

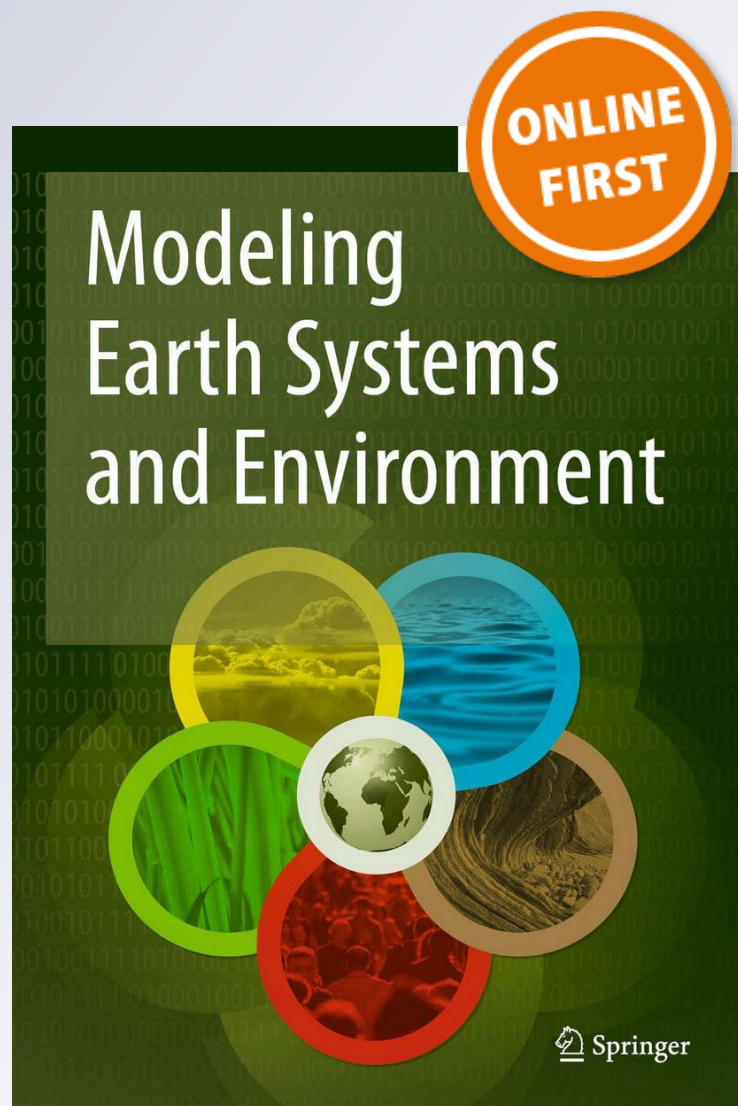
The role of vaccination in curbing tuberculosis epidemic

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The role of vaccination in curbing tuberculosis epidemic

Ayinla Ally Yeketi¹ · Wan Ainun Mior Othman¹ · M. A. Omar Awang¹

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Abstract

This work studies the impact of vaccine in controlling tuberculosis (TB) epidemic using susceptible, vaccinated, exposed, infectious and recovered compartmental model. This is necessitated due to the acclaimed ineffectiveness of BCG vaccine in combatting TB. The model is formulated using a non-linear system of ordinary differential equation which is normalised to eliminate the natural death factor (μ) so as to focus on other factors. The disease-free equilibrium and endemic equilibrium point (EEP) of the system are established alongside their local and global stabilities. Although the local stability of the EEP could not be established analytically due to the cumbersomeness of the EEP obtained, it is, however, established numerically. It is shown with the aid of numerical simulation carried out on the model that vaccination helps in reducing the tuberculosis epidemic and in fact, if the rates of contact and infectivity are reduced, further reduction in the rate of incidence (λ) can be achieved. Further more, the reason why there is the need for a better vaccine to replace BCG vis-à-vis provision of better immunity coverage ($\theta \rightarrow 0$ and $\sigma \rightarrow 0$) and also, the need for the development of drugs that confer permanent or long lasting immunity ($\delta_2 \rightarrow 0$) is as well established. More vaccination proportion gives better outcome ($\tau \rightarrow 1$) and the introduced controls show their relevance in reducing the infection. The novelty of this research is the provision of guiding frame work for the pharmacists on the intrinsic features expected of any proposed vaccine to replace BCG while the expected recommendations from the doctors are established using optimal control.

Keywords Tuberculosis model · Vaccination · Optimal control · Basic reproduction number · Global stability · Reinfection rate

Introduction

Tuberculosis (TB) is an infection that has claimed the lives of its victims throughout much of known human history. This trend is still maintained as deaths recorded due to TB is more than any other infectious disease, (WHO 2017) and this explains the reason why it was nicknamed “captain among these men of death” in the early twentieth century. TB is caused by *Mycobacterium tuberculosis* (*Mtb*), a bacteria that might have killed more people than any other microbe (Daniel 2006). Over the years, its deadly effects have led to its different names like; Phthisis (Daniel 1997), Consumption (Major 1945) and Scrofula (Mohajan 2015). This infection was recorded to single handedly be responsible for 1.1 million deaths globally in the year 2010 (WHO 2011), 0.9 million in 2011 (WHO 2012), 1 million in 2012 (WHO 2013), 1.2 million in 2013 (WHO 2014)

and 1.1 million in 2014 (WHO 2015). As in 2015, the death due to TB has over taken those from HIV and malaria with 1.4 million deaths, (WHO 2016), 1.3 million in 2016 (WHO 2017) and 1.3 million out of 10 million reported cases in the year 2017 (WHO 2018a). This take over explains why all hands are required to be on deck to find a lasting solution to this infection whose deadly effect is growing wilder.

The work of Théophile Laennec in the early nineteenth century should be given credit as it lays the foundation to understand the pathogenesis of TB. This work was expanded by Jean-Antoine Villemin in 1865 and Robert Koch in 1882, where they, respectively, showed the transmissibility of *Mycobacterium* infection and identified tubercle bacillus as the etiological agent (Daniel 2006). These advances led to the emergence of BCG vaccine in the year 1921 whose efficacy was evaluated in 1930s through field trials (Gomes et al. 2004). BCG (Bacille Calmette–Guérin) is a prophylactic vaccine named after its inventors, Albert Calmette and Camille Guérin. The acceptability of this vaccine was low at that time until after World War II between the years 1929 and 1945 when TB became a major concern. Subsequently, UNICEF encouraged

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its use and was supported by the Danish Red Cross Society (Luca and Mihaescu 2013). Despite the existence of some arguments pertaining to the effectiveness of BCG in the prevention of TB, its use is greatly embraced by many nations, each setting their policies regarding its use (Gerberry 2009).

In recent time, there have been discussions over the need for a new vaccine to replace BCG. This is because its ineffectiveness in preventing adult pulmonary TB has been greatly proven as corroborated by the annual TB-induced death stated above. Kernodle (2010), Moliva et al. (2015), Bhandari (2016) and Jalan (2018) are among those who have discussed the likely reasons of the ineffectiveness of BCG in fighting TB. According to WHO (2018b), the achievement of 95% reduction in the TB-induced death and 90% decrement in the incident of TB, world wide by the year 2035, requires a new vaccine to replace the existing BCG.

Different researchers at different times have modelled TB mathematically, either to assess its rampaging effect, see e.g. Aparicio and Castillo-Chavez (2009), Raimundo and Yang (2006), Vynnycky et al. (2015), McCluskey and van den Driessche (2004), Jia et al. (2008), and Trauer et al. (2014) or provide intervention strategies to curb its spread, see e.g. Bhunu et al. (2008), Murphy et al. (2003), Ragonnet et al. (2017) and Varughese et al. (2017). None of these researchers discussed the main consideration to be made in the formulation of an effective vaccine. As such, the novelty of our research is the provision of guiding frame work for the pharmacists on the intrinsic features expected of any proposed vaccine.

There are six sections in this paper, which is inclusive of this (Sect. 1). Section 2 explains the model formulation, Sect. 3 deals with the equilibrium points and their stabilities while Sect. 4 is about the numerical simulation of the model. Furthermore, Sect. 5 extends the model by taking optimal control variables into consideration and finally, Sect. 6 concludes the work.

Model formulation

The human population is partitioned into five groups namely; susceptible individuals (S), vaccinated individuals (V), latently infected individuals (E), infectious individuals (I) and the recovered individuals (R). The total population $N(t)$ at any time t is

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

Individuals from all compartments are assumed to be freely mixing with one another and a susceptible individual contracts TB after an effective 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.

People are recruited into the susceptible class at the rate πN from which individuals subsequently move to the exposed and the infectious stages at the rates $(1 - \tau)f\lambda$ and $(1 - \tau)(1 - f)\lambda$, respectively, while the recovered individuals can move back to the exposed and infectious compartments at the rates $f_1\lambda$ and $(1 - f_1)\lambda$, respectively, due to the loss of immunity. Also, a fraction from the susceptible class gets vaccinated at the rate τ and move to the vaccinated compartment. Individuals in the vaccinated compartment can get infected of TB at the rate θ . $\delta_1\lambda$ describes the exogenous reinfection rate and k is the endogenous reactivation rate while δ_2 is the probability that a recovered person could get reinfected after the loss of immunity. Natural death rate is μ and dying since TB infection is ε .

