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Mathematical Analysis of an Infection Age-Structured Model for Tuberculosis Disease Dynamics Incorporating Control Measures

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Abstract
An infection-age-structured mathematical model for tuberculosis (TB) disease dynamics and treatment, vaccination and public health education campaign as control parameters is developed and analyzed. Here, both the latent and infectious classes are structured according to time and age-of-infection. An explicit threshold value for the effective reproduction number R_E is obtained in terms of the demographic and epidemiological parameters of the model. Using the method of linearization, the disease-free equilibrium was found to be locally asymptotically stable when the effective reproduction number is less than unity. By constructing a suitable Lyapunov functional, the disease-free equilibrium state was found to be globally asymptotically stable whenever the associated effective reproduction number is less or equal to unity. This means that tuberculosis could be put under control in the population when the associated effective reproduction number is less than unity. Sensitivity analysis was also carried out on the effective reproduction number, R_E in order to ascertain the parameters of the model that are most sensitive and that should be targeted by way of intervention strategies. It was found out that the, infection rate α , recruitment number due to birth (Λ), treatment rates [both for latent (ρ_2) and active TB (ρ_1)], vaccination υ and public health education campaign (ψ_e) are the most sensitive parameters. From the effective reproduction number (R_E), the basic reproduction number and the reproduction numbers with single double and triple control strategies were obtained. Results from the numerical simulations of the various reproduction numbers revealed that, the more the application of the control strategies, the faster the control/eradication of TB is achieved.

Keywords: Age-of-infection, tuberculosis, sensitivity analysis, mathematical model, Age-Structured.

Introduction

Tuberculosis otherwise known as *tubercle bacillus* (TB) remains one of the top 10 world's most infectious deadly killer disease. TB ranks as the second leading cause of death from an infectious disease worldwide after the human immunodeficiency virus (HIV), World Health Organization (WHO), [26]. It is an infectious disease caused by mycobacteria mainly *mycobacterium tuberculosis*. An infected person may have latent TB infection or active TB infection. Only actively infected persons who are sick with TB in their lungs are infectious. When infectious people cough, sneeze, talk or spit, they propel TB germs, known as bacilli into the air. A susceptible person needs to inhale only a small number of these bacteria to be infected. A latent TB infected person does not show any symptoms of the disease and cannot infect others, though may live as long as possible without it degenerating into active TB [26].

Disease Control (CDC)), [9].

The epidemiology of tuberculosis varies substantially around the world. It is on records that about one-quarter of the world's populations are infected with TB. This clearly implies that many people have been infected with TB bacteria but are not (yet) ill with the disease and cannot transmit it. In 2019, 10 million people around the world feel ill with TB disease while 1.6 million people died of the disease. About 30 high TB burden countries account for 87% of new TB cases in 2019 and Nigeria accounts for two third of the total [26].

Presently, the treatment of TB uses antibiotics to kill the bacteria (CDC, 2020). TB can be treated by taking several antibiotics (drugs) for six to nine months. There are about ten drugs currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of TB. The most

commonly used drugs are: Isoniazid (INH), Rifampin (RIF), Ethambutol (EMB) and Pyrazinamide (PZA),Canadian Centre for Occupational Health and Safety (CCHS), [7].Although, the exact drugs and length of treatment depends on the patient's age, overall health, possible drugs resistance, the form of TB and the infection's location in the body [9].

Mathematical models have continued to play a key role in the formulation of TB control strategies and the establishment of interim goals for intervention programs (Colijn*et al.* 2006). In order to control and eradicate TB effectively, mathematical models have been proposed and studied by many authors in order to gain better insight into the dynamics of the disease in the last two decades(see for example, [1, 11, 12, 13, 14, 15, 18, 19, 20 and 23]).

Over the last two decades, infection-age-structured epidemic models have been extensively studied (see for example, [3, 5, 6, 11, 17, 24, and 25]). Recently, Ashezua *et al.* [5] formulated an infection-age-structured model on TB where only the infectious class was structured according to time and age-of-infection.

In this study, a realistic infection-age-structured mathematical model for tuberculosis incorporating control measures was developed to critically study the dynamics of the disease where both the latent and infectious classes are structured according to time and age-of-infection. To the best of my knowledge, this is the first mathematical model for TB where both the latent and infectious classes are structured according to time and age-of-infection.

Material and Methods

The infection-age-structured model sub-divides the total human population at time t ,denoted by $N(t)$, into the following sub-populations of the Vaccinated individuals $(V(t))$;this is the class in which members are vaccinated against TB infection; the second class is the Susceptible individuals $(S(t))$; this is the class in which members are free from TB but are open to infection as they interact with those in the infected class; the third class is the Latent individuals $(L(t))$; this is the class that have contracted TB but are not infectious; the fourth class is the Infected individuals $(I(t))$; this is the class that have contracted the disease and are infectious. The fifth class is the Treated individuals $(T(t))$; this is the classes that have recovered from both latent and active TB infections due to treatment.

The latent class $L(t)$ and Infectious class $I(t)$ as earlier stated are structured by the infection age with the density functions $l(t,\tau)$ and $i(t,\tau)$ where t the time parameter is and τ is the infection age. There is a maximum infection age T at which a member of the infected class $I(t)$ must leave the compartment via death; and so $0 \le \tau \le T$. Similarly, there is a maximum infection age, T at which the latently infected must reach and hence move to the actively infected compartment, so that

$$N(t) = S(t) + V(t) + L(t) + I(t) + T(t) \quad (1)$$

The variables and parameters of the model equations are summarized in Tables 1 and 2 below respectively.

