Effect of mixed infection on TB dynamics*

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Abstract. Poor living conditions, overcrowding, and strain diversity are some of the factors that influence mixed infection in TB at population level. We formulate a mathematical model for mixed infection in TB using non-linear ordinary differential equations where such factors were represented as probabilities of acquiring mixed infection. A qualitative analysis of the model shows that it exhibits multiple endemic equilibria and backward bifurcation for certain parameter values. The reactivation rate and transmission rate of individuals with mixed infection were of importance as well as the probabilities for latent individuals to acquire mixed infection. We calculate the prevalence of mixed infection from the model and the effect of mixed infection on TB incidence, TB prevalence and MTB infection rate. Numerical simulations show that mixed infection may explain high TB incidences in areas which have a high strain diversity, poor living conditions and are overcrowded even without HIV.

Keywords: Tuberculosis; Mixed Infection; Mathematical Model.
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1. Introduction

A disease that flourishes among the ignorant, underprivileged and poor is what some authors have taken Tuberculosis (TB) to be [17, 30]. Having existed since prehistoric times [8, 13, 14], TB thrives in areas where there is overcrowding, poor living and working conditions and poor housing facilities [9, 17, 29, 30]. It is caused by *Mycobacterium tuberculosis* (MTB) as discovered in 1882 by Sir Robert Koch [7, 8, 13, 14]. Being an airborne disease transmitted when an infected individual coughs, sneezes, laughs, speaks, spits or talks, overcrowding would aggravate TB transmission. In such conditions, individuals are more likely to be infected many times which is termed as *multiple infection*. If there happen to be many strains circulating, then individuals could be infected with more than one strain which we define as *mixed infection*. This is believed to be a rare event [3, 24, 29] due to the preconceived idea of acquired immunity after initial infection [2, 3, 5, 25, 38].

Nonetheless, some studies have shown that mixed infection could occur in areas with high TB incidence and where the risk of infection is high [9, 12, 21, 38]. It has been documented in prisons [9], mines [29], homeless shelters [22] and overcrowded areas [33, 38]. All these places have things in common such as overcrowding, poor living and working conditions and bad housing facilities. Hence there is a connection between such conditions and mixed infection in TB.

Mixed infection is only possible if there are many strains circulating in a population. Different strains were first noticed with the discovery of drugs. In 1944, when streptomycin was developed, treatment with this drug alone led to resistant mutants [8]. Moreover, with mutations, strains have evolved over time and there have been different strains in different regions. In fact, some strains are named according to their purported areas of origin: for example Beijing strain which is believed to have its origins in Beijing, China. With present day globalisation, strains have been transported all over the world and this has resulted in a great diversity of strains in some places [4, 19, 28, 35, 36]. In Africa, where there is a lot of urbanisation, people have moved from villages to towns which has led to formation of slums. It is thus not surprising that mixed infection has been documented in slums, mines, prisons and homeless shelters [9, 22, 29, 38].

It was originally thought that active TB was due to one strain infection only and that infected individuals had acquired immunity against reinfection [2, 3, 5, 35]. This could be one of the reasons as to why there are few mathematical models that incorporate mixed infection in TB. Castillo-Chavez and Zhilan Feng [6] investigated a TB model with two strains; i.e sensitive strain and resistant strain. Their model considered that latent individuals infected with a sensitive strain could also get infected with the resistant strain and this dual infection with two different strains formed the mixed infected compartment. However, nothing much was done with the mixed infection compartment. Their main focus was on whether co-existence of strains was possible in presence of treatment. Rodrigues *et al* [27] developed a two strain model of TB. The strains were drug resistant and drug sensitive. They

assumed that when an individual was infected with both strains (mixed infection), only the resistant strain could be activated or transmitted. Thus our model is formulated particularly to study mixed infection which was not the case with the models of Castillo-Chavez and Zhilan Feng [6] and Rodrigues *et al* [27]. The paper is organized as follows. In section 2, the mixed infection model is formulated. Section 3 presents the mathematical analysis where the equilibrium points are discussed. In section 4 numerical simulations are given and section 5 has the discussion of results.

2. Mixed Infection model

This model is based on two major ideas of simultaneous infection and reinfection. Simultaneous infection happens when an individual is infected by more than one strain at the same time and we consider reinfection to occur when an individual gets another infection with a different strain years after initial infection already occurred. Reinfection with the same strain could occur but it is not possible to quantify it because methods that are available only confirm a reinfection event if it is with a different strain [34].

The model consists of 3 groups of individuals; susceptibles, S_1, latents, E_1 and infectives, I_1. The latents and infectives are each divided into two subgroups, $E_{11},\ E_{12}$ and $I_{11},\ I_{12}$ respectively. The subgroups' subscripts take a two digit format where the first digit is the default definition of the group and the second digit represents number of strains an individual is infected with though 2 stands for more than one strain, that is, 2+. Some parameters used in the model also have subscripts in a two digit format and they also take the same description.

Individuals are recruited into the susceptible group (S_1) at a constant rate B. Infection occurs when susceptibles interact with infectives with one strain infection (I_{11}) or those with mixed infection (I_{12}). We assume that when susceptibles mix with infectives in I_{12}, they can get infected with either one of the strains resulting into a one strain infection or more than one strain resulting into mixed infection. The forces of infection for the one strain infection and mixed infection are modeled by standard incidence with transmission rates, k_{11} and k_{12} respectively.

After infection, a proportion p of the susceptible population progresses fast to disease (in the first 5 years after initial infection) joining the infectious subgroups, $I_{11},\ I_{12}$ and $(1-p)$ denoted p' progresses slowly to disease forming the latent subgroups, E_{11} and E_{12}. Due to the interaction between susceptibles and infectives in I_{12}, a proportion p_1 of those who progress fast to disease moves to infectious subgroup I_{11} while the other proportion goes to I_{12}. Similarly, we assume that a proportion, p_2 of those who move to the latent stage joins latent subgroup E_{11} and the other proportion moves to E_{12}.

Latent individuals in E_{11} enter I_{11} by reactivation (which occurs at a rate a_{11}) or by reinfection which results from contact of the latent individuals in E_{11} with individuals in I_{11} and I_{12}. Latent individuals in E_{11} can get mixed infection by interacting with infectious individuals.

We define η as the probability of E_{11} individuals getting into contact with an infectious individual with a one strain infection who has a different strain from theirs and η_1 is the probability of E_{11} individuals getting into contact with an infectious individual with mixed infection who has at least a different strain from theirs. A proportion, r_1 of those reinfected progress fast (in the first 5 years following a reinfection) to I_{12} and the other, $(1-r_1)$ denoted r_1' joins E_{12}. Those in E_{12} join I_{12} by reactivation at a rate, a_{12}.

Susceptibles and latents die naturally at a rate μ_1. Infectives die at a rate m_{ij} and they recover at a rate b_{ij} where $i = 1$ and $j = 1$ or 2. Subscripts are defined as before. We assume that after recovery, they return to their respective latent subgroups. Furthermore, we assume that individuals with active TB do not get reinfected during the time of their sickness (this explains why we did not consider any transfers from I_{11} to I_{12}).

The flows between the different groups are shown in Fig. 1 and Table. 1 gives definitions of all the parameters used in system of equations (2.1)

The differential equations of the model are given as:

$$\begin{aligned}
\frac{dS_1}{dt} &= B - S_1(f^{^1} + f^{^2}) - \mu_1 S_1,\\
\frac{dE_{11}}{dt} &= p'S_1(f^{^1} + p_2 f^{^2}) - E_{11}(\eta f^{^1} + \eta_1 f^{^2}) - (a_{11} + \mu_1)E_{11} + b_{11}I_{11},\\
\frac{dE_{12}}{dt} &= p_2'p'S_1 f^{^2} + r_1'E_{11}(\eta f^{^1} + \eta_1 f^{^2}) - (a_{12} + \mu_1)E_{12} + b_{12}I_{12},\\
\frac{dI_{11}}{dt} &= pS_1(f^{^1} + p_1 f^{^2}) - (b_{11} + m_{11})I_{11} + a_{11}E_{11},\\
\frac{dI_{12}}{dt} &= p_1'pS_1 f^{^2} + r_1E_{11}(\eta f^{^1} + \eta_1 f^{^2}) - (b_{12} + m_{12})I_{12} + a_{12}E_{12},
\end{aligned} \tag{2.1}$$

where, $f^{^1} = k_{11}I_{11}/P$ and $f^{^2} = k_{12}I_{12}/P$ are the forces of infection for one strain infection and mixed infection respectively and

$$P = S_1 + E_{11} + E_{12} + I_{11} + I_{12},$$

is the total population.