The infectious individuals may recover naturally at the rate ω or due to treatment at the rate γ . Since there is no total immunity against reinfection of bacterial infection, a fraction of the recovered class is expected to move back to the susceptible class at the rate α . The model is diagrammatically shown in Fig. 1 below and it is governed by the non-linear system

$$\frac{dS}{dt} = \pi N + \sigma V + \alpha R - [\tau + (1 - \tau)\lambda + \mu]S, \quad (3)$$

$$\frac{dV}{dt} = \tau S - (\theta\lambda + \sigma + \mu)V, \quad (4)$$

$$\begin{aligned} \frac{dE}{dt} = & (1 - \tau)f\lambda S + \theta f\lambda V \\ & + f_1\delta_2\lambda R - (\delta_1\lambda + k + \mu)E, \end{aligned} \quad (5)$$

$$\begin{aligned} \frac{dI}{dt} = & (1 - \tau)(1 - f)\lambda S + \theta(1 - f)\lambda V + (1 - f_1)\delta_2\lambda R \\ & + (\delta_1\lambda + k)E - (\gamma + \omega + \varepsilon + \mu)I \end{aligned} \quad (6)$$

and

$$\frac{dR}{dt} = (\gamma + \omega)I - (\delta_2\lambda + \alpha + \mu)R, \quad (7)$$

with initial conditions

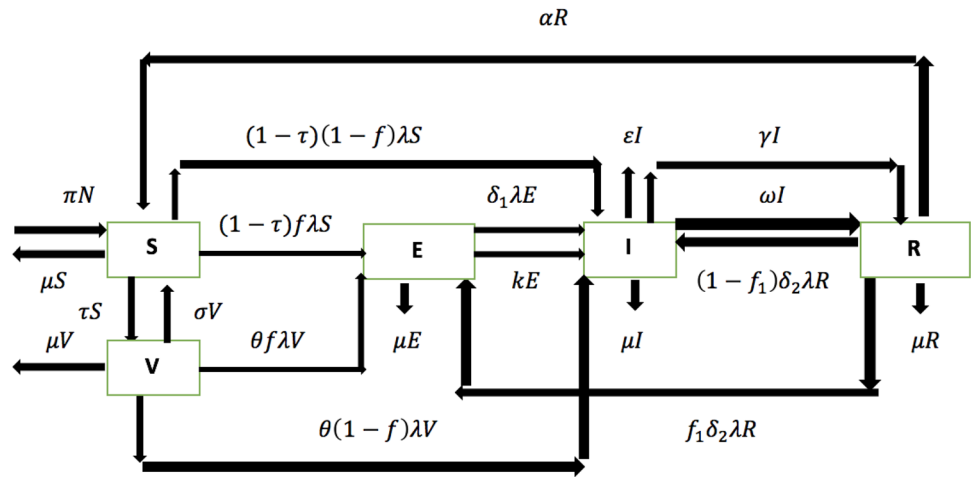
$$\begin{aligned} S(0) = S_0 \geq 0, \quad V(0) = V_0 \geq 0, \quad E(0) = E_0 \geq 0, \\ I(0) = I_0 \geq 0, \quad R(0) = R_0 \geq 0. \end{aligned}$$

Adding (3)–(7) gives

$$\frac{dN}{dt} = (\pi - \mu)N - \varepsilon I. \quad (8)$$

The above non-linear system (3)–(7) can be normalised by dividing throughout by N . If $\frac{S}{N}$, $\frac{V}{N}$, $\frac{E}{N}$, $\frac{I}{N}$ and $\frac{R}{N}$ are consecutively denoted by s , v , e , i and r , then the system becomes

Fig. 1 Vaccination model for tuberculosis



$$\frac{1}{N} \frac{dS}{dt} = \pi + \sigma v + \alpha r - [\tau + (1-\tau)\beta ci + \mu]s, \quad (9)$$

$$\frac{1}{N} \frac{dV}{dt} = \tau s - (\theta\beta ci + \sigma + \mu)v, \quad (10)$$

$$\frac{1}{N} \frac{dE}{dt} = (1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\beta cir - (\delta_1\beta ci + k + \mu)e, \quad (11)$$

$$\frac{1}{N} \frac{dI}{dt} = (1-\tau)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e - (\gamma + \omega + \epsilon + \mu)i \quad (12)$$

and

$$\frac{1}{N} \frac{dR}{dt} = (\gamma + \omega)i - (\delta_2\beta ci + \alpha + \mu)r, \quad (13)$$

with initial conditions

$$s(0) = s_0 \geq 0, \quad v(0) = v_0 \geq 0, \quad e(0) = e_0 \geq 0, \\ i(0) = i_0 \geq 0, \quad r(0) = r_0 \geq 0.$$

From $S = sN$,

$$\frac{1}{N} \frac{dS}{dt} = \frac{ds}{dt} + s[(\pi - \mu) - \epsilon i]. \quad (14)$$

Similarly, from $v = \frac{V}{N}$, $e = \frac{E}{N}$, $i = \frac{I}{N}$ and $r = \frac{R}{N}$, now the appropriate governing non-linear equations become

$$\frac{ds}{dt} = \pi + \sigma v + \alpha r - [\pi + \tau + [(1-\tau)\beta c - \epsilon]i]s, \quad (15)$$

$$\frac{dv}{dt} = \tau s - [\pi + \sigma + (\theta\beta c - \epsilon)i]v, \quad (16)$$

$$\frac{de}{dt} = (1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\beta cir - [\pi + k + (\delta_1\beta c - \epsilon)i]e, \quad (17)$$

$$\frac{di}{dt} = (1-\tau)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e - [\pi + \gamma + \omega + \epsilon(1-i)]i, \quad (18)$$

and

$$\frac{dr}{dt} = (\gamma + \omega)i - [\pi + \alpha + (\delta_2\beta c - \epsilon)i]r. \quad (19)$$

Equilibrium points, basic reproduction number (R_0) and stability of the equilibrium points

Equilibrium points

At equilibrium point, the non-linear system (15)–(19) becomes

$$0 = \pi + \sigma v + \alpha r - [\pi + \tau + [(1-\tau)\beta c - \epsilon]i]s, \quad (20)$$

$$0 = \tau s - [\pi + \sigma + (\theta\beta c - \epsilon)i]v, \quad (21)$$

$$0 = (1-\tau)f\beta cis + \theta f\beta civ + f_1\delta_2\beta cir - [\pi + k + (\delta_1\beta c - \epsilon)i]e, \quad (22)$$

$$0 = (1-\tau)(1-f)\beta cis + \theta(1-f)\beta civ + (1-f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e - [\pi + \gamma + \omega + \epsilon(1-i)]i \quad (23)$$

and

$$0 = (\gamma + \omega)i - [\pi + \alpha + (\delta_2\beta c - \varepsilon)i]r. \quad (24)$$

From (24),

$$r = \frac{(\gamma + \omega)i}{[\pi + \alpha + (\delta_2\beta c - \varepsilon)i]}. \quad (25)$$

Using (21) and (25) in (20) produces

$$s = \frac{[\pi + \sigma + (\theta\beta c - \varepsilon)i]\{\pi[\pi + \alpha + (\delta_2\beta c - \varepsilon)i] + \alpha(\gamma + \omega)i\}}{[\pi + \alpha + (\delta_2\beta c - \varepsilon)i]\{\pi + \sigma + (\theta\beta c - \varepsilon)i\}[\pi + \tau + [(1 - \tau)\beta c - \varepsilon]i] - \sigma\tau}, \quad (26)$$

whilst substituting (26) in (21) gives

$$v = \frac{\tau[\pi + \sigma + (\theta\beta c - \varepsilon)i]\{\pi[\pi + \alpha + (\delta_2\beta c - \varepsilon)i] + \alpha(\gamma + \omega)i\}}{[\pi + \sigma + (\theta\beta c - \varepsilon)i]\{\pi + \alpha + (\delta_2\beta c - \varepsilon)i\}\{\pi + \tau + [(1 - \tau)\beta c - \varepsilon]i] - \sigma\tau}, \quad (27)$$

and subsequently inserting (25)–(27) in (22) implies

$$e = \frac{(1 - \tau)f\beta c i s + \theta f\beta c i v + f_1\delta_2\beta c i r}{[\pi + k + (\delta_1\beta c - \varepsilon)i]}. \quad (28)$$

