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Modelling the dynamics of tuberculosis in Nigeria

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Abstract

Mathematical models for the population dynamics of tuberculosis under the implementation of the direct observation therapy strategy (DOTS) in Nigeria are presented. The models establish conditions for the minimization and eradication of tuberculosis in Nigeria based on the fraction of infectious individuals treated under DOTS. The results from the models showed that there existed a stable disease free equilibrium provided the fraction of treated infectious individuals exceeded a critical value. The results showed that DOTS expansion in Nigeria must include a significant increase in the number of infectious individuals treated under DOTS else the effect in reducing the incidence of tuberculosis in Nigeria may not be achieved.

Keywords: Tuberculosis, DOTS, prevention and control, mathematical model.

1.0 Introduction

Tuberculosis (TB) was assumed to be on its way out in developed countries until the number of TB cases began to increase in the late 1980s [28]. TB is an airborne transmitted disease. Mycobacterium tuberculosis droplets are released in the air by coughing or sneezing infectious individuals [28]. Tubercle bacillus carried by such droplets lives in the air for a short period time (about two hours) and, therefore, it is believed that occasional contacts with TB-active persons (infectious individuals) rarely lead to transmission and that most secondary cases are the result of prolonged and sustained close contacts with a primary case.

Latently infected individuals (inactive TB) become infectious (active TB) after a variable (typically long) latency period which range from months to decades. Most infected individuals never progress towards the active TB state. On the other hand, average infectious periods are relatively short (few months) and becoming shorter in developing nations due to the availability of treatment.

Tuberculosis has continued to cause a high mortality in humans especially in developing countries, with Sub-Saharan Africa having the highest incidence in per-capita rate [20, 22]. It is estimated that a third of the world's population is infected with *Mycobacterium tuberculosis*. Of the 1.7 billion people estimated to be infected with TB, 1.3 billion live in developing countries [29]. Those infected are responsible for 8 to 12 million active cases of TB and 3 million deaths [20, 26].

A global control strategy adopted by the WHO to help reduce the number of active TB cases *as well as* effect proper treatment of patients with tuberculosis is the Direct Observation Therapy Strategy (DOTS). DOTS have evolved as a strategy that makes it compulsory for patients to complete their treatment. The DOTS program uses a nurse or surrogate to deliver and observe the patients taking all the doses of their drugs rather than relying on the patients to take the drugs on their own [10]. The patients may either come to a health facility (clinic based DOT) [10, 13] or be visited wherever the patients is found e.g. at work, home or shelter (community based DOT) [11].

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DOTS is seen to be highly effective at promoting successful treatment. Although a program like DOTS is essential to reducing TB relapse and emergence of drug resistant strains, its impact on the control of tuberculosis transmission is not clear [2, 4].

Nigeria has been ranked fourth among the 22 countries designated by the WHO as high-burden countries for TB. Nigeria is also said to have the highest number of new TB cases in Africa [23, 33]. An estimated 300,000 TB cases are recorded each year, resulting in 30,000 deaths annually. The total notified cases of all forms of TB increased from 46,473 in 2003 to 59, 493 in 2004.

With DOTS implementation in Nigeria, the detection rate remained at a low 21% while treatment rate is 59% in 2003, the lowest among any HBC [33]. What condition(s) can we impose on the fraction of infectious individuals receiving treatment under a DOTS program that could help eradicate TB in Nigeria or at least minimize the incidence of the disease?

In this paper, we will be formulating mathematical models to investigate the overall effect of DOTS on the dynamics of tuberculosis in Nigeria.

2.0 Model formulation

We will formulate a mathematical model that incorporates parameters for case detection and treatments under the DOTS program. In the formulation, we assume that there is a homogenous mixing of the population when all people are equally likely to be infected by the infectious individuals in case of contact.

We have the following system of nonlinear ordinary differential equations for the TB model:

$$\frac{dS}{dt} = \Lambda - \beta_1 SI/N - \mu S \tag{2.1a}$$

$$\frac{dE}{dt} = (\beta_1 S + \beta_2 (T_1 + T_2))I/N - (k + \mu + r_0)E + (1-m)(1-n_1)qr_1 I + (1-n_2)pr_1 I \tag{2.1b}$$

$$\frac{dI}{dt} = kE - (d + \mu + r_1)I \tag{2.1c}$$

$$\frac{dT_1}{dt} = r_0 E + n_1 qr_1 I + n_2 pr_1 I - \mu T_1 - \beta_2 T_1 I/N \tag{2.1d}$$

$$\frac{dT_2}{dt} = m(1-n_1)qr_1 I - \mu T_2 - \beta_2 T_2 I/N \tag{2.1e}$$

where $0 \le n_1 \le 1, 0 \le n_2 \le 1, 0 \le m \le 1,\ p = 1-q, and\ N = S + E + I + T_1 + T_2$ is the total population.

The mathematical model (2.1a-b) is based on the typical TB treatment models (for example see [29, 32] and the treatment models in the survey article by Castillo-Chavez, et al. [9]) usually written as SEIT (susceptible-latent-infected-treated) models. We incorporated into the SEIT framework, DOTS implementation parameters and divided the 'treated' class into two: treated individuals and re-treated individuals who initially failed treatments. Hence our model can be called a $SEIT_1T_2$ (susceptible - latent - infected - treated - re-treated) model.