3. Mathematical Analysis of the model

For biological feasibility of system (2.1), it is important that all variables stay positive at all times and as such we analyse this system in the region

$$\Omega = \left\{(S_1, E_{11}, E_{12}, I_{11}, I_{12}) \in \Re_+^5 : S_1 + E_{11} + E_{12} + I_{11} + I_{12} \leq \frac{B}{\mu}\right\}.$$

Solutions of the system, remain positive for all time $t \geq 0$ and are bounded in Ω.

Proposition 3.1. *System (2.1) has for each positive initial condition, a unique solution that is positive. Moreover, the region Ω is positively invariant.*

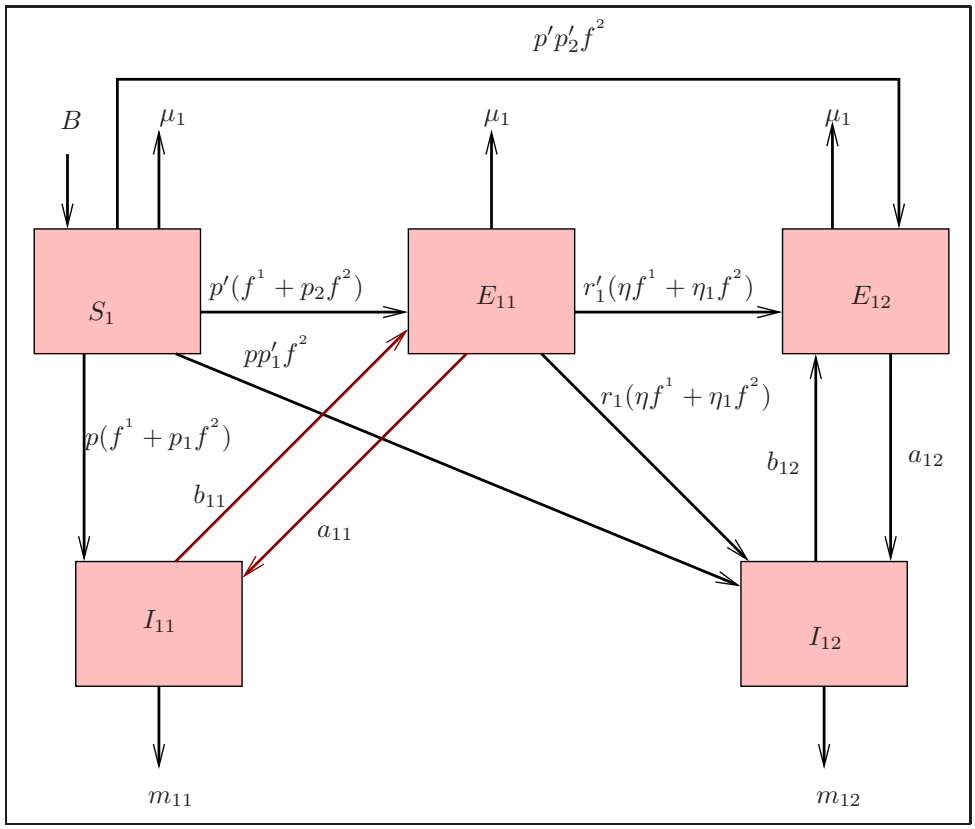


Fig. 1. Compartmental diagram showing mixed infection in TB. It comprises of susceptibles, S_1, latents, $E_{11},\ E_{12}$ and infectives, $I_{11},\ I_{12}$ and the subscripts, the first one is default definition of the group and the second subscript represents whether they have one strain infection or mixed infection. The arrows show the in and out flows between the compartments.

Proof. Let $t_1 = \sup\ \{t > 0 : S_1 > 0,\ E_{11} > 0,\ E_{12} > 0,\ I_{11} > 0,\ I_{12} > 0\ \}$. Thus $t_1 > 0$. If $t_1 < \infty$, then necessarily S_1 or E_{11} or E_{12} or I_{11} or I_{12} is equal to zero at t_1. Using the variation of constants formula, we have:

$$S_1(t_1) = S_1(0)exp[-\int_0^{t_1}(\mu_1 + f^{1} + f^{2})(s)ds] + B\int_0^{t_1} exp[-\int_0^{t_1-s}(\mu_1 + f^{1} + f^{2})(\tau)d\tau]ds > 0.$$

Moreover, since all the variables are positive in $[0, t_1]$, it can be shown in a similar way that $E_{11}(t_1) > 0,\ E_{12}(t_1) > 0,\ I_{11}(t_1) > 0$ and $I_{12}(t_1) > 0$. Hence $t_1 = \infty$ which is a contradiction.

For the invariance of Ω, we add the equations of system (2.1) to obtain:

$$\frac{dP(t)}{dt} = B - \mu_1 P(t) - (m_{11} - \mu_1)I_{11}(t) - (m_{12} - \mu_1)I_{12}(t).$$

Since the initial condition is in Ω, then $0 \leq I_{12}(t) \leq P(t)$ and $0 \leq I_{11}(t) \leq P(t)$.

Moreover, because $m_{11} > \mu_1$ and $m_{12} > \mu_1$, then

$$\frac{dP(t)}{dt} \leq B - \mu_1 P(t).$$

Therefore, $P(t) \leq P(0)e^{-\mu_1 t} + B/\mu_1(1 - e^{-\mu_1 t})$ and if $P(0) \leq B/\mu_1$ then so is $P(t)$. Moreover, whenever $P(t) > B/\mu_1$, $P(t)' < 0$. Thus every solution of the model equations (2.1) with initial conditions in $\mathbb{R}^5_+$ approaches and stays in Ω as $t \to \infty$.

3.1. *Equilibrium points*

These are time-independent states of a system. In finding them, we set time derivatives of model equations (2.1) to zero. For convenience, we introduce the fraction notation: $s_1^* = S_1^*/P^*$, $e_{11}^* = E_{11}^*/P^*$, $e_{12}^* = E_{12}^*/P^*$, $i_{11}^* = I_{11}^*/P^*$, $i_{12}^* = I_{12}^*/P^*$, $\mathbb{B} = B/P^*$, where $P^* = S_1^* + E_{11}^* + E_{12}^* + I_{11}^* + I_{12}^*$. We write the forces of infection as: $f^{^1} = k_{11} i_{11}^*$ and $f^{^2} = k_{12} i_{12}^*$. We are unable to find the equilibrium points explicitly, thus we express them in terms of forces of infection, $f^{^1}$ and $f^{^2}$ as shown in equations (3.2).

$$\begin{aligned}
s_1^* &= \frac{\mathbb{B}}{\theta},\\
e_{11}^* &= \frac{\mathbb{B}(pb_{11}(f^{^1} + f^{^2}p_1) + (b_{11} + m_{11})(f^{^1} + f^{^2}p_2)p')}{\theta\beta},\\
e_{12}^* &= \frac{\mathbb{B}(\alpha(b_{12} + m_{12}r_1') + \beta f^{^2}(pb_{12}p_1' + \sigma p' p_2'))}{\beta\theta\gamma},\\
i_{11}^* &= \frac{\mathbb{B}(\beta p(f^{^1} + f^{^2}p_1) + a_{11}(pb_{11}(f^{^1} + f^{^2}p_1) + (b_{11} + m_{11})(f^{^1} + f^{^2}p_2)p'))}{(b_{11} + m_{11})\theta\beta},\\
i_{12}^* &= \frac{\mathbb{B}((\alpha r_1'((a_{12} + \mu_1)\sigma - \gamma)) + \beta f^{^2}((a_{12} + \mu_1)(pb_{12}p_1' + \sigma p' p_2') - \gamma p' p_2'))}{b_{12}\beta\theta\gamma}.
\end{aligned} \tag{3.1}$$

where, $\theta = f^{^1} + f^{^2} + \mu_1$, $\beta = b_{11}\mu_1 + m_{11}(a_{11} + \mu_1) + (b_{11} + m_{11})(\eta f^{^1} + \eta_1 f^{^2})$, $\alpha = (\eta f^{^1} + \eta_1 f^{^2})(pb_{11}(f^{^1} + f^{^2}p_1) + (b_{11} + m_{11})(f^{^1} + f^{^2}p_2)p')$, $\gamma = m_{12}(a_{12} + \mu_1) + b_{12}\mu_1$, $\sigma = b_{12} + m_{12}$.

