrition may change the pathogenesis of TB is to increase the risk of progression from TB infection to primary disease in the short term, or to increase the risk of reactivation of TB disease in the longer term. Furthermore, nutritional status may also influence the progression from TB infection to disease by altering the availability of essential nutrients to meet the metabolic needs of the pathogen and the individual. Additionally, concomitant malnutrition could diminish the pharmacodynamic effectiveness of anti-mycobacterial drug regimens, which must be taken for several months to cure the patient. Malnutrition-induced loss of some immune functions is reversed fairly rapidly upon correction of the nutritional deficiencies. Thus, nutritional intervention in combination with an appropriate pharmaceutical therapy, as is the case in HIV infected patients, could improve the outcome in malnourished TB patients. Malnutrition could also impair the protective efficacy of Bacillus Calmette-Guerin (BCG) vaccine, thereby increasing the disease burden in vaccinated populations that are nutritionally vulnerable or deficient.

A brief survey on previous studies provides the context of this paper. Zachariah et al. [13] has conducted a study on new patients registered with TB in a rural district of Malawi to determine (i) the prevalence of malnutrition on admission and (ii) the association between malnutrition and early mortality (defined as death within the first 4 weeks of treatment). There were included 1181 patients with TB (576 men and 605 women), whose overall rate of infection with human immunodeficiency virus (HIV) was 80%. 673 TB patients (57%) were malnourished on admission (body mass index [BMI] $< 18.5 \text{ kg/m}^2$). There were 259 patients (22%) with mild malnutrition (BMI $17.0 - 18.4 \text{ kg/m}^2$), 168 (14%) with moderate malnutrition (BMI $16.0 - 16.9 \text{ kg/m}^2$) and 246 (21%) with severe malnutrition (BMI $< 15.9 \text{ kg/m}^2$). 95 patients (8%) died during the first 4 weeks. Significant risk factors for early mortality

included increasing degrees of malnutrition, age >35 years, and HIV seropositivity. Among all the 1181 patients, 10.9% of the 414 patients with moderate to severe malnutrition died in the first 4 weeks compared with 6.5% of the 767 patients with normal to mild malnutrition (odds number 1.8, 95% confidence interval 1.1-2.7). In patients with TB, BMI $< 17.0 \text{ kg/m}^2$ is associated with an increased risk of early death. In their paper, Gupta et al. [14] found that nutritional supplementation may represent a novel approach for fast recovery in tuberculosis patients. In addition, raising nutritional status of population may prove to be an effective measure to control tuberculosis in underdeveloped areas of the earth. Paton et al. [15] performed the first known randomized controlled trial of nutritional supplementation in patients with tuberculosis and showed that in the initial stage there is a significant effect on lean mass and functional status.

A number of theoretical studies has been carried out on the mathematical modelling of TB transmission dynamics [8,16-19]. However, none of these studies has considered the effect of malnutrition on the transmission dynamics of TB. Since mathematical models on the effect of malnutrition in the spread of TB are lacking, it is therefore the intention of this study to investigate the impact of malnutrition on the transmission dynamics of TB in the community. The model incorporates some key epidemiological features of TB such as exogenous reinfections, chemoprophylaxis and treatment. The main objective in this study is to forecast future trends in the incidence of TB and also to quantify the association between malnutrition and TB in the community.

The paper is structured as follows. In the next section, our TB transmission model is formulated and results on the long-term dynamics are presented. Simulation results are presented in Section 3. Concluding remarks and discussions round up the paper.

2. The Model

The model sub-divides the human population into susceptible individuals ($S_i(t)$), latently-infected individuals ($E_i(t)$) and infectious individuals ($I_i(t)$) where $i = (1, 2)$ with $i = 1$ denoting nourished individuals and $i = 2$ denoting malnourished individuals. Thus, the total human population at time t is given by $N(t)$ where

$$N(t) = S_1(t) + E_1(t) + I_1(t) + S_2(t) + E_2(t) + I_2(t). \quad (1)$$

As a first step, we assume random mixing of the population, even though nourished and malnourished individuals may well have different mixing patterns. The potential effect of non-random mixing patterns will be addressed in the next study. It is assumed that susceptible humans are recruited into the population at a constant rate Λ . A proportion π of these individuals are assumed to be nourished (categorized

in the S_1 class) and the complementary proportion $(1 - \pi)$ are malnourished and are categorized in the S_2 class.

Transmission of *M. tuberculosis* occurs due to adequate contacts between susceptible and infectious individuals. Then, susceptible individuals acquire TB infection from individuals with active TB at a rate λ , given by

$$\lambda = \frac{\beta(I_1 + \varepsilon I_2)}{N}, \quad (2)$$

where β is the effective contact rate of nourished and malnourished infectious individuals that is sufficient to transmit infection to nourished and malnourished susceptible individuals, and ε models the increased susceptibility to TB infection of the malnourished infectious individuals.

We assume that chemoprophylaxis of latently infected individuals reduces their reactivation and that the initiation of therapeutics immediately removes individuals from the active status I_i and places them into a latent state E_i . We denote by r and γ the rates of chemoprophylaxis of latently-infected individuals and the treatment of infectious individuals, respectively. Thus, rE_i is the number of latently-infected individuals who received chemoprophylaxis. Nourished individuals become malnourished individuals at a constant rate α due to food shortages. In other words, individuals in the nourished classes S_1 , E_1 and I_1 may move to the malnourished classes S_2 , E_2 and I_2 , respectively, at a constant rate α . Also, we assume that individuals in the malnourished classes S_2 , E_2 and I_2 may move to the nourished classes S_1 , E_1 and I_1 , respectively, at a constant rate δ due to food abundance.

Nourished susceptible individuals are infected with *Mtb* at a rate λ . A proportion p of newly infected nourished susceptible individuals develops fast TB (development of active TB within the first five years following infection) and the complementary part $(1 - p)$ becomes latently infected. Latently infected nourished individuals who does not received effective chemoprophylaxis develop active TB through endogenous reactivation (most people have tuberculosis which can be activated in situations of malnutrition which turns off the production of cell-mediated immunity in the lungs, rendering the patient more susceptible to the development of progressive disease from latent *Mtb* infection [12]) and exogenous reinfections at rates $k(1 - r)$ and $\sigma(1 - r)\lambda$, respectively, with $\sigma \in (0, 1)$, since primary infection confers some degree of immunity (see [20], and the references therein). Secondary tuberculosis may follow reinfections or endogenous reactivation and knowledge about the relative importance of these mechanisms in specific communities are important possible drivers of the disease dynamics. After receiving an effective therapy, nourished infectious individuals leave the class (I_1) to the class (E_1) at a constant rate γ .

Malnourished susceptible individuals are infected with *Mtb* at a rate $\theta\lambda$ with $\theta > 1$, since malnutrition acts as a carrier of *Mtb* [10,21]. A proportion p of malnourished latently-infected individuals develops fast TB and the remainder $(1 - p)$ develop latent TB. Malnourished latently infected individuals develop active TB through

endogenous reactivation and exogenous re-infection at rates $\tau k(1-r)$ and $\theta\sigma(1-r)\lambda$, respectively. It is worth noting here that $\tau > 1$, since malnourished latently infected individuals tend to develop active TB at a faster rate than latently infected nourished individuals [10,22,23]. Also, $\sigma \in (0, 1)$ since primary infection confers some degree of immunity. Malnourished active TB patients have a reduced rate of recovery if they are put on treatment and move to the (E_2) class at a rate $\phi\gamma$ with $\phi \leq 1$.

Individuals in all sub-classes experience natural death at a constant rate μ . It is assumed that death from natural causes is not influenced by individuals's status (nourished or malnourished). Individuals with active TB experience disease induced death rates d and ηd for nourished and malnourished active TB patients, respectively. It is important to note here that $\eta > 1$ as malnutrition experience greater disease induced deaths than their corresponding non-malnutrition counterparts.

The structure of the model is shown in Fig. 1.

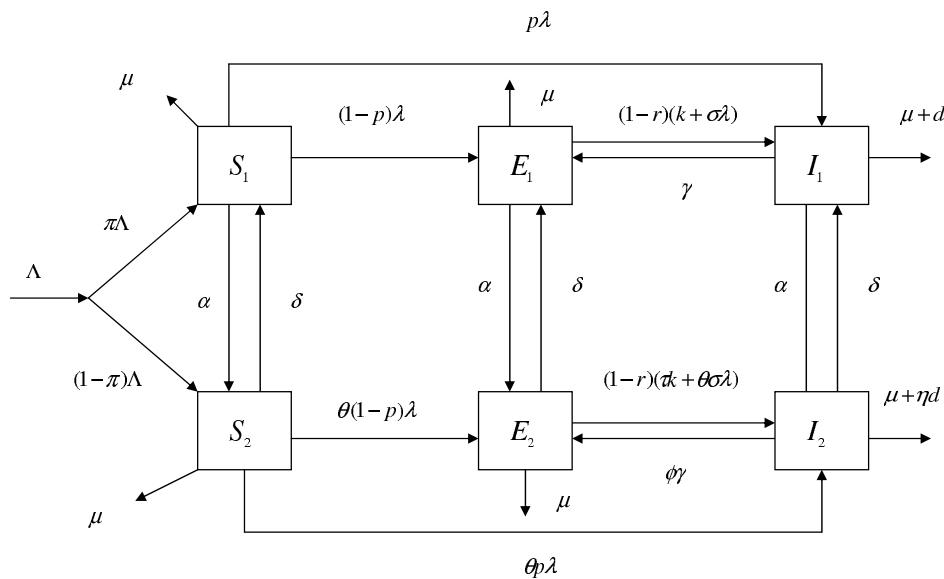


Figure 1: Structure of the model.