Table 1: Variables of the model

S/No.	Variable	Description
1	$V(t)$	Vaccinated individuals at time, t
2	$S(t)$	Susceptible individuals at time, t
3	$L(t)$	Latently infected individuals at time, t
4	$I(t)$	Actively infected individuals at time, t
5	$T(t)$	Treated individuals at time, t

Table 2: Parameters of the model

S/No.	Parameter Description
1	τ Age-of-infection
2	T Maximum infection age
3	α Infection rate
4	μ Natural death rate for the population
5	ω Waning rate of the BCG vaccine
6	θ Probability of the susceptible individuals acquiring active TB Infection
7	$(1-\theta)$ Probability of the susceptible individuals acquiring latent TB Infection
8	γ Breakdown rate of individuals from the latent TB to the infectious TB
9	Λ Recruitment number due to birth
10	$\upsilon\Lambda$ Proportion of the susceptible new births vaccinated against TB infection
11	$(1-\upsilon)\Lambda$ Proportion of the susceptible new births not vaccinated against TB infection
12	$\alpha\theta$ Proportion of the susceptible individuals acquiring active TB infection
13	$\alpha(1-\theta)$ Proportion of the susceptible individuals acquiring latent TB infection
14	υ Effective vaccination rate
15	δ Death rate due to TB infection
16	ρ_1 Treatment rate for the actively infected individuals
17	ρ_2 Treatment rate for the latently infected individuals
18	ψ_e Public health education campaign

The following assumptions were made in formulating the model: The population is homogeneous; the vaccine is 75% effective and administered to children at birth; treatment is effective and administered to both the latently and actively infected individuals; $l(i,\tau)$ denote infection age-density for the latent individuals of infection age τ at time t. Then $\int_0^T l(t,\tau)d\tau$ is the total number of latent individuals at time t of infection ages between 0 and T; $i(i,\tau)$ denote infection age-density for the infectious individuals of infection age τ at time t. Then $\int_0^T i(t,\tau)d\tau$ is the total number of infectious individuals at time t of infection ages between 0 and T.It is also assume that the total population consists entirely of the vaccinated, susceptible, latently infected, actively infected and treated individuals; all successfully treated individuals (i.e. the latently and actively infected) will move to the susceptible compartment; It is assumed further that latently infected individuals who are diagnosed of having latent TB, will move to the treated compartment while those not identified for having latent TB will later move to active TB compartment; The natural death rate μ is same for the susceptible, vaccinated, latently infected and the treated individuals. The actively infected individuals will die due to natural death, μ and death due to TB at a rate δ ; The initial age distributions $l(0,\tau)=\phi_1(\tau)$ and $i(0,\tau)=\phi_2(\tau)$ are also continuous, nonnegative and integrable function of $\tau\in[0,T]$.

The model flow diagram is shown in Figure 1

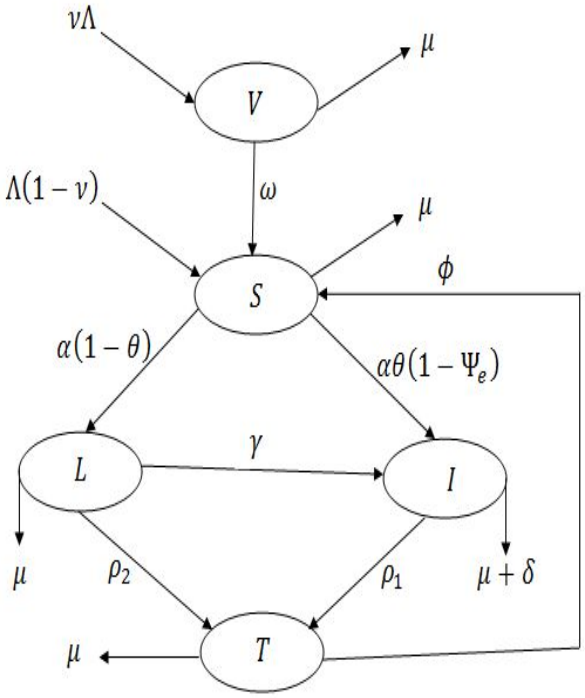

Figure 1: Flow Diagram of the TB model

Putting the above formulations , the flow diagram in Figure 1 and assumptions together gives the following integro-differential equations.

$$\frac{dS(t)}{dt} = (1-\upsilon)\Lambda - \alpha(1-\theta)S(t)I(t) - \alpha\theta(1-\psi_e)S(t)I(t) + \omega V(t) + \phi T(t) - \mu S(t) \quad (2)$$

$$\frac{dV(t)}{dt} = \upsilon\Lambda - (\mu+\omega)V(t) \quad (3)$$

$$\frac{\partial l(t,\tau)}{\partial t} + \frac{\partial l(t,\tau)}{\partial \tau} + (\mu+\gamma+\rho_2)l(t,\tau) = 0 \quad (4)$$

$$\frac{\partial i(t,\tau)}{\partial t} + \frac{\partial i(t,\tau)}{\partial \tau} + (\mu+\delta+\rho_1)i(t,\tau) = 0 \quad (5)$$

$$\frac{dT(t)}{dt} = \rho_2 L(t) + \rho_1 I(t) - (\mu+\phi)T(t) \quad (6)$$

$$l(t,0) = B_1(t) = \alpha(1-\theta)S(t)I(t) \quad (7)$$

$$i(t,0) = B_2(t) = \alpha\theta(1-\psi_e)S(t)I(t) + \gamma L(t) \quad (8)$$

where

$$L(t) = \int_0^T l(t,\tau)d\tau \tag{9}$$

$$I(t) = \int_0^T i(t,\tau)d\tau \tag{10}$$

$$S(0) = S_0, V(0) = V_0, L(0) = L_0, I(0) = I_0, N(0) = N_0 \tag{11}$$

$$l(0,\tau) = \phi_1(\tau) \tag{12}$$

$$i(0,\tau) = \phi_2(\tau) \tag{13}$$

Integrating (4) over τ and using (7) yields

$$\frac{dL}{dt} = \alpha(1-\theta)S(t)I(t) - (\mu + \gamma + \rho_2)L(t) \tag{14}$$

