

A mathematical analysis of the tuberculosis epidemic.

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Abstract: Long latency period has been seen as a major setback in the control of tuberculosis (TB) [33], because an individual infected of TB can be latent for years [26, 27]. In this paper, a four compartment deterministic model is presented to change the narrative. It is established that making sure every individual infected of TB pass through the latent stage would actually reduce the TB incident rate. Also established from the model is that prevention against TB re-infection has no significant contribution to the disease incident rate, which implies the money meant to guard against TB reinfection should not be wasted. The formulated model was shown to be locally asymptotically stable at the disease free equilibrium (DFE) whenever $R_0 < 1$ and the global asymptotic stability (GAS) at this point was as well established. It is as well shown that the endemic equilibrium point (EEP) is locally asymptotically stable with the aid of phase portrait and the GAS of the EEP was established by defining a suitable Lyapunov function.

Keywords: Tuberculosis Model, Latency Stage Bypass, Lyapunov Function, Immunity Loss.

AMS 2010 Subject Classification: 34D20, 92D25, 92D30

1 Introduction

In this 21st century, tuberculosis (TB) is the 9th cause of death globally [2]. In fact, it is the number one cause of death from a single infectious agent. This infection is responsible for 1.4 million deaths in 2015 [3], 1.3 million deaths in 2016 [2] and also 1.3 million deaths in 2017 [5]. Depending on the body part(s) affected, this infection caused by *Mycobacterium tuberculosis* (*Mtb*) can either be pulmonary or extrapulmonary. Pulmonary affect the lungs while extrapulmonary affect other body parts like; kidney, brain, spine, bones and joints. The release of *Mycobacterium tuberculosis* to the air through cough is the most common mode of its transmission, but having contact with the infected sputum could also be another way of getting the infection [1].

Numerous deterministic mathematical models have been formulated to study this epidemic. Okunoghae and Omosigho [8] focused their attention on detection of TB. Their model revealed that effective awareness program and active cough identification are ways to increase the TB case detection. Porco and Blower [11] came up with a model to understand the transmission dynamics of TB in the absence of treatment, leading them to conclude that disease reactivation rate, number of persons infected by an infectious individual annually, disease rate death rate and the recruitment rate contribute significantly to the severity of TB epidemic.

Khajanchi et al. [31] demonstrated the relevance of TB transmission and exogenous re-infection rates to TB dynamics. These two factors promote the disease incidence and should be properly addressed. Nkamba et al. [28] on the other hand showed that vaccination of individuals do not totally eradicate TB and as such, HIV control, poverty reduction and sensitization should be key strategies employed to combat TB. This result is in agreement with that discussed in [16] where awareness was shown to be a key measure to reducing TB incident rate. In the

research of Herrera et al. (2013) [12], it was demonstrated that attention should be focused on semi-closed communities as they are major sources of TB spread. Since densely populated environments promote high contact rate, Bhunu et al. [13] showed that poverty (which could lead to dense population) in a particular area has significant impact on the rise of TB cases. Smoking is another contributor to the spread of TB as the authors in [21] have shown that smoking increase the chances of getting infected with TB. Immigration is another factor that increases TB infection and has been established by [14], [9] and [29]. Tuberculosis is basically treated with rifampicin and isoniazid (the first line anti-tubercular drugs). This infection is of different strains, depending on the level of its resistance to the recommended medications. The variations are; drug susceptible TB (DS-TB), rifampicin resistant TB (RR-TB), multidrug resistant TB (MDR-TB), extensively drug resistant TB (XDR-TB) and totally drug resistant TB (TDR-TB). Drug susceptible is the most common one and so, the focus of this research. Also, this infection is characterised by long latency period [4], which implies that the time at which the infected person becomes infectious is not easily determined. Presently, a quarter of the world population is estimated to have latent tuberculosis infection (LTBI) [6] out of which 10% develops active TB [10]. This is an improvement as compared to the previous estimate of one-third of the world population [7]. However, rather than seeing the latent period as a set back in dealing with the infection, the advantage of latency is presented here. This paper consists of five sections with this part being the first (introduction). The second part introduces the model formulation where the design of the model is discussed, the third part deals with the analytical results of the model and section four presents the numerical results. The conclusion is presented in the fifth section.

2 Model Formulation

2.1 Introduction

Human population is divided into four groups; susceptible individuals S , infected asymptomatic individuals (exposed) E , infected with symptoms (infectious) I and the recovered individuals R . The source of recruitment into the population is through the susceptible compartment with recruitment rate πN and the total population $N(t)$ at any time t is

$$N(t) = S(t) + E(t) + I(t) + R(t). \quad (1)$$

Homogenous mixing is assumed and a susceptible individual contracts TB infection after a contact with an infectious individual at the rate

$$\lambda = \frac{\beta c I}{N}, \quad (2)$$

where β is the probability of a susceptible individual getting infected and c is the per capita contact rate.

Susceptible individuals progress to the exposed and the infectious stages at the rates $f\lambda$ and $(1 - f)\lambda$ respectively while the recovered individuals get back to the exposed and infectious compartments at the rates $f_1\lambda$ and $(1 - f_1)\lambda$ respectively. $\delta\lambda$ is the exogenous re-infection rate while k is the endogenous re-activation rate. People are assumed to die naturally at the rate μ and die of TB infection at the rate ε , while infectious individuals recover naturally at the rate ω and recover due to treatment at the rate σ . Since there is no total immunity against re-infection in the case of bacterial infection, a fraction of the recovered class is expected to move back to the susceptible class at the rate α . Note that except for c , all parameter values here are in the interval $(0, 1]$. The mathematical system describing the model is

$$\frac{dS}{dt} = \pi N + \alpha R - (\lambda + \mu)S, \quad (3)$$

$$\frac{dE}{dt} = f\lambda S + f_1\lambda R - (\delta\lambda + k + \mu)E, \quad (4)$$

$$\frac{dI}{dt} = (1-f)\lambda S + (1-f_1)\lambda R + (\delta\lambda + k)E - (\sigma + \omega + \varepsilon + \mu)I, \quad (5)$$

and

$$\frac{dR}{dt} = (\sigma + \omega)I - (\lambda + \alpha + \mu)R, \quad (6)$$

with the initial conditions:

$$S(0) = S_0 \leq 0, \quad E(0) = E_0 \leq 0, \quad I(0) = I_0 \leq 0, \quad R(0) = R_0 \leq 0,$$