Putting the formulations and the assumptions together gives the following sys-

tem of differential equations:

$$\left\{ \begin{array}{l} S'_1 = \pi\Lambda + \delta S_2 - (\mu + \alpha + \lambda)S_1, \\ E'_1 = (1 - p)\lambda S_1 + \gamma I_1 + \delta E_2 - (1 - r)(k + \sigma\lambda)E_1 - (\mu + \alpha)E_1, \\ I'_1 = p\lambda S_1 + (1 - r)(k + \sigma\lambda)E_1 + \delta I_2 - (\mu + d + \gamma + \alpha)I_1, \\ S'_2 = (1 - \pi)\Lambda + \alpha S_1 - (\mu + \delta + \theta\lambda)S_2, \\ E'_2 = \theta(1 - p)\lambda S_2 + \phi\gamma I_2 + \alpha E_1 - (1 - r)(\tau k + \theta\sigma\lambda)E_2 - (\mu + \delta)E_2, \\ I'_2 = \theta p\lambda S_2 + (1 - r)(\tau k + \theta\sigma\lambda)E_2 + \alpha I_1 - (\mu + \delta + \phi\gamma + \eta d)I_2. \end{array} \right. \quad (3)$$

System (3) can be written in the following compact form:

$$\left\{ \begin{array}{l} x'(t) = \Gamma + A_x x(t) - \lambda \sum_{i=1}^2 B_i \langle e_i | x(t) \rangle, \\ y'(t) = \lambda \left[\sum_{i=1}^2 K_i \langle e_i | x(t) \rangle + B_3 \langle e_3 | y(t) \rangle + B_4 \langle e_4 | y(t) \rangle \right] + A_y y(t), \end{array} \right. \quad (4)$$

where $x(t) = (x_1(t), x_2(t))^T = (S_1(t), S_2(t))^T \in \mathbb{R}_+^2$, $y(t) = (y_1(t), y_2(t), y_3(t), y_4(t))^T = (E_1(t), I_1(t), E_2(t), I_2(t))^T \in \mathbb{R}_+^4$, $\Gamma = (\pi\Lambda, (1 - \pi)\Lambda)^T$, $\lambda = \langle B | y \rangle / N$, $B = (0, \beta, 0, \beta\epsilon)^T$, $B_1 = (1, 0)^T$, $B_2 = (0, \theta)^T$, $B_3 = (-\sigma(1 - r), \sigma(1 - r), 0, 0)^T$, $B_4 = (0, 0, -\theta\sigma(1 - r), \theta\sigma(1 - r))^T$, $e_1 = (1, 0)$, $e_2 = (0, 1)$, $e_3 = (1, 0, 0, 0)$, $e_4 = (0, 0, 1, 0)$, $K_1 = (1 - p, p, 0, 0)^T$, $K_2 = (0, 0, \theta(1 - p), \theta p)^T$,

$$A_x = \begin{pmatrix} -(\mu + \alpha) & \delta \\ \alpha & -(\mu + \delta) \end{pmatrix}, \quad A_y = \begin{pmatrix} -A_1 & \gamma & \delta & 0 \\ k(1 - r) & -A_2 & 0 & \delta \\ \alpha & 0 & -A_3 & \phi\gamma \\ 0 & \alpha & \tau k(1 - r) & -A_4 \end{pmatrix},$$

with

$$\begin{aligned} A_1 &= \mu + \alpha + k(1 - r), & A_2 &= \mu + d + \alpha + \gamma, \\ A_3 &= \mu + \delta + \tau k(1 - r) & \text{and} & \quad A_4 = \mu + \delta + \phi\gamma + \eta d. \end{aligned}$$

In Eq. (4), $\langle a | b \rangle = a^T b$ is the usual inner scalar product. Note that A_x and A_y are Metzler matrices. A Metzler matrix is a matrix with off-diagonal entries non-negative [24-26].

The parameter values used for numerical simulation are given in Table 1.

Table 1: Numerical values for the parameters of the model (3)

Definition	Symbols	Estimated(Range)	Source
Recruitment rate	Λ	397800/yr	[27]
Proportion of nourished individuals	π	0.7	Assumed
Transmission coefficient of infectious	β	Variable	Assumed
Natural mortality rate	μ	0.019896/yr	[27]
Endogenous reactivation rate	k	0.00013/yr	[16]
Chemoprophylaxis rate	r	0/yr	[28]
Treatment rate	γ	0.7372/yr	[28]
Protective factor for latently-infected individuals (E_1, E_2)	σ	0.7	Assumed
Modification parameter	θ	1.07	Assumed
Modification parameter	ε	1.05	Assumed
Modification parameter	τ	1.06	Assumed
Modification parameter	η	1.04	Assumed
Modification parameter	ϕ	0.75	Assumed
Rate of becoming malnourished	α	0.07/yr	Assumed
Rate of becoming nourished	δ	0.0701/yr	Assumed
TB induced mortality	d	0.0575/yr	Assumed
Rate of developing active TB among susceptibles (S_1, S_2)	p	0.015	Assumed

Due to lack of data, the parameters that are not estimated are assumed within realistic ranges (for the purpose of illustration) based on current understanding of the qualitative and the essential biological and epidemiological features of TB.

3. Analysis of the Model

3.1. Basic Properties

3.1.1. Positivity and Boundedness of Solutions

For model system (3) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all time. In other words, solutions of model system (3) with positive initial data remain positive for all time $t > 0$.

Theorem 1. : *Let the initial data be $S_1(0) > 0$, $E_1(0) > 0$, $I_1(0) > 0$, $S_2(0) > 0$, $E_2(0) > 0$ and $I_2(0) > 0$. Then, the solutions $(S_1, E_1, I_1, S_2, E_2, I_2)$ of*

model system (3) are positive for all $t > 0$. Furthermore,

$$\limsup_{t \rightarrow \infty} N(t) \leq \frac{\Lambda}{\mu}. \tag{5}$$

Proof: Suppose, for example, the variable S_1 becomes zero for some time $\bar{t} > 0$, i.e., $S_1(\bar{t}) = 0$, while all other variables are positive. Then, from the S_1 equation, we have $dS_1(\bar{t})/dt > 0$. Thus, $S_1(t) \geq 0$ for all $t > 0$. Similarly, it can be shown that all variables remain nonnegative for all $t > 0$.

Now, adding all the equations in the differential equation system (3) gives

$$N'(t) = \Lambda - \mu N - dI_1 - \eta dI_2. \tag{6}$$

It follows from Eq. (6) that

$$\Lambda - (\mu + d + \eta d)N(t) \leq N'(t) \leq \Lambda - \mu N(t).$$

Thus,

$$\frac{\Lambda}{\mu + d + \eta d} \leq \liminf_{t \rightarrow \infty} N(t) \leq \limsup_{t \rightarrow \infty} N(t) \leq \frac{\Lambda}{\mu}.$$

so that

$$\limsup_{t \rightarrow \infty} N(t) \leq \frac{\Lambda}{\mu}.$$

This completes the proof. □

3.1.2. Invariant Region

Model system (3) will be analyzed in a suitable region as follows. We first show that model system (3) is dissipative. That is all solutions are uniformly bounded in a proper subset $\Omega \subset \mathbb{R}_+^6$. Let $(S_1, E_1, I_1, S_2, E_2, I_2) \in \mathbb{R}_+^6$ be any solution with non-negative initial conditions.

Model system (3) has a varying population size ($N \neq 0$) and therefore a trivial equilibrium is not feasible. Let $\xi = \min(d, \eta d)$, then, from Eq. (3), it follows that

$$\begin{aligned} N'(t) &= \Lambda - \mu N - dI_1 - \eta dI_2, \\ &\leq \Lambda - \mu N(t) - \zeta(I_1(t) + I_2(t)), \\ &\leq \Lambda - \mu N(t). \end{aligned} \tag{7}$$

So that (cf. [29])

$$0 \leq N(t) \leq \frac{\Lambda}{\mu} + \left(N(0) - \frac{\Lambda}{\mu} \right) e^{-\mu t}, \tag{8}$$

where $N(0)$ represents the value of $N(t)$ evaluated at the initial values of the respective variables. The lower limit comes naturally from the fact that the model variables and parameters are non-negative ($t \geq 0$), since they monitor human populations. Thus, as $t \rightarrow \infty$, $0 \leq N(t) \leq \Lambda/\mu$. Therefore, all feasible solutions of model system (3) enter the region

$$\Omega = \left\{ (S_1, E_1, I_1, S_2, E_2, I_2) \in \mathbb{R}_+^6, N(t) \leq \frac{\Lambda}{\mu} \right\}. \quad (9)$$

Thus, Ω is positively invariant (it can also be shown that Ω is attracting) and it is sufficient to consider solutions of model system (3) in Ω . Existence, uniqueness and continuation results for model system (3) hold in this region. It can be shown that all solutions of model system (3) starting in Ω remain in Ω for all $t \geq 0$. All parameters and state variables for model system (3) are assumed to be non-negative for $t \geq 0$.

3.2. Stability of the Disease-Free Equilibrium (DFE)

The disease-free equilibrium of model system (4) is given by $Q_0 = (x^0, 0)$ where $x^0 = (-A_x)^{-1}\Gamma$. With the notations of Eq. (4), the disease-free equilibrium of model system (3) is

$$Q_0 = (S_1^0, E_1^0, I_1^0, S_2^0, E_2^0, I_2^0) = \left(\frac{\Lambda(\pi\mu + \delta)}{\mu(\mu + \alpha + \delta)}, 0, 0, \frac{\Lambda[\alpha + \mu(1 - \pi)]}{\mu(\mu + \alpha + \delta)}, 0, 0 \right). \quad (10)$$

It can be shown that Q_0 attracts the region:

$$\Omega_{Q_0} = \{(S_1, S_2, E_1, E_2, I_1, I_2) \in \Omega, E_1 = E_2 = I_1 = I_2 = 0\}. \quad (11)$$

3.2.1. The Basic Reproduction Number and its Analysis

The linear stability of Q_0 is governed by the basic reproductive number \mathcal{R}_0 [30,31]. The stability of this equilibrium will be investigated using the next generation operator (van den Driessche and Watmough, 2002). Using the notations in van den Driessche and Watmough [31] for model system (4), the matrices F and V for the new infection terms and the remaining transfer terms are, respectively, given by

$$F = \frac{1}{N_0} \sum_{i=1}^2 \mathcal{K}_i B S_i^0 \quad \text{and} \quad V = -A_y,$$

where $N_0 = \Lambda/\mu$, giving

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{1}{N_0} \sum_{i=1}^2 \langle B | (-A_y)^{-1} \mathcal{K}_i \rangle S_i^0, \quad (12)$$

where ρ represents the spectral radius. We use the expression $(-A_y^{-1})$ to emphasize that $(-A_y^{-1}) \geq 0$ because the matrix A_y is Metzler stable [24-26].

Thus, using Theorem 2 of van den Driessche and Watmough [31] yields the following result.

Lemma 1. : *The disease-free equilibrium Q_0 of model system (4) is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The basic reproductive number measures the average number of new infections generated by a single infected individual in a completely susceptible population. Thus, Theorem 1 implies that TB can be eliminated from the community (when $\mathcal{R}_0 < 1$) if the initial sizes of the sub-populations of the model are in the basin of attraction of the disease-free equilibrium. Now, let us analyze the basic reproduction number \mathcal{R}_0 .