Also, integrating (5) over τ and using (8) gives

$$\frac{dI}{dt} = \alpha\theta(1-\psi_e)S(t)I(t) + \gamma L(t) - (\mu + \delta + \rho_1)I(t) \tag{15}$$

Adding (2), (3), (6), (14) and (15) gives

$$\frac{dN(t)}{dt} = \Lambda - \mu N(t) - \delta I(t), \tag{16}$$

Results and Discussion

The results and discussions obtained are presented and discussed under the following sub-headings:

The Disease-Free Equilibrium State

The TB model is analyzed by first solving equations (2)-(13) simultaneously to get the disease-free equilibrium as:

$$E^0 = \begin{pmatrix} S \\ V \\ L \\ I \\ T \end{pmatrix} = \begin{pmatrix} \left(\frac{(1-\upsilon)\Lambda}{\mu} + \frac{\upsilon\omega\Lambda}{\mu(\mu+\omega)}\right) \\ \frac{\upsilon\Lambda}{(\mu+\omega)} \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad (17)$$

Consider the region:

$$\Omega = \left\{ (S,V,L,I,T) \in \Re_+^5 \middle| S+V+L+I+T \le \frac{\Lambda}{\mu} \right\}.$$

It can be shown (see, for instance, [5, 12]) that all solutions of the system in (2)-(13) starting Ω in remain in Ω for all $t \ge 0$. Thus, Ω is positively-invariant (hence it is sufficient to consider the dynamics of (2)-(13) in Ω).

Equation (17) represents the state where there is no TB infection.

Effective Reproduction Number, R_E

$$R_E = \alpha\theta(1-\psi_e)x^0 \int_0^T \pi_2(\tau)d\tau + \gamma \int_0^T \pi_1(\tau)d\tau \quad (18)$$

The threshold value (18) is in the form:

$$R_E = R_i + R_L \text{ ,(19)}$$

where

$$R_i = \alpha\theta x^0 \int_0^T \pi_2(\tau)d\tau \quad (20)$$

is the number of secondary TB cases generated by individuals in the actively infected class and

$x^0 = \left(\frac{(1-\upsilon)\Lambda}{\mu} + \frac{\upsilon\omega\Lambda}{\mu(\mu+\omega)}\right)$ represents the number of susceptible individuals in the absence of TB. This threshold quantity represents the expected number of secondary TB cases produced, in a completely susceptible population by a typical infective individual. For ordinary differential equations, the next generation operator approach as used by Gumel and Song [14] is often used to compute R_E. For infection-age-structured mathematical models, the effective reproduction number is often expressed as the sum of the infectivity of each infected compartment. In view of the above explanation, the effective reproduction number for the infection-age-structured model becomes:

The term $\pi_1(\tau) = e^{-\int_0^\tau (\mu+\gamma+\rho_1)ds}$ is the survival probability of a function of infection age τ in the latently infected class while $\pi_2(\tau) = e^{-\int_0^\tau (\mu+\delta+\rho_2)ds}$ is the

survival probability as a function of infection age τ in the actively infected class.

$$R_L = \gamma \int_0^T \pi_1(\tau) d\tau \quad (21)$$

From (21), γ represents the number of latently infected individuals breaking down from latent TB to active TB.

The effective reproduction number obtained in (18) aids to determine the local stability of the disease-free equilibrium state as can be seen in the Theorem I below. Following the idea as outlined in the works of Wang and Zhang, [25]. Theorem I is established next.

Theorem I

The DFE state E^0 is locally asymptotically stable if $R_E < 1$ and unstable if $R_E > 1$.

Proof

Here, we consider the local stability of the DFE state given by (17).

Let,

$$V(t) = \frac{\upsilon\Lambda}{(\mu+\omega)} + y(t) \quad (22)$$

$$S(t) = \left(\frac{(1-\upsilon)\Lambda}{\mu} + \frac{\upsilon\omega\Lambda}{\mu(\mu+\omega)} \right) + x(t) \quad (23)$$

$$L(t) = q(t) \quad (24)$$

$$i(t,\tau) = z(t,\tau) \quad (25)$$

$$T(t) = w(t) \quad (26)$$

Linearizing equations (2)-(6) using (22)-(26) about E^0, gives the following equations

$$\frac{dx(t)}{dt} = -\mu x(t) + \omega y(t) + \phi w(t) - \alpha(1-\theta)x^0 \int_0^T z(t,\tau) d\tau - \alpha\theta x^0 \int_0^T z(t,\tau) d\tau \quad (27)$$

$$\frac{dy(t)}{dt} = -(\mu+\omega) y(t) \quad (28)$$

$$\frac{\partial q(t,\tau)}{\partial t} + \frac{\partial q(t,\tau)}{\partial \tau} + (\mu+\gamma+\rho_2) q(t,\tau) = 0 \quad (29)$$

$$\frac{\partial z(t,\tau)}{\partial t} + \frac{\partial z(t,\tau)}{\partial \tau} + (\mu+\delta+\rho_1) z(t,\tau) = 0 \quad (30)$$

$$q(t,0) = \alpha(1-\theta)x^0 \int_0^T z(t,\tau) d\tau \quad (31)$$

and

$$z(t,0) = \alpha\theta(1-\psi_e)x^0\int_0^T z(t,\tau)d\tau - \gamma\int_0^T q(t,\tau)d\tau \quad (32)$$

To study system (2)-(11),we look for solutions of the form:

$x(t) = \bar{x}e^{\lambda t}$, $y(t) = \bar{y}e^{\lambda t}$, $q(t,\tau) = \bar{q}(\tau)e^{\lambda t}$, $z(t,\tau) = \bar{z}(\tau)e^{\lambda t}$ and $w(t) = \bar{w}e^{\lambda t}$.