which is normalized to give

$$\frac{ds}{dt} = \pi + \alpha r - [\pi + (\beta c - \varepsilon)i]s, \quad (7)$$

$$\frac{de}{dt} = f\beta c i s + f_1\beta c i r - [\pi + k + (\delta\beta c - \varepsilon)i]e, \quad (8)$$

$$\frac{di}{dt} = (1-f)\beta c i s + (1-f_1)\beta c i r + (\delta\beta c i + k)e - [\pi + \sigma + \omega + \varepsilon(1-i)]i \quad (9)$$

and

$$\frac{dr}{dt} = (\sigma + \omega)i - [\pi + \alpha + (\beta c - \varepsilon)i]r. \quad (10)$$

with the initial conditions:

$$s(0) = s_0 \leq 0, \quad e(0) = e_0 \leq 0, \quad i(0) = i_0 > \leq 0, \quad r(0) = r_0 \leq 0, \quad (*)$$

where

$$s + e + i + r = 1$$

such that $\frac{S}{N}$, $\frac{E}{N}$, $\frac{I}{N}$ and $\frac{R}{N}$ are consecutively denoted by s , e , i and r .

2.2 Positivity of the Solution

The formulated model (nonlinear system (7)-(10)) above shall only be epidemiologically meaningful if all the variables are non-negative at any time t . Hence, the positivity of the model is thus established.

Lemma 2.1 *Given that the initial conditions of (nonlinear system (7)-(10)) are as given in (*), then the solutions $s(t)$, $e(t)$, $i(t)$, and $r(t)$ are positive for all $t > 0$.*

Proof. Suppose that $t^* = \sup\{t > 0 : s(t) > 0, e(t) > 0, i(t) > 0, r(t) > 0\} > 0$, then from the first equation of system (7)-(10),

$$\frac{ds}{dt} = \pi + \alpha r - [\pi + (\beta c - \varepsilon)i]s,$$

let $(\beta c - \varepsilon)i = \Lambda_1$, then

$$\begin{aligned} \frac{ds}{dt} &= \pi + \alpha r - [\pi + \Lambda_1]s \geq \pi - [\pi + \Lambda_1]s, \\ \frac{d}{dt} \left[s(t) e^{(\pi t + \int_0^t \Lambda_1(\xi) d\xi)} \right] &\geq \pi e^{(\pi t + \int_0^t \Lambda_1(\xi) d\xi)} \\ \Rightarrow s(t^*) e^{(\pi t^* + \int_0^{t^*} \Lambda_1(\xi) d\xi)} - s(0) &\geq \int_0^{t^*} \pi e^{(\pi y + \int_0^y \Lambda_1(\xi) d\xi)} dy \\ \Rightarrow s(t^*) &\geq e^{-(\pi t^* + \int_0^{t^*} \Lambda_1(\xi) d\xi)} \left[s(0) + \int_0^{t^*} \pi e^{(\pi y + \int_0^y \Lambda_1(\xi) d\xi)} dy \right] > 0. \end{aligned}$$

$e(t)$, $i(t)$ and $r(t)$ can similarly be shown to be positive.

3 Equilibrium Points, Basic Reproduction Number (R_0) and Stability of the Equilibrium Points

3.1 Equilibrium Points

At equilibrium, the nonlinear system [(7)-(10)] becomes

$$0 = \pi + \alpha r - [\pi + (\beta c - \varepsilon)i]s \quad (11)$$

$$0 = f\beta cis + f_1\beta cir - [\pi + k + (\delta\beta c - \varepsilon)i]e \quad (12)$$

$$0 = (1 - f)\beta cis + (1 - f_1)\beta cir + (\delta\beta ci + k)e - [\pi + \sigma + \omega + \varepsilon(1 - i)]i \quad (13)$$

$$0 = (\sigma + \omega)i - [\pi + \alpha + (\beta c - \varepsilon)i]r. \quad (14)$$

The system of equations (11)-(14) was expressed in terms of i to establish the set of equilibria $\{P_1, P_2, P_3, P_4, P_5\}$.

$$A_5 i^5 + A_4 i^4 + A_3 i^3 + A_2 i^2 + A_1 i = 0, \quad (15)$$

where A_1, A_2, A_3, A_4 and A_5 are given in the Appendix.

$$P_1 = (s_1, e_1, i_1, r_1) = (1, 0, 0, 0),$$

$$P_2 = (s_2, e_2, i_2, r_2),$$

$$P_2 = \left\{ \frac{\pi\beta c + \alpha(\sigma + \omega + \varepsilon)}{\beta c[\alpha\varepsilon + \pi\beta c]}, \frac{\pi f\varepsilon[\pi\beta c + \alpha(\sigma + \omega + \varepsilon)] + \pi^2 f_1\beta c(\sigma + \omega)}{[\pi\beta c + \alpha\varepsilon][\pi\delta\beta c + k\varepsilon]}, \frac{\pi}{\varepsilon}, \frac{\pi(\sigma + \omega)}{[\alpha\varepsilon + \pi\beta c]} \right\}.$$

$P_3 - P_5$ are too long to be expressed here.

The validity of the solutions (equilibrium points) gotten is investigated by subjecting them to two conditions;

- i. Substitution of the value of i into (15) is expected to give its LHS as 0.
- ii. The sum of s, e, i and r is 1.

All the equilibrium points passed the tests except P_2 that failed the second condition and as such was rejected, hence the equilibrium points reduce to four (4). By inspection, P_1 coincides with the disease free equilibrium (DFE) which can easily be verified by setting $i = 0$ in the nonlinear system [(7)-(10)]

3.2 Basic Reproduction Number (R_0) and Stability Analysis

3.2.1 Establishing the Basic Reproduction Number (R_0)

Basic reproduction number (R_0) is simply the number of secondary infections due to one singly recorded case. Using the next generation matrix (see [18] for details), the basic reproduction number, R_0 of the model is

$$R_0 = \frac{\beta c[k + \pi(1 - f)]}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)}. \quad (16)$$

Theorem 3.1 *Whenever $f = 1$ in R_0 , that is when there is no bypassing of the exposed class, the infection becomes less rampaging.*

Proof. Since $f \leq 1$,

$$0 \leq \pi(1 - f). \quad (17)$$

$$\Rightarrow k \leq k + \pi(1 - f), \quad (18)$$

multiplying (18) by βc and subsequently dividing by $(\pi + k)(\pi + \sigma + \omega + \varepsilon)$ gives

$$\frac{\beta c k}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)} \leq \frac{\beta c [k + \pi(1 - f)]}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)}. \quad (19)$$

That is

$$R_{0_1} \leq R_0,$$

where

$$R_{0_1} = \frac{\beta c k}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)}.$$

When

$$f < 1 \Rightarrow R_{0_1} < R_0 \quad (20)$$

and when

$$f = 1 \Rightarrow R_{0_1} = R_0. \quad (21)$$

(21) concludes the proof.