Substituting $\frac{f^{^1}}{k_{11}}$ for i_{11}^* in equation (3.2) and $\frac{f^{^2}}{k_{12}}$ for i_{12}^* in equation (3.2), we end up with a system of coupled equations given by:

$$\begin{aligned}
(f^{^1})^3 + \mathsf{a}^1(f^{^1})^2 + \mathsf{b}^1 f^{^2}(f^{^1})^2 + \mathsf{c}^1 f^{^2} f^{^1} + \mathsf{d}^1(f^{^2})^2 f^{^1} + \mathsf{e}^1 f^{^1} +\\
\mathsf{g}^1 f^{^2} + \mathsf{h}^1(f^{^2})^2 = 0,\\
(f^{^2})^3 + \mathsf{a}^2(f^{^2})^2 + \mathsf{b}^2 f^{^1}(f^{^2})^2 + \mathsf{c}^2 f^{^1} f^{^2} + \mathsf{d}^2(f^{^1})^2 f^{^2} + \mathsf{e}^2 f^{^2} +\\
\mathsf{g}^2 f^{^1} + \mathsf{h}^2(f^{^1})^2 = 0.
\end{aligned} \tag{3.2}$$

where,

$$\mathsf{a}^1 = \frac{(X_1 + X\eta\mu_1) - Bk_{11}p\eta}{X\eta},\ \mathsf{b}^1 = \frac{\eta + \eta_1}{\eta},\ \mathsf{c}^1 = \frac{(X_1 + X\eta_1\mu_1) - Bk_{11}(\eta p_1 + \eta_1)p}{X\eta},$$

$$\mathsf{d}^1 = \frac{\eta_1}{\eta}, \quad \mathsf{e}^1 = \frac{XX_1\mu_1 - Bk_{11}(pX_1 + a_{11}X_2)}{X^2\eta}, \quad \mathsf{g}^1 = \frac{-Bk_{11}(pp_1X_1 + a_{11}X_3)}{X^2\eta},$$

$$\mathsf{h}^1 = \frac{-Bk_{11}(pp_1\eta_1)}{X\eta}, \quad \mathsf{a}^2 = \frac{X_8 - \mathbb{B}k_{12}((X_3(b_{12} + m_{12}r') + XX_6)\eta_1X_7 - X_4\eta_1(Xp'p_2' + r'X_3))}{b_{12}XX_4\eta_1},$$

$$\mathsf{c}^2 = \frac{X_8 - \mathbb{B}k_{12}((XX_6\eta + (X_2\eta_1 + X_3\eta)(b_{12} + m_{12}r'))X_7 - X_4(r'(\eta_1X_2 + \eta X_3) + Xp'p_2'\eta))}{b_{12}XX_4\eta_1},$$

$$\mathsf{b}^2 = \frac{\eta + \eta_1}{\eta_1}, \quad \mathsf{e}^2 = \frac{X_9 - \mathbb{B}k_{12}((-a_{11}b_{11}X_6 + XX_6(a_{11} + \mu_1))X_7 - X_4(a_{11}m_{11} + X\mu_1)p'p_2')}{b_{12}XX_4\eta_1},$$

$$\mathsf{d}^2 = \frac{\eta}{\eta_1}, \quad \mathsf{g}^2 = 0, \quad \mathsf{h}^2 = \frac{-\mathbb{B}k_{12}(X_2\eta(X_7(b_{12} + m_{12}r') - r'X_4))}{b_{12}XX_4\eta_1},$$

with, $X = b_{11} + m_{11},\ X_1 = b_{11}\mu_1 + m_{11}(a_{11} + \mu_1),\ X_2 = pb_{11} + Xp',\ X_3 = pb_{11}p_1 + Xp_2p'$, $X_4 = b_{12}\mu_1 + m_{12}(\mu_1 + a_{12}),\ X_5 = b_{12} + m_{12},\ X_6 = pb_{12}p_1' + X_5p'p_2',\ X_7 = a_{12} + \mu_1$, $X_8 = b_{12}X_4(X\mu_1(1 + \eta) + a_{11}m_{11}),\ X_9 = b_{12}X_4\mu_1(X\mu_1 + a_{11}m_{11})$.

If $f^1 = 0$, then from equation (3.2), $f^2 = 0$ or $f^2 = -\mathsf{g}^1/\mathsf{h}^1$ which is not biologically feasible. Then necessarily $f^2 = 0$. Similarly, setting $f^2 = 0$ in equation (3.2), we obtain $f^1 = 0$.

Therefore, we conclude that $f^1 = 0$ if and only if $f^2 = 0$. This means that for our model, it is not possible to have one strain infected individuals if there are no mixed infected individuals and the reverse is true. This is because one strain infected individuals are infected with different strains thus there is a possibility of them interacting with one another to lead to a mixed infection. For mixed infected individuals, they can spread one or more strains thus it is possible that their interaction with susceptible individuals would lead to one strain infections. We thus investigate only two cases; $f^1 = f^2 = 0$ and $f^1 \neq 0$ and $f^2 \neq 0$.

If $f^1 = f^2 = 0$, we have the disease free equilibrium (DFE) and if $f^1 \neq 0$ and $f^2 \neq 0$, there is possibility of multiple endemic equilibria (EEP).

DFE of system of equations (2.1) is given as:

$$DFE = (B/\mu, 0, 0, 0, 0).$$

Whether it is stable or unstable depends on the basic reproductive number, R_0.

Definition 3.2. *R_0 is the mean number of infected individuals caused by an infected individual introduced into a wholly susceptible population during the individual's infectious period.*

This number gives us an insight of how fast the disease is spreading. $R_0 < 1$ means that on average, an infected individual causes less than one new infected individual over the course of his/her infectious period and $R_0 > 1$ implies that an infected individual produces more than one new infected individual. Therefore for many cases, the disease will die out when $R_0 < 1$ and it will invade the population

with $R_0 > 1$. For simple cases, R_0 is given by the product of the infection rate and the mean duration of infection [32]. However, in complicated cases like ours, we calculate it by using the next generation matrix method in [32]. It comprises of two matrices $\mathscr{F}$ and $\mathscr{V}$ where $\mathscr{F}$ is the appearance of new infections and $\mathscr{V}$ is the transfer in and out of the compartments through other means. We find the derivatives of $\mathscr{F}$ (F) and $\mathscr{V}$ (V) with respect to the infected classes. The dominant eigenvalue of FV^{-1} gives R_0. This is carried out as follows in our case:

$$\mathscr{F} = \begin{pmatrix} (1-p)S_1(f^{1} + p_2 f^{2}) \\ (1-p_2)(1-p)S_1 f^{2} \\ pS_1(f^{1} + p_1 f^{2}) \\ p(1-p_1)S_1 f^{2} \end{pmatrix},$$

and

$$\mathscr{V} = \begin{pmatrix} E_{11}(\eta f^{1} + \eta_1 f^{2}) + (a_{11} + \mu_1)E_{11} - b_{11}I_{11} \\ (a_{12} + \mu_1)E_{12} - b_{12}I_{12} - (1-r_1)E_{11}(\eta f^{1} + \eta_1 f^{2}) \\ (b_{11} + m_{11})I_{11} - a_{11}E_{11} \\ (b_{12} + m_{12})I_{12} - a_{12}E_{12} - r_1 E_{11}(\eta f^{1} + \eta_1 f^{2}) \end{pmatrix}.$$