Thus, the following eigen-value problem was obtained.

$$(\mu+\omega+\lambda)\bar{y} = 0 \quad (33)$$

$$(\mu+\lambda)\bar{x} = \phi\bar{w} - \alpha(1-\theta)x^0\int_0^T \bar{z}(\tau)d\tau + \alpha(1-\theta)\bar{x}\int_0^T \bar{z}(\tau)d\tau - \alpha\theta(1-\psi_e)x^0\int_0^T \bar{z}(\tau)d\tau$$

$$\alpha\theta(1-\psi_e)\bar{x}\int_0^T \bar{z}(\tau)d\tau \quad (34)$$

$$\frac{d\bar{q}(\tau)}{d\tau} = -(\lambda+\mu+\gamma+\rho_2)\bar{q}(\tau) \quad (35)$$

$$\frac{d\bar{z}(\tau)}{d\tau} = -(\lambda+\mu+\delta+\rho_1)\bar{z}(\tau) \quad (36)$$

$$\bar{q}(0) = \alpha(1-\theta)x^0\int_0^T \bar{q}(\tau)d\tau \quad (37)$$

$$\bar{z}(0) = \alpha\theta(1-\psi_e)x^0\int_0^T \bar{z}(\tau)d\tau + \gamma\int_0^T \bar{q}(\tau)d\tau \quad (38)$$

Solving (35) and (36) gives

$$\bar{q}(\tau) = \bar{q}(0)e^{-(\lambda+\mu+\gamma+\rho_2)\tau} \quad (39)$$

and

$$\bar{z}(\tau) = \bar{z}(0)e^{-(\lambda+\mu+\delta+\rho_1)\tau} \quad (40)$$

Further simplification of (39) and (40) gives

$$\bar{q}(\tau) = \bar{q}(0)e^{-\lambda\tau}\pi_1(\tau) \quad (41)$$

and

$$\bar{z}(\tau) = z(0)e^{-\lambda\tau}\pi_2(\tau) \quad (42)$$

where

$\pi_1(\tau)$ and $\pi_2(\tau)$ are defined as in (18).

Substituting (41) and (42) into (38) gives

$$\bar{z}(0) = \alpha\theta(1-\psi_e)x^0\int_0^T \bar{z}(0)e^{-\lambda\tau}\pi_2(\tau)d\tau + \gamma\int_0^T \bar{q}(0)e^{-\lambda\tau}\pi_1(\tau)d\tau \quad (43)$$

dividing both sides of (43) by $\bar{z}(0)$, we obtain

$$1 = \alpha\theta(1-\psi_e)x^0 \int_0^T e^{-\lambda\tau}\pi_2(\tau)d\tau + \gamma\frac{\bar{q}(0)}{\bar{z}(0)}\int_0^T e^{-\lambda\tau}\pi_1(\tau)d\tau \quad (44)$$

where x^0 is defined as in (18).

The right hand side of (44) is defined by the function $G(\lambda)$. Obviously, $G(\lambda)$ is a continuously differentiable function with $\lim_{\lambda\to\infty} G(\lambda) = 0$. By direct computation, it can be shown that $G'(\lambda) < 0$, and therefore, $G(\lambda)$ is a decreasing function. Hence, any real solution of equation (44) is negative if $G(0) < 1$, and positive if $G(0) > 1.$ Thus, if $G(0) > 1$, the DFE state is unstable.

Next, we show that equation (44) has no complex solution with non-negative real part if $G(0) < 1$. In fact, we set

$$H(\tau) = \alpha\theta(1-\psi_e)x^0\pi_2(\tau) \quad (45)$$

$$F(\tau) = \gamma\frac{\bar{q}(0)}{\bar{z}(0)}\pi_1(\tau) \quad (46)$$

Thus, substituting (45) and (46) into (44) gives

$$G(\lambda) = \int_0^T e^{-\lambda\tau}H(\tau)d\tau + \int_0^T e^{-\lambda\tau}F(\tau)d\tau \quad (47)$$

Suppose $G(0) < 0.$ Assume that $\lambda = a_1 + b_1 i$ is a complex solution of equation (47) with $a_1 \geq 0$,then,

$$|G(\lambda)| = \left|\int_0^T e^{-\lambda\tau}H(\tau)d\tau + \int_0^T e^{-\lambda\tau}F(\tau)d\tau\right|$$

$$\leq \left|\int_0^T e^{-(a_1+ib_1)\tau}H(\tau)d\tau\right| + \left|\int_0^T e^{-(a_1+ib_1)\tau}F(\tau)d\tau\right|$$

$$= \int_0^T \left|e^{-(a_1+ib_1)\tau}\right|H(\tau)d\tau + \int_0^T \left|e^{-(a_1+ib_1)\tau}\right|F(\tau)d\tau$$

$$\leq \int_0^T e^{-a_1\tau}H(\tau)d\tau + \frac{1}{a_1+\gamma+\mu}\int_0^T e^{-a_1\tau}F(\tau)d\tau$$

$$= |G(a_1)| \leq G(0) < 1 \quad (48)$$

It follows from equation (48) that equation (44) has solutions $\lambda = a_1 + ib_1$ only if $a_1 < 0.$ Thus, every solution of (44) must have a negative real part. Observe that $R_E = G(0).$ Therefore, the DFE state E^0 is locally asymptotically stable if $G(0) < 1.$ This completes the proof of the Theorem 1.

