A Mathematical Model for the Epidemiology of Tuberculosis with Estimate of the Basic Reproduction Number

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Abstract: *In this paper, we study a vaccination model for tuberculosis (TB) dynamics at the population level. We prove that the solution to the model is positive and bounded. The basic reproduction number R_0 is determined. We show that the disease-free equilibrium (DFE) is globally asymptotically stable if $R_0 \leq 1$ and the existence of at least one endemic equilibrium of the model. Numerical simulations of the model is also carried out to show the efficacy of the vaccine. Numerical experiments suggest that a strategy of continuous vaccination would result in a more stable DFE for disease elimination.*
Keywords: *mathematical model; epidemiology; infectious disease; basic reproduction number; equilibrium; stability; vaccine; uniform persistence*

I. Introduction

Tuberculosis (TB) epidemics have had a large impact on the human population [6, 7, 19, 25]. Despite many decades of study, the widespread availability of a vaccine and a highly visible WHO effort to promote unified global TB control strategy, tuberculosis remains a leading cause of death by infectious disease depending on the source [6, 24]. It is responsible for approximately 2 million deaths each year [6, 24]. One third of the world's population is estimated to be infected with TB and new infections occur at a rate of about one per second [6, 25]. In 2003, Africa alone had 8.8million new infections which results in 1.7 million deaths [24]. In 2007, there were an estimated 13.7 million chronic active TB cases, 9.3 million new cases and 1.8 million deaths mostly in developing countries [24, 25].

Although TB is currently well controlled in most countries, numerous studies indicate that the overall global incidence of TB is rising as a result of resurgence of the disease in Africa and parts of Eastern Europe and Asia [9, 12, 25]. In these regions, the emergence of drug-resistance TB strains and the convergence of HIV and TB epidemics have made TB control an herculean task [6]. In more than half of all HIV-related deaths in most developing countries, TB is the 'opportunistic infection' which takes advantage of an immune system already compromised by HIV [6].

The distribution of TB is not uniform across the globe; about 80% of the population in many Asian and African countries test positive in TB test while only 5-10% of the US population test positive [5]. Of all African countries, Nigeria has the highest TB burden and is ranked 4th among the 22 high burden countries in the world [24]. According to WHO reports, it has 311 TB cases for every 100,000 population [34]. Nigeria's level of new TB cases rose from 15% in 2002 to 26.7% in 2004 [24].

In this paper, we study a vaccination model for the transmission of tuberculosis disease. We focus on vaccination of expectant mothers in a country at the brink of eradicating TB infection. The work is based on numerous TB transmission models which have been formulated by previous researchers. Consequently, the result of this paper is related to and complements those of Blower et al. [1, 2], Dye et al. [8], Porco et al. [13], Salpeter and Salpeter [14], Vynncky and Fine [20, 21], Waaler [21, 22], Ziv et al. [28] and the others cited in the references which deal with TB dynamics.

II. Mathematical Formulation

2.1 The Model

Let S, V, E, I denote, respectively, the classes of susceptible, vaccinated, latently infected and actively infected. We describe the transmission dynamics of tuberculosis by the following system of ordinary differential equations

$$\frac{dS}{dt} = (1 - \gamma)(1 - k)\pi + qV - \beta IS/N - \mu S \tag{2.1}$$

$$\frac{dV}{dt} = k(1 - \gamma)\pi - qV - (1 - f_1)\beta IV/N - \mu V \tag{2.2}$$

$$\frac{dE}{dt} = (1 - \rho)\beta IV/N - (v + \mu)E + \rho\beta IE/N \tag{2.3}$$

$$\frac{dI}{dt} = dvE + \rho\beta IS/N + \rho(1 - f_1)(1 - f_2)\beta IV/N - (\mu + \mu_T + \varepsilon)I \tag{2.4}$$

where $N = S + V + E + I$ is the total size of the population. See Table 1 for detailed descriptions of the model parameters and reference [28] for further description of the model formulation