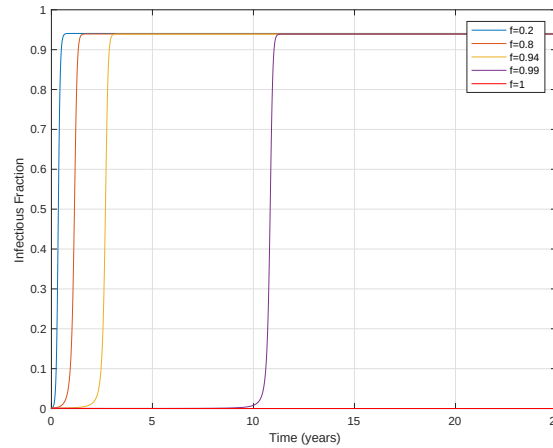


Figure 1: Impact of f on the TB infection

Theorem 3.1 above explains the role of the exposed compartment in the endemicity of the infection, it slows down the infection and in fact, drastically reduces its incidence. This is supported by Figure 1 where the value of f is varied. $f = 0.2$, $f = 0.8$, and $f = 0.94$ show early outbreak of TB infection, $f = 0.99$ delays the outbreak while $f = 1$ (every infected individual passes through the exposed state before proceeding to the infectious) almost annihilate the infection. Since exposed state refers to an asymptomatic stage of the infection, great efforts are required to identify the *Mycobacterium tuberculosis* (*Mtb*) carriers at this stage.

4 Stability Analysis of the Equilibrium Points of Equations (7)-(10)

4.1 Stability of the DFE

4.1.1 Local Stability

Theorem 4.1 *The DFE of the model [equations (7)-(10)] is locally asymptotically stable whenever $R_0 < 1$ and unstable otherwise.*

Proof. Establishing the Jacobian matrix of the system (7)-(10) and subsequently evaluating at the DFE, $(1, 0, 0, 0)$ gives

$$J = \begin{pmatrix} -\pi & 0 & -(\beta c - \varepsilon) & \alpha \\ 0 & -(\pi + k) & f\beta c & 0 \\ 0 & k & (1-f)\beta c - (\pi + \sigma + \omega + \varepsilon) & 0 \\ 0 & 0 & (\sigma + \omega) & -(\pi + \alpha) \end{pmatrix}. \quad (22)$$

The eigenvalues of (22) denoted as η_i ($i = 1, 2, 3, 4$) are $\eta_1 = -\pi$ and $\eta_2 = -(\pi + \alpha)$. The remaining two eigenvalues η_3 and η_4 are gotten from the equation below

$$\begin{aligned} &\eta^2 + \{(\pi + k) + (\pi + \sigma + \omega + \varepsilon) - \beta c(1-f)\}\eta \\ &+ \{(\pi + k)(\pi + \sigma + \omega + \varepsilon) - \beta c[k + \pi(1-f)]\} = 0. \end{aligned} \quad (23)$$

$$\eta_3, \eta_4 = \frac{-b \pm \sqrt{b^2 - 4\{(\pi + k)(\pi + \sigma + \omega + \varepsilon) - \beta c[k + \pi(1-f)]\}}}{2} \quad (24)$$

$$= \frac{-b \pm \sqrt{b^2 - 4(\pi + k)(\pi + \sigma + \omega + \varepsilon) \left\{1 - \frac{\beta c[k + \pi(1-f)]}{(\pi + k)(\pi + \sigma + \omega + \varepsilon)}\right\}}}{2}, \quad (25)$$

where $b = (\pi + k) + (\pi + \sigma + \omega + \varepsilon) - \beta c(1-f)$.

Hence,

$$\eta_3, \eta_4 = \frac{-b \pm \sqrt{b^2 - 4(\pi + k)(\pi + \sigma + \omega + \varepsilon)(1 - R_0)}}{2}. \quad (26)$$

Since the eigenvalues of (26) depend on R_0 , $R_0 < 1 \Rightarrow \eta_3, \eta_4 < 0$ while $R_0 > 1 \Rightarrow \eta_3 > 0 (< 0)$ and $\eta_4 < 0 (> 0)$. Hence, $R_0 < 1$ guarantees the stability and as such completes the proof.

4.1.2 Global Stability

The global stability theorem as discussed by [19] and used by [21], [22] and [23] is employed to establish the global stability of the nonlinear system (7)-(10).

If the system of equations (7)-(10) can be written in the form:

$$\frac{dX}{dt} = F(X, Y) \quad \text{and} \quad \frac{dY}{dt} = G(X, Y) \quad \ni : G(X, \mathbf{0}) = 0,$$

where the uninfected and infected compartments are respectively represented as $X = (s, r)^T$ and $Y = (e, i)^T$, and also, the DFE, P_1 is simply expressed as

$$P_1 = (X_0^*, \mathbf{0})$$

where

$$X_0^* = (1, \mathbf{0}),$$

then the DFE is globally asymptotically stable (GAS) provided $R_0 < 1$ and as well satisfies the conditions H_1 and H_2 given below.

H_1 : for $\frac{dX}{dt} = F(X_0, \mathbf{0})$, X_0^* is globally asymptotically stable.

H_2 : for $G(X, Y) = AY - \hat{G}(X, Y)$, $\hat{G}(X, Y) \geq 0$,

where $A = D_Y G(X_0^*, \mathbf{0})$ is M-matrix (that is, all the non-diagonal elements of the matrix are non-negative).