Substituting (25)–(28) as functions of i in (23) yields

$$A_6i^6 + A_5i^5 + A_4i^4 + A_3i^3 + A_2i^2 + A_1i = 0. \quad (29)$$

The analytical solution of (29) as well as $A_1 - A_6$ is too long to be displayed here. The six values of i obtained, that is $(i_1, i_2, i_3, i_4, i_5, i_6)$ are subsequently used in (25)–(28) to establish $(s_1, s_2, s_3, s_4, s_5, s_6)$, $(v_1, v_2, v_3, v_4, v_5, v_6)$, $(e_1, e_2, e_3, e_4, e_5, e_6)$ and $(r_1, r_2, r_3, r_4, r_5, r_6)$, and six sets of equilibrium points are produced. Among the equilibrium points obtained is the disease-free equilibrium (DFE) solution $p_1 = \left\{ \frac{\pi(\pi + \sigma)}{(\pi + \sigma)(\pi + \tau) - \sigma\tau}, \frac{\pi\tau}{(\pi + \sigma)(\pi + \tau) - \sigma\tau}, 0, 0, 0 \right\}$ and $p_2 = \{s_2, v_2, e_2, i_2, r_2\}$ where

$$\begin{aligned} s_2 &= \frac{\varepsilon\pi\psi\Lambda}{\Gamma\{\pi\beta c(1 - \tau) + \tau\varepsilon\}\Lambda - \varepsilon^2\sigma\tau}, \\ v_2 &= \frac{\varepsilon^2\tau\pi\psi\Lambda}{\Gamma\Lambda\{\Lambda[\pi\beta c(1 - \tau) + \tau\varepsilon] - \varepsilon^2\sigma\tau\}}, \\ e_2 &= \frac{(\pi\beta c\delta_1 + k\varepsilon)\{\beta cf\pi^2(1 - \tau)\Lambda^2\psi + \beta cf\theta\pi^2\varepsilon^2\tau\Lambda\psi\}}{\Gamma\Lambda\{\pi\beta c(1 - \tau) + \tau\varepsilon\}\Lambda - \varepsilon^2\sigma\tau} \\ &\quad + \frac{\beta c\delta_2f_1\pi^2(\gamma + \omega)}{\Gamma(\pi\beta c\delta_1 + k\varepsilon)}, \\ i_2 &= \frac{\pi}{\varepsilon} \text{ and } r_2 = \frac{\pi(\gamma + \omega)}{\Gamma}. \end{aligned}$$

such that

$$\psi = \pi\beta c\delta_2 + \alpha(\gamma + \omega + \varepsilon),$$

$$\Lambda = (\pi\beta c\theta + \sigma\varepsilon) \text{ and } \Gamma = (\pi\beta c\delta_2 + \alpha\varepsilon).$$

P_2 is dropped out of the solutions because its sum could not give unity. By the normalisation method adopted, all true solutions are expected to sum up to unity. Expectedly, there are five true solutions (equilibrium points) as there are five variables (compartments).

Basic reproduction number (R_0)

Establishing the basic reproduction number (R_0)

Basic reproduction number (R_0) can simply be defined as the number of secondary infections from a single primary one. Out of the different ways of establishing the basic reproduction number of an infectious disease, we shall consider the use of the next generation matrix as explained in van den Driessche and Watmough (2002). This is defined as

$$R_0 = \rho \quad (30)$$

where ρ is the spectral radius (dominant eigenvalue) of FV^{-1} . F is a matrix that represents the rate of appearance of new infections in the infected compartments and V is a matrix representing the inward and outward movement at the infected compartments.

V is defined as

$$V = V_i^- - V_i^+,$$

where

V_i^- = the rate of inward movement of individuals into the infected compartments

and

V_i^+ = the rate of outward movement of individuals from the infected compartments.

From the above system, F and V are, respectively,

$$F = \begin{pmatrix} 0 & \beta c\{[f(1 - \tau)s + \theta v] + f_1\delta_2r\} \\ \delta_1\beta ci & \beta c[(1 - f)s + (1 - f_1)\delta_2r] \end{pmatrix} \quad (31)$$

and

$$V = \begin{pmatrix} [\pi + k + (\delta_1 \beta c - \varepsilon)i] & (\delta_1 \beta c - \varepsilon)e \\ -k & [\pi + \gamma + \omega + \varepsilon(1-i)] \end{pmatrix}. \quad (32)$$

Evaluating (31) and (32) at the DFE $\left\{ \frac{\pi(\pi+\sigma)}{(\pi+\sigma)(\pi+\tau)-\sigma\tau}, \frac{\pi\tau}{(\pi+\sigma)(\pi+\tau)-\sigma\tau}, 0, 0, 0 \right\}$ gives

$$F = \begin{pmatrix} 0 & \beta c f [(1-\tau)s + \theta v] \\ 0 & \beta c (1-f) [(1-\tau)s + \theta v] \end{pmatrix} \quad (33)$$

and

$$V = \begin{pmatrix} [\pi + k] & 0 \\ -k & [\pi + \gamma + \omega + \varepsilon] \end{pmatrix}, \quad (34)$$

and from (34),

$$V^{-1} = \frac{1}{(\pi + k)(\pi + \gamma + \omega + \varepsilon)} \times \begin{pmatrix} (\pi + \gamma + \omega + \varepsilon) & 0 \\ k & (\pi + k) \end{pmatrix}. \quad (35)$$

From (33) and (35), we obtained

$$FV^{-1} = \frac{1}{(\pi + k)(\pi + \gamma + \omega + \varepsilon)} \times \begin{pmatrix} 0 & \beta c f [(1-\tau)s + \theta v] \\ 0 & \beta c (1-f) [(1-\tau)s + \theta v] \end{pmatrix} \times \begin{pmatrix} (\pi + \gamma + \omega + \varepsilon) & 0 \\ k & (\pi + k) \end{pmatrix}. \quad (36)$$

Simplification of (36) and subsequently establishing its eigenvalues produces the dominant eigenvalue ρ as

$$\frac{\beta c \pi (\pi + \sigma) [k + \pi(1-f)] [(1-\tau)(\pi + \tau) + \tau\theta]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \varepsilon) [(\pi + \tau)(\pi + \sigma) - \sigma\tau]}. \quad (37)$$

Hence basic reproduction number R_0 is given by

$$R_0 = \frac{\beta c \pi (\pi + \sigma) [k + \pi(1-f)] [(1-\tau)(\pi + \tau) + \tau\theta]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \varepsilon) [(\pi + \tau)(\pi + \sigma) - \sigma\tau]}. \quad (38)$$

Theorem 1 *Tuberculosis infection shall be more rampaging whenever $\tau = 0$ [that is when there is no vaccination compartment].*

Proof Since $0 \leq \tau \leq 1$,

$$1 \geq (1 - \tau). \quad (39)$$

When (39) is multiplied through by $(\pi + \tau)$ and $\tau\theta$ is subsequently added to both sides, the result is

$$(\pi + \tau) + \tau\theta \geq (\pi + \tau)(1 - \tau) + \tau\theta. \quad (40)$$

Multiplication by $\frac{\beta c \pi (\pi + \sigma) [k + \pi(1-f)]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \varepsilon) [(\pi + \tau)(\pi + \sigma) - \sigma\tau]}$ gives

$$\frac{\beta c \pi (\pi + \sigma) [k + \pi(1-f)] [(\pi + \tau) + \tau\theta]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \varepsilon) [(\pi + \tau)(\pi + \sigma) - \sigma\tau]} \geq \frac{\beta c \pi (\pi + \sigma) [k + \pi(1-f)] [(\pi + \tau)(1 - \tau) + \tau\theta]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \varepsilon) [(\pi + \tau)(\pi + \sigma) - \sigma\tau]} \quad (41)$$

implies

$$R_{0_1} \geq R_0$$

where

$$R_{0_1} = \frac{\beta c \pi (\pi + \sigma) [k + \pi(1-f)] [(\pi + \tau) + \tau\theta]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \varepsilon) [(\pi + \tau)(\pi + \sigma) - \sigma\tau]}$$

and

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

When $\tau = 0$,

$$\Rightarrow R_{0_1} = R_0 \quad (42)$$

and when $\tau = 1$,

$$\Rightarrow R_{0_1} > R_0. \quad (43)$$

Theorem 1 explains the importance and relevance of vaccination in curbing the spread of TB infection. $\tau = 1$ explains the scenario when there is vaccination program in place while $\tau = 0$ explains the non-existence of vaccination program. A fraction of susceptible is expected to be vaccinated at the rate τ . From (42), it is obvious that $\tau = 0$ makes no difference in the number of secondary infection as $R_{0_1} = R_0$. On the other hand, (43) explains the importance of why efforts should be concerted on making sure $\tau = 1$. It is clear that doing so reduces the number of secondary infection as $R_{0_1} > R_0$. $\square$

Theorem 2 $\theta = 0$ [that is the vaccine confers total immunity] shall always minimise the rate of tuberculosis infection.

Proof Since $0 \leq \theta \leq 1$,

$$\theta \leq 1. \quad (44)$$

Multiplying both sides of (44) by τ and subsequently adding $(1 - \tau)(\pi + \tau)$ to both sides produce

$$(1 - \tau)(\pi + \tau) + \tau\theta \leq (1 - \tau)(\pi + \tau) + \tau. \quad (45)$$

Multiplying this by $\frac{\beta c \pi (\pi + \sigma) [k + \pi (1 - f)]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \epsilon)[(\pi + \tau)(\pi + \sigma) - \sigma \tau]}$, it results to

$$\begin{aligned} & \frac{\beta c \pi (\pi + \sigma) [k + \pi (1 - f)] [(1 - \tau)(\pi + \tau) + \tau\theta]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \epsilon)[(\pi + \tau)(\pi + \sigma) - \sigma \tau]} \\ & \leq \frac{\beta c \pi (\pi + \sigma) [k + \pi (1 - f)] [(1 - \tau)(\pi + \tau) + \tau]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \epsilon)[(\pi + \tau)(\pi + \sigma) - \sigma \tau]} \end{aligned} \quad (46)$$

implies

$$R_0 \leq R_{0_2}$$

where

$$R_{0_2} = \frac{\beta c \pi (\pi + \sigma) [k + \pi (1 - f)] [(1 - \tau)(\pi + \tau) + \tau\theta]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \epsilon)[(\pi + \tau)(\pi + \sigma) - \sigma \tau]}$$

and

$$R_{0_2} = \frac{\beta c \pi (\pi + \sigma) [k + \pi (1 - f)] [(1 - \tau)(\pi + \tau) + \tau]}{(\pi + \tau)(\pi + k)(\pi + \gamma + \omega + \epsilon)[(\pi + \tau)(\pi + \sigma) - \sigma \tau]}.$$