We first suppose that every person is well-nourished, which is typical for some regions of the world. In this case, the disease-free equilibrium Q_0 will have $S_2^0 = \frac{\Lambda[\alpha + \mu(1 - \pi)]}{\mu(\mu + \alpha + \delta)} = 0$ which implies that $\alpha = 0$ and $\pi = 1$, and the basic reproduction number, \mathcal{R}_0 becomes the general treatment-induced reproduction number given by

$$\mathcal{R}_0^1 = \frac{\beta[p\mu + k(1 - r)]}{(\mu + d)[\mu + k(1 - r)] + \gamma\mu}. \quad (13)$$

From of above expression, on can easily see that when the treatment rate γ increasing, the basic reproduction number \mathcal{R}_0^1 decreases. This means that the treatment of TB infectives in a non-malnutrition population would have a positive impact in TB control.

Now suppose that every person is not well-nourished which is typical for some African countries. In this case, the disease-free equilibrium Q_0 will have $S_2^0 = \frac{\Lambda(\pi\mu + \delta)}{\mu(\mu + \delta + \alpha)} = 0$ which implies that $\pi = \delta = 0$. As such the basic reproduction number, \mathcal{R}_0 becomes the undernutrition-induced basic reproduction number for TB given by

$$\mathcal{R}_0^2 = \frac{\beta\epsilon\theta[p\mu + \tau k(1 - r)]}{(\mu + \eta d)[\mu + \tau k(1 - r)] + \mu\phi\gamma}. \quad (14)$$

Note that the above expression of the basic reproduction number will decrease when the treatment rate γ increases. But, when the reduced rate of recovery ϕ decreases, the basic reproduction number increases. Then treatment of TB infectives will have beneficial effects on malnourished infectious populations if the reduced rate of recovery is large. Now, we have to compare the basic reproduction number \mathcal{R}_0^1 and the undernutrition induced reproduction number \mathcal{R}_0^2 . Subtracting \mathcal{R}_0^1 from \mathcal{R}_0^2 , one has

$$\mathcal{R}_0^2 - \mathcal{R}_0^1 = \beta \frac{A_0}{(\mu + \eta d)(\mu + \tau k)(\mu + d)(\mu + k)}, \quad (15)$$

where

$$\begin{aligned} A_0 &= \mu[p\mu^2 + \tau k^2(1-r)^2](\varepsilon\theta - 1) + [pd\mu^2 + \tau\mu\gamma k(1-r) + d\tau k^2(1-r)^2](\varepsilon\theta - \eta) \\ &+ \mu pdk(1-r)(\varepsilon\theta - \eta\tau) + p\mu^2\gamma(\varepsilon\theta - \phi) + \mu dk(1-r)(\varepsilon\theta\tau - \eta) \\ &+ \mu^2 k(1-r)(\varepsilon\theta\tau - 1) + \mu\gamma k(1-r)(\varepsilon\theta\tau - \phi) + p\mu^2 k(1-r)(\varepsilon\theta - \tau). \end{aligned}$$

All the terms in Eq. (15) are positive except for $\varepsilon\theta - \eta$, $\varepsilon\theta - \tau\eta$, $\varepsilon\theta\tau - \eta$ and $\varepsilon\theta - \tau$. But these four negative expressions are dominated by the positive ones (based on the particular parameters chosen in this study), and consequently $\mathcal{R}_0^2 - \mathcal{R}_0^1 > 0$ (which excludes any possibility that malnourished may reduce transmission of TB). Thus, in this case, malnourished promotes the transmission and disease progression of TB. This result is solely driven by the choice of the model parameters and, therefore, $\mathcal{R}_0^2 < \mathcal{R}_0^1$ may occur in some circumstances, especially with the modifications parameters τ , θ , η and ϕ which are intrinsically difficult to estimate. So, what one can say for sure is that the first, fourth, sixth and seventh terms in the expression of A_0 in Eq. (15) are positive. The remaining terms could be negative if η was to be very large for example, in which case the disease induced death of malnutrition is increased. This could reduce the disease spread because it would be reducing the infective population before they could spread the disease, thereby making $\mathcal{R}_0^2 < \mathcal{R}_0^1$.

Figures 2-4 present the 3-D and contour plot showing the effects of the susceptibility to TB θ , proportion of nourished individuals in the population π , the rate at which nourished individuals become malnourished individuals α and the rate at which malnourished individuals become nourished individuals δ on the basic reproduction number \mathcal{R}_0 . All other parameters are as in Table 1.

In Fig. 2, we illustrate the effect of the parameters θ and π on the basic reproduction number \mathcal{R}_0 when $\beta = 1.5 \times 10^{-6}$. It clearly appears that an increase susceptibility to TB due to malnutrition θ results in an increase in \mathcal{R}_0 . One can also observe that \mathcal{R}_0 decreases if π increases (see Fig. 2(a)) even in the case of large values of θ . This means that if π is sufficiently large, TB infection could be eliminated even if θ is large. This means that the abundance of food in combination with treatment can reduce the burden of TB.

Figure 3 shows the effects of θ and α on the basic reproduction number \mathcal{R}_0 when $\beta = 1.3 \times 10^{-6}$. It shows that for the chosen parameter values, if the susceptibility to TB due to malnutrition does not exceed 1.15 ($\theta < 1.15$), then TB can be controlled irrespective of the value of α . The infection will equally persist for $\theta > 1.15$.

The combined effects of θ and δ on the basic reproduction number \mathcal{R}_0 when $\beta = 1.3 \times 10^{-6}$ are shown in Fig. 4. This figure suggests that whenever more individuals in the community change their food habit by nourishing better, this may influence the spread of TB in the community. But if the reverse is true, with

the basic reproduction number greater than unity, then a number of factors may play a crucial role on the spread of TB.

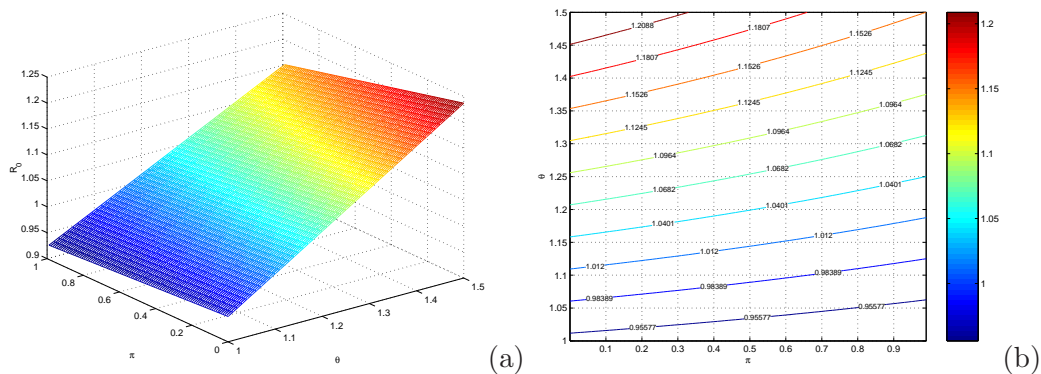


Figure 2: (a) 3-D and (b) contour plot showing the effect of varying the parameters θ and π on the basic reproduction number \mathcal{R}_0 when $\beta = 1.5 \times 10^{-6}$. All other parameters are as in Table 1.

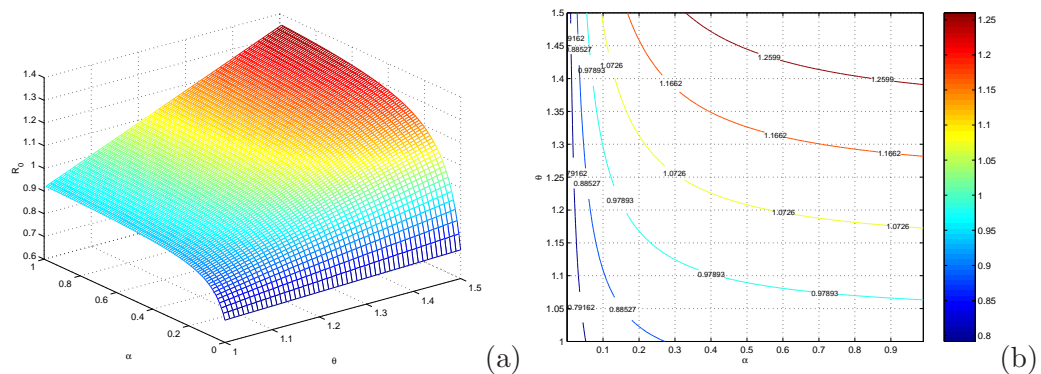


Figure 3: (a) 3-D and (b) contour plot showing the effect of varying the parameters θ and α on the basic reproduction number \mathcal{R}_0 when $\beta = 1.3 \times 10^{-6}$. All other parameters are as in Table 1.

3.2.2. Sensitivity Analysis

Sensitivity analysis is used to determine the relative importance of model parameters to TB transmission and its prevalence. We perform the analysis by calculating the sensitivity indices of the basic reproduction number, \mathcal{R}_0 . According to Chitnis et al. [33], sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values, since there are usually uncertainties in data

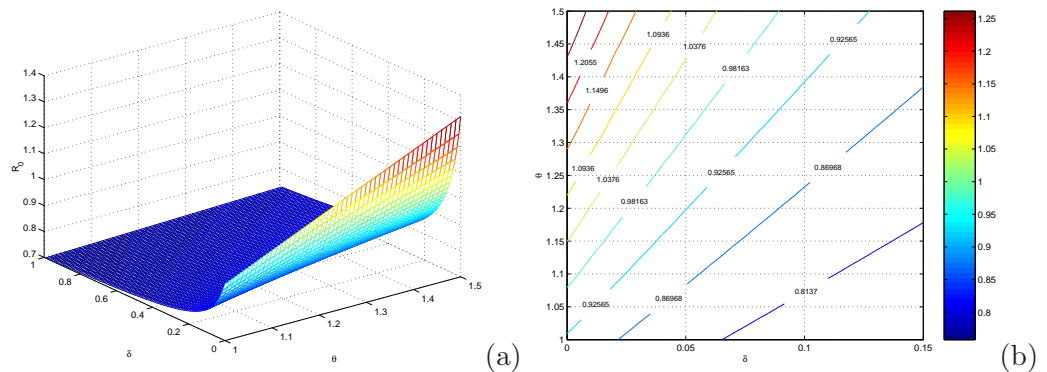


Figure 4: (a) 3-D and (b) contour plot showing the effects of varying the parameters θ and δ on the basic reproduction number \mathcal{R}_0 when $\beta = 1.3 \times 10^{-6}$. All other parameters are as in Table 1.

collection and estimated values. We are thus interested in parameters that significantly affect the basic reproduction number, since these are the parameters that should be taken into consideration when considering intervention strategies. Sensitivity analysis also permits us to measure the relative change in a state variable when a parameter changes. The normalized forward sensitivity index of a variable to a parameter is the number of the relative change in the variable to the relative change in the parameter. Since the basic reproduction number is a differentiable function of the parameters, the sensitivity index may alternatively be defined using partial derivatives. For instance, the computation of the sensitivity index of \mathcal{R}_0 with respect to β using the parameter values in Table 2 is given by

$$\prod_{\beta}^{\mathcal{R}_0} = \left(\frac{\partial \mathcal{R}_0}{\partial \beta} \right) \left(\frac{\beta}{\mathcal{R}_0} \right) = 1 > 0. \tag{16}$$

This shows that \mathcal{R}_0 is an increasing function of β and the parameter β has a strong influence on the spread of TB. We tabulate the indices of the remaining parameters in Table 2. From Table 2, parameters whose sensitivity indices have negative signs decrease the value of the basic reproduction number as their values increase, while those with positive signs increase the value of \mathcal{R}_0 as they increase. Those with no signs have no effect on the value of the basic reproduction number. The system is most sensitive to μ , followed by π . It is important to note that increasing (decreasing) μ by 10% decreases (increases) \mathcal{R}_0 by 0.055%. However, increasing (decreasing) the parameter β by 10% increases (decreases) \mathcal{R}_0 by 10%.