Theorem 4.2 *The DFE, $P_1 = (X_0^*, \mathbf{0})$ of the nonlinear system (7)-(10) is globally asymptotically stable (GAS) provided it satisfies the conditions H_1 and H_2 above, as well as $R_0 < 1$.*

Proof. From the above, the following are established

$$F(X_0, \mathbf{0}) = \begin{pmatrix} \pi - \pi s \end{pmatrix}$$

and

$$G(X, Y) = AY - \hat{G}(X, Y),$$

where

$$A = \begin{pmatrix} -[\pi + k + (\delta\beta c - \varepsilon)i] & f\beta cs + f_1\beta cr - (\delta\beta c - \varepsilon)e \\ \delta\beta ci + k & (1-f)\beta cs + (1-f_1)\beta cr + \delta\beta ce - (\pi + \sigma + \omega + \varepsilon) + 2\varepsilon i \end{pmatrix}, \quad (27)$$

and

$$\hat{G}(X, Y) = \begin{pmatrix} \hat{G}_1(X, Y) \\ \hat{G}_2(X, Y) \end{pmatrix} = \begin{pmatrix} f\beta cis + f_1\beta cir \\ (1-f)\beta cis + (1-f_1)\beta cir + \delta\beta cie \end{pmatrix}. \quad (28)$$

Recall that $Y_0 = Y(0) \geq 0 \Rightarrow Y(t) \geq 0$. Since A is an M-matrix, then e^{At} is a positive semigroup. Using the variation of constant formula, see e.g [24] and [25] gives

$$\begin{aligned} 0 \leq Y(t) &= e^{At}Y_0 - \int_0^t e^{A(t-w)} \hat{G}(X(w), Y(w))dw \\ &\leq e^{At}Y_0. \end{aligned} \quad (29)$$

It is obvious from (26) that A has dominant eigenvalue $m(A) < 0$ for $R_0 < 1$.

As such,

$$\lim_{t \rightarrow \infty} \|e^{At}\| = 0, \Rightarrow \lim_{t \rightarrow \infty} Y(t) = 0.$$

X^* is a GAS equilibrium point of $\frac{dX}{dt} = F(X, \mathbf{0})$ which is a limiting system of $F(X(t), Y(t))$. Thus,

$$\lim_{t \rightarrow \infty} X(t) = X^*$$

which satisfies condition H_1 .

Also, evaluating (27) and (28) at the DFE $(X_0, \mathbf{0})$ gives

$$A = \begin{pmatrix} -[\pi + k] & f\beta c \\ k & (1-f)\beta c - (\pi + \sigma + \omega + \varepsilon) \end{pmatrix} \quad (30)$$

and

$$\hat{G}(X, Y) = \mathbf{0}. \quad (31)$$

Obviously, the non-diagonal elements of A are non-negative and also since $f \leq 1$ and $f_1 \leq 1$, $\hat{G}(X, Y) \geq 0$, hence the satisfaction of condition H_2 is established. Then, the DFE, P_1 of the nonlinear system (7)-(10) is GAS.

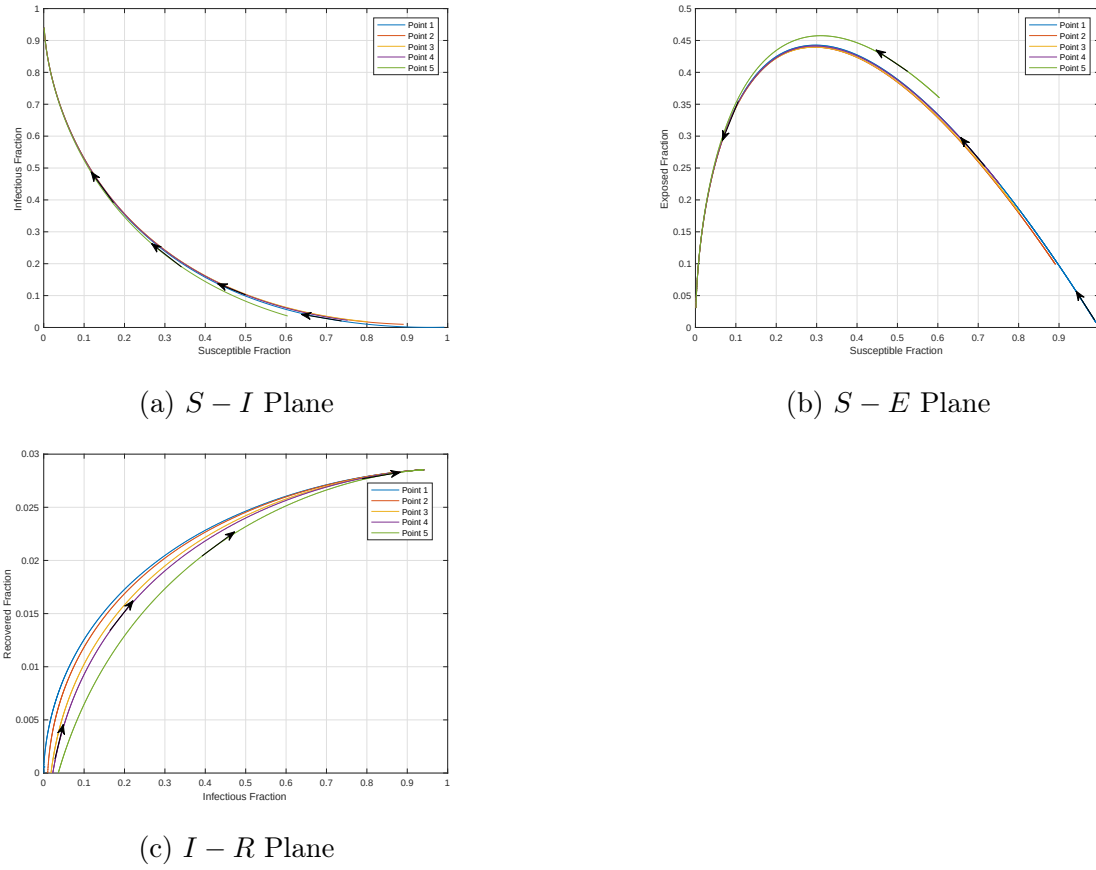


Figure 2: Phase portraits of the system

4.2 Stability of the EEP

4.2.1 Local Stability

Due to the hugeness of the gotten expressions for the EEP, phase portraits (Figures 2a- 2c) is adopted to show the endemic stability of the system with randomly chosen initial conditions as well as the parameter values given in Table 1 below. All the points converge to the same point which implies the local asymptotic stability of the EEP.