When $\theta = 0$,

$$\Rightarrow R_0 < R_{0_2} \quad (47)$$

and when $\theta = 1$,

$$\Rightarrow R_0 = R_{0_2}. \quad (48)$$

Theorem 2 provides information on how the vaccine should be designed. Since R_0 , i.e. (38) is the number of secondary infection from a primary, a value lesser to the established R_0

shall reduce the tuberculosis incidence while a greater value does the opposite. From (47), $\theta = 0$ implies the situation where the administered vaccination gives 100% immunity against tuberculosis. By that, vaccinated individuals are totally protected from contracting TB. $\theta = 1$ on the other hand, i.e. (48) gives an explanation on how there shall be no impact of the vaccine felt as all those vaccinated shall still contract the TB infection. As such, if the vaccines to prevent the contraction of TB are designed to give 100% protection against the infection, then the TB incident rate will be dramatically reduced. $\square$

Stability analysis of the equilibrium points of Eqs. (15)–(19)

The Jacobian matrix of Eqs. (15)–(19) is expressed as

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial s} & \frac{\partial f_1}{\partial v} & \frac{\partial f_1}{\partial e} & \frac{\partial f_1}{\partial i} & \frac{\partial f_1}{\partial r} \\ \frac{\partial f_2}{\partial s} & \frac{\partial f_2}{\partial v} & \frac{\partial f_2}{\partial e} & \frac{\partial f_2}{\partial i} & \frac{\partial f_2}{\partial r} \\ \frac{\partial f_3}{\partial s} & \frac{\partial f_3}{\partial v} & \frac{\partial f_3}{\partial e} & \frac{\partial f_3}{\partial i} & \frac{\partial f_3}{\partial r} \\ \frac{\partial f_4}{\partial s} & \frac{\partial f_4}{\partial v} & \frac{\partial f_4}{\partial e} & \frac{\partial f_4}{\partial i} & \frac{\partial f_4}{\partial r} \\ \frac{\partial f_5}{\partial s} & \frac{\partial f_5}{\partial v} & \frac{\partial f_5}{\partial e} & \frac{\partial f_5}{\partial i} & \frac{\partial f_5}{\partial r} \end{pmatrix} \quad (49)$$

where

$$\begin{aligned} f_1 &= \pi + \sigma v + \alpha r - \{\pi + \tau + [(1 - \tau)\beta c - \epsilon]i\}s, \\ f_2 &= \tau s - [\pi + \sigma + (\theta\beta c - \epsilon)i]v, \\ f_3 &= (1 - \tau)f\beta c i s + \theta f\beta c i v \\ &\quad + f_1\delta_2\beta c i r - [\pi + k + (\delta_1\beta c - \epsilon)i]e, \\ f_4 &= (1 - \tau)(1 - f)\beta c i s + \theta(1 - f)\beta c i v + (1 - f_1)\delta_2\beta c i r \\ &\quad + (\delta_1\beta c i + k)e - [\pi + \gamma + \omega + \epsilon(1 - i)]i \end{aligned}$$

and

$$f_5 = (\gamma + \omega)i - [\pi + \alpha + (\delta_2\beta c - \epsilon)i]r.$$

Then,

$$J = \begin{pmatrix} a_{11} & \sigma & 0 & -[(1 - \tau)\beta c - \epsilon]s & \alpha \\ \tau & -[\pi + \sigma + (\theta\beta c - \epsilon)i] & 0 & -(\theta\beta c - \epsilon)v & 0 \\ (1 - \tau)f\beta c i & \theta f\beta c i & a_{33} & a_{34} & f_1\delta_2\beta c i \\ (1 - \tau)(1 - f)\beta c i & \theta(1 - f)\beta c i & (\delta_1\beta c i + k) & a_{44} & (1 - f_1)\delta_2\beta c i \\ 0 & 0 & 0 & (\gamma + \omega) - (\delta_2\beta c - \epsilon)r & -[\pi + \alpha + (\delta_2\beta c - \epsilon)i] \end{pmatrix}, \quad (50)$$

where

$$\begin{aligned} a_{11} &= -\{\pi + \tau + [(1 - \tau)\beta c - \varepsilon]i\}, \\ a_{33} &= -[\pi + k + (\delta_1\beta c - \varepsilon)i], \\ a_{34} &= (1 - \tau)f\beta cs + \theta f\beta cv + f_1\delta_2\beta cr - (\delta_1\beta c - \varepsilon)e \\ \text{and} \\ a_{44} &= (1 - \tau)(1 - f)\beta cs + \theta(1 - f)\beta cv \\ &\quad + (1 - f_1)\delta_2\beta cr + \delta_1\beta ce - (\pi + \gamma + \omega + \varepsilon - 2\varepsilon i). \end{aligned}$$

Stability of the DFE

Local stability

Theorem 3 The DFE of the model [Eqs. (15)-(19)] is locally asymptotically stable whenever $R_0 < 1$ and unstable otherwise.

Proof Evaluating (50) at DFE $\left\{ \frac{\pi(\pi + \sigma)}{(\pi + \tau)(\pi + \sigma) - \sigma\tau}, \frac{\pi\tau(\pi + \sigma)}{(\pi + \tau)[(\pi + \tau)(\pi + \sigma) - \sigma\tau]}, 0, 0, 0 \right\}$ gives

$$J = \begin{pmatrix} -(\pi + \tau) & \sigma & 0 & \frac{-\zeta_2}{\zeta_1} & \alpha \\ \tau & -(\pi + \sigma) & 0 & \frac{\zeta_1}{(\pi + \tau)\zeta_1} & 0 \\ 0 & 0 & -(\pi + k) & \frac{\zeta_4}{(\pi + \tau)\zeta_1} & 0 \\ 0 & 0 & k & \frac{\zeta_5}{(\pi + \tau)\zeta_1} & 0 \\ 0 & 0 & 0 & (\gamma + \omega) & -(\pi + \alpha) \end{pmatrix}. \quad (51)$$

where

$$\begin{aligned} \zeta_1 &= (\pi + \tau)(\pi + \sigma) - \sigma\tau \\ \zeta_2 &= \pi(\pi + \sigma)[(1 - \tau)\beta c - \varepsilon] \\ \zeta_3 &= \pi\tau(\pi + \sigma)(\theta\beta c - \varepsilon) \\ \zeta_4 &= \pi f\beta c(\pi + \sigma)[(1 - \tau)(\pi + \tau) + \tau\theta] \\ \text{and} \\ \zeta_5 &= \pi\beta c(1 - f)(\pi + \sigma)[(1 - \tau)(\pi + \tau) + \tau\theta] \\ &\quad - (\pi + \tau)\zeta_1(\pi + \gamma + \omega + \varepsilon) \end{aligned}$$

If the eigenvalue is denoted by η , then the eigenvalues of (51) shall be obtained from

$$|J - \eta I| = 0.$$

That is,

$$\begin{vmatrix} -(\pi + \tau + \eta) & \sigma & 0 & \frac{-\zeta_2}{\zeta_1} & \alpha \\ \tau & -(\pi + \sigma + \eta) & 0 & \frac{\zeta_1}{(\pi + \tau)\zeta_1} & 0 \\ 0 & 0 & -(\pi + k + \eta) & \frac{\zeta_4}{(\pi + \tau)\zeta_1} & 0 \\ 0 & 0 & k & \frac{\zeta_5 - (\pi + \tau)\zeta_1\eta}{(\pi + \tau)\zeta_1} & 0 \\ 0 & 0 & 0 & (\gamma + \omega) & -(\pi + \alpha + \eta) \end{vmatrix} = 0, \quad (52)$$

The first three eigenvalues of (52) are

$$\begin{aligned} \eta_1 &= -\pi, \\ \eta_2 &= -(\pi + \alpha) \\ \text{and} \end{aligned}$$

$$\eta_3 = -(\pi + \sigma + \tau)$$

while the reduced determinantal equation is

$$\begin{vmatrix} -(\pi + k + \eta) & \frac{\zeta_4}{(\pi + \tau)\zeta_1} \\ k & \frac{\zeta_5 - (\pi + \tau)\zeta_1\eta}{(\pi + \tau)\zeta_1} \end{vmatrix} = 0, \quad (53)$$

then

$$a\eta^2 + b\eta + c = 0, \quad (54)$$

where

$$\begin{aligned} a &= 1, \\ b &= (\pi + k) + (\pi + \gamma + \omega + \varepsilon) - \frac{[\zeta_5 + (\pi + \tau)\zeta_1]}{(\pi + \tau)\zeta_1} \\ \text{and} \end{aligned}$$

$$\begin{aligned} c &= (\pi + k)(\pi + \gamma + \omega + \varepsilon) \\ &\quad - \frac{[\zeta_5 + (\pi + \tau)\zeta_1][k + \pi(1 - f)]}{(\pi + \tau)\zeta_1}. \end{aligned}$$

The fourth and fifth eigenvalues, η_4 and η_5 , respectively, are

$$\eta_{4,5} = \frac{-b \pm \sqrt{b^2 - 4(\pi + k)(\pi + \gamma + \omega + \varepsilon)\{1 - R_0\}}}{2}. \quad (55)$$

Eigenvalues η_4, η_5 from (55) depend on R_0 . $R_0 < 1 \Rightarrow \eta_4, \eta_5 < 0$ while $R_0 > 1 \Rightarrow \eta_4 > (<)0$ and

$\eta_5 < (>)0$. Hence, $R_0 < 1$ guarantees the stability and as such completes the proof. $\square$

Global stability

The global stability theorem as discussed by Castillo-Chavez et al. (2002) and used by Bhunu et al. (2011), Srivastav and Ghosh (2016) and Goswami et al. (2018) is employed to establish the global stability of the non-linear system (17)–(20).

