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Transmission Dynamics Of Tuberculosis With Exogenous Reinfection And Vaccination Control

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Abstract
This paper presents a deterministic mathematical model on the transmission dynamics of tuberculosis with exogenous reinfection and vaccination control. A non-linear compartmental model for the disease transmission was developed. Stability analysis of disease-free equilibrium point was estimated to be both locally and globally asymptotically stable if $R_0 < 1$ *and unstable*$R_0 > 1$ *using the next-generation matrix and the comparison theorem. The findings indicate that transmission of tuberculosis can be reduced by ensuring adequate intervention by continuous vaccination and sensitization.*

Keywords: *Tuberculosis, Exogenous Reinfection, Sensitivity and Vaccination*

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I. Introduction

Tuberculosis is an ancient scourge that has been in existence for long; though, it took years of research before the microbial causes (Mycobacterium tuberculosa, Mtb) was discovered by a German microbiologist Robert koch in 1882. Tuberculosis is an infectious disease which can be easily contracted because it spreads quickly through the air medium. When an infected individual sneezes, coughs, spits etc. the bacteria known as bacillus is propelled into the air. Only a small amount of the bacillus is needed to be inhaled to cause an infection [W.H.O, 2011]. Tuberculosis is classified as active or inactive (latent). Active means the bacteria are active in the body which means the immune system is unable to stop the bacteria from causing illness; symptoms include coughing, breathlessness, fever, weight loss, night sweats etc. Inactive tuberculosis or (latent) on the other hand implies the body has been able to fight the bacteria successfully from causing illness thereby making it latent. An inactive individual shows no symptoms and cannot spread the disease. Tuberculosis usually affects the lungs (pulmonary) but it also occurs outside the lungs (extra-pulmonary) which is more common among people with weak immune system.

Tuberculosis is a chronic relapsing infection and remains a leading cause of infectious mortality by a single infectious agent second only to HIV. The epidemiology is complex and not completely understood which makes the planning for control measures difficult [C.D.C, 2000]. About one-third of the world's population is believed to have latent and a new infection are occurring at a rate of one person per second [W.H.O, 2010]. Once latently infected, an individual can remain so for life or progress towards active tuberculosis though the chances are not much. [C.D.C, 2000] says a latently infected individual has a 10% chance of progressing but it is much higher in people with complicated immune system e.g people living with HIV, Smokers. Progression may also accelerate with re-exposure to bacteria through repeated contacts with the bacteria known as exogenous reinfection. An infected individual will infect about 10 to 15 people each year [C.D.C, 2000], as a result, it is responsible for about 2 to 3 million deaths each year. In order to curb this figures, global initiatives spearheaded by (WHO) came into existence. Presently, the only effective vaccine for is the BCG (Bacillus Calmette Guerrin); a notable medical contribution to be used on infants and in general population. Vaccinated individuals have 70% to 80% chance of immunity from the infection. According to [W.H.O, 2011], all cases of tuberculosis are curable with proper treatment but without proper treatment, up to two-third of people with tuberculosis will die. Treatment consists of combination of drugs that must be used judicially for about 6 to 9 months e.g Isomiazid (INH), Rifampicin (RIF), Ethambutol. [C.D.C, 2010] says most people with active tuberculosis who have received appropriate treatment for at least 2weeks are no longer contagious.

Modeling of infectious diseases is that which has been used to study the mechanism by which diseases spread to predict future causes of an outbreak and evaluate strategies to control the epidemic [Daley and Gani, 2005]. The earliest account of mathematical model of spread of diseases was carried out in 1766 by David Bernulli. He created a mathematical model to defend the practice of innoculation against small pox. The ability to make predictions about diseases has enabled scientist to evaluate innoculations or isolations plans which have a significant effect on the mortality rate of a particular epidemic.

The rest of this paper is structured as follows: Method which includes model formulation and analysis are described in "Method" section. Next section consist of Sensitivity analysis, discussion of results is given in "Discussion" section. Finally, in "Conclusion" section, we have provided conclusions of this article.

