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A tuberculosis model : Validating to study transmission dynamics with vaccination and treatment

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Abstract

In this paper, we have analyzed the validation of the tuberculosis model for its transmission dynamics. Here, we have seen the existence and uniqueness of solution, invariant region, positivity of solution, equilibrium points and basic reproduction number. We have calculated disease free equilibrium points and R.

1 Introduction

Tuberculosis (TB) is one of the top 10 causes of death worldwide. It is caused by bacteria (Mycobacterium tuberculosis) that most often affects the lungs. TB is curable and preventable. TB is spread from person to person through the air. When people with lungs TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected. About one-third of the world population has latent TB, which means people have been

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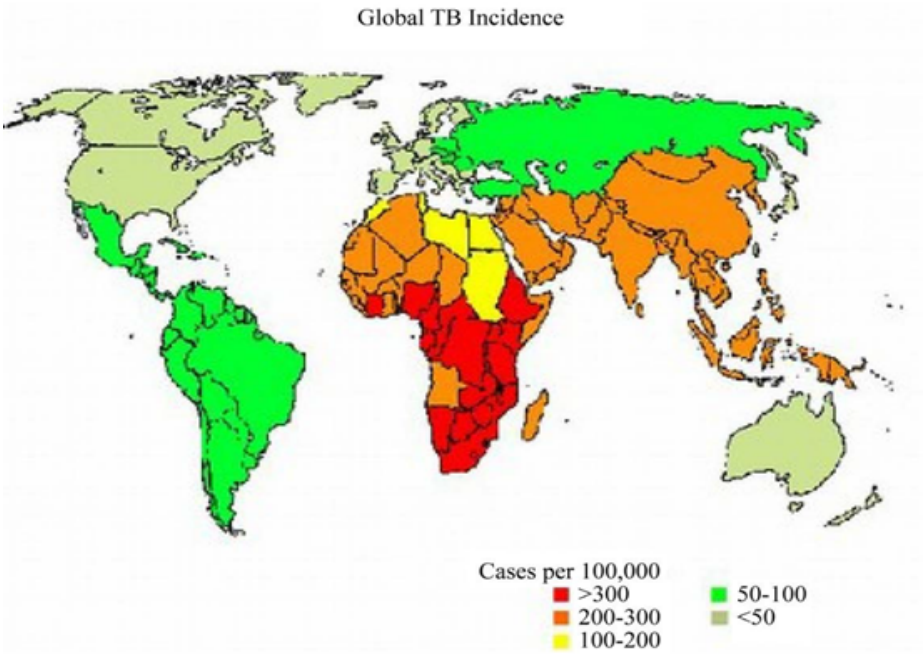
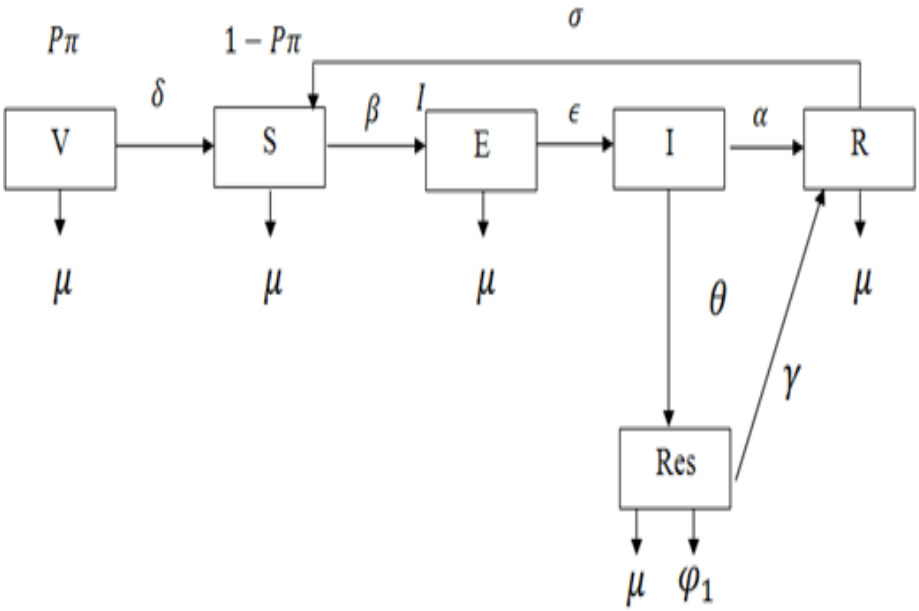
infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease. People infected with TB bacteria have a 10% lifetime risk of falling ill with TB. However, persons with compromised immune systems, such as people living with HIV, malnutrition or diabetes or people who use tobacco, have a much higher risk of falling ill. When a person develops active TB disease the symptoms may be mild for many months. This can lead to delays in seeking care and results in transmission of the bacteria to other [1]. Today, this disease ranks as the second leading cause of morbidity and mortality in the world from a single infectious agent, after the human immunodeficiency virus (HIV) [8]. Interestingly, about one-third of the world's population is infected with Mtb with approximately nine million people developing active tuberculosis and up to nearly two million people worldwide die from the disease every year.