Each equation in (2.1) represents the rate of change, with respect to time, of the sub-populations. The first term on the right hand side of equation (2.1a) is the recruitment term, Λ (newborns and/or uninfected immigrants who enter into the susceptible class). The second term is the change in the S population due to their encounter with actively infected individuals where β_1 is the transmission coefficient while the third term shows the number of susceptible that die naturally at the rate μ. (Usually a positive sign in front of a term indicates movements *into* the class or compartment while a negative sign will indicate movements *out* of the class or compartment).

We now examine Equation (2.1b), which describes the rate of change of the latent class. The first term on the right hand side of (2.1b) is the combination of (latent) infections produced when susceptible, treated and re-treated individuals come in contact with actively infected persons with β_2 being the transmission coefficient for the treated and re-treated classes. The second term is made up of

the rates at which latent individuals progress to the active TB case (k), die naturally (μ) or gets treated (r_0). The third term is the number of actively infected individuals that fail treatment and re-treatment under the DOTS program. These revert back to the latent stage. The fourth term is the number of actively infected individuals that fail treatment under a non-DOTS program; these also revert back to the latent class.

In Equation (2.1c), we have the rate of change of the actively infected class. The first term on the right hand side is the number of latently infected individuals that progress to the active TB stage at the rate k. The second term is the combination of the number of actively infected individuals who leave the class due to TB-induced death, at the rate d, due to natural death, at the rate μ and due to treatment, at the rate r_1.

In Equation (2.1d), we have the rate of change of the treated class. The first term on the right hand side is the number of latently infected individuals that were successfully treated at the rate r_0. The second term is the number of successfully treated active TB cases under the DOTS where q is the fraction of active cases treated under DOTS while n_1 is the fraction of these that were successfully treated. The third term is the number of successfully treated active TB cases under non-DOTS program where $p = 1 - q$ is the fraction of active cases treated under non-DOTS program while n_2 is the fraction of these that were successfully treated. The fourth term is the number of treated individuals that die naturally at the rate μ while the fifth term is the number of treated individuals that's get infected when they come in contact with actively infected individuals.

Finally, we examine Equation (2.1e) which describes the rate of change of the re-treated individuals under the DOTS program. The first term on the right hand side of (2.1e) is the number of failed treatments that were successfully re-treated where m is the fraction of the retreated cases that were successful. The second term is the number of re-treated individuals that die naturally at the rate μ while the third term is the number of re-treated individuals that gets infected due to their contact with actively infected individuals.

If we let $T = T_1 + T_2$ in (2.1) above, we will be having a system of four nonlinear differential equations viz:

$$\frac{dS}{dt} = \Lambda - \beta_1 SI / N - \mu S$$

$$\frac{dE}{dt} = (\beta_1 S + \beta_2 T)I / N - (k + \mu + r_0)E + (1-m)(1-n_1)qr_1 I + (1-n_2)pr_1 I$$

$$\frac{dI}{dt} = kE - (d + \mu + r_1)I$$

$$\frac{dT}{dt} = r_0 E + n_1 qr_1 I + n_2 pr_1 I - \mu T - \beta_2 T\, I / N + mr_1 q(1-n_1)I \qquad (2.2)$$

with $N = S + E + I + T$.

3.0 Sub-models without re-infection of treated individuals (β_2)

We analyze sub-models where the treatment class (T) is omitted for ease of analysis as well as set the transmission parameter, β_2 to zero.

Doing this, we will have the following system of equations:

$$\frac{dS}{dt} = \Lambda - \beta_1 SI / N' - \mu S \tag{3.1a}$$

$$\frac{dE}{dt} = \beta_1 SI / N' - (k + \mu + r_0)E + (1 - n_1)qr_1 I + (1 - n_2)pr_1 I \tag{3.1b}$$

$$\frac{dI}{dt} = kE - (d + \mu + r_1)I \tag{3.1c}$$

The model (3.1) helps us explore the effect of treatment under DOTS on the infectious class without the 'complications' of treated individuals getting infected again. It is assumed that there is no re-treatment of failed treatments i.e. $m = \mathbf{0}$.

A suitable domain for the model is: $F = \{(S, E, I) \in R^3_{\geq 0}; S + E + I \leq \Lambda / \mu\}$

First let us show that the compact set F is a positively invariant set of the flow described by (3.1).

***Lemma* 3.1**

The set F *is positively invariant*

Proof

At $S = 0, \frac{dS}{dt} = \Lambda > 0 \text{ for all } E, I \in F.$ Hence the two dimensional 'EI' plane is impenetrable from F. At $E = 0, \frac{dE}{dt} = \beta SI / N' + (1 - n_1)qr_1 I + (1 - n_2)pr_1 I > 0 \text{ for all } S, I \in F.$

Hence the EI plane is impenetrable from $R^3_{\geq 0}$. At $I = 0, \frac{dI}{dt} = kE > 0 \text{ for all } S, E \in F$. Hence the S, E plane is impenetrable from F. Define a Lyapunov function $W(S, E, I) = S + E + I$. This satisfies $\dot{W} = \dot{S} + \dot{E} + \dot{I} = \Lambda - \mu(S + E + I) - r_0 E - dI - n_1 qr_1 I - n_2 pr_1 I$. At the plane $S + E + I = \Lambda / \mu,\ \dot{W} = -r_0 E - dI - n_1 qr_1 I - n_2 pr_1 I \leq 0$

Hence, $\dot{W}(S, E, I) \leq 0 \text{ for all } (S, E, I) \in \{R^3_+ \setminus F\}$, and there is no flux through the plane $S + E + I = \Lambda / \mu$. By virtue of the Lyapunov-LaSalle asymptotic stability theorem, the set F is an attractor for the system. Therefore the set $F = \{(S, E, I) \in R^3_{\geq 0}; S + E + I \leq \Lambda / \mu\}$ is positively invariant under the flow described in (3.1a) – (3.1c). Hence no solution path leaves through any boundary of F. This ends the proof.