Table 1: Description of Parameters for the Model

Parameter	Description
π	Recruitment rate into the population
k	Proportion of immigrants that are vaccinated
v	Rate of slow progression
ρ	Rate of fast progression
μ	Natural death rate
μ_T	Mortality rate due to TB infection
β	Transmission rate of active TB
s	Treatment rate of active TB
d	Detection rate of active TB
q	Rate at which the vaccine wanes
ε	Rate at which susceptible individuals recover
f_1	Efficacy of vaccine in preventing initial infection
f_2	Efficacy of vaccine in preventing fast progression
γ	Proportion of recruitment due to immigration

2.2 Basic Properties of Solutions
In this section, we study some results of the solutions of the system (2.1) – (2.4) which will be very useful in the section which follow.

Let $\mathbb{R}_+^n = (0, \infty)$ denote the set of positive vectors $x = (x_1, x_2, \ldots, x_n)$ with $x_j > 0$ for $j = 1, 2, \ldots, n$. We will use the following results in Thieme [18].

Lemma 2.1: Let $F: \mathbb{R}_+^n \to \mathbb{R}^n$ such that

$$F(x) = (F_1(x), F_2(x), \ldots, F_n(x)), x = (x_1, x_2, \ldots, x_n)$$

be continuous and have partial derivatives $\frac{\partial F_j}{\partial x_k}$ which exist and are continuous in $\mathbb{R}_+^n$ for all $j, k = 1, 2, \ldots, n$. Then F is locally Lipschitz continuous in $\mathbb{R}_+^n$.

Theorem 2.1: Let $F: \mathbb{R}_+^n \to \mathbb{R}^n$ be locally Lipschitz continuous and for each $j, k = 1, 2, \ldots, n$ satisfying

$$F_j(x) \geq 0 \quad \text{whenever } x \in \mathbb{R}_+^n, x_j = 0.$$

Then for every $x_0 \in \mathbb{R}_+^n$, there exists a unique solution of $x' = F(x), x(0) = x_0$ with values in $\mathbb{R}_+^n$ which is defined in some interval $(0, b)$ with $b \in (0, \infty)$, then

$$\sup_{0 \le t \le b} \sum_{j=1}^{n} x_j(t) = \infty \qquad \text{If } b < \infty.$$

III. Methodology

3.1 Existence, Uniqueness and Positivity

Lemma 3.1: Let $S, V, E, I : \mathbb{R}^4 \rightarrow \mathbb{R}$ be continuous differentiable function of S, V, E, I respectively.

Theorem 3.1:   Assume Lemma 3.1 holds. For all $S(0) > 0, V(0) > 0, E(0) > 0, I(0) > 0$ there exists $S, V, E, I : (0, \infty) \rightarrow (0, \infty)$ which   solve   (2.1)   –   (2.4)   with   initial   conditions $S = S(0), V = V(0), E = E(0), I = I(0)$

Proof: We will apply Theorem 2.1, let

$$F_1(x) = (1 - \gamma)(1 - k)\pi + qV - \beta IS/N - \mu S$$

$$F_2(x) = k(1 - \gamma)\pi - qV - (1 - f_1)\beta IV/N - \mu V$$

$$F_3(x) = (1 - \rho)\beta IV/N - (v + \mu)E + \rho\beta IE/N \qquad \qquad (3.1)$$

$$F_4(x) = dvE + \rho\beta IS/N + \rho(1 - f_1)(1 - f_2)\beta IV/N - (\mu + \mu_T + \varepsilon)I$$

where $x = (S, V, E, I)$. By Lemma 3.1 and the properties of continuity over operations, we have the continuity of F_i for all $i = 1, \dots, 4$. Further the partial derivatives

$$\frac{\partial F_1}{\partial x_1} = \beta I/N - \mu < \infty, \qquad \frac{\partial F_1}{\partial x_2} = q < \infty, \qquad \frac{\partial F_1}{\partial x_3} = -\beta S/N < \infty, \frac{\partial F_1}{\partial x_4} = 0 < \infty$$

These partial derivatives exist and are continuous. In the same way, the other partial derivatives exist and are continuous. In consequence, by Lemma 2.1, F is locally Lipschitz continuous.   Let $x_1 = S = 0$ and $x_2 = I > 0, x_3 = V > 0, x_4 = I > 0$ then $F_1(x) = qV > 0$.