If the system of Eqs. (15)–(19) can be written in the form:

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

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.

$$\begin{aligned} H_1 : & \text{for } \frac{dX}{dt} = F(X_0, \mathbf{0}), X_0^* \text{ is globally asymptotically stable.} \\ H_2 : & \text{for } G(X, Y) = AY - \hat{G}(X, Y), \hat{G}(X, Y) \geq 0, \end{aligned}$$

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 *The DFE, $P_1 = (X_0^*, \mathbf{0})$ of the non-linear system (15)–(19) is globally asymptotically stable (GAS) provided it satisfies the conditions H_1 and H_2 above, as well as $R_0 < 1$.*

Proof From Theorem 3, the following are established

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

and

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

where

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

Recall that $Y_0 = Y(0) \geq 0 \Rightarrow Y(t) \geq 0$. Since A is an M-matrix, e^{At} is a positive semigroup. Using the variation of constant formula, see e.g. Wu (2003) and Carrasco and Leiva (2007) gives

$$\begin{aligned} 0 \leq Y(t) &= e^{At} Y_0 - \int_0^t e^{A(t-s)} \hat{G}(X(w), Y(w)) dw \\ &\leq e^{At} Y_0. \end{aligned} \quad (56)$$

It is obvious from (55) that A has dominant eigenvalue $m(A)$ for $R_0 < 1$.

As such,

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

X^* is GAS equilibrium point of $\frac{dX}{dt} = F(X, 0)$ 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,

$$\begin{aligned} \hat{G}(X, Y) &\Rightarrow \begin{pmatrix} \hat{G}_1(X, Y) \\ \hat{G}_2(X, Y) \end{pmatrix} \\ &= \begin{pmatrix} f\beta_{cis} + f_1\beta_{cir} \\ (1-f)\beta_{cis} + (1-f_1)\beta_{cir} + \delta\beta_{cie} \end{pmatrix}. \end{aligned} \quad (57)$$

and

$$A = \begin{pmatrix} -[\pi + k + (\delta\beta_c - \epsilon)i] & f\beta_{cs} + f_1\beta_{cr} - (\delta\beta_c - \epsilon)e \\ \delta\beta_{ci} + k & (1-f)\beta_{cs} + (1-f_1)\beta_{cr} + \delta\beta_{ce} - (\pi + \sigma + \omega + \epsilon) + 2\epsilon i \end{pmatrix}, \quad (58)$$

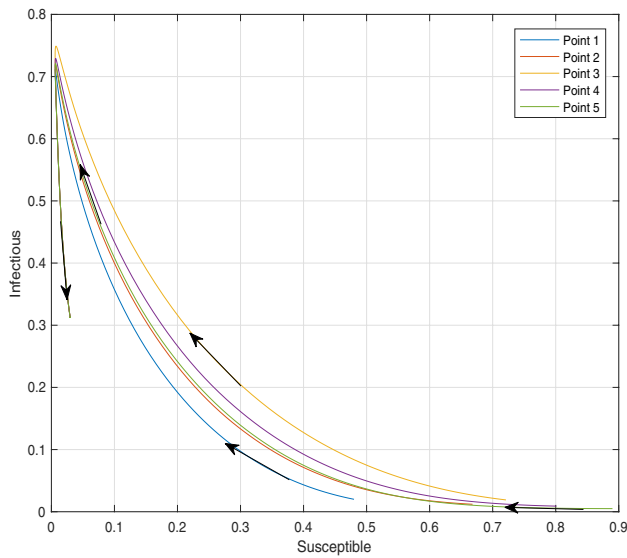


Fig. 2 Phase portrait of the system (15)–(19) in S - I Plane

which at the DFE $(X_0, \mathbf{0})$ gives

$$A = \begin{pmatrix} -[\pi + k] & f\beta c \\ k & (1-f)\beta c - (\pi + \sigma + \omega + \varepsilon) \end{pmatrix}. \quad (59)$$

Obviously, the non-diagonal elements of A are non-negative since $f < 1$ and $f_1 < 1$, $\hat{G}(X, Y) \geq 0$. Then the DFE, P_1 of the non-linear system (15)–(19) is GAS. $\square$

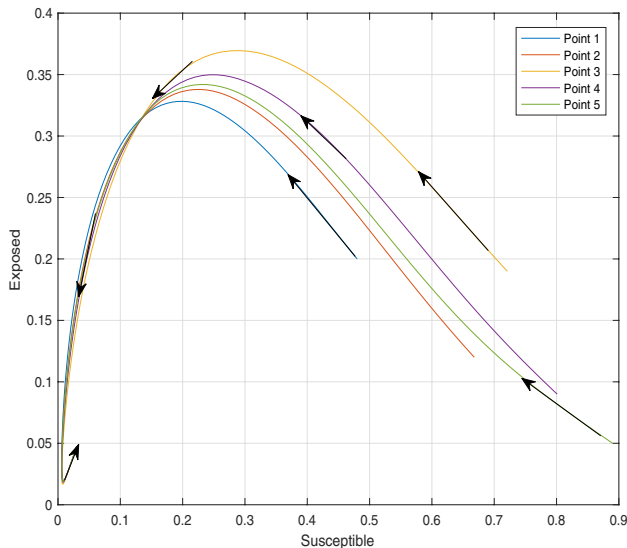


Fig. 3 Phase portrait of the system (15)–(19) in S - E Plane

Stability of the EEP

Local stability

The expressions for the EEP of the non-linear system (15)–(19) from solving Eq. (29) are too long to be written here, and to show the local stability of the EEP analytically is challenging. As such, we employed the phase portrait in establishing the stability of the EEP using five random initial conditions (points 1–5) which are: $\{[s(0) = 0.4800, v(0) = 0.3000, e(0) = 0.2000, i(0) = 0.0200, r(0) = 0], [s(0) = 0.6680, v(0) = 0.2000, e(0) = 0.1200, i(0) = 0.0120, r(0) = 0], [s(0) = 0.7200, v(0) = 0.0700, e(0) = 0.1900, i(0) = 0.0190, r(0) = 0], [s(0) = 0.8010, v(0) = 0.1000, e(0) = 0.0900, i(0) = 0.0090, r(0) = 0], [s(0) = 0.8890, v(0) = 0.1000, e(0) = 0.0100, i(0) = 0.0010, r(0) = 0]\}$ as well as the parameter values in Table 1 below. The graphs emanating from the chosen points eventually converge to the same point. The phase portraits are shown in Figs. 2, 3 and 4 below.

Global stability

Theorem 5 *The endemic equilibrium point $\{E_1 = (s^*, e^*, i^*, r^*) \in \Phi\}$ of the system (15)–(19) with the special case $\varepsilon = 0$ is globally asymptotically stable whenever $R_0 > 1$.*

Proof From (17) and (18), $\varepsilon = 0$

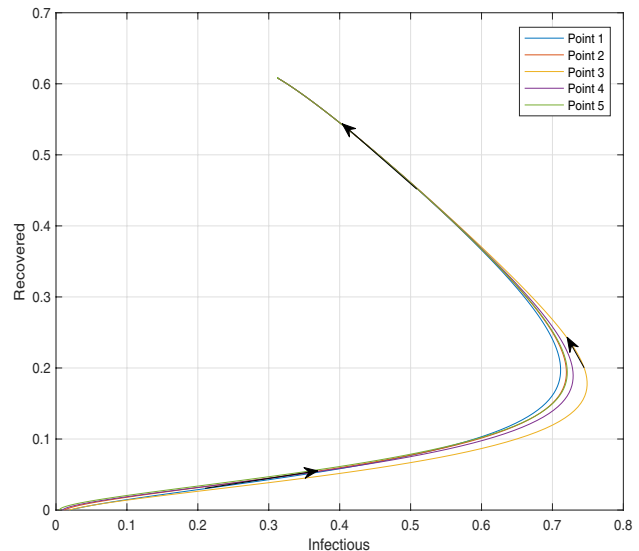


Fig. 4 Phase portrait of the system (15)–(19) in I - R Plane

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	Bhunu et al. (2008)
2	π	Recruitment rate	0.03000	Bhunu et al. (2008)
3	c	Contact rate	80.0000	Bhunu et al. (2008)
4	μ	Natural mortality rate	0.01000	Estimate
5	ε	TB-induced death	0.30000	Bhunu et al. (2008)
6	k	Endogenous reactivation	0.00013	Bhunu et al. (2008)
7	α	Rate of the recovered moving back to susceptible	0.30000	Estimate
8	δ_1	Exogenous reinfection	0.70000	Bhunu et al. (2008)
9	δ_2	Probability of the recovered individuals being reinfected	0.02000	Estimate
10	τ	Vaccination rate	0.20000	Estimate
11	ω	Natural recovery rate	0.20000	Bhunu et al. (2008)
12	σ	Rate of movement to susceptible class after loss of immunity given by vaccine	0.50000	Estimate
13	f	Probability that the infected will enter the latent stage of the disease	0.99000	Bhunu et al. (2008)
14	f_1	Probability of the reinfected R moving to E	0.70000	Bhunu et al. (2008)
15	γ	Treatment Rate	0.60000	Estimate
16	θ	Rate of the vaccinated getting infected	0.28500	WHO (2018c)
17	u_1	Reduction in the exposure rate of the susceptible individuals to the infectious	0.50000	Estimate
18	u_2	Boosting of the immune system by eating healthy meals	0.20000	Estimate

$$\Rightarrow e' = (1 - \tau)f\beta ci + \theta f\beta civ + f_1\delta_2\beta cir - [\pi + k + \delta_1\beta ci]e \quad (60)$$

and

$$i' = (1 - \tau)(1 - f)\beta ci + \theta(1 - f)\beta civ + (1 - f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e - [\pi + \gamma + \omega]i. \quad (61)$$

$$\Rightarrow e' = (1 - \tau)f\beta ci[1 - (v + e + i + r)] + \theta f\beta civ + f_1\delta_2\beta cir - [\pi + k + \delta_1\beta ci]e \quad (62)$$

and

$$i' = (1 - \tau)(1 - f)\beta ci[1 - (v + e + i + r)] + \theta(1 - f)\beta civ + (1 - f_1)\delta_2\beta cir + (\delta_1\beta ci + k)e - [\pi + \gamma + \omega]i. \quad (63)$$