The right sides of (3.1a) - (3.1c) are smooth, hence initial value problem have unique solutions that exist on maximal intervals [18]. Since paths cannot leave F, solutions remain nonnegative for nonnegative initial conditions; solutions exist for all positive time. Thus the model (3.1a) - (3.1c) is mathematically and epidemiologically well posed.

3.1 Equilibria and Threshold

To study the behaviour of the system of differential equations, we find the equilibrium solution. The equilibrium solutions are obtained by setting the equations (3.1) to zero and then solve for *S*, *E* and *I*.

For the system under consideration, there are two equilibrium points, the disease free equilibrium (DFE) and the endemic equilibrium (EE). At the DFE, we have that $(S_0, E_0, I_0) = (\Lambda/\mu, 0, 0)$, where $S_0 = \Lambda / \mu$ is the asymptotic population size. At the EE, let S_1, E_1 ,I_1 be the equilibrium point, if it exists. After some algebraic calculations, and writing this equilibrium in terms of R^1_0, we have that

$$S_1 = \frac{d+k+\mu+r_1}{\rho_0},\ E_1 = \frac{d+\mu+r_1}{\rho_0}(R_0^1-1),\ I_1 = \frac{k}{\rho_0}(R_0^1-1),$$

where R_0^1 is the basic reproduction number obtained using the next generation matrix approach in [32] and is given by $R_0^1 = f_1 Q_1$ where $f_1 = \dfrac{k}{(k+\mu+r_0)-k(q(1-n_1)r_1+p(1-n_2)r_1)/\gamma}$ and

$Q_1 = \dfrac{\beta}{\gamma}, \gamma = (d+\mu+r_1)$. Also from the definition of the EE

$$\rho_0 = \frac{\Lambda}{k(\beta+q(1-n_1)r_1+p(1-n_2)r_1-r_1-d)-(d+\mu+r_1)r_0}.$$

Hence S_1 exists only if $\rho_0 > 0$. This extends to the other components of the EE. Therefore, the EE exists only if $\rho_0 > 0$ and $R_0^1 > 1$.

In the definition of R_0^1, Q_1 is the number of secondary (latent) infections produced by a typical infectious individual during the mean infectious period, $1/\gamma$ where $\gamma = \mu + d + r_1$. Also, f_1 is the fraction of infected individuals that develop active TB during his/her lifespan. Hence our mathematical definition of the basic reproduction number, which is the product of the number of infected individuals produced by a typical infectious individual during his/her mean infectious period and the fraction of these infections that progresses to active tuberculosis is epidemiologically correct.

Tuberculosis infection and re-infection are always existent in a community due to respiratory contact between the susceptible individuals, treated individuals and the infectious individuals. Whether the disease becomes persistence or dies out depends on the magnitude of the basic reproduction number. In most cases, the stability (local or global) of the equilibrium points can be analyzed using R_0^1. If R_0^1 is less than one, then on average an infected person produces less than one infected individuals over the course of its infectious period, and the infection cannot grow and invade the population.

Conversely, if R_0^1 is greater than one, then each infected individual produces, on average, more than one new infection, and the disease can invade the population leading to an epidemic. Hence any control strategy to be proposed must be such that will drive R_0^1 below one.

3.2 Analysis of equilibria

To determine the behaviour of the different compartments near each of the equilibrium solutions, we need to compute the linearization of the system, which is obtained from the Jacobian of the system.

Evaluating the Jacobian of (3.1) at the DFE, we have the following matrix:

$$J_0 = \begin{pmatrix} -\mu & 0 & -\beta \\ 0 & -(k+\mu+r_0) & \beta+(1-n_1)qr_1+p(1-n_2)r_1 \\ 0 & k & -\gamma \end{pmatrix}$$

Let $\lambda_i, i = 1,2,3$ be the eigenvalues of J_0. We then have that

$$(-\mu-\lambda)\det\begin{pmatrix} -(k+\mu+r_0)-\lambda & \beta+(1-n_1)qr_1+p(1-n_2)r_1 \\ k & -\gamma-\lambda \end{pmatrix} = 0$$

Let $$M = \begin{pmatrix} -(k+\mu+r_0) & \beta + (1-n_1)qr_1 + p(1-n_2)r_1 \\ k & -\gamma \end{pmatrix}$$

Then from M, we have $\det(M) = (k+\mu+r_0)\gamma - k(\beta + (1-n_1)qr_1 + p(1-n_2)r_1)$ and $Trace(M) = -(k+\mu+r_0) - \gamma$. Clearly, Trace ($M$) < 0 since all parameter values are positive. For the Det(M) > 0, we should have that $-k\beta + \gamma(k+\mu+r_0) - k(q(1-n_1)r_1 + p(1-n_2)r_1) > 0$. This implies that $R_0^1 < 1$, where R_0^1 is the basic reproduction number of the model (3) given above.

Therefore the DFE is locally asymptotically stable if $R_0^1 < 1$ and tuberculosis will not successfully invade the population. If $R_0^1 > 1$, the DFE will become unstable; TB invasion on the population becomes possible.