Table 2: Sensitivity indices for the basic reproduction number \mathcal{R}_0

Parameter	Index	Parameter	Index	Parameter	Index
β	1	θ	0.538	Λ	0
ε	0.5633	π	-0.0221	p	0.6892
k	0.3123	τ	0.1796	η	0
σ	0	d	0	r	0
γ	0.006	δ	0.5296	α	0.6658
ϕ	0.0029	μ	-0.0055		

3.2.3. Local Stability of the Disease-Free Equilibrium

Using a theorem from Castillo-Chavez et al. [33], we now show that the disease-free equilibrium may not be globally asymptotically stable in the case that the basic reproduction number is less than unity ($\mathcal{R}_0 < 1$).

Following Castillo-Chavez et al. [33], we rewrite model system (3) as

$$\begin{cases} X'(t) = FX, Y, \\ Y'(t) = G(X, Y), \quad G(X, 0) = 0, \end{cases} \tag{17}$$

where $X \in \mathbb{R}_+^2$ is the number of nourished and malnourished susceptible individuals and $Y \in \mathbb{R}_+^4$ denoting (its components) the number of nourished and malnourished infected individuals including latent and infectious individuals. The DFE is now denoted by $Q_0 = (X_0, 0)$ where $X_0 = \left(\frac{\Lambda(\pi\mu + \delta)}{\mu(\mu + \delta + \alpha)}, \frac{\Lambda[\alpha + \mu(1 - \pi)]}{\mu(\mu + \alpha + \delta)} \right)$.

The conditions (H_1) and (H_2) below must be met to guarantee the global asymptotic stability of Q_0 .

$$H_1 : \quad \text{For } X'(t) = F(X, 0), \quad X_0 \text{ is globally asymptotically stable (GAS),}$$

$$H_2 : \quad G(X, Y) = BY - \hat{G}(X, Y), \quad \hat{G}(X, Y) \geq 0 \quad \text{for } (X, Y) \in \Omega, \tag{18}$$

where $B = D_Y G(X_0, 0)$ is an M-matrix (the off diagonal elements of B are non-negative) and Ω is the region where the model makes biological sense. We refer the reader to Refs. [24-26] for more details about the properties of a M-matrix. If model system (3) satisfies the conditions in (18), then the following result holds.

Theorem 2. : *The fixed point $Q_0 = (X_0, 0)$ is a globally asymptotically stable equilibrium of model system (3) provided that $\mathcal{R}_0 < 1$ and the assumptions in Eq. (18) are satisfied.*

Proof in Lemma 1, Q_0 is locally asymptotically stable for $\mathcal{R}_0 < 1$.

Consider

$$F(X, 0) = \begin{bmatrix} \pi\Lambda + \delta S_2 - (\mu + \alpha + \lambda)S_1 \\ (1 - \pi)\Lambda + \alpha S_1 - (\mu + \delta + \lambda)S_2 \end{bmatrix},$$

$$B = \begin{bmatrix} -A_1 & (1-p)\beta \frac{\pi\mu + \delta}{\mu + \delta + \alpha} + \gamma & 0 & (1-p)\varepsilon\beta \frac{\pi\mu + \delta}{\mu + \delta + \alpha} \\ k(1-r) & p\beta \frac{\pi\mu + \delta}{\mu + \delta + \alpha} - A_2 & 0 & p\varepsilon\beta \frac{\pi\mu + \delta}{\mu + \delta + \alpha} + \delta \\ \alpha & \theta(1-p)\beta \frac{\alpha + \mu(1-\pi)}{\mu + \alpha + \delta} & -A_3 & \theta(1-p)\varepsilon\beta \frac{\alpha + \mu(1-\pi)}{\mu + \alpha + \delta} \\ 0 & \theta p\beta \frac{\alpha + \mu(1-\pi)}{\mu + \alpha + \delta} & \tau k(1-r) & \theta p\varepsilon\beta \frac{\alpha + \mu(1-\pi)}{\mu + \alpha + \delta} - A_4 \end{bmatrix}.$$

Thus,

$$\begin{aligned} \widehat{G}(X, Y) &= \begin{pmatrix} \widehat{G}_1(X, Y) \\ \widehat{G}_2(X, Y) \\ \widehat{G}_3(X, Y) \\ \widehat{G}_4(X, Y) \end{pmatrix}, \\ &= \begin{pmatrix} (1-p)\lambda N \left(\frac{\pi\mu + \delta}{\mu + \delta + \alpha} - \frac{S_1}{N} \right) + \sigma\lambda(1-r)E_1 \\ p\lambda N \left(\frac{\pi\mu + \delta}{\mu + \delta + \alpha} - \frac{S_1}{N} \right) - \sigma\lambda(1-r)E_1 \\ \theta(1-p)\lambda N \left(\frac{\alpha + \mu(1-\pi)}{\mu + \alpha + \delta} - \frac{S_2}{N} \right) + \theta\sigma\lambda(1-r)E_2 \\ \theta p\lambda N \left(\frac{\alpha + \mu(1-\pi)}{\mu + \alpha + \delta} - \frac{S_2}{N} \right) - \theta\sigma\lambda(1-r)E_2 \end{pmatrix}. \end{aligned}$$

The sign of $\widehat{G}_i(X, Y)$, $i = 1, \dots, 4$ is not obvious, but based on the model parameters, $G(X, Y)$ is neither positive nor equal to zero. Condition (H_2) in (18) is therefore violated and as such, Q_0 may not be a globally asymptotically stable. But, in the absence of exogenous re-infections, Q_0 is globally asymptotically stable. This achieved the proof. □

3.3. Endemic Equilibria and Stability Analysis

Model system (3) has basically three possible endemic equilibria, that is nourished only endemic equilibrium, malnourished only endemic equilibrium and the equilibrium point where both nourished and malnourished co-exist.

3.3.1. Nourished-Only Equilibrium

This equilibrium is $Q^* = (S_1^*, E_1^*, I_1^*, 0, 0, 0)$. Expressing S_1^* , E_1^* and I_1^* in terms

of the force of infection at the steady state λ^* gives

$$S_1^* = \frac{\Lambda}{\mu + \lambda^*}, \quad E_1^* = \frac{\Lambda\lambda^*[(1-p)(\beta\mu + d\lambda^*) + \gamma(\mu + \lambda^*)]}{(\mu + \lambda^*)(\beta\mu + d\lambda^*)[B_1 + \sigma(1-r)\lambda^*]} \quad \text{and} \quad I_1^* = \frac{\Lambda\lambda^*}{\beta\mu + d\lambda^*}, \tag{19}$$

where $B_1 = [\mu + k(1-r)]$. In Eq. (19), λ^* satisfies the following quadratic equation:

$$a_2(\lambda^*)^2 + a_1\lambda^* + a_0 = 0, \tag{20}$$

where

$$\begin{aligned} a_2 &= \sigma\mu(1-r), \\ a_1 &= (\mu + d)(1-r)(\sigma\mu + k) - \beta\mu\sigma - d[p\mu + k(1-r)], \\ a_0 &= [(\mu + d)[\mu + k(1-r)] + \mu\gamma](1 - \mathcal{R}_0^1), \end{aligned}$$

with \mathcal{R}_0^1 defined as in Eq. (13). The quadratic equation (20) can be analyzed for the possibility of multiple endemic equilibria. It is worth noting that the coefficient a_2 is always positive, and a_0 is positive (negative) if \mathcal{R}_0^1 is less than (greater than) unity, respectively.

Solving the quadratic equation (20) yields

$$\lambda^* = \frac{-a_1 + \sqrt{a_1^2 - 4a_0a_2}}{2a_2}, \tag{21}$$

and the remaining one root is complex roots which are discarded because we are dealing with a population of individuals and is always positive. We only consider conditions for a_2 , a_1 and a_0 which gives us $a_1^2 - 4a_0a_2 \geq 0$ and a positive λ^* since a negative force of infection is epidemiologically irrelevant. Note that $a_0 < 0$ whenever $\mathcal{R}_0^1 > 1$. This implies that $a_1^2 - 4a_0a_2 > 0$. Also, one has that $\sqrt{a_1^2 - 4a_0a_2} > a_1$ which leads to a positive λ^* . Then, we have proved the following result.

Lemma 2. : *Model system (3) without malnutrition have a unique endemic equilibrium whenever $\mathcal{R}_0^1 > 1$.*

In order to analyze the stability of the endemic equilibrium point, we make use of the Centre Manifold theory [34] as described by Theorem 4.1 of Castillo-Chavez and Song [18], stated below (Theorem 3) for convenience, to establish the local asymptotic stability of the nutrition only endemic equilibrium. To apply this theory, the following simplification and change of variables are made first of all. Let $z_1 = S_1$, $z_2 = E_1$ and $z_3 = I_1$ so that $N = z_1 + z_2 + z_3$. Further, by using vector notation $z = (z_1, z_2, z_3)^T$, the TB (3) without malnutrition can be written in the

form $\dot{z} = f(z)$, with $f = (f_1, f_2, f_3)^T$, as follows:

$$\begin{cases} z'_1 &= f_1 = \Lambda - (\mu + \lambda)z_1, \\ z'_2 &= f_2 = (1 - p)\lambda z_1 + \gamma z_3 - (1 - r)\sigma\lambda z_2 - A_1 z_2, \\ z'_3 &= f_3 = p\lambda z_1 + (1 - r)(k + \sigma\lambda)z_2 - A_2 z_3, \end{cases} \quad (22)$$

where $A_1 = \mu + k(1 - r)$, $A_2 = \mu + d + \gamma$ and

$$\lambda = \frac{\beta z_3}{z_1 + z_2 + z_3}.$$

System (22) has a DFE given by $Q_0^1 = (\Lambda/\mu, 0, 0)$. The Jacobian of system (22), at the DFE Q_0^1 , is given by

$$J(Q_0^1) = \begin{pmatrix} -\mu & 0 & -\beta \\ 0 & -A_1 & \gamma + \beta(1 - p) \\ 0 & k(1 - r) & \beta p - A_2 \end{pmatrix}.$$

Consider, next, the case when $\mathcal{R}_0^1 = 1$.