Theorem 2

The disease free equilibrium E^0 of the model equations (2)-(6) is globally asymptotically stable (GAS) in Ω if $R_E \leq 1$ while unstable if $R_E > 1$.

Proof

Inthis section, we study the global stability of the disease-free equilibrium E^0 by providing the proof for Theorem 2.

Following the approach by Huang *et al.*[17]and Shuai and Van Den Driessche [24], a suitable Lyapunov functional is constructed as follows:

$$V_1(t) = \left(x - x^0 - x^0 \ln\frac{x}{x^0}\right) + \left(y - y^0 - y^0 \ln\frac{y}{y^0}\right) + \int_0^T q(\tau)\frac{l(t,\tau)}{\pi_1(\tau)}d\tau + \int_0^T q(\tau)\frac{i(t,\tau)}{\pi_2(\tau)}d\tau \quad (49)$$

Solving for $l(t,\tau)$ and $i(t,\tau)$ along the characteristics lines and substituting in (49) gives

$$V_1(t) = \left(x - x^0 - x^0 \ln\frac{x}{x^0}\right) + \left(y - y^0 - y^0 \ln\frac{y}{y^0}\right) + \int_0^T q(\tau)B_1(t-\tau)d\tau + \int_0^T q(\tau)B_2(t-\tau)d\tau \quad (50)$$

Let

$$q(\tau) = \alpha\theta(1-\psi_e)x^0\int_\tau^T \pi_2(\tau)d\tau + \gamma\int_\tau^T \pi_1(\tau)d\tau \quad (51)$$

and

$$q(0) = \alpha\theta(1-\psi_e)x^0\int_0^T \pi_2(\tau)d\tau + \gamma\int_0^T \pi_1(\tau)d\tau\ , \quad (52)$$

Directdifferentiation of (50) gives

$$\frac{dV_1(t)}{dt} = \left(\frac{x-x^0}{x}\right)\frac{dS}{dt} + \left(\frac{y-y^0}{y}\right)\frac{dV}{dt} + \left(q(0)B_1(t) + \int_0^T q'(\tau)B_1(t-\tau)d\tau\right)$$

$$+\left(q(0)B_2(t) + \int_0^T q'(\tau)B_2(t-\tau)d\tau\right) \quad (53)$$

substituting (2), (3), (51) and (52) into (53) and simplifying gives

$$= -\frac{\mu}{x}(x-x^0)^2 - \frac{(\mu+\omega)}{y}(y-y^0)^2 - (1-R_E)l(t,0) - (1-R_E)i(t,0) \leq 0 \text{ for } R_E \leq 1 \quad (54)$$

The equality $\frac{dV_1(t)}{dt} = 0$ holds if and only if $x = x^0$, $y = y^0$, $l(t,0) = i(t,0) = 0$. Thus, from the solution of the model equations (4)-(5) along the characteristics lines, we have that $l(t,\tau) = i(t,\tau) = 0$ for all $t > \tau$. Hence, we have $l(t,\tau) \to 0$ and $i(t,\tau) \to 0$ as $t \to \infty$. It can be verified that $\{E^0\}$ is the maximal compact invariant set. Therefore, from the LaSalle invariant principle (see [16]), it is concluded that the disease-free equilibrium E^0 is globally asymptotically stable if $R_E \leq 1$. This completes the proof of the Theorem 2.

Analysis of the Effective Reproduction Number

Recall that the effective reproduction number for the TB model is given in its expanded form as:

$$R_E = \frac{\alpha\theta(1-\psi_e)x^0\left[1-\exp(-(\delta+\mu+\rho_1)\right]}{\left(\delta+\mu+\rho_1\right)} + \frac{\alpha\gamma(1-\theta)x^0\left[\exp(-(\gamma+\mu+\rho_2)-1\right]\left[\exp(-(\mu+\delta+\rho_1)-1\right]}{\left(\mu+\gamma+\rho_2\right)\left(\delta+\mu+\rho_1\right)} \quad (55)$$

where

x^0 is earlier defined as in (18).

Thus (55) above is the effective reproduction number (the basic reproduction number with control strategy (interventions)).

So, when there are no control strategies, that is when $\psi_e = \upsilon = \rho_1 = \rho_2 = 0$ thus (55) becomes:

$$R_E = \frac{\alpha\theta\Lambda\left[1-\exp(-(\delta+\mu+\rho_1)\right]}{\mu\left(\mu+\delta\right)} + \frac{\alpha\gamma(1-\theta)\Lambda\left[\exp(-(\gamma+\mu)-1\right]\left[\exp(-(\mu+\delta)-1\right]}{\mu\left(\mu+\gamma\right)\left(\delta+\mu\right)} \quad (56)$$

Equation (56) is the basic reproduction number R_0 for our model equations (2)-(8).

Analysis of the Effective Reproduction Number (R_E) with Unique ControlStrategy.

In this section, we use the effective reproduction number in (55) to compute the reproduction numbers for individual control strategy (intervention). This approach adopted here in computing the reproduction numbers for the individual control strategy is similar to the ones by Nyerereet *al.*[21].