***Theorem* 3.1**

The disease free equilibrium of the *system* (3.1) ***is locally asymptotically stable*** *in* F ***if*** $R_0^1 < 1$

Next, we carry out the stability analysis for the EE. Evaluating the Jacobian of (3.1) at the EE, we have that

$$J_E = \begin{pmatrix} -\beta I_1 / N' - \mu & 0 & -\beta S_1 / N' \\ \beta I_1 / N' & -(k+\mu+r_0) & \beta S_1 / N' + (1-n_1)qr_1 + p(1-n_2)r_1 \\ 0 & k & -\gamma \end{pmatrix}$$

The characteristic equation corresponding to J_E is a third-degree polynomial, which has the form

$a_0\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$ where $\alpha_0 = -1 < 0$.

Hence by the third-order Routh-Hurwitz (R-H) criteria, all roots of the characteristic polynomial will be negative if $\alpha_1 < 0, \alpha_3 < 0$ and $\alpha_1\alpha_2 - \alpha_0\alpha_3 > 0$. The other coefficients of the polynomial are:

$$a_1 = \frac{1}{d+k+\mu+r_1}(-d^2 + dk + k^2 + k\beta + 3(d+k)\mu + 2\mu^2 + r_1(2d + k(1+p+q) + 3\mu - k(qn_1 + pn_2) + kr_0))$$

$$a_2 = \frac{1}{d+k+\mu+r_1}(d+k+2\mu+r_1+r_0)(k(d-\beta) + (1-p-q-qn_1+pn_2)r_1) + (d+\mu+r_1)r_0),$$

$$a_3 = \frac{1}{d+k+\mu+r_1}(k(d-\beta) + (d+k)\mu + \mu^2 + (d+\mu)r_0 + r_1(-k(-1+p+q) + \mu + kqn_1 + kpn_2 + r_0))((d+\mu)(k+\mu+r_0) + r_1(-k(-1+p+q) + \mu + kqn_1 + pkn_2 + r_0)).$$

It is easy to verify that all the R-H criteria are satisfied. From the expression for $\alpha_3 < 0$, after much algebraic simplifications, we have $1 - \frac{k\beta}{\gamma(k+\mu+r_0) - k(q(1-n_1)r_1 + p(1-n_2)r_1)} < 0$

This leads to $R_0^1 > 1$, with the expression of R_0^1 giving above.

Hence, the EE is locally asymptotically stable if $R_0^1 > 1$; the disease will invade the population leading to an epidemic that will eventually settle to an endemic state.

***Theorem* 3.2**

The Endemic equilibrium of the system (3.1) *is locally asymptotically stable in* F *if* $R_0^1 > 1$

We can use the Lyapunov function approach to provide a sufficient condition for the global stability of the DFE when $R_0^1 < 1$.

Consider the Lyapunov function $V = kE + (k + \mu + r_0)I$. Then $V > 0$ except at the DFE. To show this, differentiate V with respect to time. This yield

$$\dot{V} = k\dot{E} + (k + \mu + r_0)\dot{I} = I(k\beta S / N' + k(q(1-n_1)r_1 + p(1-n_2)r_1) - \gamma(k + \mu + r_0))$$

on $F, S \le N' \le \Lambda / \mu$, and so

$$\dot{V} \le I(k\beta + k(q(1-n_1)r_1 + p(1-n_2)r_1) - \gamma(k + \mu + r_0))$$
$$= I(\gamma(k + \mu + r_0) - k(q(1-n_1)r_1 + p(1-n_2)r_1))(R_0^1 - 1)$$

with equality only at the DFE. For R_0^1, we have that $\dot{V} \le 0$ with equality only if I = 0. By LaSalle's extension to Lyapunov's method [19], the limit set of each solutions is contained in the largest invariant set for which $\boldsymbol{I = 0}$, which is the singleton {DFE}.

***Theorem* 3.3**

The Disease free equilibrium of the system (3.1) *is globally asymptotically stable in* F *if* $R_0^1 \le 1$

Conversely, if $R_0^1 > 1$, the DFE becomes unstable and the EE is globally stable if it exists.

Putting all of these together, we can say that the DFE will be locally and globally asymptotically stable if $R_0^1 \le 1$. Hence tuberculosis will not be able to invade the population. However, if $R_0^1 > 1$, the DFE loses is stability and the EE becomes stable, if it exists; the disease will be able to invade the population leading to an epidemic that could eventually settles to the endemic state.

3.3 Condition for the minimization of TB

For us to minimize the incidence of tuberculosis, we require that the population sizes of the latently infected individuals as well as the infectious individuals decrease. This we will obtain when $\frac{dE}{dt} < 0, \frac{dI}{dt} < 0$. Combining these inequalities, we have a condition on $\boldsymbol{q}$ for us to be able to minimize the incidence of TB: $q > \frac{1}{(n_1 - n_2)r_1}(\beta S / N' + (1 - n_2)r_1 - \gamma(k + \mu + r_0)/k) = q_m$ with $n_1 \neq n_2$. Hence, q must be greater than the quantity on the right hand side of the inequality in magnitude for there to be a reduction in the incidence of TB.

From the definition of R_0^1 given earlier, we can find a condition on q for the eradication of tuberculosis in the population. For $R_0^1 < 1$, we have that

$$q > \frac{1}{(n_1 - n_2)r_1}(\beta + (1 - n_2)r_1 - \gamma(k + \mu + r_0)/k) = q_c$$

with $n_1 \neq n_2$.

Both conditions (q_m for minimization and $\boldsymbol{q_c}$ for eradication) are quite similar except that in $\boldsymbol{q_m}$, the transmission rate is multiplied with the fraction of susceptible which will make the value of $\boldsymbol{q_c}$ 'higher' than q_m.