Using the Dulac multiplier $\Theta = \frac{1}{ei}$ with the below Dulac function as discussed in Mukandavire et al. (2009) and Omondi et al. (2018)

$$\frac{\partial(\Theta e')}{\partial e} + \frac{\partial(\Theta i')}{\partial i},$$

produces

$$\frac{-\beta c}{e^2} \{f(1 - \tau)[1 - (v + i + r)] + \theta f v + f_1 \delta r\} - \frac{(1 - \tau)(1 - f)\beta c}{e} - \frac{k}{i^2} \quad (64)$$

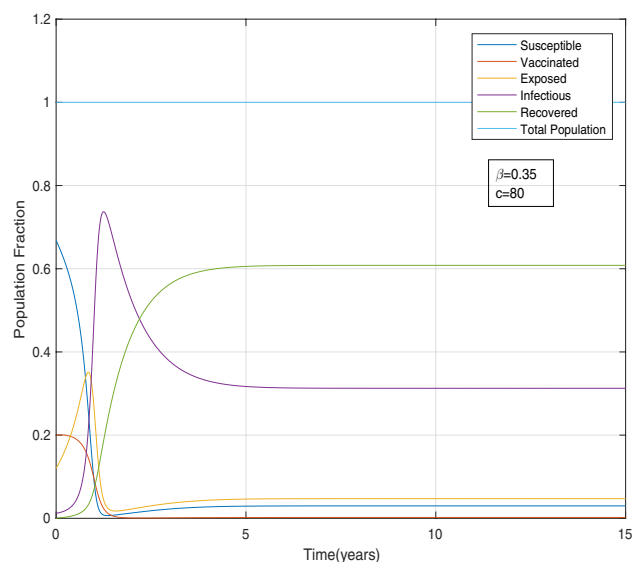


Fig. 5 SVEIR Relationship within 15 Years

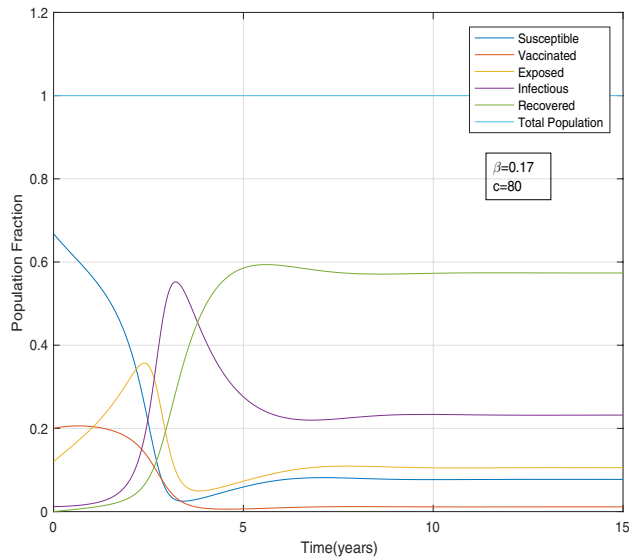


Fig. 6 SVEIR Relationship within 15 Years

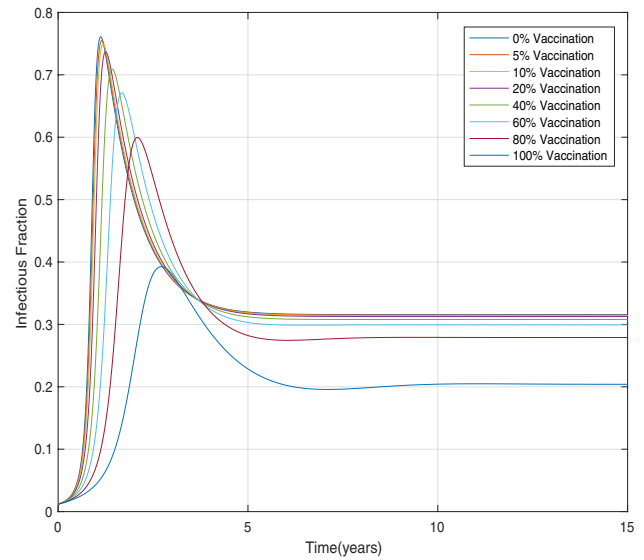


Fig. 8 Effect of the vaccination rate

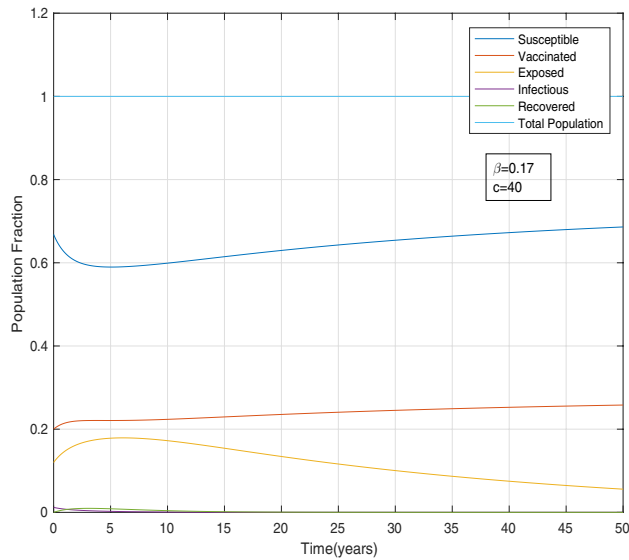


Fig. 7 SVEIR Relationship within 50 Years

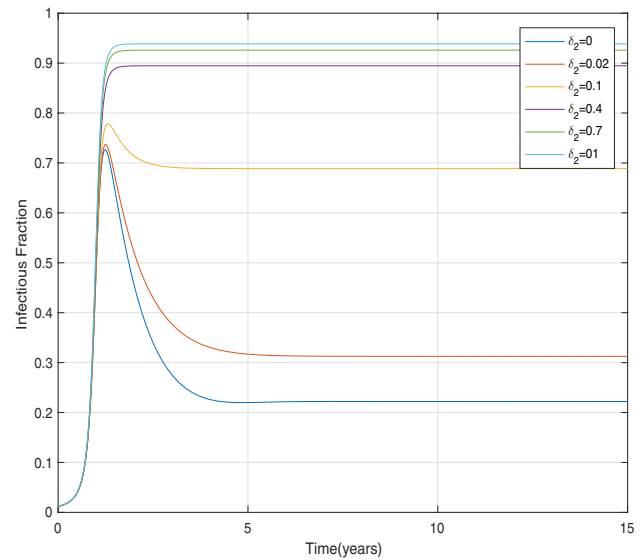


Fig. 9 Effect of δ_2 (probability of recovered being reinfected) in reducing TB infection

$$\Rightarrow -\left\{ \frac{\beta c}{e^2} \{f(1-\tau)[1-(v+i+r)] + \theta f v + f_1 \delta r\} + \frac{(1-\tau)(1-f)\beta c}{e} + \frac{k}{i^2} \right\} < 0 \quad (65)$$

As such, we can infer by the Dulac's criterion that there are no periodic orbits in Φ . Since Φ is positively invariant and the EEP of the model exists only when $R_0 > 1$, using Poincaré–Bendixson theorem (Perko 2001) all solutions of the limiting system emanating in Φ remain in Φ for all t . Also, the uniqueness of the globally asymptotically stable EEP of

the special case is established by the absence of the periodic orbits in Φ . $\square$

Numerical simulation of the model

The above non-linear system (15)–(19) was solved using ODE45 package of MATLAB with known values given in Table 1. Most of the values used for graphical purposes here are from Bhunu et al. (2008) while others are reasonably chosen estimates. The initial fractions of the susceptible,