If vaccination is the only control strategy used, that is $\upsilon \neq 0, \psi_e = \rho_1 = \rho_2 = 0$, then the basic reproduction number with only vaccination is given by

$$R_\upsilon = \frac{\alpha\theta x^0\left[\exp(-\left(\mu+\delta\right)-1)\right]}{\left(\mu+\delta\right)} + \frac{\alpha\gamma(1-\theta)x^0\left[\exp(-(\gamma+\mu)-1\right]\left[\exp(-(\mu+\delta)-1\right]}{\left(\mu+\gamma\right)\left(\mu+\delta\right)} \quad (57)$$

If public health education campaign is the only control strategy used, that is $\psi_e \neq 0, \upsilon = \rho_1 = \rho_2 = 0$, then the basic reproduction number with only public health education campaign is given by

$$R_{\psi_e} = \frac{\alpha\theta\Lambda\left(1-\psi_e\right)\left[1-\exp\left[-\left(\mu+\delta\right)\right]\right]}{\mu\left(\mu+\delta\right)} + \frac{\alpha\gamma(1-\theta)\Lambda\left[\exp\left[-(\gamma+\mu)\right]-1\right]\left[\exp-\left[(\mu+\delta)\right]-1\right]}{\mu\left(\mu+\gamma\right)\left(\mu+\delta\right)} \quad (58)$$

If treatment is the only control strategy used, that is $\rho_1 \neq \rho_2 \neq 0, \psi_e = \upsilon = 0$, then the basic reproduction number with only treatment is given by

$$R_{\rho_1,\rho_2} = \frac{\alpha\theta\Lambda\left[1-\exp\left[-\left(\mu+\delta+\rho_1\right)\right]\right]}{\mu(\mu+\delta+\rho_1)} + \frac{\alpha\gamma\Lambda(1-\theta)\left[\exp\left[-(\gamma+\mu+\rho_1)\right]-1\right]\left[\exp-\left[(\mu+\delta+\rho_1)\right]-1\right]}{\mu(\mu+\gamma+\rho_2)(\mu+\delta+\rho_1)} \quad (59)$$

Analysis of the Effective Reproduction Number (R_E) with Two Control Strategies.

In this section, we further analyze the effective reproduction number in (55) to compute the reproduction numbers for the combination of two control strategies (intervention). If the combination of vaccination and public health education campaign are the only control strategy used, that is $\upsilon \neq 0, \psi_e \neq 0, \rho_1 = \rho_2 = 0$, then the basic reproduction number with only vaccination and public health education campaign is given by:

$$R_{\upsilon\psi_e} = \frac{\alpha\theta(1-\psi_e)x^0\left[1-\exp(-\left(\mu+\delta\right))\right]}{\left(\mu+\delta\right)} + \frac{\alpha\gamma(1-\theta)x^0\left[\exp(-(\gamma+\mu)-1\right]\left[\exp(-(\mu+\delta)-1\right]}{\left(\mu+\gamma\right)\left(\mu+\delta\right)} \quad (60)$$

If the combination of treatment and public health education campaign are the only control strategy used, that is $\upsilon \neq 0, \psi_e \neq 0, \rho_1 = \rho_2 = 0$, then the basic reproduction number with only treatment and public health education campaign is given by:

$$R_{\rho_1,\rho_1,\psi_e} = \frac{\alpha\theta(1-\psi_e)\Lambda\left[1-\exp(-(\mu+\delta+\rho_1)\right]}{\mu\left(\mu+\delta+\rho_1\right)} + \frac{\alpha\gamma(1-\theta)\Lambda\left[\exp(-(\gamma+\mu+\rho_2)-1\right]\left[\exp(-(\mu+\delta+\rho_1)-1\right]}{\mu\left(\mu+\gamma+\rho_2\right)\left(\mu+\delta+\rho_1\right)} \quad (61)$$

If the combination of vaccination and treatment are the only control strategy used, that is $\upsilon \neq 0, \rho_1 \neq 0, \rho_2 \neq 0, \psi_e = 0$, then the basic reproduction number with only vaccination and treatment is given by:

$$R_{\upsilon,\rho_1,\rho_1} = \frac{\alpha\theta x^0\left[\exp(-(\mu+\delta+\rho_1)-1\right]}{\left(\mu+\delta+\rho_1\right)} + \frac{\alpha\gamma(1-\theta)x^0\left[\exp(-(\gamma+\mu+\rho_2)-1\right]\left[\exp(-(\mu+\delta+\rho_1)-1\right]}{\left(\mu+\gamma+\rho_2\right)\left(\mu+\delta+\rho_1\right)} \quad (62)$$

Analysis of the Effective Reproduction Number (R_E) with Three Control Strategies.

In this section, we analyze the effective reproduction number for the situation where all the control strategies (treatment, vaccination and public health education campaign) are used, then the basic reproduction number with all the control strategies is given by equation (55) above.

Numerical Simulations

The following variables and parameters on Tables 3 and 4 were estimated using information from Central Intelligence Agency, CIA [8], WHO [26]whileothers were assumed. A guide of how the estimations were carried out can be found in the works of Ashezua *et al.* [5].

Table 3: Values for population-dependent parameters of the model

S/NO	Variable/Parameter	Value	Source
1	S	36,368,808	WHO [26]
2	V	44,961,946	WHO [26]
3	L	73,197,680	WHO [26]
4	I	8,133,076	WHO [26]
5	T	51,366,792	WHO [26]
6	N	214,028,302	CIA [8]
7	μ	0.0181 yr^{-1}	CIA [8]
8	Λ	3,873,912	CIA [8]

Table 4: Values for population-independent parameters of the model

S/NO	Parameter	Value	Source
1	α	0.0000722 yr^{-1}	WHO [26]
2	ω	0.067 yr^{-1}	WHO [26]
3	γ	0.5 yr^{-1}	Assumed
4	θ	0.1 yr^{-1}	WHO [26]
5	$\rho_1, \rho_2, \tau, \upsilon, \psi_e$	(0-1) yr^{-1}	Assumed

Sensitivity Analysis (SA) with Respect to the Model Parameters

In this section, sensitivity analysis is carried out on the effective reproduction number, R_E in order to determine parameters of the model that are most sensitive and are targeted by way of intervention strategy. It is therefore critical to take various actions to control the system parameters so that the effective reproduction number R_E is remarkably kept below one. In determining how best to reduce human mortality and morbidity due to TB, the sensitivity indices of the effective reproduction number to the parameters in the model is calculated following similar approach as in Abdulrahman *et al.* [1]. The normalized forward sensitivity index of a variable to a parameter is thus defined as the ratio of the relative change in the variable to the relative change in the parameter. Mathematically, the normalized forward sensitivity indices with respect to a parameter value, X is defined as:

$$S_X^{R_0} = \frac{\partial R_E}{\partial X} \times \frac{X}{R_E}, \qquad (63)$$

where $X = \{\Lambda, \alpha, \omega, \theta, \upsilon, \gamma, \psi_e, \rho_1, \rho_2, \mu\}$.