4.2.2 Global Stability

Theorem 4.3 *The endemic equilibrium point $\{E_1 = (s^*, e^*, i^*, r^*) \in \Phi\}$ of the system (7)-(10) is globally asymptotically stable whenever $f = 1$.*

Proof. Consider the Lyapunov function

$$V = K_1 \left(s - s^* - s^* \ln \frac{s}{s^*} \right) + K_2 \left(e - e^* - e^* \ln \frac{e}{e^*} \right) + K_3 \left(i - i^* - i^* \ln \frac{i}{i^*} \right), \quad (32)$$

then the time derivative of V is

$$V' = K_1 \left(\frac{s - s^*}{s} \right) \frac{ds}{dt} + K_2 \left(\frac{e - e^*}{e} \right) \frac{de}{dt} + K_3 \left(\frac{i - i^*}{i} \right) \frac{di}{dt}. \quad (33)$$

Substituting $\frac{ds}{dt}$, $\frac{de}{dt}$ and $\frac{di}{dt}$ as expressed in (7)-(9) in (33),

$$V' = K_1 \left(\frac{s - s^*}{s} \right) [\pi + \alpha r - [\pi + (\beta c - \varepsilon) i] s] + K_2 \left(\frac{e - e^*}{e} \right) [f \beta c i s + f_1 \beta c i r - [\pi + k + (\delta \beta c - \varepsilon) i] e]$$

$$+K_3 \left(\frac{i-i^*}{i} \right) ((1-f)\beta cis + (1-f_1)\beta cir + (\delta\beta ci)e + ke - (\pi + \sigma + \omega + \varepsilon)i + \varepsilon ii). \quad (34)$$

At equilibrium, $\pi = \pi s^* + (\beta c - \varepsilon)i^* s^* - \alpha r^*$, $(k + \mu) = \frac{f\beta ci^* s^* + f_1\beta cir^* - (\delta\beta c - \varepsilon)i^* e^*}{e^*}$ and $(\pi + \sigma + \omega + \varepsilon) = \frac{(1-f)\beta ci^* s^* + (1-f_1)\beta ci^* r^* + \delta\beta ci^* e^* + ke^* + \varepsilon i^* i^*}{i^*}$ which upon substitution into (34) gives

$$\begin{aligned} V' &= K_1 \left(\frac{s-s^*}{s} \right) [\pi s^* + (\beta c - \varepsilon)i^* s^* - \alpha r^* + \alpha r - (\pi + (\beta c - \varepsilon))s] \\ &+ K_2 \left(\frac{e-e^*}{e} \right) \left(f\beta cis + f_1\beta cir - \left[\frac{f\beta ci^* s^* + f_1\beta ci^* r^* - (\delta\beta c - \varepsilon)i^* e^*}{e^*} \right] e - (\delta\beta c - \varepsilon)ie \right) \\ &+ K_3 \left(\frac{i-i^*}{i} \right) \left((1-f)\beta cis + (1-f_1)\beta cir + \delta\beta cie + ke - \left(\frac{K_3^*}{i^*} \right) i + \varepsilon ii \right), \quad (35) \\ K_3^* &= (1-f)\beta ci^* s^* + (1-f_1)\beta ci^* r^* + \delta\beta ci^* e^* + ke^* + \varepsilon i^* i^*. \end{aligned}$$

From $s + e + i + r = 1$,

$$i = 1 - (s + e + r) \Rightarrow i^* = 1 - (s^* + e^* + r^*). \quad (36)$$

Using (36) in (35) gives

$$\begin{aligned} V' &= \frac{-K_1\pi(s-s^*)^2}{s} + K_1 \left(\frac{s-s^*}{s} \right) [(\beta c - \varepsilon)(i^* s^* - is) - \alpha r^* + \alpha r] \\ &+ K_2 \left(\frac{e-e^*}{e} \right) \left(f\beta cis + f_1\beta cir - \left[\frac{f\beta ci^* s^* + f_1\beta ci^* r^* - (\delta\beta c - \varepsilon)i^* e^*}{e^*} \right] e - (\delta\beta c - \varepsilon)ie \right) \\ &+ K_3 \left(\frac{i-i^*}{i} \right) ((1-f)\beta cis + (1-f_1)\beta cir + \delta\beta cie + ke + \varepsilon i(1 - (s + e + r))) \\ &- K_3 \left(\frac{i-i^*}{i} \right) \left(\frac{(1-f)\beta ci^* s^* + (1-f_1)\beta ci^* r^* + \delta\beta ci^* e^* + ke^* + \varepsilon i^*(1 - (s^* + e^* + r^*))}{i^*} \right) i. \quad (37) \end{aligned}$$

Let $\frac{s}{s^*} = x_1$, $\frac{e}{e^*} = x_2$, $\frac{i}{i^*} = x_3$, $i^* s^* = a$, $i^* e^* = b$, $i^* r^* = d$, $kE^* = g$, $\varepsilon i^* = m$ and $\alpha r^* = h$, then (37) is

$$\begin{aligned} V' &= -\frac{K_1\pi(s-s^*)^2}{s} + K_1 \left(1 - \frac{1}{x_1} \right) [(\beta c - \varepsilon)(i^* s^* - i^* x_3 s^* x_1) - \alpha r^* + \alpha r^* x_4] \\ &+ K_2 \left(1 - \frac{1}{x_2} \right) (f\beta ci^* x_3 s^* x_1 + f_1\beta ci^* x_3 r^* x_4 - (f\beta ci^* s^* + f_1\beta ci^* r^* - (\delta\beta c - \varepsilon)i^* e^*)x_2 \\ &- (\delta\beta c - \varepsilon)i^* x_3 e^* x_2) + K_3 \left(1 - \frac{1}{x_3} \right) ((1-f)\beta ci^* x_3 s^* x_1 + (1-f_1)\beta ci^* x_3 r^* x_4 + \delta\beta ci^* x_3 e^* x_2 \\ &+ ke^* x_2 + \varepsilon i^* x_3 (1 - (s^* x_1 + e^* x_2 + r^* x_4))) - K_3 \left(1 - \frac{1}{x_3} \right) \left(\frac{K_3^{**}}{i^*} \right) i, \quad (38) \\ K_3^{**} &= (1-f)\beta ci^* s^* + (1-f_1)\beta ci^* r^* + \delta\beta ci^* e^* + ke^* + \varepsilon i^* (1 - (s^* + e^* + r^*)) \\ V' &= \frac{-K_1\pi(s-s^*)^2}{s} + K_1 \left(1 - \frac{1}{x_1} \right) [(\beta c - \varepsilon)(i^* s^* - ax_1x_3) - h + hx_4] \\ &+ K_2 \left(1 - \frac{1}{x_2} \right) (f\beta cax_1x_3 + f_1\beta cdx_3x_4 - (f\beta ca + f_1\beta cd - (\delta\beta c - \varepsilon)b)x_2 - (\delta\beta c - \varepsilon)bx_2x_3) \\ &+ K_3 \left(1 - \frac{1}{x_3} \right) ((1-f)\beta cax_1x_3 + (1-f_1)\beta cdx_3x_4 + \delta\beta cbx_2x_3 + gx_2 + mx_3 - \varepsilon ax_1x_3 - \varepsilon bx_2x_3) \end{aligned}$$