Now let, $x_2 = E = 0$ and $x_3 = S > 0, x_4 = I > 0$, then $F_2(x) = (1 - f_1)\beta IV/N > 0$.   Further, let $x_3 = V = 0$ and $x_1 = E > 0, x_2 = E > 0, x_3 = I > 0, x_4 = I > 0$, then $F_3(x) = \rho\beta IE/N > 0$. Finally, let $x_4 = I = 0$ and $x_1 = E > 0$, $x_2 = S > 0, x_3 = V > 0$, then $F_4(x) = dvE > 0$.

By Theorem 2.1, for every $x_0 = (S(0), V(0), E(0), I(0) \in \mathbb{R}_+^n$, there exists a unique solution of $x' = F(x), x(0) = x$ with values in $\mathbb{R}_+^n$ which is defined in some interval $(0, b)$ with $b \in (0, \infty)$. If $b < \infty$, then $\sup(S(t) + V(t) + E(t) + I(t)) = \infty$.

Suppose that $b < \infty$ and set $T(t) = S(t) + V(t) + E(t) + I(t)$, then

$$T' = -\mu S + (\beta - q - \mu)V + (\beta - v - \mu)E + (\beta - \mu - \mu_T - \varepsilon)I - \mu T^2 \qquad (3.2)$$

such that
$$T' \le \beta I \le \beta T$$

In consequence

$$\frac{T'}{T} \leq \beta$$

Integrating the above inequality, we obtain

$$\ln T(t) \leq \ln T(0) + \beta t$$

which implies that

$$T(t) \leq T(0)e^{\beta t}, t \in (0, b)$$

so, $S(t) + V(t) + E(t) + I(t)$ is bounded, a contradiction with Theorem 3.1. In consequence, $b = \infty$. Then the solutions of the system are positive and defined on $(0, \infty)$.

3.2 Boundedness of Solutions

Theorem 3.2: All the solutions of the system (2.1) – (2.4) are bounded.

Using the equation (3.2), we have

$$T' = -\mu S + (\beta - q - \mu)V + (\beta - v - \mu)E + (\beta - \mu - \mu_T - \varepsilon)I - \mu T^2$$
$$\leq \beta I - rT^2$$
$$\leq \beta T - rT^2, r \neq 0$$

Proposition 3.1: $T(t) \leq U$ for all $t \geq 0$ where

$$U = \max\left\{T(0), \frac{\beta}{r} + 1\right\}, \quad r \neq 0$$

Next, the proof is divided into two cases.

Case 1: If $U = \frac{\beta}{r} + 1$.

Assume that the proposition is not true, there exists a $t_1 > 0$ such that

$$T(t_1) = \frac{\beta}{r} + 1, \quad T(t) < \frac{\beta}{r} + 1, \ t < t_1, \ T'(t_1) \geq 0$$
$$T'(t_1) \leq \beta T(t_1) - rT^2(t_1)$$
$$= \beta\left(\frac{\beta}{r} + 1\right) - r\left(\frac{\beta}{r} + 1\right)^2$$
$$= -\beta\left(\frac{\beta}{r} + 1\right)$$

then $T'(t_1) < 0$ which is a contradiction. In consequence, the proposition is true.

Case 2: If $U = T(0)$.

Suppose the proposition is not true; there exists a $t_1 > 0$ such that

$$T(t_1) = U, \quad T'(t_1) \geq 0$$
$$T'(t_1) \leq \beta T(t_1) - rT^2(t_1)$$
$$= \beta U - rU^2$$
$$= U(\beta - rU)$$

as $\frac{\beta}{r} < \frac{\beta}{r} + 1 \leq U$, then $\beta - rU < 0$ and $T'(t_1) < 0$, a contradiction. In consequence, the proposition is true.