In 2013, approximately nine million people contracted active tuberculosis and this included 1.1 million cases among people living with HIV and 550,000 children. Out of these nine million cases 1.5 million people succumbed to the disease and this included 360,000 among people who were HIV-positive, 510,000 were women out of which 180,000 were HIV-positive. Africa recorded the highest tuberculosis/HIV burden with three out of four Tuberculosis patients knowing their HIV status. Approximately 480,000 people developed multidrug-resistant (MDR) tuberculosis globally with 210,000 of those who developed MDR tuberculosis succumbing to it [8]. **Figure 1** showed the global incidence of tuberculosis in 2008 [9]. Figure 1. Global distribution of tuberculosis.[9], Figure 2. A Compartmental Diagram for the Tuberculosis transmission Dynamics.

2 Model Formulation and Description

The human population is categorized into six classes such that at time $t \geq 0$ there are V, vaccinated humans S, susceptible humans, E, exposed human to tuberculosis, I, infected humans with active tuberculosis, Res, resistant humans to the first line of treatment, R, recovered humans. Thus the size of the human population is given as N=V+S+E+I+Res+R. In our model, the recruitment into the susceptible human population is by birth λ. The size of the human population is further increased by the partially immune humans in R after they lose their immunity at the rate σ. The size of the human population is decreased by natural deaths (μ) and exposure to (Mtb) mycobacterium tuberculosis. The exposed susceptible to Mtb move to the exposed classes E with the force of infection being β resulting in an increase in the exposed class. The exposed class is further decreased by natural deaths (μ), and the proportion who moves to the infected class I after developing active


Global TB Incidence
Cases per 100,000
>300
200-300
100-200
50-100
<50


$P\pi$
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σ
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μ
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θ
μ
γ
Res
μ
φ_1

Table 1: Description of state Variables

Variable	Description
V(t)	Vaccinated humans
S(t)	Susceptible humans
E(t)	Exposed humans
I(t)	Infected humans
Res(t)	Resistant to the first line of treatment
R(t)	Recovered humans

tuberculosis. The infected class I is also reduced by natural deaths (μ), disease induced deaths (ϕ), those recover (α) and also by those resistant to the first line of treatment (θ). Thus both the infected class (I) and the resistant class (Res) gain partial immunity at the rates (α) and (γ) respectively. Thus moving to the recovered class R thus reducing their respective classes and also increasing the recovered class. The resistant class (Res) is also reduced by natural death (μ) and disease induced deaths $(\phi 1)$ while the recovered class is reduced by natural deaths (μ) and those who lose their partial immunity at the rate σ. Let δ be the rate of waning of vaccines.