$$-\varepsilon dx_3x_4)) - K_3 \left(1 - \frac{1}{x_3}\right) ((1-f)\beta cax_3 - (1-f_1)\beta cdx_3 - \delta\beta cbx_3 - gx_3 - mx_3 + \varepsilon ax_3 + \varepsilon bx_3 + \varepsilon dx_3). \quad (39)$$

$$\begin{aligned} V' = & \frac{-K_1\pi(s-s^*)^2}{s} + (K_1(\beta c - \varepsilon)a + K_2f\beta ca + K_3(1-f)\beta ca - K_3\varepsilon a)x_1x_3 + (-K_2(\delta\beta c - \varepsilon)b \\ & + K_3\delta\beta cb - K_3\varepsilon b)x_2x_3 + (K_2f_1\beta cd + K_3(1-f_1)\beta cd - K_3\varepsilon d)x_3x_4 + (-K_3(1-f)\beta ca + K_3\varepsilon a)x_1 \\ & + (-K_2f\beta ca - K_2f_1\beta cd + K_2(\delta\beta c - \varepsilon)b + K_3g - K_3\delta\beta cb + K_3\varepsilon b)x_2 \\ & + (K_1(\beta c - \varepsilon)a + K_2(\delta\beta c - \varepsilon)b - K_3(1-f)\beta ca - K_3(1-f_1)\beta cd - K_3\delta\beta cb - K_3g \\ & + K_3\varepsilon a + K_3\varepsilon b + K_3\varepsilon d)x_3 + (K_1h - K_3(1-f_1)\beta cd + K_3\varepsilon d)x_4 + K_1(\beta c - \varepsilon)a - K_1h - K_1h\frac{x_4}{x_1} \\ & + K_1\frac{h}{x_1} - K_1(\beta c - \varepsilon)\frac{a}{x_1} - K_2f\beta ca\frac{x_1x_3}{x_2} - K_2f_1\beta cd\frac{x_3x_4}{x_2} + K_2f\beta ca + K_2f_1\beta cd - K_2(\delta\beta c - \varepsilon)b \\ & - K_3g\frac{x_2}{x_3} + K_3(1-f)\beta ca + K_3(1-f)\beta cd + K_3\delta\beta cb + K_3g - K_3\varepsilon a - K_3\varepsilon b - K_3\varepsilon d. \end{aligned} \quad (40)$$

Equating the coefficients of x_1x_3 , x_2x_3 , x_3x_4 , x_1 , x_2 , x_3 and x_4 to 0 gives $K_1 = K_2 = K_3$; $g = f\beta ca$; $\varepsilon = (1-f)\beta c$, $d = h = 0$.

Choosing the values of $K_1 = K_2 = K_3 = f = 1$ and substituting the values of g , ε , d and h gives

$$V' = \frac{-\pi(s-s^*)^2}{s} + \beta ca \left(3 - \frac{1}{x_1} - \frac{x_1x_3}{x_2} - \frac{x_2}{x_3}\right). \quad (41)$$

Since arithmetic mean (AM) is greater than or equal to geometric mean (GM) ($AM \geq GM$), then

$$\frac{1}{x_1} + \frac{x_1x_3}{x_2} + \frac{x_2}{x_3} \geq 3.$$

It can be seen from (41) that $V' \leq 0$ for which the equality holds when $x_1 = x_2 = x_3 = 1$ (which implies $s = s^*$, $e = e^*$ and $i = i^*$). From the LaSalle's invariance principle [30], the endemic equilibrium point EEP is globally asymptotically stable whenever $f = 1$.

5 Numerical Simulation

The above model was solved using *ODE45* package of MATLAB with the parameter values given in Table 1 below. Most of the values are extracted from [17] while others are reasonably chosen estimates. The initial fractional populations of the susceptible, exposed, infectious and recovered are 0.99175, 0.00750, 0.00075 and 0 respectively and the resulting graphs are presented below.

Table 1: Table of values

S/No	Parameter	Meaning	Value (yr^{-1})	Source
1	β	Probability of being infected after effective contact with an infectious being	0.35000	[17]
2	π	Recruitment rate	0.03000	[17]
3	c	Contact rate	80.0000	[17]
4	μ	Natural mortality rate	0.01000	Estimate
5	ε	TB induced death	0.30000	[17]
6	k	Endogenous re-activation	0.00013	[17]
7	α	Rate of the recovered moving back to susceptible	0.30000	Estimate
8	δ	Exogenous re-infection	0.70000	[17]
9	ω	Natural recovery rate	0.20000	[17]
10	σ	Effectiveness of the treatment	0.60000	Estimate
11	f	Probability that the infected will enter the latent stage of the disease	0.99000	[17]
12	f_1	Probability of the re-infected R moving to E	0.70000	[17]

5.1 Graphical Results

5.1.1 SEIR Relationship Graphs

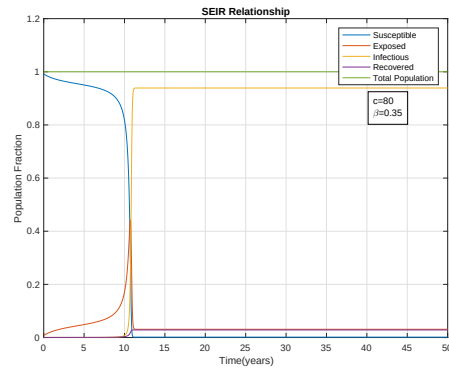
Here, the relationship between each compartments are shown. Figures 3a, 3b and 3c show the behaviour of each proportion of the population (compartment) as time evolves and also their proportions under various contact rates (c) are shown. In Figure 3b, 6.25% reduction in the original value of contact rate $c = 80$ shows a delay for the occurrence of the epidemic and in Figure 3c, the infection tends to disappear when there is 10% reduction in the contact rate.