II. Method

We propose a deterministic mathematical model on the transmission dynamics of tuberculosis with exogenous reinfection and vaccination control. The total population is divided into five compartments. Individuals are classified based on their epidemiological status spread out within the five compartments; the Vaccinated (M), the susceptible (S), the Exposed or latently infected (E), the Infected (I) and the Recovery class (R). Recruitment's are into the vaccinated and the susceptible class at a constant rate θk and $(1-\theta)k$. Natural Mortality leaves all the compartments at a rate $\mu > 0$ while mortality as a result of the disease leaves the infected class at a rate $\delta > 0$. The vaccinated compartment reduces due to the waning of vaccine and increases the susceptible class at a constant rate $\alpha > 0$. The model is governed by the following set of nonlinear differential equations below:

Fig 1: Schematic representation of the model

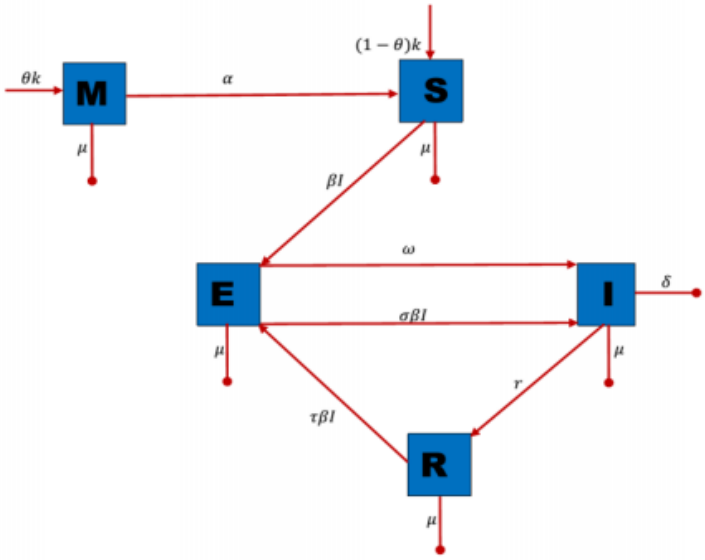

Table 1 Parameters Values used for the simulations

Parameter	Value	Description
k	0.2	Recruitment rate of humans
θ	0.4	Proportion of vaccinated Individuals
μ	0.03	Natural death rate
α	0.004	Expiration of duration of vaccine efficacy
β	0.017	Effective Contact Rate
ω	0.017	Rate at which an individual's leaves the latent class by becoming infective
σ	0.04	Level reinfection progression rate (Exogenous Reinfection)
r	0.036	Recovery rate
δ	0.02	Disease Induced Death Rate
τ	0.04	Removal of immunity

$$\begin{aligned}
\frac{dM}{dt} &= \theta k - (\alpha + \mu)M \\
\frac{dS}{dt} &= (1-\theta)k + \alpha M - (\beta I + \mu)S \\
\frac{dE}{dt} &= \beta IS + \tau\beta IR - (\omega + \mu)E - \sigma\beta EI \\
\frac{dI}{dt} &= \sigma\beta EI - \omega E - (\mu + \delta + r)I \\
\frac{dR}{dt} &= rI - (\mu + \tau\beta I)R
\end{aligned} \tag{1}$$

Subject to the following nonnegative initial conditions:

$$M(0) \geq 0, S(0) \geq 0, E(0) \geq 0, I(0) \geq 0, R(0) \geq 0 \tag{2}$$

$$M(0) + S(0) + E(0) + I(0) + R(0) \leq N(0) \tag{3}$$

Model Analysis

The Model analysis begins by showing that all feasible solutions of the model are uniformly bounded in a proper subset of **Ω**. Thus the feasible region

$$\Omega = \{(M, S, E, I, R) \in R^5{}_+ : N \leq \frac{K}{\mu} \tag{4}$$

is considered. Therefore, after differentiation of (2) and (13) and proper substitutions, we have

$$\frac{dN(t)}{dt} = k - \mu N \leq k - \mu N \tag{5}$$

Applying [Birkhof, G. and Rota, G. C., 1989] on the differential inequalities in (5) , we obtained:

$$N(t) \leq N(0)e^{-\mu t} + \frac{k}{\mu}(1 - e^{-\mu t}) \tag{6}$$

Where $N(0)$ is the initial populations of the human population. Therefore $0 \leq N \leq \frac{k}{\mu}$ as $t \to \infty$. This implies that, $\frac{k}{\mu}$ is upper bound for $N(t)$ as long as $N(0) \leq \frac{k}{\mu}$. Hence the feasible solution of the model equations in (1) enters the region **Ω** which is a positively invariant set. Thus, the system is mathematically and epidemiologically well-posed. Therefore, for an initial starting point $x \in \Omega$, the trajectory lies in **Ω**, and so it sufficient to restrict our analysis on **Ω**. Clearly, under the dynamics described by the model equations, the closed set **Ω** is hence a positively invariant set.