It means that $T(t) \leq U$ for all $t \geq 0$, then we have proved the theorem.

IV. Global Stability of the DFE

Let the right hand side of (2.1) – (2.4) be zero, then it can be seen that the system has a disease-free equilibrium H_0 given by

$$= \left(\frac{1 - \gamma[(1 - k)(\mu + q) - q\pi]}{\mu(\mu + q)}, \frac{(1 - \gamma)\pi}{\mu + q}, 0, 0 \right) \qquad (4.2)$$

Proposition 4.1: The basic reproduction number for model system (2.1) – (2.4) is

$$R_0 = \frac{\rho\beta[\mu(1 - k) + q]\pi}{\mu(\mu + q)(\mu + \rho)(\mu + \varepsilon)} \qquad (4.2)$$

Theorem 4.1: The DFE of system (2.1) – (2.4) is globally asymptotically stable (GAS) if $R_0 \le 1$ and unstable if $R_0 > 1$.

Proof: We follow the approach in Sharomi et al. [15]. We first show that the sets

$$P = \left\{ (S, V, E, I) \in \mathbb{R}_+^4 : S + V + E + I \le \frac{\pi}{\mu} \right\} \qquad (4.3)$$

and

$$P_* = \{ (S, V, E, I) \in P : S \le S^*, V \le V^* \} \qquad (4.4)$$

are positively invariant and attracting, and we then find a Lyapunov function for the model on P. Summing the equations in the model gives

$$\frac{dN_1}{dt} = \frac{[\mu(1 - k) + q)]\pi}{\mu} - (\mu + q)N_1 - \varepsilon(E + 1) - \mu_T I \qquad (4.5)$$

Since the right hand side of (4.5) is bounded above by $\left[\frac{\mu(1-k)+q)}{\mu} \right] \pi - (\mu + q)N_1$, it follows then that $N_1'(t) < 0$, if $N_1(t) > \frac{\pi}{\mu}$. More specifically by a standard comparison theorem [10 11, 15, 16], we can show that $N_1(t) \le N_1(0)e^{-\mu t} + \frac{\pi}{\mu}(1 - e^{-\mu t})$. In particular, $N_1(t) \le \frac{\pi}{\mu}$ if $N_1(0) \le \frac{\pi}{\mu}$. Thus P is positively-invariant. If $N_1(0) > \frac{\pi}{\mu}$, then either the solution enters P in infinite time or $N_1(t)$ approaches $\frac{\pi}{\mu}$ asymptotically and the infected variables E and I approach zero. Hence, P is attracting and the proof is complete.

Now, using the Lyapunov function

$$M' = (\mu + \mu_T)E' + \rho(\mu + \varepsilon)I'$$

we have that $M' \le 0$ if $R_0 \le 1$ and $M = 0$ if and only if $E = I = 0$. Then, it follows from the Lasalle Invariant Principle [10], that $E \to 0$ and $I \to 0$ as $t \to \infty$. That is, the disease dies out. Since, the disease-free equilibrium H_0 is GAS for the reduced system with $E = I = 0$, it follows that the DFE is GAS on P. Since P is attracting as well as positively invariant, then the DFE is GAS if $R_0 \le 1$.

V. Existence and Stability of Endemic Equilibrium

Using the techniques of persistence theory [3, 10, 17, 26], we can show the uniform persistence of TB disease and the existence of at least one endemic equilibrium. Then we have the following theorem.