2.1 The model Equations :

$$\frac{dv}{dt} = p\pi - (\delta + \mu) V \tag{2.1}$$

$$\frac{ds}{dt} = (1-p)\pi + \delta s + \sigma R - \beta I - \mu s \tag{2.2}$$

$$\frac{dE}{dt} = \beta I - (\mu + \epsilon) E \tag{2.3}$$

$$\frac{dI}{dt} = \epsilon E - (\mu + \varphi + \theta + \alpha) I \tag{2.4}$$

$$\frac{dR_{es}}{dt} = \theta I - (\mu + \varphi_1 + \gamma) R_{es} \tag{2.5}$$

$$\frac{dR}{dt} = \alpha I + \gamma R_{es} - (\mu + \sigma) R \tag{2.6}$$

with initial condition $S(0) = S$, V $(0) = V_0$, E $(0) = E_0$, I $(0) = I_0$, $R_{es}(0) = R_{es0}$, R $(0) = R_0$

Parameters	Description
β	Rate at which the susceptible become exposed to Mtb
ϵ	Infection rate
Φ	Disease induced death rate
α	Recovery rate due to prompt treatment
γ	Recovery rate after second line of resistance treatment
θ	Resistance rate due to treatment
σ	Rate at which the recovered lose their immunity
$\phi 1$	Disease induced death rate after resistance
$p\pi$	The proportion of new births that is passively immune
$(1-p)\pi$	Remaining proportion without passive immunity
μ	Rate of natural death

Table 2: Description of Parameters

3 Model Analysis :

3.1 Existence and uniqueness of solution :

The validity and authenticity of any mathematical model depends on whether the given system of equations has a solution or not and we will check for our equations (1.1) to (1.6)

Theorem 3.1. *Derrick and Grossman, 1976)*
Let Ω *denotes the region* $|t-t_0| \leq a,\ ||x-x_0|| \leq b, x = (x_1, x_2.....x_n)$*, satisfies the Lipschitz condition.* $||f(t,x_1) - f(t,x_2)|| \leq K||x_1 - x_2||$

Proof. The pairs (t, x^1) and (t, x^2) belongs to Ω and K is the positive constant, hence there is a constant $\overline{\delta} > 0$ such that there exists a unique continuous vector solution x(t) of the system in the interval $|t-t^0|^{\leq \overline{\delta}\cdot}$ It is important to note that the condition is satisfied by $\frac{\delta f_i}{\delta x_i}, i, j, = 1, 2...$ be continuous and bounded in Ω . Let the system of equation (1.1) to (1.6) be as follows.

$$F_1 = P\pi - (\delta + \mu) V \tag{3.1}$$

$$F^2 = (1-P)\,\pi + \delta s + \sigma R - \beta I - \mu s \tag{3.2}$$

$$F_3 = \beta I - (\mu + \epsilon)\, E \tag{3.3}$$

$$F_4 = \epsilon E - (\mu + \varphi + \theta + \alpha) \tag{3.4}$$

$$F_5 = \theta I - (\mu + \varphi_1 + \gamma)\, R_{es} \tag{3.5}$$

$$F_6 = \alpha I + \gamma R_{es} - (\mu + \sigma)\, R \tag{3.6}$$

we are interested in the region $0 \leq \chi \leq R$ & bounded solution in the region and whose partial derivatives satisfy f $\leq \chi \leq 0$ where $\overline{\delta}\ and\ \chi$ are positive constant. □

Theorem 3.2. *Let Ω denote the region $0 \leq \chi \leq R$, then the eqution (2.1) to (2.6) has a unique solution if $\frac{\delta f_i}{\delta x_j}$ i, j = 1, 2, ... 6 are continuous and bounded in Ω*
The equation from (2.1) to (2.6) we obtain the following partial derivatives

$$|\frac{dF_1}{dv}| = |-(\delta + \mu)\,| < \infty \tag{3.7}$$

$$|\frac{dF_2}{ds}| = |\delta - \mu| < \infty; |\frac{dF_2}{dI}| = |-\beta| < \infty \tag{3.8}$$

$$|\frac{dF_2}{dR}| = |\sigma| < \infty; |\frac{dF_3}{dE}| = |-(\mu + \epsilon)\,| < \infty \tag{3.9}$$