Tuberculosis-free equilibrium state

This occurs in the absence of disease. Thus in the absence of infection, we set M, S, E, I and R to zero in (1) and the resulting solution gives the tuberculosis-free equilibrium states given below:

$$\emptyset_{TFE} = (M^*, S^*, E^*, I^*, R^*) = \left(\frac{\theta k}{(\alpha + \mu)}, \frac{k(\alpha + (1-\theta)\mu)}{\mu(\alpha + \mu)}, 0, 0, 0\right) \tag{7}$$

Endemic Equilibrium

This occurs when the infection persist in the population represented by $\emptyset_{TEE} = (M^*, S^*, E^*, I^*, R^*)$.
Thus,

$$\begin{aligned}
M^* &= \frac{\theta k}{(\alpha + \mu)} \\
S^* &= \frac{k(\alpha + (1-\theta)\mu)}{\mu(\alpha + \mu)} \\
E^* &= \frac{\beta SI + \tau\beta IR}{(\omega + \mu + \sigma\beta I)} \\
I^* &= \frac{-\omega E}{(\sigma\beta E - \mu - \delta - r)} \\
R^* &= \frac{rI}{(\mu + \tau\beta I)}
\end{aligned} \tag{8}$$

Basic Reproduction Number

The basic reproduction number is one of the critical parameters to examine the long-term behavior of an epidemic. It can be defined as number of secondary cases generated by a typical infected in an entirely susceptible population. We have used the next-generation matrix technique explained in [Diekmann et al. 2010, Peter et al. 2020] to obtain the expression of reproduction numberR_0.

It is defined to be largest eigenvalue or spectral radius of the characteristic equation$|FV^{-1} - \psi I| = 0$. Using the notations in [Van D. P. and Watmough, J. 2002] for the model system (1) , the associated matrices F and V for the new infectious terms and the remaining transition terms, evaluated at the disease-free equilibrium are respectively given by

$$F = \begin{bmatrix} 0 & \beta S^* \\ 0 & 0 \end{bmatrix} \quad (9)$$

and

$$V = \begin{bmatrix} (\omega + \mu) & 0 \\ -\omega & (\mu + \delta + r) \end{bmatrix} \quad (10)$$

Therefore,

$$FV^{-1} = \begin{bmatrix} \frac{\omega\beta S^*}{(\omega+\mu)(\mu+\delta+r)} & \frac{\beta S^*}{(\mu+\delta+r)} \\ 0 & 0 \end{bmatrix} \quad (11)$$

Hence, the basic reproduction numbers of the model is given as:

$$R_0 = \frac{\omega\beta k(\alpha + \mu - \mu\theta)}{\mu(\alpha+\mu)(\omega+\mu)(\mu+\delta+r)} \quad (12)$$

Theorem 1: The disease-free equilibrium is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$ with $R_0 = \max\{R_0\}$.

Stability of disease-free equilibrium

To obtain the conditions for the global stability for E_0, we used the comparison theorem.

Theorem 2: The disease-free equilibrium is globally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.

Proof: By the comparison theorem, the rate of change of the variables representing the infectious classes in the model can be compared in the following inequality:

$$\begin{bmatrix} E' \\ I' \end{bmatrix} \leq (F - V)\begin{bmatrix} E \\ I \end{bmatrix} - P_1\theta_1\begin{bmatrix} E \\ I \end{bmatrix} - P_2\theta_2\begin{bmatrix} E \\ I \end{bmatrix} - \theta_2\begin{bmatrix} E \\ I \end{bmatrix} \quad (13)$$

Where F and V are defined (9) and (10) respectively, $P_1 = 1 - \frac{S^0}{N^0}$, $P_2 = 1 - \frac{M^0}{N^0}$, $\theta_1, \theta_2 \; and \; \theta_3$ are nonnegative matrices. And since $S^0 \leq N^0$, then $M^0 \leq N^0$.Therefore, from (13) we get:

$$\begin{bmatrix} E' \\ I' \end{bmatrix} \leq (F - V)\begin{bmatrix} E \\ I \end{bmatrix} \quad (14)$$