Since R_E depends on ten parameters, an analytical expression for its sensitivity indices with respect to each of the parameters using the normalized forward sensitivity index as follows:

$$S_\alpha^{R_0} = \frac{\partial R_E}{\partial \alpha} \times \frac{\alpha}{R_E} = +0.999962$$

In a similar manner, we compute the sensitivity indices of the parameters of the effective reproduction number R_E using the values on Table 3 with the aid of Maple 17 mathematical software. Table 5 shows the sensitivity indices of R_E with respect to the ten parameters.

Table 5: Sensitivity indices of R_E with respect to the ten parameters.

S/NO	Parameter	Sensitivity Index	Sign
1	α	0.999962	+
2	Λ	0.999962	+
3	θ	0.999962	+
4	ω	0.149421	+
5	γ	0.000037	+
6	ρ_1	0.000013	-
7	υ	0.189787	-
8	ρ_2	0.269137	-
9	ψ_e	0.999962	-
10	μ	1.157502	-

Table 5 shows that all the parameters have either positive or negative impact on the effective reproduction number.

Simulation of the Effective Reproduction Number (R_E) with Various Control Strategies.

In this section, the impact of the control strategies (measures or intervention) is studied. Here, the basic reproduction numbers obtained in (55)-(62) above are analyzed.

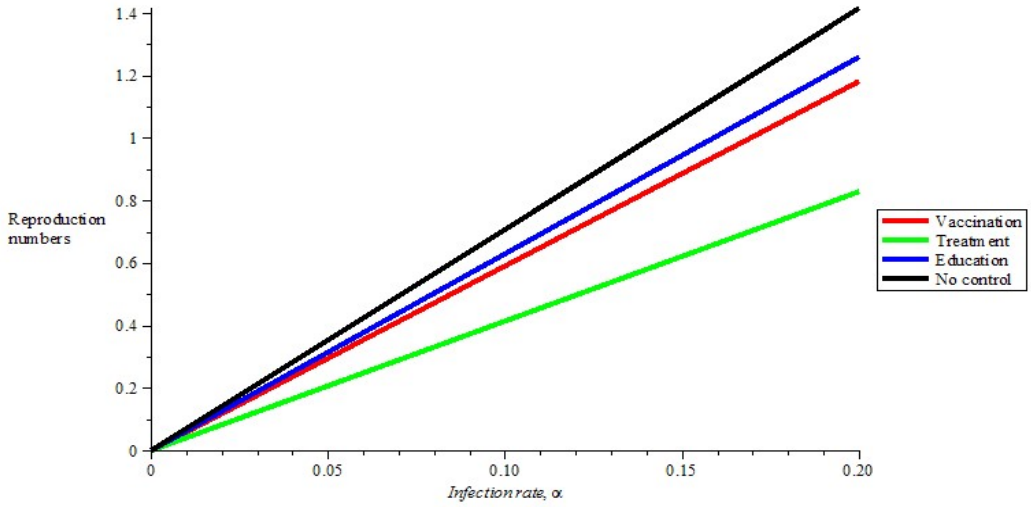

Figure 2: Variation of mono-control strategy reproduction numbers and basic reproduction number with respect to the infection rate. Parameter values used are as shown on Tables 3 and 4.

Figure 2 shows that the reproduction number with treatment (R_T) is less than the reproduction number with vaccination (R_V). Furthermore, the reproduction number with public health education campaign (R_{Ed}) is less than the reproduction number without any intervention strategy (R_0). Mathematically speaking, this is represented as $R_T < R_V < R_{Ed} < R_0$. It is observed from Figure 2 that the reproduction number without any intervention strategy has the worst scenario as it occurred when there was no control strategy for TB. The reproduction number (R_0) in this case grows very sharp beyond one (as compared to the reproduction number with vaccination and public health education campaign) with respect to the infection rate (α). Such an increment in R_0 above one indicates that there is a high outbreak of TB in the population. The best scenario as can be seen from Figure 2 occurs with the reproduction number with treatment (R_T). In this case, treatment was the only intervention strategy given to the latently and actively infected individuals. Finally we can see from Figure 2 showed that, the reproduction number with treatment (R_T) is less than one while others are above one. This implies that, TB dies out with the reproduction number with treatment.

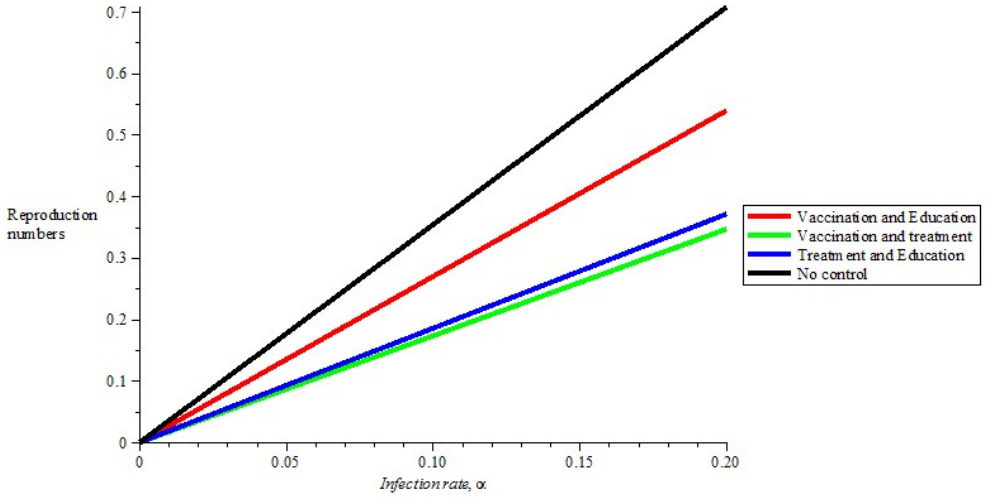

Figure 3: Variation of bi-control strategy reproduction numbers and the basic reproduction number with respect to the infection rate.Parameter values used are as shown on Tables 3 and 4.