$$|\frac{dF_3}{dI}| = |\beta| < \infty; \quad |\frac{dF_4}{dI}| = |-(\mu + \varphi + \theta + \alpha)\,| < \infty \tag{3.10}$$

$$|\frac{dF_4}{dE}| = |\epsilon| < \infty; \quad |\frac{dF_5}{dR_{es}}| = |-(\mu + \varphi_1 + \gamma)\,| < \infty \tag{3.11}$$

$$|\frac{dF_5}{dI}| = |\theta| < \infty; \quad |\frac{dF_6}{dR}| = |-(\mu + \sigma)\,| < \infty \tag{3.12}$$

$$|\frac{dF_6}{dI}| = |\alpha| < \infty; \quad |\frac{dF_6}{dR_{es}}| = |\gamma| < \infty \tag{3.13}$$

These partial derivates exists, continuous and are bounded. Hence the model (2.7) to (2.13) has a unique solution.

Theorem 3.3. *Invariant Region : To obtain the invariant region in which the model solution is bounded. Consider the total human population (N) where N = V+S+E++I+R_{es}+R. Differentiating N both sides with respect to t gives*

$$\frac{dN}{dt} = \frac{dV}{dt} + \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR_{es}}{dt} + \frac{dR}{dt} \tag{3.14}$$

$$\Longrightarrow \frac{dN}{dt} = \pi - \mu N - \varphi I - \varphi_1 R_{es} \leq \pi - \mu N \tag{3.15}$$

In the absence of mortality due to tuberculosis (2.15) becomes,

$$\frac{dN}{dt} \leq \pi - \mu N \tag{3.16}$$

By the separation of variable, equation (2.16) becomes

$$\frac{dN}{\pi - \mu N} \leq dt \tag{3.17}$$

Integrating equation (2.17) give

$$\int \frac{dN}{\pi - \mu N} \leq \int dt. \tag{3.18}$$

$$\Longleftrightarrow -\frac{1}{\mu} \ln (\pi - \mu N) \leq t + c \tag{3.19}$$

$$\Longrightarrow \pi - \mu N \geq A e^{-\mu t} \tag{3.20}$$

$$(-\mu N) \geq (\pi - \mu N_0)\, e^{-\mu t} \tag{3.21}$$

$$\Longrightarrow N \leq \frac{\pi}{\mu} - \left(\frac{\pi - \mu N_0}{\mu}\right) e^{-\mu t} \tag{3.22}$$

as t $\to \infty$ *the population size N* $\to \frac{\pi}{\mu}$ *. which shows that* $0 \leq N \leq \frac{\pi}{\mu}$ *. Hence the feasible solution set of the system equation of the model enters* & *remains in the region.*

$$\Omega = \left\{ (V, S, C, I, R_{es}, R)\ \epsilon R_+^6 : N \leq \frac{\pi}{\mu} \right\} \tag{3.23}$$

This shows that N(t) is bounded and we can study the dynamics of the model in Ω *.*

Theorem 3.4. *Positivity of the Solution :*

Let $\Omega = \left\{ (V, S, C, I, R_{es}, R)\ \epsilon R_+^6 \ : V_0 > 0,\ S_0 > 0,\ C_0 > 0,\ I_0 > 0,\ R_{es0} > 0,\ R_0 > 0 \right\}$,

then the solutions of $\{V,S,C,I,Res, R\}$ *are positive for* $t \geq 0$

Proof. We take first equation (1.1) of the system

$$\frac{dv}{dt} = p\pi - (\delta + \mu) V$$

$$\Longrightarrow \frac{dv(t)}{dt} \geq -(\delta + \mu) V$$

$$\Longrightarrow \int \frac{dv(t)}{v(t)} \geq \int -(\delta + \mu)\ d(t)$$

solving by separation of variable and applying condition, we obtain

$$V(t) \geq V_0\, e^{-(\delta+\mu)\ t} \geq 0 \tag{3.24}$$

Similarly taking second, third, fourth, fifth and sixth equations of the system and solving by variable separable method, we get,