Suppose, further, that $\beta = \beta^*$ is chosen as a bifurcation parameter. Solving for β from $\mathcal{R}_0^1 = 1$ gives

$$\beta = \frac{(\mu + d)[\mu + k(1 - r)] + \mu\gamma}{p\mu + k(1 - r)}.$$

It follows that the Jacobian ($J(Q_0^1)$) of system (22) at the DFE Q_0^1 , with $\beta = \beta^*$, denoted by J_{β^*} has a simple zero eigenvalue (with all other eigenvalues having negative real parts). Hence, the Centre Manifold theory [34] can be used to analyze the dynamics of system (22). In particular, the theorem in Castillo and Song [18], reproduced below for convenience, will be used to show that when $\mathcal{R}_0^1 > 1$, there exists a unique endemic equilibrium of system (22) (as shown in Lemma 1) which is locally asymptotically stable for \mathcal{R}_0^1 near 1 under certain condition.

Theorem 3. (Castillo-Chavez & Song [18]): Consider the following general system of ordinary differential equations with a parameter ϕ :

$$\frac{dz}{dt} = f(z, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \rightarrow \mathbb{R} \quad \text{and} \quad f \in C^2(\mathbb{R}^n, \mathbb{R}), \quad (23)$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ for all ϕ) and assume

1. $A = D_z f(0, 0) = \left(\frac{\partial f_i}{\partial z_j}(0, 0) \right)$ is the linearization matrix of system (23) around the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

2. Matrix A has a right eigenvector u and a left eigenvector v (each corresponding to the zero eigenvalue).

Let f_k be the k^{th} component of f and

$$a = \sum_{k,i,j=1}^n v_k u_i u_j \frac{\partial^2 f_k}{\partial z_i \partial z_j}(0, 0),$$

$$b = \sum_{k,i=1}^n v_k u_i \frac{\partial^2 f_k}{\partial z_i \partial \phi}(0, 0),$$

then, the local dynamics of the system around the equilibrium point 0 is totally determined by the signs of a and b .

1. $a > 0, b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative, locally asymptotically stable equilibrium;
2. $a < 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable equilibrium, and there exists a positive unstable equilibrium;
3. $a > 0, b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;
4. $a < 0, b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.

Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

In order to apply the above theorem, the following computations are necessary (it should be noted that we use β^* as the bifurcation parameter, in place of ϕ in Theorem (Castillo-Chavez & Song [18])).

Eigenvectors of J_{β^*} : For the case when $\mathcal{R}_0^1 = 1$, it can be shown that the Jacobian of system (22) at $\beta = \beta^*$ (denoted by J_{β^*}) has a right eigenvector (corresponding to the zero eigenvalue), given by $U = (u_1, u_2, u_3)^T$, where,

$$\begin{cases} u_1 = -\frac{\beta u_3}{\mu}, \\ u_2 = \frac{[\gamma + \beta(1-p)]u_3}{A_1}, \\ u_3 = u_3 > 0. \end{cases} \quad (24)$$

Similarly, the components of the left eigenvectors of J_{β^*} (corresponding to the zero eigenvalue), denoted by $V = (v_1, v_2, v_3)^T$, are given by,

$$\begin{cases} v_1 = 0, \\ v_2 = \frac{k(1-r)v_3}{A_1}, \\ v_3 = v_3 > 0. \end{cases} \tag{25}$$

Computation of b: For the sign of b , it can be shown that the associated non-vanishing partial derivatives of f are

$$\frac{\partial^2 f_1}{\partial z_3 \partial \beta^*}(0, 0) = -1 \quad \frac{\partial^2 f_2}{\partial z_3 \partial \beta^*}(0, 0) = p - 1 \quad \text{and} \quad \frac{\partial^2 f_3}{\partial z_3 \partial \beta^*}(0, 0) = p.$$

Substituting the respective partial derivatives into the expression

$$b = v_2 \sum_{i=1}^3 u_i \frac{\partial^2 f_3}{\partial z_i \beta^*}(0, 0) + v_3 \sum_{i=1}^3 u_i \frac{\partial^2 f_4}{\partial z_i \beta^*}(0, 0),$$

gives

$$b = \frac{[p\mu + k(1-r)]u_3v_3}{A_1} > 0. \tag{26}$$

Computation of a: For system (22), the associated non-zero partial derivatives of f (at the DFE Q_0^1) are given by

$$\begin{aligned} \frac{\partial^2 f_2}{\partial z_3 \partial z_1} &= \frac{\beta^*(1-p)}{N_0}, \\ \frac{\partial^2 f_2}{\partial z_3 \partial z_2} &= -\frac{\beta^*\sigma(1-r)}{N_0} - \frac{\beta^*(1-p)}{N_0}, \quad \frac{\partial^2 f_2}{\partial z_3^2} = -\frac{\beta^*(1-p)}{N_0}, \\ \frac{\partial^2 f_3}{\partial z_3 \partial z_1} &= \frac{\beta^*p}{N_0}, \quad \frac{\partial^2 f_3}{\partial z_3 \partial z_2} = \frac{\beta^*\sigma(1-r)}{N_0} - \frac{\beta^*p}{N_0}, \quad \frac{\partial^2 f_3}{\partial z_3^2} = -\frac{\beta^*p}{N_0}, \end{aligned}$$

where $N_0 = \Lambda/\mu$. Then, it follows that

$$\begin{aligned} a &= v_2 \sum_{i,j=1}^3 u_i u_j \frac{\partial^2 f_2}{\partial z_i \partial z_j}(0, 0) + v_3 \sum_{i,j=1}^3 u_i u_j \frac{\partial^2 f_3}{\partial z_i \partial z_j}(0, 0), \\ &= \frac{\beta^*u_3^2v_3}{A_1^2N_0\mu} [-[p\mu + k(1-r)][A_1(\beta^* + \mu) + \mu[\gamma + \beta^*(1-p)]] \\ &\quad + \sigma(1-r)[\gamma + \beta^*(1-p)]\mu^2], \end{aligned}$$

so that the bifurcation coefficient $a > 0$ if and only if

$$\sigma > \frac{[p\mu + k(1 - r)][A_1(\beta^* + \mu) + \mu[\gamma + \beta^*(1 - p)]]}{(1 - r)[\gamma + \beta^*(1 - p)\mu]} \tag{27}$$

Thus, $b > 0$ and $a > 0$ or $a < 0$ depending on whether inequality (27) is satisfied. This sign of b may be expected in general for epidemic models because, in essence, using β as a bifurcation parameter often ensures $b > 0$. Using Theorem 3 items (i) and (iv), we established Theorem 4.

Theorem 4. : *If condition (27) is satisfied, $a > 0$, then, system (22) without malnutrition undergoes a backward bifurcation at $\mathcal{R}_0^1 = 1$, otherwise $a < 0$ and a unique endemic equilibrium Q^* guaranteed by Lemma 2 is locally asymptotically stable for $\mathcal{R}_0^1 > 1$, but close to 1.*

The phenomenon of backward bifurcation in disease models, where a stable endemic equilibrium coexists with a stable disease-free equilibrium when the associated reproduction number is less than unity, has important implications for disease control [35]. In such a scenario, the classical requirement of the reproduction number being less than unity becomes only a necessary, but not sufficient condition for disease elimination. For $a < 0$, the model exhibits a forward bifurcation. The bifurcations which occur for different signs of a are shown in Fig. 5.

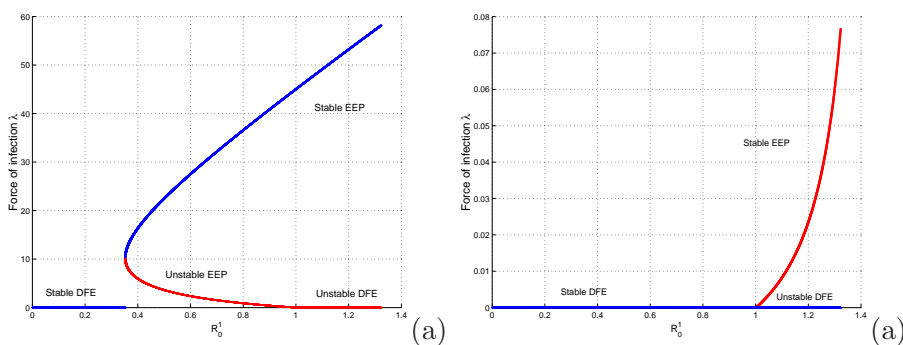


Figure 5: Bifurcation diagram for system (22) when $\sigma = 0.7$. The notation EEP stands for endemic equilibrium point. All other parameters are as in Table 1.

3.3.2. Malnourished-Only Endemic Equilibrium

This occurs when the entire community consists of malnourished individuals only, i.e., $\pi = 1$, $\alpha = \delta = 0$ and $S_1 = E_1 = I_1 = 0$. Using similar analysis as in Section 3.3.1, it can easily be shown that the nonzero endemic equilibrium is $Q_2^* = (0, 0, 0, S_2^*, E_2^*, I_2^*)$ where

$$S_2^* = \frac{\Lambda}{\mu + \theta\lambda_1^*}, \quad E_2^* = \frac{\Lambda\lambda_1^*[\theta(1-p)(\beta\varepsilon\mu + \eta d\lambda_1^*) + \phi\gamma(\mu + \theta\lambda_1^*)]}{(\mu + \theta\lambda_1^*)(\beta\varepsilon\mu + \eta d\lambda_1^*)[B_2 + \sigma\theta(1-r)\lambda_1^*]},$$

$$\text{and } I_2^* = \frac{\Lambda\lambda_1^*}{\beta\varepsilon\mu + \eta d\lambda_1^*}, \quad (28)$$

where $B_2 = [\mu + \tau k(1-r)]$ and λ_1^* is the force of infection which satisfies the following quadratic equation:

$$b_2(\lambda_1^*)^2 + b_1\lambda_1^* + b_0 = 0, \quad (29)$$

where

$$b_2 = \sigma\theta\mu(1-r),$$

$$b_1 = (\mu + \eta d)(1-r)(\sigma\mu + \tau k) - \beta\varepsilon\theta\mu\sigma - \eta d[p\mu + \tau k(1-r)],$$

$$b_0 = [(\mu + \eta d)[\mu + \tau k(1-r)] + \mu\phi\gamma](1 - \mathcal{R}_0^2),$$

with \mathcal{R}_0^2 defined as in Eq. (14). The quadratic equation (29) can be analyzed for the possibility of multiple endemic equilibria. It is worth noting that the coefficient b_2 is always positive, and b_0 is positive (negative) if \mathcal{R}_0^2 is less than (greater than) unity, respectively.