Figure 3showedthat the reproduction number without any intervention strategy had the worst scenario as it occurred when there was no control strategy for TB. The reproduction number (R_0) in this case grew very sharp around 0.7 but less than one with respect to the infection rate (α). The best scenario as can be seen from Figure 3 occurs with the reproduction number with vaccination and treatment (R_{VT}). In this case, vaccination and treatment was the only intervention strategy that was given to the latently and actively infected individuals. Finally it is observed from Figure 3 that, the reproduction number with vaccination and treatment (R_{VT}) was around 0.3 while others were above 0.3. This implies that, TB can be eradicated faster with the reproduction number that had vaccination and treatment as controls.

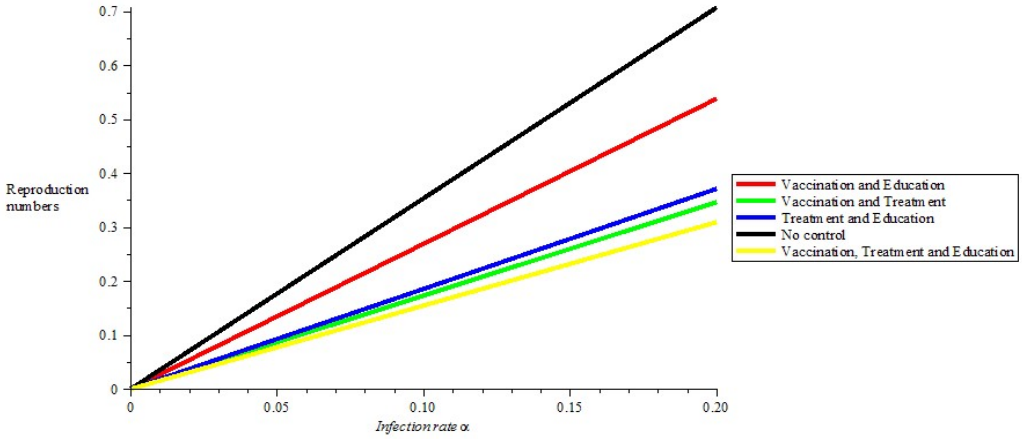

Figure 4: Effective reproduction number with two and three control strategies and the basic reproduction number with respect to the infection rate. Parameter values used are as shown on Tables 3 and 4.

Figure 4revealedthat the reproduction number without any intervention strategy has the worst scenario as it occurs when there was no control strategy for TB. The reproduction number (R_0) in this case grew very sharp around 0.7 but less than one with respect to the infection

rate $(\dot{\alpha})$. The best scenario as can be seen from Figure 4 occurred with the reproduction number that had vaccination, treatment and education (R_{VTEd}) as controls. Finally, it was also observed from Figure 4 that, the reproduction number with vaccination, treatment and education (R_{VTEd}) was around 2.5 while all others were above 0.3. This implies that, TB can be eradicated faster with the reproduction number having vaccination, treatment and education (R_{VTEd}) as control strategies.

Conclusion

In this research work, an infection-age-structured mathematical model for tuberculosis disease dynamics incorporating three control strategies namely: treatment, vaccination and public health education campaign was developed and analyzed. An explicit threshold value for the effective reproduction number (R_E) was obtained in terms of the demographic and epidemiological parameters of the model equations. From the effective reproduction number (R_E), the basic reproduction number and the reproduction numbers with single,double and triple control strategies were obtained. The threshold value (R_E) represents the average number of secondary TB infections produced in a completely susceptible population by an infective TB individual after intervention strategies are successfully applied. Results from the stability analysis showed that the disease-free equilibrium is locally asymptotically stable when $R_E < 1$ and unstable when $R_E > 1$. The global stability of the disease-free equilibrium state was found to be globally asymptotically stable for $R_E \leq 1$.

Sensitivity analysis was also carried out on the effective reproduction number, R_E in order to ascertain the parameters of the model that were most sensitive and that should be targeted by way of intervention strategies. It was found out that, the infection rate α ,the recruitment number due to birth, treatment rates (both for latent and active TB), vaccination and public health education campaign are the most sensitive parameters. These parameters need the desired attention by government and public health practitioners if TB must be put under control in Nigeria and other developing countries where the disease remains endemic. The least sensitive parameters are the human natural death rate and the proportion of the susceptible acquiring active TB infection (θ).

Numerical simulations of the effective reproduction numbers showed that whenever the control strategies are solely applied, then the treatment rates are the best control strategies. When the combinations of two control strategies are applied, results reveal that treatment and vaccination are the best control strategies to be applied in the prevention and control of TB. Furthermore, when the combinations of the two and three control strategies are applied, it was observed that the best control strategy is the combination of treatment, vaccination and public health education campaign as shown on Figure 4. Finally it was observed that, the more the combination of the control strategies implemented, the faster the control and eradication of TB in Nigeria within a finite time.

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Declaration of conflicting interests

The authors declared no potential conflicts of interest

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