$$S(t) \geq S_0\, e^{(\delta-\mu)t} \geq 0 \tag{3.25}$$

$$E(t) \geq E_0\, e^{-(\mu+\varepsilon)t} \geq 0 \tag{3.26}$$

$$I(t) \geq I_0\, e^{-(\mu+\varphi+\theta+\alpha)t} \geq 0 \tag{3.27}$$

$$R_{\text{es}}(t) \geq R_{es0}\, e^{-(\mu+\varphi_1+\gamma)t} \geq 0 \tag{3.28}$$

$$R(t) \geq R_0 e^{-(\mu+\sigma)t} \geq 0 \tag{3.29}$$

Thus the solution of (V,S,C,I,Res, R) are positive for $t \geq 0$ □

3.2 Equilibrium states of the model the disease free equilibrium (DFE):

The disease free equilibrium of model (1.1) to (1.6) is obtained by equating it to zero.

$$i.e. \frac{dV}{dt} = \frac{dS}{dt} = \frac{dC}{dt} = \frac{dI}{dt} = \frac{dR_{es}}{dt} = \frac{dR}{dt} = 0 \tag{3.30}$$

$$i.e. \frac{dv}{dt} = p\pi - (\delta + \mu) v = 0 \tag{3.31}$$

$$\frac{ds}{dt} = (1-p)\pi + \delta s + \sigma R - \beta I - \mu s = 0 \tag{3.32}$$

$$\frac{dE}{dt} = \beta I - (\mu + \epsilon) E = 0 \tag{3.33}$$

$$\frac{dI}{dt} = \epsilon E - (\mu + \varphi + \theta + \alpha) I = 0 \tag{3.34}$$

$$\frac{dR_{es}}{dt} = \theta I - (\mu + \varphi_1 + \gamma) R_{es} = 0 \tag{3.35}$$

$$\frac{dR}{dt} = \alpha I + \gamma R_{es} - (\mu + \sigma) R = 0 \tag{3.36}$$

Calculation results in two equilibrium points, one being the disease free equilibrium while the other being the endemic equilibrium. Disease free equilibrium points (V, S, E, I, Res, R) is expressed as follows:

$$(V, S, E, I, R_{es}, R) = \left(\frac{\pi p}{\delta + \mu}, \frac{\pi}{\mu} \frac{(\delta + \mu (1 - p))}{(\delta + \mu)}, 0, 0, 0, 0 \right) \tag{3.37}$$

3.3 Reproduction Number (R^0) :

The reproduction numbers R_0 is defined as the average number of secondary cases arising from an average primary case in an entirely susceptible population over the period of infection. The reproduction number is used to predict whether the epidemic will spread or die out. Any epidemiological model has a disease free equilibrium (DFE) at which the population remains in the absence of the disease. According to Diekmann and Heesterbeek (2000) [7], we call FV^{-1} the next generation matrix for the model and set the reproduction number, $R_0 = \rho(FV^{-1})$
where

$$F = \left[\frac{\delta F_i (x_0)}{dx_j} \right] and V = \left[\frac{\delta V_i (x_0)}{dx_j} \right]$$

for $i \geq 1$ for the number of compartments, and $1 \leq j \leq m$ for the infected compartment only $\rho(FV^{-1})$ denotes the spectral radius of a matrix A. F and V are $m \times m$ matrices, where m is the number of infected class. Let us take at the following system of differential equations.