We find the derivatives of $\mathscr{F}$ and $\mathscr{V}$:

$$F = \begin{pmatrix} 0 & 0 & k_{11}(1-p) & (1-p)p_2 k_{12} \\ 0 & 0 & 0 & (1-p)(1-p_2)k_{12} \\ 0 & 0 & pk_{11} & pp_1 k_{12} \\ 0 & 0 & 0 & p(1-p_1)k_{12} \end{pmatrix},$$

$$V = \begin{pmatrix} (a_{11} + \mu_1) & 0 & -b_{11} & 0 \\ 0 & (a_{12} + \mu_1) & 0 & -b_{12} \\ -a_{11} & 0 & b_{11} + m_{11} & 0 \\ 0 & -a_{12} & 0 & b_{12} + m_{12} \end{pmatrix}.$$

R_0^{TB} is the spectral radius of FV^{-1}. Using mathematica, we obtain $R_0^{TB} = \max\{R_1, R_2\}$ where $R_i, i = 1, 2$ is the reproduction number for i strain infection given by

$$R_1 = \frac{k_{11}(a_{11} + p\mu_1)}{b_{11}\mu_1 + m_{11}(a_{11} + \mu_1)},$$

$$R_2 = \frac{k_{12}(pp_1'(a_{12} + \mu_1) + a_{12}p'p_2')}{b_{12}\mu_1 + m_{12}(a_{12} + \mu_1)}.$$

3.2. *Local stability of the DFE*

Theorem 3.3. *The DFE is locally asymptotically stable if* $R_0^{TB} < 1$ *and unstable if* $R_0^{TB} > 1$

Proof. The Jacobian matrix of the system at DFE is given by

$$J = \begin{pmatrix} -\mu_1 & 0 & 0 & -k_{11} & -k_{12} \\ 0 & -(a_{11}+\mu_1) & 0 & b_{11}+(1-p)k_{11} & p_2(1-p)k_{12} \\ 0 & 0 & -(a_{12}+\mu_1) & 0 & b_{12}+(1-p)(1-p_2)k_{12} \\ 0 & a_{11} & 0 & -(b_{11}+m_{11})+k_{11}p & pp_1k_{12} \\ 0 & 0 & a_{12} & 0 & -(b_{12}+m_{12})+p(1-p_1)k_{12} \end{pmatrix}.$$

Using Mathematica software, we find that the eigenvalues of J are given by the roots of the following characteristic polynomial:

$$(\lambda+\mu_1)(\lambda^2+B_1\lambda+C_1)(\lambda^2+B_2\lambda+C_2),$$

where,

$$\begin{aligned} B_1 &= \frac{(a_{11}+b_{11}+m_{11}+\mu_1-pk_{11})}{2}, \\ C_1 &= \frac{((b_{11}\mu_1+m_{11}(a_{11}+\mu_1))(1-R_1))}{4}, \\ B_2 &= \frac{(a_{12}+b_{12}+m_{12}+\mu_1-pk_{12}(1-p_1))}{2}, \\ C_2 &= \frac{((b_{12}\mu_1+m_{12}(a_{12}+\mu_1))(1-R_2))}{4}. \end{aligned}$$

Clearly, $C_i > 0$ if and only if $R_i < 1$, $i = 1, 2$. Moreover, when C_i is non-negative then so is B_i. In fact, if $C_1 > 0$ then $R_1 < 1$. This implies that $pk_{11} < b_{11} + m_{11} + \frac{(m_{11}-k_{11})a_{11}}{\mu_1}$. We have two cases; either $m_{11} \leq k_{11}$ or $m_{11} > k_{11}$. If $m_{11} \leq k_{11}$, then $pk_{11} \leq b_{11} + m_{11}$ which implies that $B_1 > 0$. While if, $m_{11} > k_{11}$, then using the expression of B_1 one can see that $B_1 > 0$. One can prove in a similar way that $B_i > 0$ when $C_i > 0$. By Routh-Hurwitz criterion, we conclude that the DFE is locally asymptotically stable if $R_1 < 1$ and $R_2 < 1$, in other words if $R_0^{TB} < 1$.

3.3. *Existence and stability of EEP near* $R_0^{TB} = 1$

In this subsection, we apply the center manifold theory used in [7] to determine the existence and local stability of a branch of endemic equilibria that bifurcates from the DFE at $R_0^{TB} = 1$. To apply the center manifold theory in [7], we change variables of model equations (2.1) as follows: $S_1 = x_1,\ E_{11} = x_2,\ E_{12} = x_3,\ I_{11} = x_4,\ I_{12} = x_5$ and $P = x_1 + x_2 + x_3 + x_4 + x_5$ and as such $X = (x_1, x_2, x_3, x_4, x_5)^T$

and $\frac{dX}{dt} = F = (f_1, f_2, f_3, f_4, f_5)^T$. Therefore system (2.1) becomes;

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = B - (x_1(k_{11}x_4 + k_{12}x_5)/P - \mu_1 x_1,\\
\frac{dx_2}{dt} &= f_2 = (p'x_1(k_{11}x_4 + p_2k_{12}x_5) + x_2(\eta k_{11}x_4 + \eta_1 k_{12}x_5))/P - (a_1 + \mu)x_2 + b_1x_4,\\
\frac{dx_3}{dt} &= f_3 = (p_2'p'x_1k_{12}x_5 + r_1'x_2(\eta k_{11}x_4 + \eta_1 k_{12}x_5))/P - (a_2 + \mu)x_3 + b_2x_5,\\
\frac{dx_4}{dt} &= f_4 = (px_1 * (k_{11}x_4 + p_1k_{12}x_5))/P - (b_{11} + m_{11})x_4 + a_1x_2,\\
\frac{dx_5}{dt} &= f_5 = (p_1'px_1k_{12}x_5 + r_1x_2(\eta k_{11}x_4 + \eta_1 k_{12}x_5))/P - (b_{12} + m_{12})x_5 + a_{12}x_3.
\end{aligned} \tag{3.3}$$

The Jacobian matrix of system (3.3) at DFE is given by:

$$J = \begin{pmatrix}
-\mu_1 & 0 & 0 & -k_{11} & -k_{12}\\
0 & -(a_{11} + \mu_1) & 0 & b_{11} + (1-p)k_{11} & p_2(1-p)k_{12}\\
0 & 0 & -(a_{12} + \mu_1) & 0 & b_{12} + (1-p)(1-p_2)k_{12}\\
0 & a_{11} & 0 & -(b_{11} + m_{11}) + k_{11}p & pp_1k_{12}\\
0 & 0 & a_{12} & 0 & -(b_{12} + m_{12}) + p(1-p_1)k_{12}
\end{pmatrix}.$$

which is the same as for system (2.1). To determine the occurrence of a bifurcation, we need to set $R_0^{TB} = 1$. In our case, we have two possible R_0^{TB}'s, i.e, R_1 and R_2. Thus we consider two cases:

3.3.1. *Case 1:* $R_1 > R_2$, $R_0^{TB} = R_1 = 1$.

Taking $R_1 = R_0^{TB} = 1$, we let the transmission rate for one strain infection, k_{11} to be the bifurcation parameter. Therefore at $R_0^{TB} = 1$,

$$k_{11} = k_{11}^* = \frac{m_{11}(a_{11} + \mu_1) + \mu_1 b_{11}}{a_{11} + p_1\mu_1},$$

which means that if $k_{11} < k_{11}^*$ then $R_0^{TB} < 1$ and if $k_{11} > k_{11}^*$ then $R_0^{TB} > 1$.

The Jacobian of system (3.3) at $k_{11} = k_{11}^*$ has the following eigenvalues.

$$\left\{0, -\mu_1, l_1, l_2, l_3\right\},$$

where, $l_1 = -(a_{11}(a_{11} + b_{11} + m_{11}(1-p)) + \mu_1(a_{11}(1+p) + \mu_1))/(a_{11} + p\mu_1)$ and $l_2, l_3 = -\frac{1}{2}(h \pm \sqrt{h^2 - h_1})$, with $h = a_{12} + b_{12} + m_{12} + \mu_1 - pk_{12}p_1'$ and $h_1 = 4(b_{12}\mu_1 + m_{12}(\mu_1 + a_{12}))(1 - R_2)$.