Solving the quadratic equation (20) yields

$$\lambda_1^* = \frac{-b_1 + \sqrt{b_1^2 - 4b_0b_2}}{2b_2}, \quad (30)$$

and the remaining one root is a complex root which is discarded because we are dealing with a population of individuals and is always positive. We only consider conditions for b_2 , b_1 and b_0 which gives us $b_1^2 - 4b_0b_2 \geq 0$ and a positive λ_1^* since a negative force of infection is epidemiologically irrelevant. Furthermore, using the analysis done in sec. 3.3.1, the stability of Q_2^* can be established. We now discuss the co-existence of nourished and malnourished individuals in the community.

3.3.3. Co-Existence of Nourished and Malnourished Endemic Equilibrium and Bifurcation Analysis

Let $Q^{**} = (x^{**}, y^{**})$ be the positive endemic equilibrium of Eq. (4). This positive endemic equilibrium (steady state with $y(t) > 0$) is obtained by setting the right hand side of Eq. (4) to zero, giving:

$$\begin{cases} \Gamma + A_x x^{**} - \lambda^{**} \sum_{i=1}^2 B_i \langle e_i | x^{**} \rangle = 0, \\ \lambda^{**} \left[\sum_{i=1}^2 \mathcal{K}_i \langle e_i | x^{**} \rangle + B_3 \langle e_3 | y^{**} \rangle + B_4 \langle e_4 | y^{**} \rangle \right] + A_y y^{**} = 0, \end{cases} \quad (31)$$

where λ^{**} is the force of infection at the endemic equilibrium, given by

$$\lambda^{**} = \frac{\langle B | y^{**} \rangle}{N^{**}}. \tag{32}$$

Using the first equation of Eq. (31), one has

$$\begin{aligned} S_1^{**} &= \frac{\Lambda[\pi(\mu + \theta\lambda^{**}) + \delta]}{(\mu + \theta\lambda^{**})(\mu + \alpha + \lambda^{**}) + \delta(\mu + \lambda^{**})} \quad \text{and} \\ S_2^{**} &= \frac{\Lambda[\alpha + (1 - \pi)(\mu + \lambda^{**})]}{(\mu + \theta\lambda^{**})(\mu + \alpha + \lambda^{**}) + \delta(\mu + \lambda^{**})}. \end{aligned} \tag{33}$$

Multiplying the second equation of Eq. (31) by $(-A_y)^{-1}$ yields

$$y^{**} = \lambda^{**} \left[\sum_{i=1}^2 \mathcal{K}_i \langle e_i | x^{**} \rangle (-A_y)^{-1} \mathcal{K}_i + \langle e_3 | y^{**} \rangle (-A_y)^{-1} B_3 + \langle e_4 | y^{**} \rangle (-A_y)^{-1} B_4 \right]. \tag{34}$$

Then, one can deduce that

$$\begin{aligned} \langle B | y^{**} \rangle &= \lambda^{**}(a_1 S_1^{**} + a_2 S_2^{**} + a_3 \langle e_3 | y^{**} \rangle + a_4 \langle e_4 | y^{**} \rangle), \\ \langle e_3 | y^{**} \rangle &= \lambda^{**}(a_5 S_1^{**} + a_6 S_2^{**} + a_7 \langle e_3 | y^{**} \rangle + a_8 \langle e_4 | y^{**} \rangle), \\ \langle e_4 | y^{**} \rangle &= \lambda^{**}(a_9 S_1^{**} + a_{10} S_2^{**} + a_{11} \langle e_3 | y^{**} \rangle + a_{12} \langle e_4 | y^{**} \rangle), \end{aligned} \tag{35}$$

where

$$\begin{aligned} a_1 &= \langle B | (-A_y)^{-1} \mathcal{K}_1 \rangle, & a_2 &= \langle B | (-A_y)^{-1} \mathcal{K}_2 \rangle, & a_3 &= \langle B | (-A_y)^{-1} B_3 \rangle, \\ a_4 &= \langle B | (-A_y)^{-1} B_4 \rangle, & a_5 &= \langle e_3 | (-A_y)^{-1} \mathcal{K}_1 \rangle, & a_6 &= \langle e_3 | (-A_y)^{-1} \mathcal{K}_2 \rangle, \\ a_7 &= \langle e_3 | (-A_y)^{-1} B_3 \rangle, & a_8 &= \langle e_3 | (-A_y)^{-1} B_4 \rangle, & a_9 &= \langle e_4 | (-A_y)^{-1} \mathcal{K}_1 \rangle, \\ a_{10} &= \langle e_4 | (-A_y)^{-1} \mathcal{K}_2 \rangle, & a_{11} &= \langle e_4 | (-A_y)^{-1} B_3 \rangle \quad \text{and} \quad a_{12} = \langle e_4 | (-A_y)^{-1} B_4 \rangle. \end{aligned}$$

Using the second and third equations of Eq. (35), one can deduce that

$$\begin{aligned} \langle e_3 | y^{**} \rangle &= \frac{\lambda^{**}[(a_5 S_1^{**} + a_6 S_2^{**})(1 - a_{12} \lambda^{**}) + a_8(a_9 S_1^{**} + a_{10} S_2^{**})\lambda^{**}]}{(1 - a_{12} \lambda^{**})(1 - a_7 \lambda^{**}) - a_8 a_{11} (\lambda^{**})^2} \quad \text{and} \\ \langle e_4 | y^{**} \rangle &= \frac{\lambda^{**}[(a_9 S_1^{**} + a_{10} S_2^{**})(1 - a_7 \lambda^{**}) + a_{11}(a_5 S_1^{**} + a_6 S_2^{**})\lambda^{**}]}{(1 - a_{12} \lambda^{**})(1 - a_7 \lambda^{**}) - a_8 a_{11} (\lambda^{**})^2} \end{aligned} \tag{36}$$

Combining the first equation of (35) and Eq. (32) yields

$$N^{**} = a_1 S_1^{**} + a_2 S_2^{**} + a_3 \langle e_3 | y^{**} \rangle + a_4 \langle e_4 | y^{**} \rangle. \tag{37}$$

Now, let $w_1 = (0, 1, 0, 0)^T$ and $w_2 = (0, 0, 0, 1)^T$. From Eq. (34), one can deduce that

$$\begin{aligned} I_1^{**} &= \lambda^{**} (a_{13} S_1^{**} + a_{14} S_2^{**} + a_{15} \langle e_3 | y^{**} \rangle + a_{16} \langle e_4 | y^{**} \rangle), \\ I_2^{**} &= \lambda^{**} (a_{17} S_1^{**} + a_{18} S_2^{**} + a_{19} \langle e_3 | y^{**} \rangle + a_{20} \langle e_4 | y^{**} \rangle), \end{aligned} \tag{38}$$

where

$$\begin{aligned} a_{13} &= \langle w_1 | (-A_y)^{-1} \mathcal{K}_1 \rangle, & a_{14} &= \langle w_1 | (-A_y)^{-1} \mathcal{K}_2 \rangle, & a_{15} &= \langle w_1 | (-A_y)^{-1} B_3 \rangle, \\ a_{16} &= \langle w_1 | (-A_y)^{-1} B_4 \rangle, & a_{17} &= \langle w_2 | (-A_y)^{-1} \mathcal{K}_1 \rangle, & a_{18} &= \langle w_2 | (-A_y)^{-1} \mathcal{K}_2 \rangle, \\ a_{19} &= \langle w_2 | (-A_y)^{-1} B_3 \rangle & \text{and} & & a_{20} &= \langle w_2 | (-A_y)^{-1} B_4 \rangle. \end{aligned}$$

Remind that at the steady state, the size of the total population satisfies the following equation:

$$\Lambda - \mu N^* - d_1 I_1^* - d_2 I_2^*. \tag{39}$$

With this in mind, using Eq. (8), one has

$$\begin{aligned} N^{**} &= \frac{\Lambda}{\mu} - \frac{d\lambda^{**}}{\mu} [(a_{13} + \eta a_{17}) S_1^{**} \\ &\quad + (a_{14} + \eta a_{18}) S_2^{**} + (a_{15} + \eta a_{19}) \langle e_3 | y^{**} \rangle + (a_{16} + \eta a_{20}) \langle e_4 | y^{**} \rangle]. \end{aligned} \tag{40}$$

Equating Eqs. (37) and (40), and using Eqs. (33) and (36), it can be shown that the non-zero equilibria of model system (4) satisfy the following equation in term of λ^* :

$$f_4(\lambda^{**})^4 + f_3(\lambda^{**})^3 + f_2(\lambda^{**})^2 + f_1 \lambda^{**} + f_0 = 0, \tag{41}$$

where

$$f_4 = (a_7a_{12} - a_8a_{11})[\theta\pi C_1 + (1 - \pi)C_2 - \theta] + C_3[\theta\pi C_5 + (1 - \pi)C_6] \\ + C_4[\theta\pi C_7 + (1 - \pi)C_8],$$

$$f_3 = (a_7a_{12} - a_8a_{11})[\mu\theta\pi a_1 + (\pi\mu + \delta)C_1 + \mu(1 - \pi)a_2 \\ + [\alpha + \mu(1 - \pi)]C_2 - \mu - \delta - \theta(\mu + \alpha)] - (a_7 + a_{12})[\theta\pi C_1 + (1 - \pi)C_2 - \theta] \\ + C_3[\theta\pi a_5 + (\pi\mu + \delta)C_5 + (1 - \pi)a_6 + [\alpha + \mu(1 - \pi)]C_6] \\ + C_4[\theta\pi a_9 + (\pi\mu + \delta)C_7 + (1 - \pi)a_{10} + [\alpha + \mu(1 - \pi)]C_8] \\ + \mu\pi\theta(a_3C_5a_4C_7) + \mu(1 - \pi)(a_3C_6 + a_4C_8),$$

$$f_2 = (a_7a_{12} - a_8a_{11})[\mu(\pi\mu + \delta)a_1 + \mu[\alpha + \mu(1 - \pi)]a_2 - \mu(\mu + \alpha + \delta)] \\ - (a_7 + a_{12})[\mu\theta\pi a_1 + (\pi\mu + \delta)C_1 + \mu(1 - \pi)a_2 \\ + [\alpha + \mu(1 - \pi)]C_2 - \mu - \delta - \theta(\mu + \alpha)] \\ + \theta\pi(C_1 + \mu a_3a_5 + \mu a_4a_9) + (1 - \pi)(C_2 + \mu a_3a_6 + \mu a_4a_{10}) \\ + (\pi\mu + \delta)(a_5C_3 + a_9C_4 + \mu a_3C_5 + \mu a_4C_7) \\ + [\alpha + \mu(1 - \pi)](a_6C_3 + a_{10}C_4 + \mu a_3C_6 + \mu a_4C_8) - \theta,$$

$$f_1 = -\mu(a_7 + a_{12})[(\pi\mu + \delta)a_1 + [\alpha + \mu(1 - \pi)]a_2 - \mu - \alpha - \delta] \\ + \mu\theta\pi a_1 + \mu(1 - \pi)a_2 + (\pi\mu + \delta)[C_1 + \mu a_3a_5 + \mu a_4a_9] \\ + [\alpha + \mu(1 - \pi)][C_2 + \mu a_3a_6 + \mu a_4a_{10}] - \mu - \delta - \theta(\mu + \alpha),$$

$$f_0 = \mu(\mu + \delta + \alpha)(\mathcal{R}_0 - 1),$$

with

$$C_1 = d(a_{13} + \eta a_{17}), \quad C_2 = d(a_{14} + \eta a_{18}), \quad C_3 = d(a_{15} + \eta a_{19}), \quad C_4 = d(a_{16} + \eta a_{20}),$$

$$C_5 = a_8a_9 - a_5a_{12}, \quad C_6 = a_8a_{10} - a_6a_{12}, \quad C_7 = a_5a_{11} - a_7a_9, \quad C_8 = a_6a_{11} - a_7a_{10}.$$