Therefore the matrix (F - V) is obtained as:

$$(F - V) = \begin{bmatrix} -(\omega + \mu) & \beta S^* \\ \omega & -(\mu + \delta + r) \end{bmatrix} \quad (15)$$

From the matrix (15), let λ be an eigenvalue. Then, the characteristic equation $|(F - V) - \lambda I| = 0$ gives the following eigenvalues:

$$\lambda_1 = -\left[\left(\mu + \frac{1}{2}\delta + \frac{1}{2}r + \frac{1}{2}\omega\right) - \frac{1}{2}\sqrt{4\beta S^*\omega + \delta^2 - 2\delta\omega + 2\delta r + \omega^2 - 2\omega r + r^2}\right] \quad (16)$$

$$\lambda_1 = -\left[\left(\mu + \frac{1}{2}\delta + \frac{1}{2}r + \frac{1}{2}\omega\right) + \frac{1}{2}\sqrt{4\beta S^*\omega + \delta^2 - 2\delta\omega + 2\delta r + \omega^2 - 2\omega r + r^2}\right] \quad (17)$$

Therefore, all the row eigenvalues of the matrix (15) have negative real part, showing that the matrix (15) is stable if $R_0 < 1$. Consequently, using the model equations, $(M, S) \Rightarrow (0, 0)$ as $t \Rightarrow \infty$. Thus by the comparison theorem as used in [Shaban, N. and Hawa, M. 2014] , $(M, S) \Rightarrow (0, 0)$ as $t \Rightarrow \infty$. Evaluating the model system at $M = S = 0$ gives $M^0 = \frac{\theta k}{(\alpha+\mu)}$, $S^0 = \frac{k(\alpha+(1-\theta)\mu)}{\mu(\alpha+\mu)}$ and $R_0 \Rightarrow (0)$ as $t \Rightarrow \infty$ for $R_0 < 1$. Hence, the disease-free equilibrium is globally asymptotically stable for $R_0 < 1$.

III. Sensitivity Analysis of Parameters in the Model

A sensitivity analysis determines how different values of independent variable affect a particular dependent variable under a given set of assumptions [Kalyan et al 2021;Victorr et al. 2020]. The normalized forward sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. When variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives.

Since the basic reproduction number R_0 helps us to predict the future course of the disease, the sensitivity analysis is performed to understand which parameters involved in the model effect the value of R_0 relatively more. We have used the following expression of the sensitivity for R_0 which depends on the parameter v

$$\psi_v^{R_0} = \frac{v}{R_0} \times \frac{\partial R_0}{\partial v} \quad (18)$$

A negative index of sensitivity shows that the parameter and $R_0$are inversely proportional. A positive sensitivity index, however, denotes that the value of R_0increases with an increase in the value of the parameter concerned.

The estimated sensitivity indices for R_0 are presented in Table 2. From the values, we can see that an increase θ will results in a decrease in the value of R_0 . On the other hand, an increase in the value of β, k and ω will increase the tuberculosis cases.

Table 2 Sensitivity index of parameters

Parameter	Expression of the sensitivity index	Value
β	1	1
k	1	1
θ	$\frac{-\mu\theta}{(\alpha+\mu-\mu\theta)}$	-0.5454
ω	$\frac{\mu}{(\omega+\mu)}$	0.9463

IV. Discussion

The basic reproduction number is a crucial parameter in disease dynamics which gives us major information about the disease. To understand the effect of various disease transmission parameters on the basic reproduction number, we have obtained the sensitivity indices from R_0 and parameters in Table 1. The sensitivity indices suggest that, the indices with positive signs increases the value of R_0 when the corresponding parameters are increased and indices with negative signs decreases the value of R_0 with increase in the corresponding parameters.

V. Conclusion

A non-linear compartmental model has been proposed to understand the transmission dynamics of tuberculosis exogenous reinfection and vaccination control. We carried out analysis on the developed model. The disease-free equilibrium was found to be both locally and globally asymptotically stable if $R_0 < 1$ and unstable$R_0 > 1$. Sensitivity analysis revealed that, the interventions offer an optimal control on the tuberculosis reinfection with increase in the control parameter rates of vaccination and treatment.

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