We find the right and left eigenvectors associated with the zero eigenvalue. The

right eigenvector, $w = [w_1, w_2, w_3, w_4, w_5]^T$ is given as:

$$\begin{aligned} w_1 &= -(\frac{m_{11}(a_{11}+\mu_1)+b_{11}\mu_1}{\mu_1(a_{11}+\mu_1 p)}), \\ w_2 &= -(\frac{-b_{11}-m_{11}+m_{11}p}{a_1+\mu_1 p_1}), \\ w_3 &= w_5 = 0, \quad w_4 = 1. \end{aligned}$$

The left eigenvector, $v = [v_1, v_2, v_3, v_4, v_5]^T$ is given as:

$$\begin{aligned} v_1 &= 0, \quad v_3 = \frac{a_{12}}{a_{12}+\mu_1}, \quad v_5 = 1, \\ v_2 &= \frac{a_{11}(1-R_2)(b_{12}\mu_1 + m_{12}(a_{12}+\mu_1))}{k_{12}(a_{12}+\mu_1)(pp_1(a_{11}+\mu_1)+a_{11}p_2(1-p))}, \\ v_4 &= \frac{(a_{11}+\mu_1)(1-R_2)(b_{12}\mu_1 + m_{12}(a_{12}+\mu_1))}{(a_{12}+\mu_1)((1-p)a_{11}k_{12}p_2 + pk_{12}p_1(a_{11}+\mu_1))}. \end{aligned}$$

We then compute a and b. We look for the non-zero partial derivatives of f at DFE. Since $v_1 = 0$, then the partial derivatives of f_1 will cancel out after substitution. The non-zero partial derivatives of $f_2,\ f_3,\ f_4,\ f_5$ are:

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_4} = -\frac{k_{11}^* \mu_1 (1-p)}{B}, \quad \frac{\partial^2 f_2}{\partial x_2 \partial x_4} = -\frac{k_{11}^* \mu_1 (\eta + (1-p))}{B}, \quad \frac{\partial^2 f_2}{(\partial x_4)^2} = \frac{-2k_{11}^*(1-p)\mu_1}{B},$$

$$\frac{\partial^2 f_3}{\partial x_2 \partial x_4} = \frac{k_{11}^* \eta (1-r_1)\mu_1}{B}, \quad \frac{\partial^2 f_4}{\partial x_2 \partial x_4} = \frac{-k_{11}^* p \mu_1}{B}, \quad \frac{\partial^2 f_4}{(\partial x_4)^2} = \frac{-2k_{11}^* p \mu_1}{B}, \quad \frac{\partial^2 f_5}{\partial x_2 \partial x_4} = \frac{k_{11}^* \eta r_1 \mu_1}{B}.$$

Let

$$\begin{aligned} n &= 4v_2 w_1 w_4 \frac{\partial^2 f_2}{\partial x_1 \partial x_4} + 4v_2 w_2 w_4 \frac{\partial^2 f_2}{\partial x_2 \partial x_4}, \\ n_1 &= 2v_2 w_4^2 \frac{\partial^2 f_2}{\partial x_4^2} + 4v_3 w_2 w_4 \frac{\partial^2 f_3}{\partial x_2 \partial x_4} + 4v_4 w_2 w_4 \frac{\partial^2 f_4}{\partial x_2 \partial x_4}, \\ n_2 &= 2v_4 w_4^2 \frac{\partial^2 f_4}{(\partial x_4)^2} + 4v_5 w_4 w_2 \frac{\partial^2 f_5}{\partial x_4 \partial x_2}. \end{aligned}$$

Therefore $a = n + n_1 + n_2$. Since a is a large expression, we simulate it numerically by changing the values of η and r_1 so as to determine its sign. Plot is shown in Fig. 2. For the computation of b, we look for the non-zero partial derivatives of f at DFE. We neglect the partial derivatives of f_1 since $v_1 = 0$. Thus the non-zero partial derivatives are given by:

$$\frac{\partial^2 f_2}{\partial x_4 \partial k_{11}^*} = (1-p), \quad \frac{\partial^2 f_4}{\partial x_4 \partial k_{11}^*} = p.$$

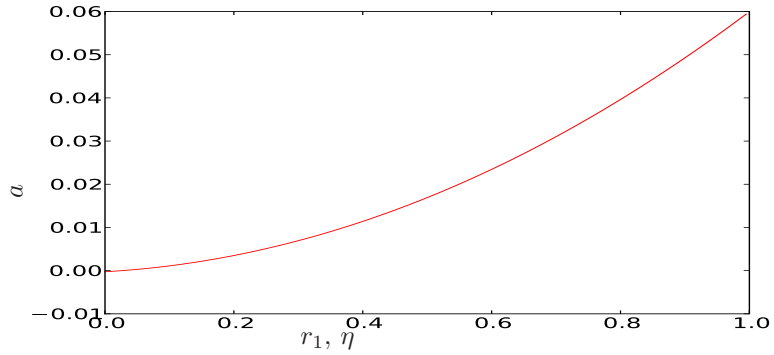


Fig. 2. Numerical result for value of a. $a > 0$ if r_1 and η are both ≥ 0.03

.

It follows from the above expressions that;

$$b = v_2 w_4 \frac{\partial^2 f_2}{\partial x_4 \partial k_{11}^*} + v_4 w_4 \frac{\partial^2 f_4}{\partial x_4 \partial k_{11}^*},$$
$$v_2 w_4 \frac{\partial^2 f_2}{\partial x_4 \partial k_{11}^*} = \frac{a_{11}(1-p)(1-R_2)(b_{12}\mu_1 + m_{12}(a_{12}+\mu_1))}{k_{12}(a_{12}+\mu_1)(pp_1(a_{11}+\mu_1) + a_{11}p_2(1-p))},$$
$$v_4 w_4 \frac{\partial^2 f_4}{\partial x_4 \partial k_{11}^*} = \frac{p(a_{11}+\mu_1)(1-R_2)(b_{12}\mu_1 + m_{12}(a_{12}+\mu_1))}{(a_{12}+\mu_1)((1-p)a_{11}k_{12}p_2 + pk_{12}p_1(a_{11}+\mu_1))}.$$

Since $R_2 < 1$, we have $b > 0$.

From the center manifold theorem in [7], if $a > 0$ and $b > 0$, we have a subcritical (backward) bifurcation at $R_0^{TB} = 1$ and if $a < 0$ and $b > 0$, we have a supercritical (forward) bifurcation at $R_0^{TB} = 1$. We also establish the following result.

Proposition 3.4. *If $R_2 < 1$, an endemic equilibrium guaranteed by center manifold theorem in [7] is locally asymptotically stable for $R_1 > 1$ but close to 1.*

3.3.2. *Case 2: $R_2 > R_1$, $R_0^{TB} = R_2 = 1$.*

We take $R_2 = R_0^{TB} = 1$ and the transmission rate for a mixed infection, k_{12} to be the bifurcation parameter. At $R_0^{TB} = 1$, we have

$$k_{12} = k_{12}^* = \frac{m_{12}(a_{12}+\mu_1) + \mu_1 b_{12}}{p(1-p_1)(a_{12}+\mu_1) + a_{12}(1-p)(1-p_2)},$$

which implies that $R_0^{TB} < 1$ with $k_{12} < k_{12}^*$ and $R_0^{TB} > 1$ with $k_{12} > k_{12}^*$.

The Jacobian of system (3.3) at $k_{12} = k_{12}^*$ has the following eigenvalues,

$$\left\{ 0, -\mu_1, ((l_4 + l_5 + l_6)/l_7), l_8, l_9 \right\},$$

where,

$$\begin{aligned}
l_4 &= a_{12}^2(1-pp_1-p_2(1-p))+p\mu_1^2(1-p_1),\\
l_5 &= a_{12}\left(b_{12}(1-pp_1-p_2(1-p))+m_{12}(1-p-p_2(1-p))\right),\\
l_6 &= a_{12}\mu_1(1+p(1-2p_1)-p_2(1-p)),\\
l_7 &= a_{12}(pp_1-1+p_2(1-p))-p\mu_1(1-p),\\
l_8, l_9 &= -\frac{1}{2}(h_2 \pm \sqrt{h_2^2-h_3}),
\end{aligned}$$

with,

$$\begin{aligned}
h_2 &= a_{11}+b_{11}+m_{11}+\mu_1-pk_{11},\\
h_3 &= 4(b_{11}\mu_1+m_{11}(a_{11}+\mu_1))(1-R_1)
\end{aligned}$$