The positive endemic equilibria Q^* are obtained by solving for λ^{**} from the equation (41) and substituting the result (positive values of λ^{**}) into the expression of the

infection force at the steady state defined as in Eq. (32). Clearly, the coefficient f_0 of (41) is positive or negative whenever \mathcal{R}_0 is greater or less than unity, respectively. Thus, the number of possible real roots that the polynomial (41) can have depends on the signs of f_4, f_3, f_2, f_1 and f_0 . This can be analyzed using the Descartes Rule of Signs on the fourth polynomial $g(\lambda^{**}) = f_4(\lambda^{**})^4 + f_3(\lambda^{**})^3 + f_2(\lambda^{**})^2 + f_1(\lambda^{**}) + f_0$ given in Eq. (41). The following result gives various possibilities of solutions of Eq. (41).

Lemma 3. : *The TB model (4)*

- (i) *could have a unique endemic equilibrium whenever $\mathcal{R}_0 > 1$.*
- (ii) *could have more than one endemic equilibrium whenever $\mathcal{R}_0 > 1$.*
- (iii) *could have a unique endemic equilibrium whenever $\mathcal{R}_0 < 1$.*
- (iv) *could have one or more endemic equilibria whenever $\mathcal{R}_0 < 1$.*

Case (i) of Lemma 3 suggests that co-existence of nourished and malnourished individuals in a TB endemic area is possible, while case (iii) of Lemma 3 indicates the possibility of a backward bifurcation in model system (3) when $\mathcal{R}_0 < 1$.

The backward bifurcation phenomenon is illustrated by simulating model system (3) and the parameter values of Table 1. The associated backward bifurcation diagram is depicted in Fig. 6. A time series of model system (3) when $\beta = 5 \times 10^{-5}$ (so that $\mathcal{R}_0 = 0.3766$) is shown in Fig. 7. This figure shows the convergence to both a disease-free equilibrium and an endemic equilibrium for model system (3) when $\mathcal{R}_0 < 1$, depending on the initial sizes of the population of the model (owing to the phenomenon of backward bifurcation). This result is summarized below for model system (3).

Theorem 5. : *The TB model (3) exhibits the phenomenon of backward bifurcation whenever $\mathcal{R}_0 < 1$ and could have a unique endemic equilibrium whenever $\mathcal{R}_0 > 1$.*

The epidemiological significance of the phenomenon of backward bifurcation is that the classical requirement of $\mathcal{R}_0 < 1$ is, although necessary, no longer sufficient for disease eradication. In such a scenario, disease elimination would depend on the initial sizes of the population (state variables) of the model. That is, the presence of backward bifurcation in TB transmission model (3) suggests that the feasibility of controlling TB when $\mathcal{R}_0 < 1$ could be dependent on the initial sizes of the population.

4. Numerical Studies

Numerical simulations using a set of reasonable parameter values in Table 1 are carried out for illustrative purpose and to support the analytical results. In all simulations, the model was simulated with the following initial conditions: $S_1(0) = 15 \times 10^6$, $E_1(0) = 15 \times 10^5$, $I_1(0) = 478 \times 10^3$, $S_2(0) = 15 \times 10^6$, $E_1(0) = 15 \times 10^5$

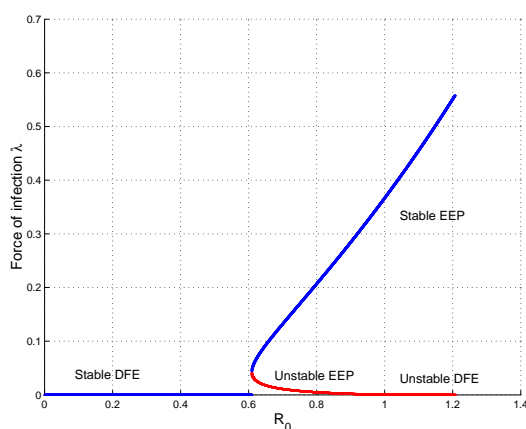


Figure 6: Bifurcation diagram for model system (3). The notation EEP stands for endemic equilibrium point. All other parameters are as in Table 1.

and $I_1(0) = 478 \times 10^3$. We point out that these initial conditions have been chosen arbitrarily. Also, in all simulations, the transmission rate β has been chosen such that $\mathcal{R}_0 > 1$ (so that case (i) of Lemma 3 is satisfied).

4.1. General Dynamics

Numerical simulations of the TB model system (3) showing the time series plots of nourished and malnourished infective populations individuals when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0 = 1.3195$) are shown in Fig. 8. The results obtained using parameter values in Table 1 indicate that more nourished latently infected individuals (E_1) are infected than malnourished latently infected individuals, while more malnourished infectious individuals (I_2) are infectious than nourished infectious individuals (I_1). This means that malnutrition accelerate the progression from latent status to active TB.

4.2. Effects of Increased Some Parameters

Effects of increased susceptibility to TB as a result of malnutrition are explored in Fig. 9 by varying θ when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0 > 1$). Figure 9 plots the number of nourished infectious individuals (I_1) and the number of malnourished infectious individuals (I_2). All other parameter values are given in Table 1. It illustrates that an increase in susceptibility to TB due to malnutrition will generally result in an increase in the number of TB infectious individuals (both nourished and malnourished) with a significant effect on the malnourished infectious individuals (as shown in Fig. 9(b)). Also, this figure shows that changes in θ do not significantly affect the

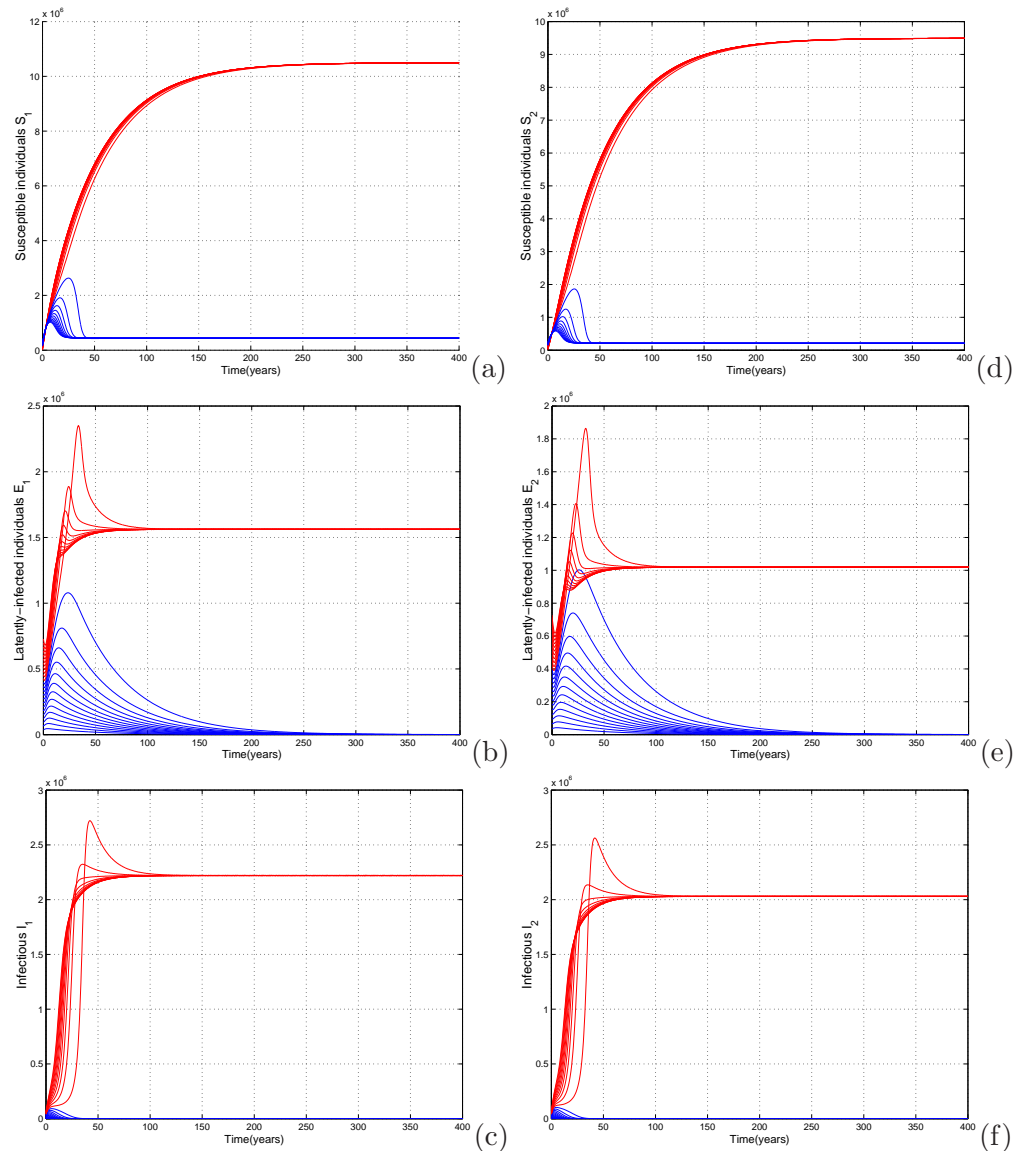


Figure 7: Simulation of model system (3). Time series of (a) nourished susceptible individuals, (b) nourished latently infected individuals, (c) nourished infectious individuals, (d) malnourished susceptible, (e) malnourished latently infected individuals and (f) malnourished infectious individuals using $\beta = 5 \times 10^{-7}$ (so that $\mathcal{R}_0 = 0.3227$). All other parameters are as in Table 1.