Fig. 10 Effect of a better vaccine

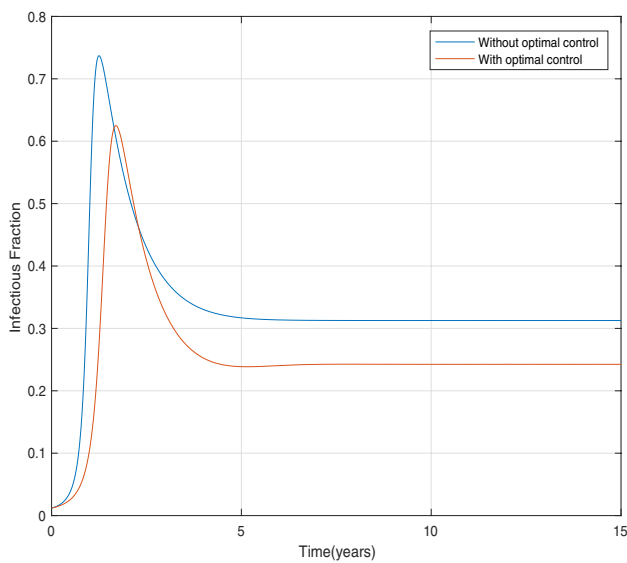
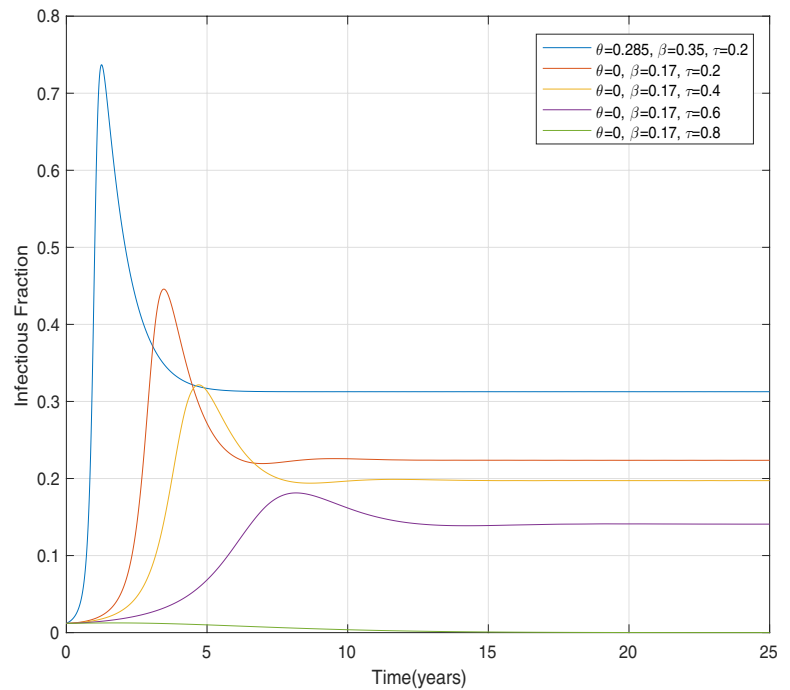


Fig. 11 Effect of the optimal control on the infectious class

vaccinated, exposed, infectious and recovered are 0.6680, 0.2000, 0.1200, 0.0120 and 0, respectively, and the resulting graphs are presented below.

Graphical results

The simulation

In this part of the work, the non-linear system of equations is solved numerically with the stated initial condition above.

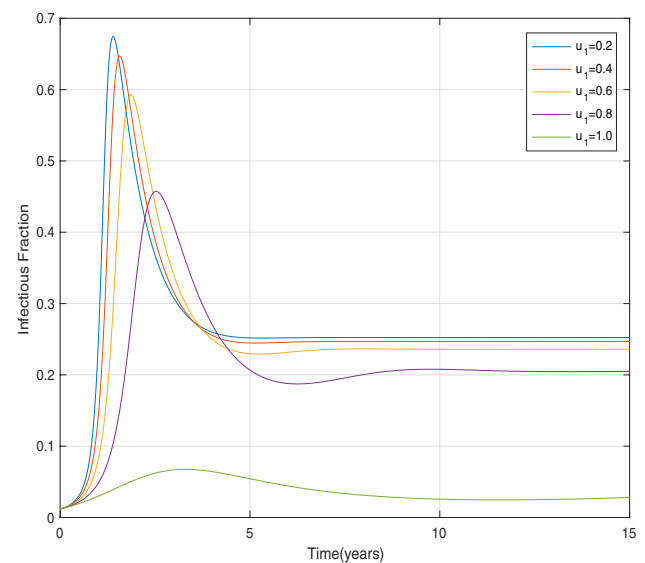


Fig. 12 Effect of the variations in optimal control u_i

Figs. 5, 6 and 7 show the behaviour of the infection under various infectivity (β) and contact (c) rates while vaccination is maintained. Figure 8 explains the impacts of different vaccination proportions and Fig. 9 gives the outcome of the infection when prevention of reinfection is not considered in the vaccination and drugs formulation. Figs. 10, 11, 12 display the outcome when the vaccine is designed to confer total immunity against tuberculosis infection.

The analysis

Drug administration in combating any epidemic can be done majorly in two ways, it is either therapeutic or prophylactic. Therapeutic is useful in managing an infection that has been contracted while prophylactic is useful in preventing the eventual contraction of the infection. Our concern dwells on the prophylactic. Fig. 5 shows how the infection would behave when we maintain the standard infectivity (β) and contact (c) rates. Reduction of the infectivity rate (β) by half gives a reduction in the peak value of the infectious fraction by 30.67% as displayed in Fig. 6. Halving both the infectivity rate (β) and contact rate (c) eventually sends the infection off the community as it gives significant 98.48% reduction in the peak of the infectious fraction as displayed in Fig. 7 below. Fig. 8. details the effect of vaccination proportion in combatting TB. The vaccination rate was varied from 0% to 100% to detect the best vaccination proportion. At 100% vaccination rate, the maximum infectious fraction is 0.5053 as compared to 0.7451, which is the maximum infectious fraction when there is no vaccination program. That shows a reduction by 32.18% in the maximum infectious fraction. In Fig. 9, we investigated the relevance of the probability of reinfection (δ_2) after being in the recovered class. It was shown that δ_2 plays a significant role in the behaviour of the infection as non-consideration of δ_2 in the model formulation, i.e. ($\delta_2 = 1$) makes the vaccination non-helpful in reducing the TB incidence. Finally, Fig. 10 probes the impact of the vaccination when it confers 100% immunity against tuberculosis infection. When the vaccine confers total immunity, it is expected that the infectivity rate of the infection is as well reduced. 20% is used as the basic vaccination proportion, variation in this proportion to 40%, 60% and 80% further reduces the infectious fraction as obviously displayed in Fig. 10.

The optimal control

In this section, the analysis on combatting TB is extended using optimal control. The objective is to further reduce the TB infection rate while maintaining the associated cost. Controls u_1 and u_2 are introduced where u_1 is the reduction in the exposure rate of the susceptible individual to the infectious while u_2 is the recommendation of healthy meals to boost the immune system of the infectious individuals, $u_1, u_2 \in [0, 1]$ as indicated in the system (66) below.

$$\left. \begin{aligned} \frac{ds}{dt} &= \pi + \sigma v + \alpha r \\ &\quad - \{ \pi + \tau + [(1-\tau)(1-u_1)\beta c - \epsilon] i \} s \\ \frac{dv}{dt} &= \tau s - [\pi + \sigma + (\theta\beta c - \epsilon) i] v \\ \frac{de}{dt} &= (1-\tau)(1-u_1)f\beta cis + \theta f\beta civ \\ &\quad + f_1\delta_2\beta cir - [\pi + k + (\delta_1\beta c - \epsilon) i] e \\ \frac{di}{dt} &= (1-\tau)(1-u_1)(1-f)\beta cis + \theta(1-f)\beta civ \\ &\quad + (1-f_1)\delta_2\beta cir + (\delta_1\beta ci + k) e \\ &\quad - [\pi + \gamma + \omega + u_2 + \epsilon(1-i)] i \\ \frac{dr}{dt} &= (\gamma + \omega + u_2) i - [\pi + \alpha + (\delta_2\beta c - \epsilon) i] r. \end{aligned} \right\} \quad (66)$$

Since the objective is to reduce the infectious (i), the objective functional for the optimal control is

$$J(u_1, u_2) = \int_0^{t_f} \left[Qi + \frac{1}{2}c_1u_1^2 + \frac{1}{2}c_2u_2^2 \right] dt \quad (67)$$

where $Q \geq 0, c_1 \geq 0, c_2 \geq 0$, represent the weight constants. The control parameters u_1^* and u_2^* are to be established such that $J(u_1^*, u_2^*) = \min_{u_1, u_2 \in \Omega} J(u_1, u_2)$ where Ω is the control set defined as $\Omega = \{u_1, u_2 : \text{measurable} \ni 0 \leq u_1, u_2 \leq 1 \text{ for all } t \in [0, t_f]\}$. As expressed in the above objective functional, we have the Lagrangian associated with the problem as

$$\begin{aligned} L(i, u_1, u_2) &= Qi + \frac{1}{2}c_1u_1^2 \\ &\quad + \frac{1}{2}c_2u_2^2 \end{aligned} \quad (68)$$

and the Hamiltonian $\mathcal{H}$

$$\begin{aligned} \mathcal{H} &= L(i, u_1, u_2) + \lambda_1^* \frac{ds}{dt} + \lambda_2^* \frac{dv}{dt} \\ &\quad + \lambda_3^* \frac{de}{dt} + \lambda_4^* \frac{di}{dt} + \lambda_5^* \frac{dr}{dt} \end{aligned} \quad (69)$$

where $\lambda_i^*, i = 1, \dots, 5$ are the adjoint variables satisfying $\frac{d\lambda_1^*}{dt} = \frac{-\partial \mathcal{H}}{\partial s}, \frac{d\lambda_2^*}{dt} = \frac{-\partial \mathcal{H}}{\partial v}, \frac{d\lambda_3^*}{dt} = \frac{-\partial \mathcal{H}}{\partial e}, \frac{d\lambda_4^*}{dt} = \frac{-\partial \mathcal{H}}{\partial i}, \frac{d\lambda_5^*}{dt} = \frac{-\partial \mathcal{H}}{\partial r}$ and the transversality condition $\lambda_i^*(t_f) = 0, i = 1, \dots, 5$.