If eradication is achieved (i.e. **E=I=0**), then the expected population size will simply be the solution of dS/dt i.e. $\frac{dS}{dt} = \Lambda - \mu S$. Solving this equation gives $S(t) = \Lambda / \mu + (S_i - \Lambda / \mu)e^{-\mu t}$, where S_i is the initial number of susceptible individuals. It is easy to see that as $t \to \infty, S \to \Lambda / \mu$, which is the asymptotic population size. Hence the entire population will be comprised wholly of susceptible individuals.

3.4 Sub-model with *m* > 0

Again, from the general equations (2.1), with $\beta_2 = 0$ and $m > 0$, while omitting the T class, we have $\frac{dS}{dt} = \Lambda - \beta_1 SI / N' - \mu S$,

$$\frac{dE}{dt} = \beta_1 SI / N' - (k + \mu + r_0)E + (1-m)(1-n_1)qr_1 I + (1-n_2)pr_1 I \quad \frac{dI}{dt} = kE - (d + \mu + r_1)I \qquad (3.2)$$

with $N' = S + E + I$. A suitable domain for (3.2) is $D = \{(S, E, I) \in R^3_{\geq 0}; S + E + I \leq \Lambda / \mu\}$

The domain is positively invariant and the model is mathematically well posed: nonnegative initial conditions lead to nonnegative solutions.

For the model in (3.2), using the next generation matrix approach in [32], the basic reproduction number is $R_0^2 = f_2 Q_2$, where $f_2 = \frac{k}{(k + \mu + r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1)/\gamma}$ and

$Q_2 = \frac{\beta}{\gamma}, \gamma = (d + \mu + r_1)$. In the definition of R_0^2, Q_2 is the number of secondary (latent) infections produced by a typical infectious individual during the mean infectious period, $1/\gamma$ while f_2 is the fraction of infected individuals that develop active TB during his/her lifespan.

The DFE for (3.2) is $(S_0, E_0, I_0) = (\Lambda / \mu, 0, 0)$ while the endemic equilibrium is

$$S_2 = \frac{d + k + \mu + r_1}{\rho_0^*}, E_2 = \frac{d + \mu + r_1}{\rho_0^*}(R_0^2 - 1),\ I_2 = \frac{k}{\rho_0^*}(R_0^2 - 1),$$

where $\rho_0^* = \frac{\Lambda}{k(\beta + q(1-m)(1-n_1)r_1 + p(1-n_2)r_1 - r_1 - d) - (d + \mu + r_1)r_0}$.

Hence S_2 exists only if $\rho_0 > 0$. This extends to the other components of the EE. Therefore, the EE exists only if $\rho_0 > 0$ and $R_0^2 > 1$. It is straight forward to show that the DFE is locally asymptotically stable as well as globally asymptotically stable if $R_0^2 \leq 1$ following the method of linearization and the use of a similar Lyapunov function as shown earlier. For $R_0^2 > 1$, the disease free equilibrium becomes unstable and an endemic equilibrium exists, which can also be shown to be stable for this condition on R_0^2.

From the models, without the treated (and re-treated) individuals getting infected again, a very important strategy to bring the value of the basic reproduction numbers below one is to increase the fraction of infectious persons receiving treatment under DOTS above a critical minimum q_c for there to be the possibility of eradication of tuberculosis.

4.0 The General Model with $\beta_2 > 0$ and $m > 0$

This is the system of equations we have in equation (2.2), reproduced here:

$$\frac{dS}{dt} = \Lambda - \beta_1 SI / N - \mu S$$

$$\frac{dE}{dt} = (\beta_1 S + \beta_2 T)I / N - (k + \mu + r_0)E + (1-m)(1-n_1)qr_1 I + (1-n_2)pr_1 I$$

$$\frac{dI}{dt} = kE - (d + \mu + r_1)I$$

$$\frac{dT}{dt} = r_0 E + n_1 q r_1 I + n_2 p r_1 I - \mu T - \beta_2 T \; I/N + m r_1 q(1-n_1) I \qquad (4.1)$$

with $N = S + E + I + T$. Under the flow described by (4.1), the region

$$A = \{(S,E,I,T) \in R^4_{\geq 0}; S + E + I + T \leq \Lambda/\mu\}$$

is positively invariant. Also each solution in $\Re^4_+$ approaches A. Since paths cannot leave A, solutions remain positive for positive initial conditions and the model is mathematical and epidemiologically well posed.

4.1 Analytic results

4.1.1 Equilibria and Threshold

Using the next generation matrix approach in [32], the basic reproduction number is obtained as $R_0 = fQ$ where $f = \dfrac{k}{(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1)/\gamma}$ and $Q = \dfrac{\beta}{\gamma}, \gamma = (d+\mu+r_1)$.

The DFE of (4.1) is given by $S_0 = \Lambda/\mu, E_0 = 0, I_0 = 0, T = 0$. There is also an EE that will exist if

$R_0 > 1$, which is rather complicated to write down.