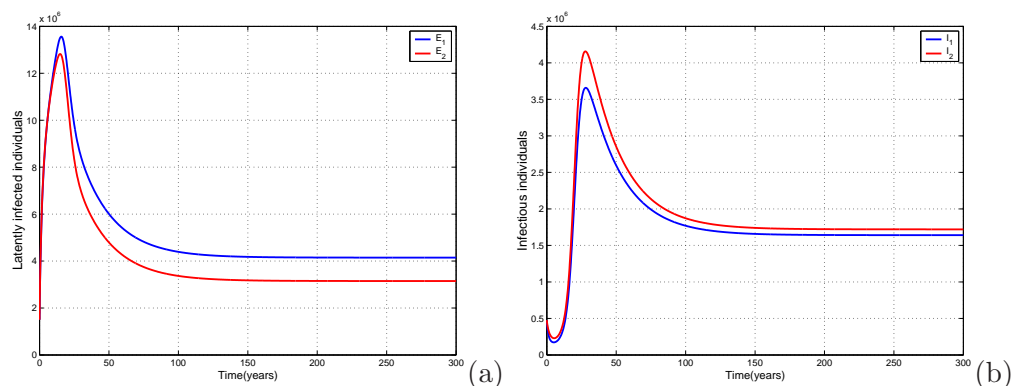


Figure 8: Simulation results showing the general trends of model system (3) when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0 = 1.3195$). (a) Nourished and malnourished latently infected individuals and (b) Nourished and malnourished infectious individuals. All other parameters are as in Table 1.

long term progression of the disease, but significant changes are observed in the initial phases of the epidemic, with more changes being observed in the malnourished infectious individuals. This result suggests that the problem of malnutrition should be addressed in impoverished communities affected with TB in order to reduce the burden of the disease.

The impact of varying the rate at which nourished individuals become malnourished individuals α when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0 > 1$) is depicted in Fig. 10. Simulation results suggest that an increase of the rate at which nourished individuals become malnourished individuals α will decrease the population of nourished infectious individuals (see Fig. 10(a)), but increase the population of malnourished infectious individuals (see Fig. 10(a)) in the community. Thus, an decrease of the rate at which nourished individuals become malnourished individuals α will have a positive impact on controlling TB in the community.

Figure 11 gives the influence of the rate of the reduced rate of recovery of malnourished infectious individuals ϕ when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0 > 1$). It suggests that a decreases of the rate of the reduced rate of recovery of malnourished infectious individuals will generally result in an increase in the number of TB infectious individuals (both nourished and malnourished) with a significant effect on the nourished infectious individuals (as shown by Fig. 11(b))

Figure 12 gives the graphical representation showing how both forms of TB fare in 100% and 0% malnourished populations in the community when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0^1 > 1$ and $\mathcal{R}_0^2 > 1$) using various initial conditions. The higher the percentage of nourished, the larger are the number of the total number of infected individuals at the endemic equilibrium point.

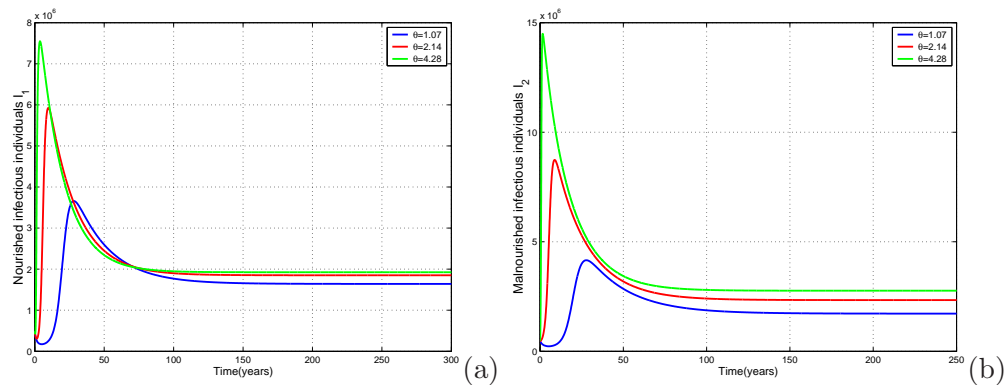


Figure 9: Simulations of model system (3) showing the effects of increasing susceptibility to TB when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0 > 1$). (a) Nourished infectious individuals and (b) malnourished infectious individuals. All other parameters are as in Table 1.

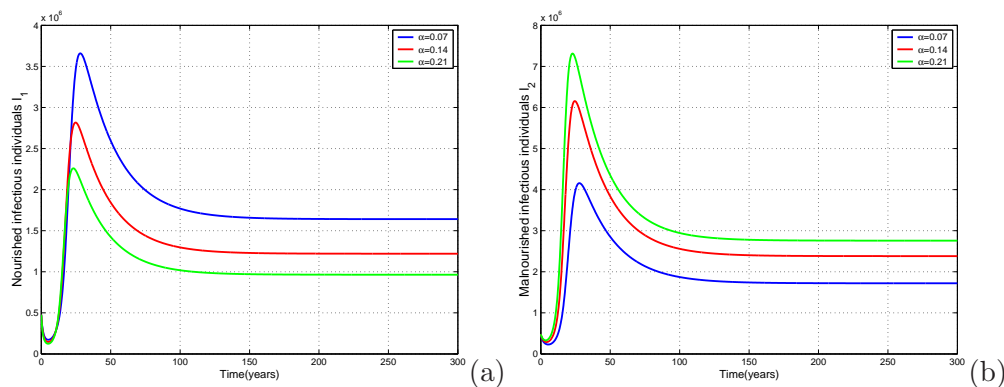


Figure 10: Simulation results showing the effect of increasing the rate at which nourished individuals become malnourished individuals when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0 > 1$). (a) Nourished infectious individuals and (b) malnourished infectious individuals. All other parameters are as in Table 1.

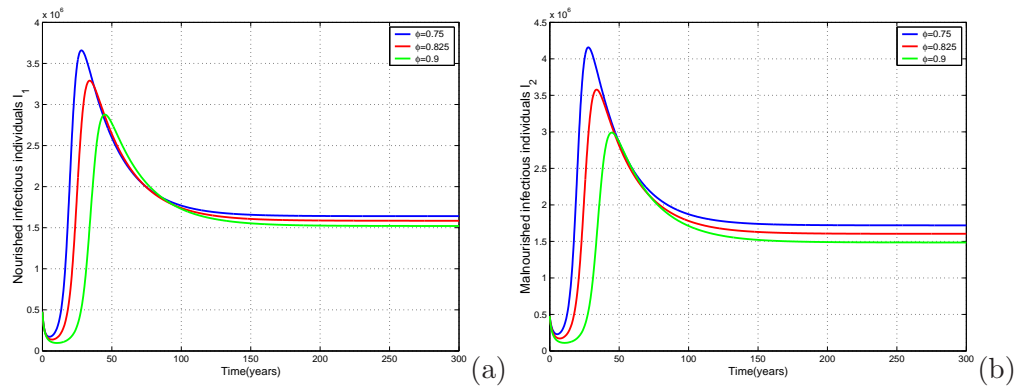


Figure 11: Simulation results showing the effect of increasing the rate of the reduced rate of recovery of malnourished infectious individuals ϕ when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0 > 1$). (a) Nourished infectious individuals and (b) malnourished infectious individuals. All other parameters are as in Table 1.

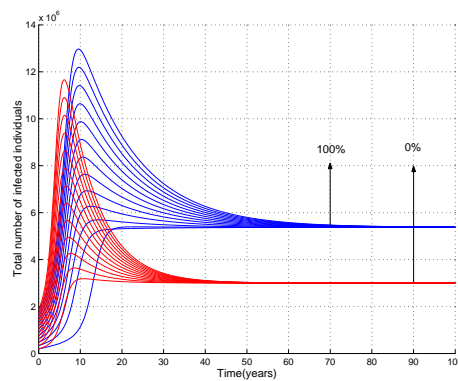


Figure 12: Time series evolution of the total number of infected individuals when the whole population is made of nourished and when the whole population is made up of malnourished when $\beta = 2 \times 10^{-6}$ (so that $\mathcal{R}_0^1 > 1$ and $\mathcal{R}_0^2 > 1$) using various initial conditions.) All other parameters are as in Table 1.

5. Discussions and Concluding Remarks

A deterministic compartmental model for investigating the effects of malnutrition on the transmission dynamics of TB in the community is formulated and analyzed. We find that the effect of malnutrition on the actual tuberculosis dynamics is twofold: it increases transmissibility from malnourished infectious individuals, and it also increases the progression from susceptible to latently infected in the malnourished population. The basic reproduction number which determines the outcome of the disease has been computed and used to assess the effects of malnutrition in the community. Also, malnutrition enhances TB, which agrees with experimental results that malnutrition is associated with specific negative health outcomes [9,11] and promotes the development of TB [4,10]. The reproduction numbers for the nourished and malnourished only sub-models are computed and analyzed. Results show that increasing the number of healthy nourished people of malnourished people who become nourished as well as effective treatment of TB infective individuals have a positive impact on TB control.

A qualitative analysis of the model has been presented. The model has been shown to exhibit the phenomenon of backward bifurcation, where a stable disease-free equilibrium co-exists with one or more stable endemic equilibria when the associated basic reproduction number is less than unity. The epidemiological consequence of this result is that the effective control of TB, when the reproduction number is less than unity, in the community would then be dependent on the initial sizes of the populations of the model. As customary in epidemiological models, disease-free and endemic equilibria are found and their stability is investigated depending on the system parameters. Due to the presence of backward bifurcation, in some parameter regimes the system exhibits a bi-stability between a disease-free and endemic steady states. The Centre Manifold theory was used to determine the local asymptotic stability of the endemic equilibrium. Numerical simulations are performed to illustrate various dynamical regimes. Graphical representations clearly show that the number of active TB people in malnourished communities is higher than the number in the nourished communities. This suggests that malnutrition promotes TB transmission.

The proposed model is not exhaustive and has some limitations. For instance, the dynamics of HIV/AIDS is not included, which may limit its applicability to sub-Saharan Africa. Also, the class of recovered is not accounted for in this study. Also, the model that we have proposed does not include some features of the very complex system involving the Mtb epidemiology. Nonetheless, the study highlights an important aspect of the dynamics of TB in the human population.

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