We find the right and left eigenvectors associated with the zero eigenvalue. The right eigenvector, $w=[w_1,w_2,w_3,w_4,w_5]^T$ is given as:

$$\begin{aligned}
w_1 &= \frac{-z}{\mu_1 z_1}+\frac{k_{11}z_2}{\mu_1 z_3},\quad w_4=-\frac{z_2}{z_3},\quad w_5=1,\\
w_2 &= \frac{-pp_1 z}{a_{11}z_1}+\frac{(-(b_{11}+m_{11})+pk_{11})z_2}{a_{11}z_3},\\
w_3 &= \frac{(b_{11}+m_{12})}{a_{12}}-\frac{p(1-p_1)z}{a_{12}z_1},
\end{aligned}$$

where,

$$\begin{aligned}
z &= b_{12}\mu_1+m_{12}(a_{12}+\mu_1),\\
z_1 &= (1-p)a_{12}(1-p_2)+p(1-p_1)(a_{12}+\mu_1),\\
z_2 &= \frac{z((1-p)a_{11}p_2+pp_1(a_{11}+\mu_1))}{z_1},\\
z_3 &= -(b_{11}\mu_1+m_{11}(a_{11}+\mu_1))(1-R_1).
\end{aligned}$$

The Left eigenvector, $v=[v_1,v_2,v_3,v_4,v_5]^T$ is given as:

$$\begin{aligned}
v_1 = v_2 &= v_4=0,\quad v_5 = 1,\\
v_3 &= \frac{a_{12}}{a_{12}+\mu_1}.
\end{aligned}$$

We then compute a and b. We look for the non-zero partial derivatives of f at DFE. Since $v_1=0$, then the partial derivatives of f_1 will cancel out after substitution. The non-zero partial derivatives of $f_3,\ f_5$ are:

$$\frac{\partial^2 f_3}{\partial x_2 \partial x_4}=\frac{(1-r_1)\eta k_{11}\mu_1}{B},\quad \frac{\partial^2 f_3}{\partial x_2 \partial x_5}=\frac{k_{12}^*\mu_1((1-r_1)\eta_1-(1-p_2)(1-p))}{B},$$

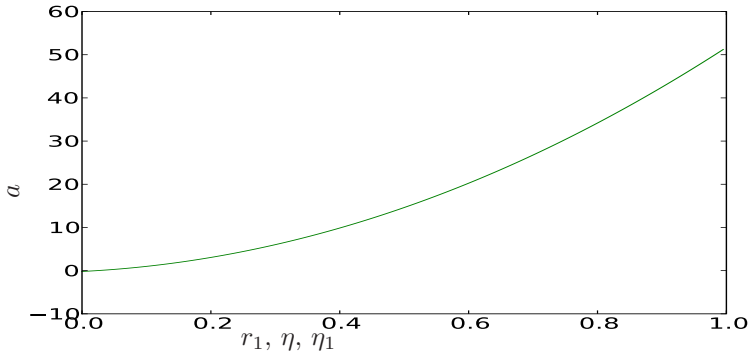


Fig. 3. As r_1, η, η_1 vary simultaneously, the sign of value of a changes from negative to positive. $a > 0$ when the values of r_1, η, η_1 are all ≥ 0.025.

$$\frac{\partial^2 f_3}{\partial x_3 \partial x_5} = -\frac{k_{12}^* \mu_1 (1-p_2)(1-p)}{B}, \quad \frac{\partial^2 f_3}{\partial x_4 \partial x_5} = -\frac{(1-p_2)(1-p) k_{12}^* \mu_1}{B},$$

$$\frac{\partial^2 f_3}{(\partial x_5)^2} = -\frac{2k_{12}^* \mu_1 (1-p_2)(1-p)}{B}, \quad \frac{\partial^2 f_5}{\partial x_2 \partial x_4} = \frac{r_1 \eta k_{11} \mu_1}{B}, \quad \frac{\partial^2 f_5}{\partial x_2 \partial x_5} = \frac{k_{12}^* \mu_1 (r_1 \eta_1 - (1-p_1)p)}{B},$$

$$\frac{\partial^2 f_5}{\partial x_3 \partial x_5} = -\frac{k_{12}^* (1-p_1) p \mu_1}{B}, \quad \frac{\partial^2 f_5}{\partial x_4 \partial x_5} = -\frac{k_{12}^* (1-p_1) p \mu_1}{B}, \quad \frac{\partial^2 f_5}{(\partial x_5)^2} = -\frac{2k_{12}^* (1-p_1) p \mu_1}{B}.$$

Let

$$n_3 = 4v_3 w_2 w_4 \frac{\partial^2 f_3}{\partial x_2 \partial x_4} + 4v_3 w_2 w_5 \frac{\partial^2 f_3}{\partial x_2 \partial x_5} + 4v_3 w_3 w_5 \frac{\partial^2 f_3}{\partial x_3 \partial x_5},$$

$$n_4 = 4v_3 w_4 w_5 \frac{\partial^2 f_3}{\partial x_4 \partial x_5} + 2v_3 w_5^2 \frac{\partial^2 f_3}{(\partial x_5)^2} + 4v_5 w_2 w_4 \frac{\partial^2 f_5}{\partial x_2 \partial x_4} + 4v_5 w_2 w_5 \frac{\partial^2 f_5}{\partial x_2 \partial x_5},$$

$$n_5 = 4v_5 w_3 w_5 \frac{\partial^2 f_5}{\partial x_3 \partial x_5} + 4v_5 w_4 w_5 \frac{\partial^2 f_5}{\partial x_4 \partial x_5} + 2v_5 w_5^2 \frac{\partial^2 f_5}{(\partial x_5)^2}.$$

Thus $a = n_3 + n_4 + n_5$. a is a large expression and to determine its value and sign, we simulate the expression with different values of r_1, η and η_1 numerically. Plot is shown in the Fig. 3. Fig. 3 shows that $a > 0$ when the values of r_1, η, η_1 are all ≥ 0.025. For the computation of b, we also need to look for the non-zero partial derivatives of f at DFE. We neglect the partial derivatives of f_1 since $v_1 = 0$. Thus the non-zero partial derivatives are given by;

$$\frac{\partial^2 f_3}{\partial x_5 \partial k_{12}^*} = (1-p_2)(1-p), \quad \frac{\partial^2 f_5}{\partial x_5 \partial k_{12}^*} = (1-p_1)p.$$

It follows from the above expressions that;

$$b = v_3 w_5 \frac{\partial^2 f_3}{\partial x_5 \partial k_{12}^*} + v_5 w_5 \frac{\partial^2 f_5}{\partial x_5 \partial k_{12}^*} = \frac{a_{12}(1-p_2)(1-p) + (a_{12} + \mu_1)(1-p_1)p}{a_{12} + \mu_1}.$$

Clearly, $b > 0$

By the center manifold theorem in [7], if $a > 0$ and $b > 0$, we have a subcritical (backward) bifurcation at $R_0^{TB} = 1$ and if $a < 0$ and $b > 0$, we have a supercritical (forward) bifurcation at $R_0^{TB} = 1$. We also establish the following result.

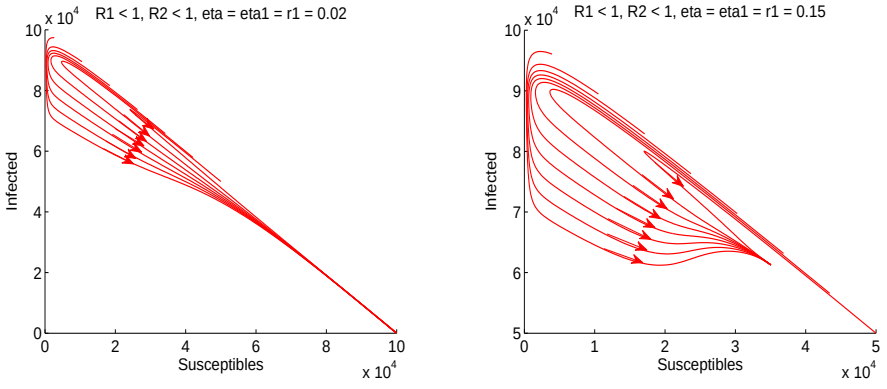
Proposition 3.5. *If $R_1 < 1$, an endemic equilibrium guaranteed by center manifold theory in [7] is locally asymptotically stable for $R_2 > 1$ but close to 1.*

3.4. *Numerical simulations for equilibrium points*

Using a hypothetical population of $100,000$ individuals, we run our model until equilibrium with different initial conditions and values of parameters in Table. 1 so as to determine and show equilibrium points. We obtain phase portraits using Matlab 5.0 and the Runge-Kutta method. Results are shown in Fig. 4 and Fig. 5.