To determine the behaviour of the different compartments near the equilibria, as usual we need to compute the linearization of the system which is obtained from the Jacobian matrix of the system. Evaluated the Jacobian of (4.1) at the DFE, we have that

$$J_0 = \begin{pmatrix} -\mu & 0 & -\beta_1 & 0 \\ 0 & -(k+\mu+r_0) & \beta_1 + (1-m)(1-n_1)qr_1 + pr_1(1-n_2) & 0 \\ 0 & k & -\gamma & 0 \\ 0 & r_0 & n_1 q r_1 + p r_1 n_2 + m r_1 q(1-n_1) & -\mu \end{pmatrix}$$

Let $\lambda_i, i = 1,2,3,4$ be the eigenvalues of J_0. We then have that

$$(\mu+\lambda)^2 \det\begin{pmatrix} -(k+\mu+r_0) - \lambda & \beta + (1-m)(1-n_1)qr_1 + p(1-n_2)r_1 \\ k & -\gamma - \lambda \end{pmatrix} = 0$$

Let $Z = \begin{pmatrix} -(k+\mu+r_0) & \beta + (1-m)(1-n_1)qr_1 + p(1-n_2)r_1 \\ k & -\gamma \end{pmatrix}$, from Z, we have that

$Det(Z) = (d+\mu)(k+\mu+r_0) - r_1(-k(p+q-1) + \mu + k(qn_1 + m(q-qn_1) + pn_2) + r_0) - k\beta_1$

and $Trace(Z) = -d - k - 2\mu - r_1 - r_0$. We observe that the trace of **Z** is less than zero since all parameter values are positive. We can show that the determinant of Z is positive precisely when $R_0 < 1$. Hence det(Z) > 0 implies that $-k\beta + \gamma(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1 > 0.$ The inequality holds if $1 - R_0 > 0$. Therefore, det(Z) > 0 if $R_0 < 1$. Therefore the DFE is locally asymptotically stable when $R_0 < 1$.

Determining the local stability of the EE in general is more complicated. However, from our previous analysis, we were able to observe that in general the EE is locally asymptotically stable when $R_0 > 1$. Hence we can say that the EE for the general model is locally stable, if it exists, as far as $R_0 > 1$.

As done earlier, a Lyapunov function can provide a sufficient condition for the global stability of the DFE when $R_0 \leq 1$. Consider the Lyapunov function

$$V = kE + (k+\mu+r_0)I.$$

Then $V > 0$ except at the DFE and

$$\dot{V} = k\dot{E} + (k+\mu+r_0)\dot{I} = I(k\beta S/N + k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1) - \gamma(k+\mu+r_0))$$

on $A, S \le N \le \Lambda/\mu$, and so

$$\dot{V} \le I(k\beta + k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1) - \gamma(k+\mu+r_0))$$

$$= I(\gamma(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1))(R_0 - 1)$$

with equality only at the DFE. For $R_0 \le 1$, we have that $\dot{V} \le 0$ with equality only if $I = 0$.\

***Theorem* 4.1**

The Disease free equilibrium of the system (7) is locally and globally.asymptotically stable in A *if* $R_0 \le 1$

If $R_0 > 1$, the disease free state becomes unstable and a nontrivial endemic equilibrium exist and is locally stable.

For the minimization of the incidence of tuberculosis, we will require that the population size of all infected classes decrease i.e. $\frac{dE}{dt} < 0, \frac{dI}{dt} < 0.$ If we combine the inequalities, we have the following condition with respect to q:

$$q > \frac{\beta_1 S/N + \beta_2 T/N + (1-n_2)r_1 - \gamma(k+\mu+r_0)/k}{(1-n_2)r_1 - (1-m)(1-n_1)r_1} = q_r$$

where n_2 and m or n_1 should not be equal to one.

For the eradication of tuberculosis, we will require that $R_0 < 1$. Writing this inequality in terms of the fraction of infectious individuals undergoing treatment under DOTS, $\boldsymbol{q}$, we have the condition on $\boldsymbol{q}$ for elimination:

$$q > \frac{\beta + (1-n_2)r_1 - \gamma(k+\mu+r_0)/k)}{(1-n_2)r_1 - (1-m)(1-n_1)r_1} = q_c$$

For the sake of disease control, if the condition for $\boldsymbol{q_c}$ is not met strictly, at least health official may look at the condition for minimization (q_r) and could then move a step further to carry out an elimination of tuberculosis, if possible.

Eradication of the disease from the population will mean that $E = I = 0$. Hence the total population becomes $N = S + T$. Therefore solving the equations for $\dot{S}$ and $\dot{T}$ with $E = I = 0$, we have $S(t) = \frac{\Lambda}{\mu} + (S_j - \Lambda/\mu)e^{-\mu t}, T(t) = T_j e^{-\mu t}$ where S_j and T_j are the initial numbers of susceptible and treated individuals, respectively. As $t \to \infty, S(t) \to \frac{\Lambda}{\mu}$, the asymptotic population size, while $T \to 0.$ Therefore the entire population returns to the initial state where there are no infected individuals and treated people but just susceptible individuals only.

5.0 Parameter estimation and numerical results

We set the year as unit of time. The constant mortality μ is estimated as the inverse of life expectancy at birth which is about 49 years in Nigeria [31]. Hence $\mu = 1/49 = 0.02041 yr^{-1}$. The recruitment rate ($\Lambda$) controls the total population size because $N \approx \Lambda/\mu$. We shall set $\Lambda = \mu \times 10^5\, yr^{-1}$ [28].

Per capita TB-induced mortality rates vary from country to country. They are around $0.07yr^{-1}$ in developed countries but could be as high as $0.395yr^{-1}$ in some African countries [1, 27]. For the purpose of this work, we shall set the TB-induced mortality rate to $0.395yr^{-1}$.

We take the recovery rates as the time between TB activation and recovery. According to Styblo, et al [30], the time between TB activation and recovery by treatment is between 4 and 6 months while in [16], the treatment period is about 6 to 9 months implying that $r_0 > 1$ per year. If we take the treatment period to be 8 months, following [29], we obtain the recovery rate to be 1/0.5 = 2 per person-year. In [30], a recovery rate of 1/0.67 = 1.5 per person-year was used. For this study, we will set r_0 and r_1 at 1.5 per person-year.