If $\hat{s}, \hat{v}, \hat{e}, \hat{i}, \hat{r}$ are the optimum values of s, v, e, i, r and also, $\hat{\lambda}_1^*, \hat{\lambda}_2^*, \hat{\lambda}_3^*, \hat{\lambda}_4^*, \hat{\lambda}_5^*$ is the solution of (66), then with the aid of Pontryagin's maximum principle, u_1 and u_2 are optimal controls that minimise the function.

Theorem 6 *There are optimal controls $u_1^*, u_2^* \in \Omega \ni J(u_1^*, u_2^*) = \min_{u_1, u_2} J(u_1, u_2)$ subject to the optimal control system.*

Proof The approach of the proof is taken from Pontryagin et al. (1962) alongside Lenhart and Workman (2007) as it is obvious that the state variables and the controls are positive. For this minimisation problem, the necessary convexity of the objective functional in (u_1, u_2) is satisfied. Likewise,

the control variable set $\Omega \ni u_1, u_2 \in \Omega$ is also convex and closed by the definition. The integrand of the functional $Qi + \frac{1}{2}c_1u_1^2 + \frac{1}{2}c_2u_2^2$ is convex on the control set Ω and the state variables are bounded. The use of Pontryagin's maximum principle (Pontryagin and Boltyanskii 1980) is adopted to minimise the objective functional and also the optimal solution.

Consider (x, u) as an optimal solution of an optimal control problem, then there is a non-trivial vector function $\lambda^* = \lambda_1^*, \lambda_2^*, \dots, \lambda_n^*$ that satisfies the following;

$$\begin{aligned} \frac{dx}{dt} &= \frac{\partial \mathcal{H}(t, x, u, \lambda^*)}{\partial \lambda^*} \\ 0 &= \frac{\partial \mathcal{H}(t, x, u, \lambda^*)}{\partial \lambda^*} \\ \frac{d\lambda}{dt} &= -\frac{\partial \mathcal{H}(t, x, u, \lambda^*)}{\partial x} \end{aligned}$$

□

Theorem 7 The optimal controls u_1^*, u_2^* that minimise the objective functional J over the region Ω are

$$u_1^* = \min\{1, \max\{0, \hat{u}_1\}\}$$

and

$$u_2^* = \min\{1, \max\{0, \hat{u}_2\}\}$$

where

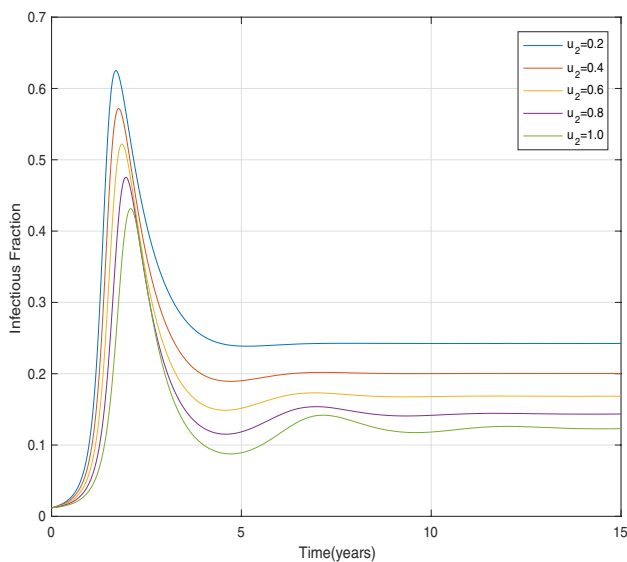


Fig. 13 Effect of the variations in optimal control u_2

$$\hat{u}_1 = \frac{\beta \text{cis}(1 - \tau)(\lambda_4^* - \lambda_1^*) + f\beta \text{cis}(1 - \tau)(\lambda_3^* - \lambda_4^*)}{c_1}$$

and

$$\hat{u}_2 = \frac{i(\lambda_5^* - \lambda_4^*)}{c_2}$$

Proof From (69),

$$\left. \begin{aligned} \frac{d\lambda_1^*}{dt} &= \tau(\lambda_1^* - \lambda_2^*) + \beta ci(1 - \tau)(1 - u_1)(\lambda_1^* - \lambda_4^*) \\ &\quad + f\beta ci(1 - \tau)(1 - u_1)(\lambda_4^* - \lambda_3^*) + (\pi - \epsilon i)\lambda_1^* \\ \frac{d\lambda_2^*}{dt} &= \sigma(\lambda_2^* - \lambda_1^*) + \theta\beta ci(\lambda_2^* - \lambda_4^*) \\ &\quad + \theta f\beta ci\lambda_4^* - \lambda_3^* + (\pi - \epsilon i)\lambda_2^* \\ \frac{d\lambda_3^*}{dt} &= k(\lambda_3^* - \lambda_4^*) + \delta_1\beta ci(\lambda_3^* - \lambda_4^*) + (\pi - \epsilon i)\lambda_3^* \\ \frac{d\lambda_4^*}{dt} &= -Q + \beta cs(1 - \tau)(1 - u_1)(\lambda_1^* - \lambda_4^*) \\ &\quad + f\beta cs(\lambda_4^* - \lambda_3^*) + \theta\beta cv(\lambda_2^* - \lambda_4^*) \\ &\quad + \theta f\beta cv(\lambda_4^* - \lambda_3^*) + M \\ \frac{d\lambda_5^*}{dt} &= \alpha(\lambda_5^* - \lambda_1^*) + \delta_2\beta ci(\lambda_5^* - \lambda_4^*) \\ &\quad + f_1\delta_2\beta ci(\lambda_4^* - \lambda_3^*) + (\pi - \epsilon i)\lambda_4^* \end{aligned} \right\} \quad (70)$$

where

$$\begin{aligned} M &= \delta_2\beta cr(\lambda_5^* - \lambda_4^*) + f_1\delta_2\beta cr(\lambda_4^* - \lambda_3^*) \\ &\quad + \delta_1\beta ce(\lambda_3^* - \lambda_4^*) + (\gamma + \omega + u_2)(\lambda_4^* - \lambda_5^*) \\ &\quad + \lambda_4^*(\pi + \epsilon) - \epsilon(\lambda_1^*s + \lambda_2^*v + \lambda_3^*e + 2\lambda_4^*i + \lambda_5^*r). \end{aligned}$$

By the optimality condition $\frac{\partial \mathcal{H}}{\partial u_1} = 0$ and $\frac{\partial \mathcal{H}}{\partial u_2} = 0$,

$$u_1 = \frac{\beta \text{cis}(1 - \tau)(\lambda_4^* - \lambda_1^*) + f\beta \text{cis}(1 - \tau)(\lambda_3^* - \lambda_4^*)}{c_1} = \hat{u}_1 \quad (71)$$

and

$$u_2 = \frac{i(\lambda_5^* - \lambda_4^*)}{c_2} = \hat{u}_2 \quad (72)$$

Numerical simulation of the optimal control model

The optimal control model (66) is solved using the numerical values in Table 1 above and the subsequent graphs are the resulting outputs. The impact of the controls u_1 and u_2 is tested and is found to be highly relevant in further reducing the incident of TB. Figure 11 queries the relevance of these controls in the model. It is shown that there is significant difference between the infectious fraction of the model with optimal control and that without control. The one with optimal control produces reduction in the infectious fraction. Furthermore, increment in the values of these controls gives far better results as shown in Figs. 12 and 13.

Conclusion

A five compartmental model of susceptible (S), vaccinated (V), exposed (E), infectious (I) and recovered (R) is formulated using a non-linear system of ODE to investigate the relevance of prophylactic vaccine in reducing the rate of TB incident. Since efforts can only be made on the controllable factors like infectivity rate, contact rate, vaccination rate, reinfection rate, TB induced death rate, etc., the model is normalised so as to eliminate the natural death factor (μ). Subsequently, the basic reproduction number (R_0) is established and the disease-free equilibrium (DFE) is shown to be stable. It is shown that the DFE is stable whenever $R_0 < 1$. The system is shown to be globally asymptotically stable using Theorems 4 and 5 alongside their proofs. From Theorem 1, it is established that vaccination helps a long way in reducing the TB incidence. Similarly, Theorem 2 explains why the vaccine should be designed to be potent enough to combat getting the infection. These theorems are corroborated by Fig. 10. In the same vein, the design of the vaccines and drugs to reduce the infectivity rate coupled with the reduction of contacts between the susceptible and infectious individuals reduces the tuberculosis incidence as shown in Figs. 5, 6, 7. Vaccination of a good proportion of the susceptible class reduces the TB incidence as displayed in Fig. 8. If the drugs are not designed to combat reinfection, little or nothing shall be achieved in the war against tuberculosis as displayed in Fig. 9. Figure 10 explains that a vaccine that could reduce the infectivity rate of *Mtb* by half and as well give a permanent immunity against TB infection will drastically reduce the incidence of TB. In furtherance to the above, an optimal control analysis is done such that controls u_1 and u_2 are introduced. u_1 is the reduction in the exposure rate of the susceptible individuals to infectious and u_2 is the boosting of the immune system by eating healthy meals. The impacts of these two controls are measured as displayed in

Figs. 11, 12, 13. The inclusion of the controls in the model shows significant reduction in the TB infectious fraction.

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