Results in this subsection show that it is possible to have backward bifurcation for certain parameter values of r_1, η, η_1. These parameters are associated with acquiring and developing active TB due to mixed infection. The phenomenon of backward bifurcation is important because it implies that even if $R_0^{TB} < 1$, the disease may persist in the population.

Phase portrait diagrams in Fig. 4 show that we can have both an endemic equilibrium and DFE when R_0^{TB} is less than unity for certain values of r_1, η and η_1 which demonstrates backward bifurcation. Phase portrait diagrams in Fig. 5 show local asymptotic stability of the DFE and EEPs.



(a) (b)

Fig. 4. Using different initial conditions, we have the DFE in FIG. 4(a) for $R_1 < 1$, $R_2 < 1$ thus $R_0^{TB} < 1$ with $r_1 = \eta = \eta_1 = 0.02$. For $r_1 = \eta = \eta_1 = 0.15$, we have an EEP even with $R_0^{TB} < 1$ as shown in FIG. 4(b). This shows the phenomenon of backward bifurcation.

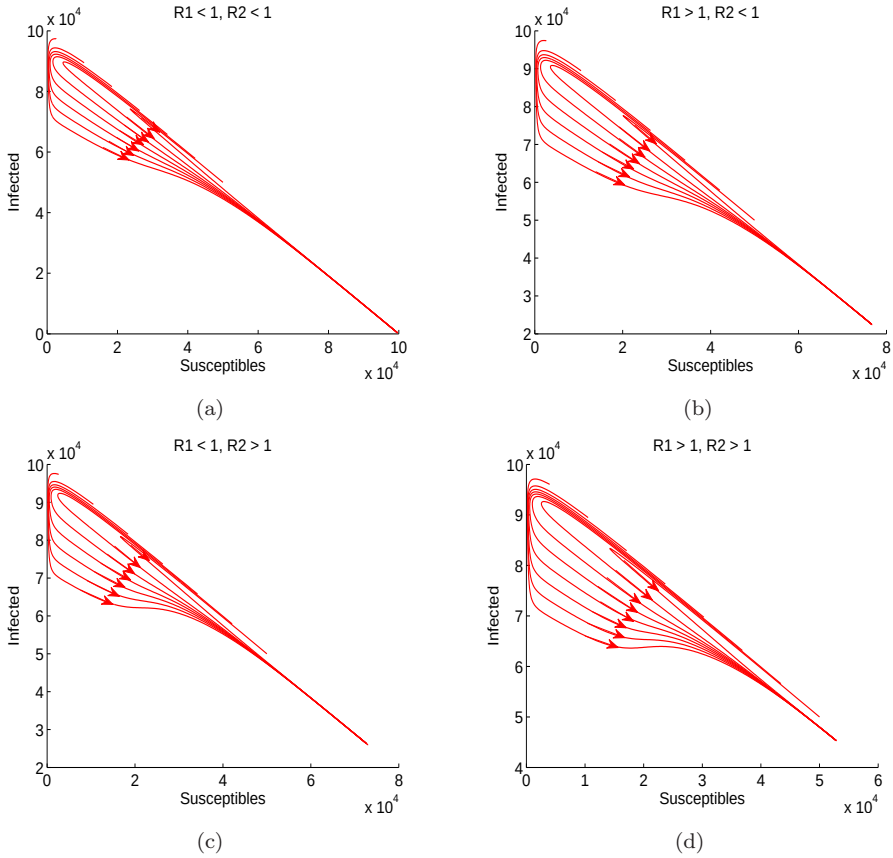


Fig. 5. Using different initial conditions, we have the DFE for $R_1 < 1$, $R_2 < 1$ thus $R_0^{TB} < 1$ in Fig. 5(a) and EEPs for $R_2 < 1 < R_1$ and $R_1 < 1 < R_2$ in Figs. 5(b) and 5(c) and for $R_1 > 1$, $R_2 > 1$ in Fig. 5(d) respectively. In these cases for the EEPs, $R_0^{TB} > 1$. These phase portraits show local asymptotic stability of the DFE and EEPs.

4. Numerical Simulations - Effect of mixed infection on TB dynamics

We use the model to find the effect of mixed infection on TB prevalence, MTB infection rate and TB incidence rate. We examine what happens to the TB dynamics when we increase parameter values associated with mixed infection. We calculate TB prevalence, MTB infection rate and TB incidence rate using formulas given in Table. 2. We run our model until equilibrium. The numerical results are shown in Figs. 6, 7, 8 and 9.

Table 1. Definitions and values of parameters in mixed infection TB model

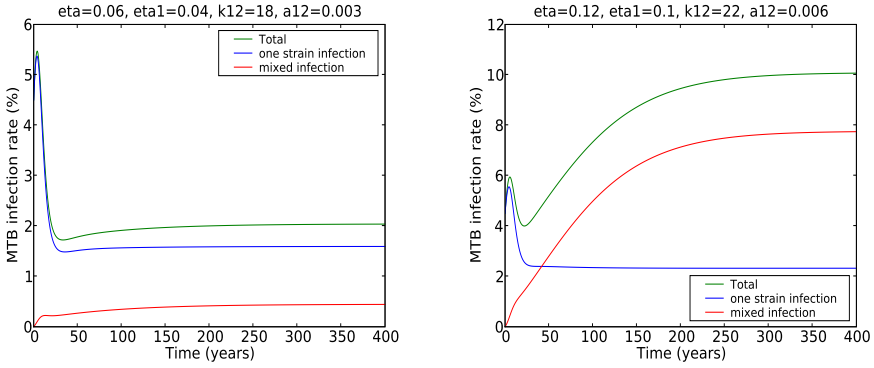
Parameter	Definition	Value	Reference
$B,\ \mu_1$	birth rate, natural death rate	$1820,\ 0.0182$	[1, 31]
a_{11}, a_{12}	reactivation rate to active TB for E_{11} and E_{12} respectively	$0.0006,\ 0.003$	[1, 18, 37]
$k_{11},\ k_{12}$	transmission rate for one strain infection and for mixed infection respectively	$9,\ 18$	[1, 16, 23]
p	proportion of infected individuals who progress fast to active TB	0.09	[1, 11, 37]
p'	proportion of infected individuals who join latent group	0.91	[1, 11, 37]
$p_1,\ p_1'$	proportion of fast progressors who go to I_{11} and I_{12} respectively	$0.9,\ 0.1$	estimate
$p_2,\ p_2'$	proportion of slow progressors who join E_{11} and E_{12} respectively	$0.9,\ 0.1$	estimate
$r_1,\ r_1'$	proportion of reinfections who join I_{12} and E_{12} respectively	$0.56p,\ (1-0.56p)$	[1, 11, 37]
η	probability of contact between E_{11} and I_{11} resulting in mixed infection	0.06	estimate
η_1	probability of contact between E_{11} and I_{12} resulting in mixed infection	0.04	estimate
m_{11}, m_{12}	death rate for I_{11} and I_{12} respectively	$0.2,\ 0.25$	[1, 10]
b_{11}, b_{12}	recovery rate for I_{11} and I_{12} respectively	$0.45,\ 0.4$	[18, 23]
γ	Percentage of active TB individuals who are tested for mixed infection	variable: $0-100\%$	

Table 2. Correspondence between some medical vocabulary and the model

Medical vocabulary	Model expression
Total population	$P = S_1 + E_{11} + E_{12} + I_{11} + I_{12}$
TB incidence (one strain)	$pS_1(k_{11}I_{11} + p_1k_{12}I_{12})/P + a_{11}E_{11}$
TB incidence (mixed)	$(pp'_1S_1k_{12}I_{12})/P + r_1E_{11}(\eta k_{11}I_{11} + \eta_1k_{12}I_{12})/P + a_{12}E_{12}$
TB prevalence	$(I_{11} + I_{12})/P$
MTB infection rate	$(k_{11}I_{11} + k_{12}I_{12})/P$
TB prevalence	I_{12}/P