In [33], we find epidemiological data on DOTS surveillance and implementation in Nigeria since 1995. With an incidence rate of 125 per 100,000 per year of *ss+* cases, the prevalence rate was 531 per 100,000 per year of all cases in 2004. Since 1997, the DOTS treatment success rate has stabilized to about 75% while re-treatment rates under DOTS have stabilized to about 79%. Fraction of detected cases undergoing treatment under DOTS has ranged from 11% to 21% in 2004 [33]. Hence from available data, we estimate q = 0.21 while n_1 = 0.5769 and n_2 = 0.05**0**5. Fraction of successfully re-treated cases, m = 0.7273. From the expression for R_0, Q depends on the average infectious periods of the infectious individuals and the transmission rate, β_1. The transmission rates, (β_1 and β_2), are chosen to match the expected number of infections produced in the $1/\gamma$ units of time. Assuming there is no significant protection against re-infection after treatment, we will have that $\beta_1 = \beta_2$.

The fraction of infected people who develop active TB, ***f***, has been estimated to be between 5% and 10% in developed countries while for developing countries, this could be about 15% and in some extreme cases, 30% [28]. For this study, we shall set f = 0.15. The average per capita rate of progression to active TB (k) is estimated from

$$f = \frac{k}{(k+\mu+r_0) - k(q(1-m)(1-n_1)r_1 + p(1-n_2)r_1)/\gamma}$$

From the above, we have that $k = \dfrac{f(\mu+r_0)}{1 - f(1 - \dfrac{q(1-m)(1-n_1)r_1 + p(1-n_2)r_1}{\gamma})}$

From data, q currently stands at 0.21 in Nigeria. With different values of q for the past eight years, ranging from 0.11 to 0.21 and f = 0.15, we observe that there was not much difference in the progression rate, where k = 0.2433, which has been almost constant over the last decade.

Figures 5.1 to 5.3 are the numerical simulation we have of the generalized model with the given parameter values and values for Q. We observe from the figures that to significantly lower R_0 below one, we need to make the number of secondary infections ***Q*** very small.

Clearly, with R_0 below one and Q = 6 in figure 5.3, the DFE was achieved after a very long time. This shows that to achieve a reduction in the incidence of tuberculosis in Nigeria, attention must be placed to isolate infectious individuals (for treatment under DOTS) so that the number of secondary infections will be greatly minimized.

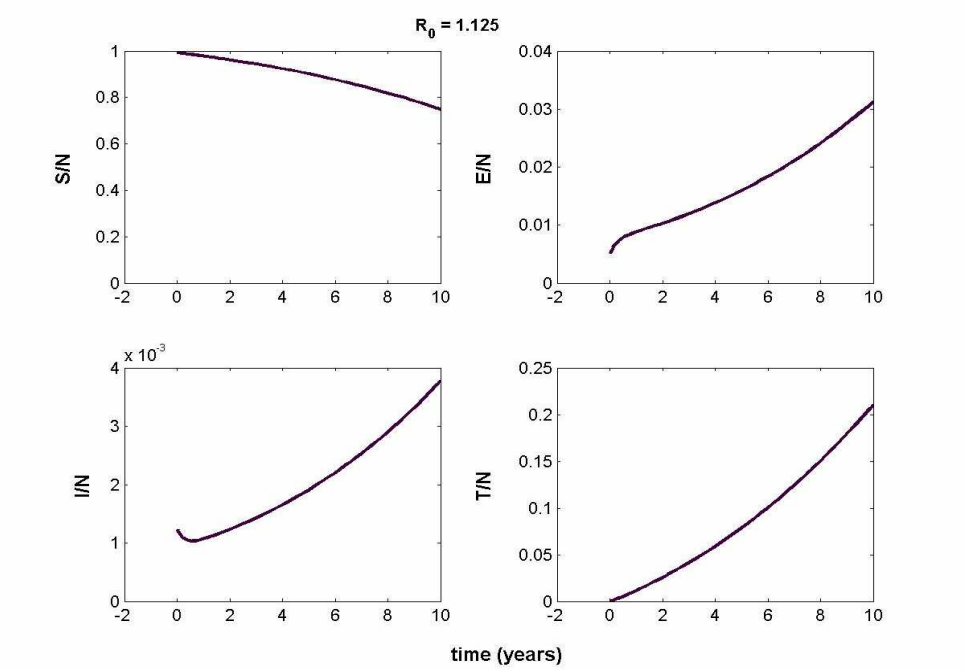

Figure 5.1: Population fractions with $Q = 7.5$

6.0 Discussion and conclusions

In Nigeria, the incidence of tuberculosis is on the increase [31]. Among other factors that may be contributing to this trend is the failure to increase the number of active TB cases undergoing treatment under the DOTS programme. Obviously, the detection rate is small and there is a large fraction of untreated cases leading to an increase on the number of secondary infections in the country. In order to control the incidence of tuberculosis, this issue must be addressed.