5.1.2 Sensitivity Analysis Graphs

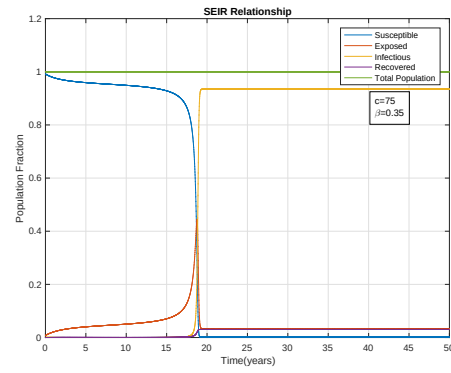
In the face of any infection, apart from the contact rate investigated above, also of importance are the recruitment and treatment rates. The recruitment is useful in maintaining the constant influx of people into the community while the treatment is useful in removing the infectious individuals out of the infectious class. Increase in the recruitment rate (Figure 4a) slightly delays the outbreak of the infection while increment in the treatment rate (Figure 4b) delays the period of infection in huge proportion with a slight reduction in the infectious population. The result due to treatment is in agreement with the findings of Khan et al. (2019) [20] where increment in the treatment rate and decrement in the transmission and immunity loss rates help in reducing TB epidemic. This delay could be optimised in tackling the spread of the infection, to manage the eventual break out of an epidemic. However, a growth rate of 7% of the population or a treatment rate of 80% of the infectious can lead the infection to extinction as displayed in Figure 4a and Figure 4b respectively. Guarding against loss of immunity after recovery may not be necessary as Figure 4c shows it has no significant impact.

6 Summary

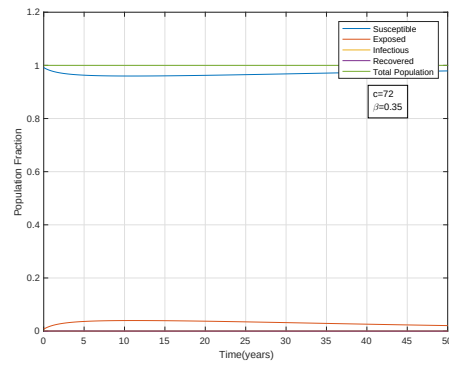
This paper studies the tuberculosis epidemiology using SEIR compartmental modelling. The possibility of a fraction of recovered R going back to susceptible S due to the fact that bacterial infection does not give a permanent immunity against the re-infection was considered. The disease free equilibrium (DFE) and the endemic equilibrium (EEP) of the model are established and their local and global stabilities are as well shown. Also the normalisation method eliminates the natural death factor (μ), hence allowing the concentrate on other factors that can be controlled,



(a) TB without intervention strategies

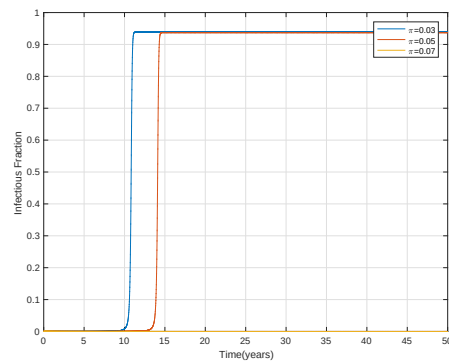


(b) Reduction of c by 6.25%

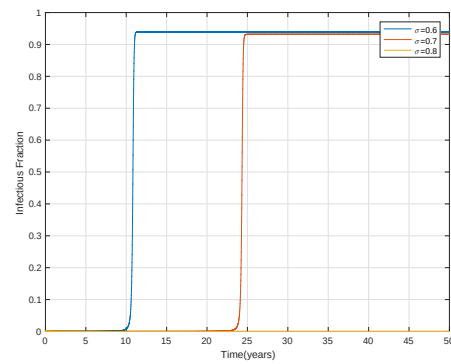


(c) Reduction of c by 10%

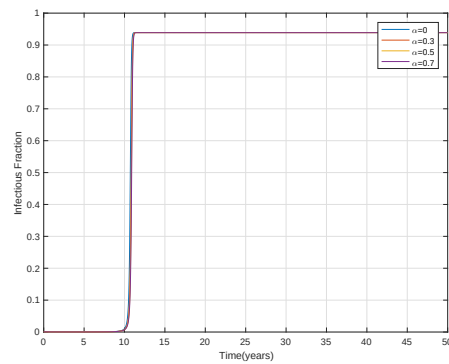
Figure 3: Disease dynamics



(a) Effect of (π) on I



(b) Effect of (σ) on I



(c) Effect of (α) on I

Figure 4: Relevance of the key factors in the disease dynamics

for example; recruitment, contact and treatment rates.

The analysis carried out on the basic reproduction number (R_0) (Theorem 3.1) reveals the relevance of the exposed class in reducing the incident rate of the TB infection. Non-direct progression of the *Mycobacterium tuberculosis* (*Mtb*) carriers to the infectious state reduces the eventual number of people with full blown infection due to the fact that $R_{0_1} = R_0$ whenever $f = 1$, which implies a reduction in the actual value of R_0 . The exposed state can be utilised in reducing the incidence of TB infection when measures are put in place to identify *Mtb* carriers at that stage as displayed in Figure 1.

The numerical simulation done on the model explains the importance of some of the factors considered in the model formulation. It is shown that the contact rate between the infectious and susceptible individuals play significant role in the rapid spread of the infection. The reduction in the value of the contact rate shows a great improvement in controlling the epidemic. In fact, this result explains part of the reasons why sanatoria used in the 18th century were effective in dealing with the epidemic. Other factors; recruitment and treatment rates have shown how important they are in delaying the infection, and as such, should be optimised in handling the infection before it becomes an epidemic. At 7% growth rate of the population or 80% treatment rate of the infectious, the infection dies out, as displayed in Figures 3c and 4a. The recruitment into the population (growth) is expected to be constituted by those that are free of *Mtb*. Money meant for the prevention against reinfection may be saved and utilised for other purposes as Figure 4c shows it may amount to waste of minimal resources.

It is worthy of note that awareness could also be of great help in reducing the incidence of the infection through e.g., education, social media, local dailies, media houses, etc., as it would help in reducing the contact rate between the infectious and susceptible individuals. This is corroborated by the resulting Figures 3a- 3c in which reasonable control of the epidemic is achieved. This is in agreement with the findings of Xiang et al. (2019) [32] where health education is shown to help in reducing TB burden. These measures are greatly needed in some parts of the developing nations and in most of the under-developed nations as they are the major victims of tuberculosis.