Theorem 5.1 [10]. For model (2.1) – (2.4), if $R_0 > 1$, then the disease is uniformly persistent i.e. there exists a constant $r > 0$ such that every solution

$$\alpha_+(x_0) \equiv (S(t), V(t), E(t), I(t)) \quad \text{of} \quad \text{system} \quad (2.1) \quad - \quad (2.4) \quad \text{with}$$

$$x_0 \equiv \{ (S(0), V(0), E(0), I(0)) \in \mathbb{R}_+^4 \times \mathbb{R}_+^4 \setminus 0 \} \text{ satisfies}$$

$$\liminf_{t \to \infty} I(t) > r, \quad r > 0$$

and (2.1) – (2.4) admit at least one endemic equilibrium.

Proof. Let

$$X = \{ (S, V, E, I) : S \ge 0, V \ge 0, E \ge 0, I \ge 0 \}$$

$$X_0 = \{(S, V, E, I) \in X : I > 0\}$$
$$\partial X_0 = X \setminus X_0 = \{(S, V, E, I) \in X : I = 0\}$$

It suffices to prove that ∂X_0 repels uniformly the solutions of system (2.1) – (2.4) in X_0. Since ∂X_0 is relatively closed in X, then it implies that X and X_0 are positively invariant.

Now, assume that

$$Q_\partial = \{x_0 \in \partial X_0 : \alpha_t(x_0) \in \partial X_0 \quad \text{for} \quad t \geq 0\} \quad \text{and}$$
$$D = \{x_0 \in X : I = 0\}$$

Clearly, $D \subset Q_\partial$ and $I(0) > 0$ for any $x_0 \in \partial X_0 \setminus D$. Since, H_0 is globally stable in Q_∂, we have that $\{H_0\}$ is an isolated invariant set and acyclic. By Theorem 4.6 in Thieme [24], the model system (2.1) – (2.4) is uniformly persistent with respect to $(X_0, \partial X_0)$. Furthermore, by

Theorem 2.4 in Zhao [27], system (2.1) – (2.4) has an equilibrium H^*. This means that H^* is an endemic equilibrium of the model (2.1) – (2.4).

VI. Numerical Approach

Consider R_0 in equation (4.2) and noting biological considerations, let $k = 0.3, q = 0.7, \pi = 0.60, \rho = 0.004, \beta = 0.0238, \varepsilon = 0.13, \mu = 0.01425$. For these parameter values, the basic reproduction number for the disease-free equilibrium is $R_0 = 0.7259 < 1$.

Remark 6.1: The susceptible subpopulation win the competition with the infected pregnant women introduced into the total population and the disease eventually dies out. In consequence, a large proportion of newborn babies are able to escape TB infections since $R_0 < 1$.

If we fix μ and let $k = 0.2, q = 0.08, \rho = 0.0088, \beta = 0.0856, \varepsilon = 0.10, \pi = 0.80,$ then the disease becomes endemic and the basic reproduction number is $R_0 = 3.2331 > 1$.

Remark 6.2: In a disease without recovery with any initial population size, if the basic reproductive number is greater than one, an average infectious pregnant woman is able to replace itself and the number of infected rises and an epidemic result. This is a bad situation that could lead to 100% of newborns from infected mothers being infected.

VII. Discussion and Conclusion

We have studied a vaccination model of TB epidemics. We have shown that the DFE is GAS if $R_0 \leq 1$ and that there exist at least one unique positive endemic equilibrium. The DFE is the most desirable result for countries with high TB burden such as Ghana, Nigeria and India . In such countries, vaccination of expectant mothers and treatment pregnant women is the best strategy and must be kept high in order to lower R_0. In the case where $R_0 > 1$, the spread of the disease may be caused by certain factors such as age at vaccination, drug-resistant TB strains and effect of HIV on tuberculosis [13]. Furthermore, based on our mathematical analysis, we are able to conclude that BCG vaccination of infected pregnant women could result in increased TB incidence for any country, including those with low burden like United Kingdom, USA and Germany. This may arise if there are no strict checks for those immigrating to ensure that they are either vaccinated or have other immunity against TB disease. In conclusion, we recommend strict border checks and vaccinations of infected mothers and measures such as good health care system for expectant mothers to ensure there is no transmission of infection from mother to child in order to produce a DFE necessary for eradication of infection.

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