$$\frac{dE}{dt} = \beta I - (\mu + \epsilon) E$$

$$\frac{dI}{dt} = \epsilon E - (\mu + \varphi + \theta + \alpha) I$$

$$\frac{dR_{es}}{dt} = \theta I - (\mu + \varphi_1 + \gamma) R_{es}$$

The above system can be represented in matrix form as shown below where F is the jacobian of the matrix of infection rates and V is the Jacobian of the matrix of transition rates at

$$\left(\frac{\pi p}{\delta+\mu}, \frac{\pi}{\mu}\frac{(\delta+\mu(1-p))}{\delta+\mu}0, 0, 0, 0\right)$$

$$F = \begin{bmatrix} 0 & \beta\pi\left(\frac{1}{\mu}-\frac{p}{\delta+\mu}\right) & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} \mu+\epsilon & 0 & 0 \\ -\epsilon & \mu+\varphi+\theta+\alpha & 0 \\ 0 & -\theta & \mu+\varphi_1+\gamma \end{bmatrix}$$

The inverse of V is obtained and given by

$$V^{\text{-}1} = \begin{bmatrix} \frac{1}{\mu+\epsilon} & 0 & 0 \\ \frac{\epsilon}{(\mu+\varphi+\theta+\alpha)(\mu+\epsilon)} & \frac{1}{\mu+\varphi+\theta+\alpha} & 0 \\ \frac{\epsilon\theta}{(\mu+\epsilon)(\mu+\varphi+\theta+\alpha)(\mu+\theta)} & \frac{\theta}{(\mu+\varphi+\theta+\alpha)(\mu+\theta)} & \frac{1}{\mu+\varphi_1+\gamma} \end{bmatrix}$$

We then obtain the spectral radius of $FV^{\text{-}1}, p(FV^{\text{-}1})$ which is define as the largest eigenvalue of $FV^{\text{-}1}$ and the spectral radius for the above system is the basic reproduction number R_0, and its expression is given by

$$R_0 = \frac{\beta\pi\epsilon(\delta+\mu-\mu\rho)}{\mu(\delta+\mu)(\delta+\varphi+\theta+\alpha)(\mu+\epsilon)} \tag{3.38}$$

Conclusion:
Here we have proved the existence and uniqueness of the solution, invariant region is shown and positivity of the solution is proved. The model is analyzed and disease free equilibrium points are derived and the basic reproduction number is calculated. The model is in complete agreement with the basic properties of the epidemiological models and is suitable to study transmission dynamics of tuberculosis disease. We have derived a basic tuberculosis model considering the most probable drug resistant effects and found the basic characteristics mentioned above. We hope more research can be done using this model as it takes into account more realization of the disease and its predicament.

References

[1] World Health Organization, et al., *Global Tuberculosis Report*, 2016.

[2] H. Waaler and S. Anderson, *The use of mathematical models in the study of the Epidemiology of Tuberculosis*, American Journal of Public Health, **52** (1962), 1002-1013.

[3] A. Mandal, *Tuberculosis causes* (2013) http : //www. news - medicals . net/ health / Tuberculosis – Cause.aspx.

[4] T. Cohen and M. Murray, *Modeling Epidemics of Multidrug - Resistant m. Tuberculosis of heterogeneous Fitness*, Nature Medicine, **10** (2004), 1117-1121, http : dx. doi. org /10 1038 / nm 1110

[5] O. P. Ogundile, S. O. Ediki, and S. O. Adewale, *A modeling technique for controlling the spread of tuberculosis*, International journal of biology and biomedical engineering, Vol. 12 2018.

[6] O. J. Peter, M. O. Ibrahim, O. B. Akinduko and M. Rabiu, *Mathematical model for the control of Typhoid Fever*, IOSR journal of Mathematics (IOSR-JM), Vol. 13, Issue - 4, 2017.

[7] O. Diekman and J. P. A. Heesterbeck, *Mathematical epidemiology of Infectious Diseases : Model Building, Analysis and Interpretation*, Wiley series in Mathematical and Computational Biology, (2000).

[8] *WHO Global Tuberculosis Report*. WHO Report (2014).

[9] CDC. *National Tuberculosis Surveillance System Highlights*.

[10] J. Semenza, J. Suk and S. Tsolova, *Social Determinants of Infectious Diseases: A Public Health Priority*, Euro Surveill, **15** (2010).

[11] K. Zaman, *Tuberculosis: A Global Health Problem. Journal of Health*, Population and Nutrition, **28** (2010), 111-113.