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Appendix

$$A_1 = \beta f \pi^3 + \alpha \beta f \pi^2 + k \pi^3 + \alpha k \pi^2 - \beta k \pi^2 + \varepsilon k \pi^2 + k \pi^2 \sigma + k \pi^2 \omega - \alpha \beta k \pi + \alpha \varepsilon k \pi + \alpha k \pi \sigma + \alpha k \pi \omega + \pi^4 + \alpha \pi^3 - \beta \pi^3 + \varepsilon \pi^3 + \pi^3 \sigma + \pi^3 \omega - \alpha \beta \pi^2 + \alpha \varepsilon \pi^2 + \alpha \pi^2 \sigma + \alpha \pi^2 \omega,$$

$$A_2 = \beta^2 f \pi^2 - 2 \beta \varepsilon f \pi^2 - \alpha \beta \varepsilon f \pi + \alpha \beta f \pi \sigma + \alpha \beta f \pi \omega + \beta f_1 \pi^2 \sigma + \beta f_1 \pi^2 \omega + \alpha \beta \varepsilon k - \alpha \varepsilon^2 k - \alpha \varepsilon k \sigma - \alpha \varepsilon k \omega + 2 \beta k \pi^2 - 3 \varepsilon k \pi^2 + \alpha \beta k \pi - 2 \alpha \varepsilon k \pi - \beta^2 k \pi + 3 \beta \varepsilon k \pi + \beta k \pi \sigma + \beta k \pi \omega - 2 \varepsilon^2 k \pi - 2 \varepsilon k \pi \sigma - 2 \varepsilon k \pi \omega + \beta \delta \pi^3 + 2 \beta \pi^3 - 4 \varepsilon \pi^3 + \alpha \beta \delta \pi^2 + \alpha \beta \pi^2 - 3 \alpha \varepsilon \pi^2 - \beta^2 \delta \pi^2 - \beta^2 \pi^2 + \beta \delta \varepsilon \pi^2 + \beta \delta \pi^2 \sigma + \beta \delta \pi^2 \omega + 4 \beta \varepsilon \pi^2 + \beta \pi^2 \sigma + \beta \pi^2 \omega - 3 \varepsilon^2 \pi^2 - 3 \varepsilon \pi^2 \sigma - 3 \varepsilon \pi^2 \omega - \alpha \beta^2 \delta \pi + \alpha \beta \delta \varepsilon \pi + \alpha \beta \delta \pi \sigma + \alpha \beta \delta \pi \omega + 2 \alpha \beta \varepsilon \pi - 2 \alpha \varepsilon^2 \pi - 2 \alpha \varepsilon \pi \sigma - 2 \alpha \varepsilon \pi \omega,$$

$$A_3 = \alpha \beta^2 \delta \varepsilon - \alpha \beta \delta \varepsilon^2 - \alpha \beta \delta \varepsilon \sigma - \alpha \beta \delta \varepsilon \omega - \alpha \beta \varepsilon^2 + \alpha \varepsilon^3 + \alpha \varepsilon^2 \sigma + \alpha \varepsilon^2 \omega - \alpha \beta \varepsilon f \sigma - \alpha \beta \varepsilon f \omega - \beta^2 \varepsilon f \pi + \beta \varepsilon^2 f \pi + \beta^2 f_1 \pi \sigma + \beta^2 f_1 \pi \omega - 2 \beta \varepsilon f_1 \pi \sigma - 2 \beta \varepsilon f_1 \pi \omega - \alpha \beta \varepsilon k + \alpha \varepsilon^2 k + \beta^2 \varepsilon k - 2 \beta \varepsilon^2 k - \beta \varepsilon k \sigma - \beta \varepsilon k \omega + \varepsilon^3 k + \varepsilon^2 k \sigma + \varepsilon^2 k \omega + \beta^2 k \pi - 4 \beta \varepsilon k \pi + 3 \varepsilon^2 k \pi + 2 \beta^2 \delta \pi^2 + \beta^2 \pi^2 - 3 \beta \delta \varepsilon \pi^2 - 6 \beta \varepsilon \pi^2 + 6 \varepsilon^2 \pi^2 + \alpha \beta^2 \delta \pi - 2 \alpha \beta \delta \varepsilon \pi - 2 \alpha \beta \varepsilon \pi + 3 \alpha \varepsilon^2 \pi - \beta^3 \delta \pi + 3 \beta^2 \delta \varepsilon \pi + \beta^2 \delta \pi \sigma + \beta^2 \delta \pi \omega + 2 \beta^2 \varepsilon \pi - 2 \beta \delta \varepsilon^2 \pi - 2 \beta \delta \varepsilon \pi \sigma - 2 \beta \delta \varepsilon \pi \omega - 5 \beta \varepsilon^2 \pi - 2 \beta \varepsilon \pi \sigma - 2 \beta \varepsilon \pi \omega + 3 \varepsilon^3 \pi + 3 \varepsilon^2 \pi \sigma + 3 \varepsilon^2 \pi \omega,$$

$$A_4 = -\alpha \beta^2 \delta \varepsilon + \alpha \beta \delta \varepsilon^2 + \alpha \beta \varepsilon^2 - \alpha \varepsilon^3 + \beta^3 \delta \varepsilon - 2 \beta^2 \delta \varepsilon^2 - \beta^2 \delta \varepsilon \sigma - \beta^2 \delta \varepsilon \omega - \beta^2 \varepsilon^2 + \beta \delta \varepsilon^3 + \beta \delta \varepsilon^2 \sigma + \beta \delta \varepsilon^2 \omega + 2 \beta \varepsilon^3 + \beta \varepsilon^2 \sigma + \beta \varepsilon^2 \omega - \varepsilon^4 - \varepsilon^3 \sigma - \varepsilon^3 \omega - \beta^2 \varepsilon f_1 \sigma - \beta^2 \varepsilon f_1 \omega + \beta \varepsilon^2 f_1 \sigma + \beta \varepsilon^2 f_1 \omega - \beta^2 \varepsilon k + 2 \beta \varepsilon^2 k - \varepsilon^3 k + \beta^3 \delta \pi - 4 \beta^2 \delta \varepsilon \pi - 2 \beta^2 \varepsilon \pi + 3 \beta \delta \varepsilon^2 \pi + 6 \beta \varepsilon^2 \pi - 4 \varepsilon^3 \pi,$$

and

$$A_5 = -\beta^3 \delta \varepsilon + 2 \beta^2 \delta \varepsilon^2 + \beta^2 \varepsilon^2 - \beta \delta \varepsilon^3 - 2 \beta \varepsilon^3 + \varepsilon^4.$$