4.1. *MTB infection rate*

This is the rate at which individuals acquire an MTB infection during a specified period. It is closely linked to the annual risk of infection (ARI) which represents the probability of becoming infected in a one year period. If MTB infection rate is high, then it implies that many new MTB infections are occuring. We are interested in knowing how many MTB infections occur in presence of mixed infection. We use the formulation in Table. 2 to calculate them. Fig. 6 gives the numerical result. In



(a) (b)

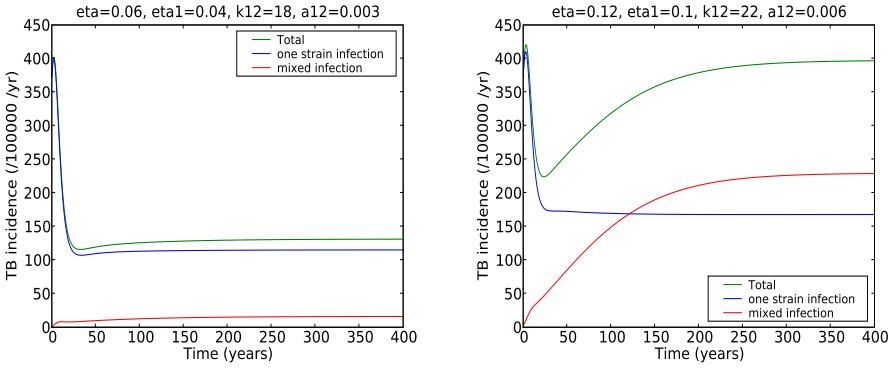
Fig. 6. MTB infection rate increases with increasing values of a_{12} and k_{12}.

Fig. 6, MTB infection rate increases with increasing values of parameters related with mixed infection. At equilibrium, total MTB infection rate is 2.0% with mixed infection imparting 21.8% in Fig. 6(a). In Fig. 6(b), total MTB infection rate is 10.1% with mixed infection imparting 76.9%. With increasing values of reactivation rate and transmission rate for individuals with mixed infection, there is increase in the MTB infection rate. This is because mixed infected individuals are more infectious than one strain infection individuals because of their potential to spread either one strain or all the strains at the same time.

4.2. *TB incidence rate*

TB incidence rate is defined as the number of new cases of TB during a specified period of time. The total TB incidence rate is the summation of the TB incidence rate for the one strain infection and that for mixed infection. We consider it as per $100,000$ people. We are also interested in the number of new cases caused by mixed infection and how much it adds to TB incidence. Fig. 7 shows how the total TB incidence rate changes with time as some parameter values change.

Total TB incidence rate rises with rising parameter values closely linked to mixed infection. In Fig. 7(a), it is $131/100,000$ to which mixed infection contributes 12.2%



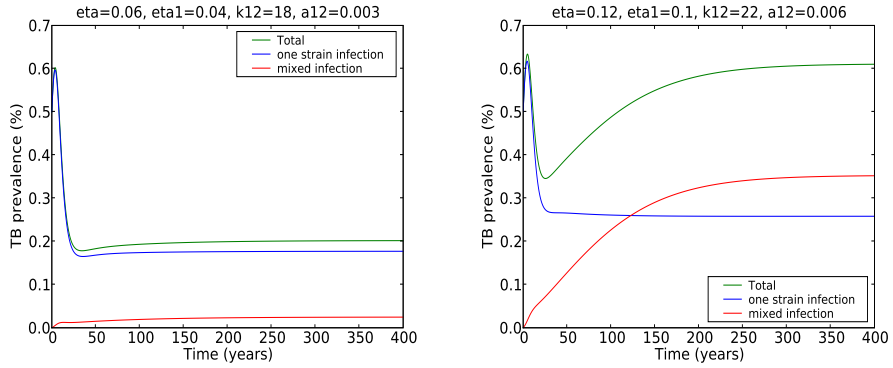
(a) (b)

Fig. 7. Increasing values of parameters of mixed infected individuals leads to a rise in the number of new active TB cases thus causing an a shoot up in Total TB incidence rate.

when model is run until equilibrium. In Fig. 7(b), it is $397/100,000$ with mixed infection imparting 57.7%. Thus mixed infection evokes rises in TB incidence rates.

4.3. *TB prevalence*

TB prevalence represents the number of people sick with TB at a given point in time. It gives the number of those that are infectious. At steady state, Total TB



(a) (b)

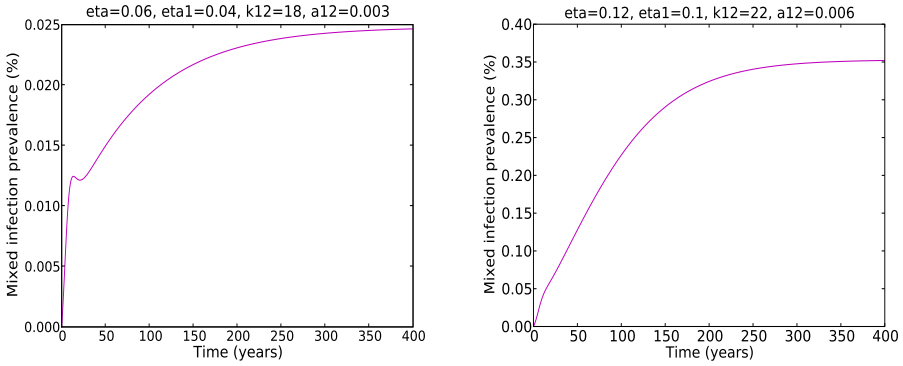
Fig. 8. TB prevalence rises with rising values of parameters linked to mixed infection. Parameters are in Table. 8.

prevalence is 0.2% with contribution of 12.2% by mixed infection as shown in Fig. 8(a). In Fig. 8(b), it is 0.61% to which mixed infection gives 57.7%. Hence the

prevalence of mixed infection in active TB individuals is 12.2% and 57.7% in Fig. 8(a) and Fig. 8(b) respectively. In studies done, it ranged from 2.3% to 75% [25, 34].

4.4. *Prevalence of mixed infection in population*

This is determined from the model. It is calculated using formulation in TABLE. 2. Numerical results are given in Fig. 9. Fig. 9(a) gives the prevalence of mixed



(a) (b)

Fig. 9. Prevalence of mixed infection is 0.025% in Fig. 9(a) and 0.35% in Fig. 9(b).

infection in the population as 0.025% at equilibrium and from Fig. 9(b), it is 0.35% with the parameter values that have been used.

A clear study of numerical results of this section shows that increasing the parameters related with mixed infection by two times leads to an increase in the MTB infection rate, TB incidence rate and TB prevalence by more than twice their initial value, with mixed infection contributing more than 50% to that value. This highlights the consequences of mixed infection in a population.

5. Discussion

In this paper, we have studied the mathematical dynamics of mixed infection in TB. The analysis of the model showed the existence of multiple endemic equilibria and backward bifurcation for certain parameter values. This means that even when $R_0^{TB} < 1$, the disease may persist in the population.
Parameters such as transmission rate, reactivation rate for mixed infected individuals as well as probabilities of latent individuals acquiring mixed infection are important in establishing mixed infection. The values of these parameters would be high in areas with poor living conditions, overcrowding and high strain diversity.
Mixed infection leads to an increase in TB incidence, TB prevalence and MTB infection rate even with no HIV and may be an explanation of what has been observed

in certain areas in Western Cape, South Africa. In one of the areas studied in [4, 20], the ARI was as high as 3.7% in 1998-1999 survey and 4.1% in 2005 survey with an HIV prevalence of less than 10% [15, 20, 26]. TB notifications had been increasing i.e from $673/100,000$ to $834/100,000$ between 1998 and 2002 yet the detection and treatment services had improved over the years. However, it was noted that the living conditions in this area were poor, there was overcrowding and high strain diversity. All these contribute greatly to mixed infection.

In conclusion, backward bifurcation occurs for certain parameter values meaning that even when $R_0^{TB} < 1$, the disease may persist in the population. Parameters such as transmission rate, reactivation rate for mixed infected individuals as well as probabilities of latent individuals acquiring mixed infection are important in establishing mixed infection and these have high values in areas of overcrowding, high strain diversity and where living conditions are poor.

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