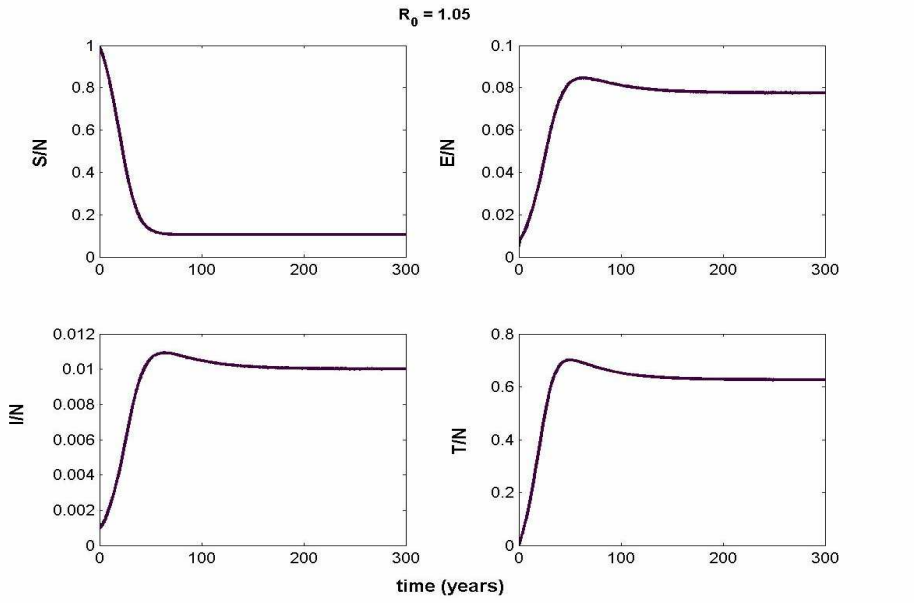

Figure 5.2: Population fractions with $Q = 7$

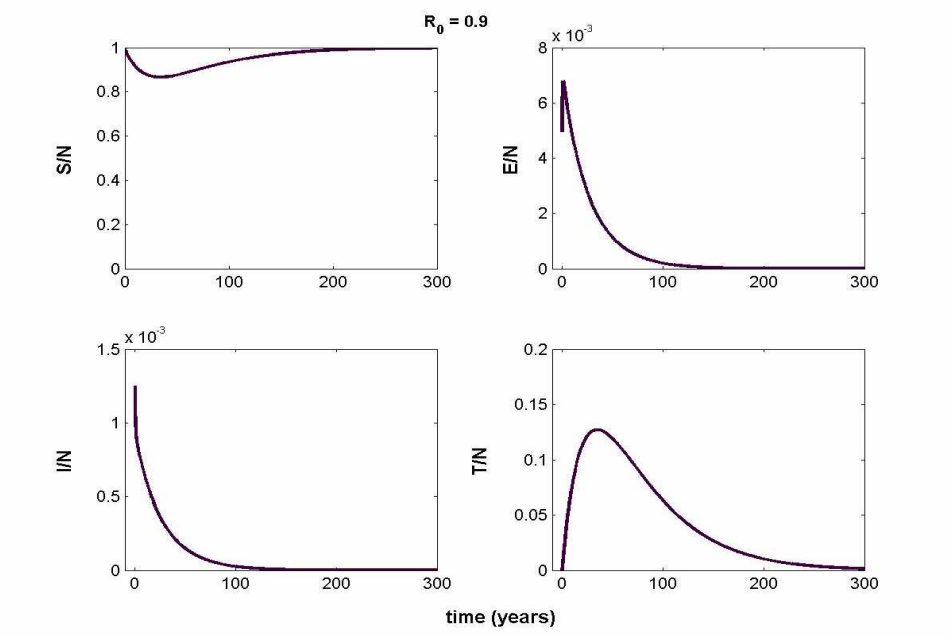

Figure 5.3: Population fractions with $Q = 6$

In this research, we have examined the effects of DOTS on the dynamics of tuberculosis vis a vis the fraction of infectious individuals undergoing treatment under DOTS. In order to understand the effects of DOTS in reducing the incidence of TB in Nigeria, a mathematical model was formulated that incorporated the fraction of active cases undergoing treatment under DOTS (including treatment and re-treatment rates).

In the qualitative analysis of the model, the existence of steady states and their stability were analyzed. The analysis showed that a disease free equilibrium existed and was found to be stable provided the fraction of active cases receiving treatment exceeds a critical value (q_c) which among other things includes the number of new infections, re-infections and failed treatments. The requirement for minimization of the incidence of tuberculosis (q_r) was obtained and is almost similar to the condition for eradication, q_c.

The results of the numerical simulations were remarkably inline with those from the qualitative analysis of the model. Both analyses showed the effect of the fraction of treated individuals under DOTS. Increasing this fraction can help in reducing the basic reproduction number and hence, the number of infectious individuals (since all infectious persons are treated under DOTS) and by extension, the number of latent infections.

The basic reproduction number, R_0 is one of the tools used in determining disease behaviour in a given population. The condition for this quantity to be less than unity will mean making the fraction of treated infectious individuals under DOTS exceed a critical value (q_c) determined by the values of the epidemiological parameters. If this critical value is not exceeded, then there is the possibility of an epidemic in the population that could end up settling to an endemic state after a long time. The number of secondary infections must be minimized to achieve a reduction in the incidence of tuberculosis in Nigeria; hence attention must shift to isolating infectious individuals for treatment under DOTS to avoid increasing the number of infections that they may cause.

DOTS expansion should not just cover treatments alone but emphases should be placed on using the dynamic nature of the programme to screen close contacts of infectious cases of TB in order to know how many of these could be having either latent or active cases of tuberculosis. The approach of screening household contacts by Becerra, et al [3] is quite useful and timely for Nigeria. The object of the study in [3] was to access the feasibility and yield of a simple active case finding strategy in a high incidence population in northern Lima, Peru. The results showed that the tuberculosis prevalence detected through combined active and passive case finding among 1,094 household contacts was 0.91% (914 per 100,000),

much higher than with passive case finding alone (0.18% ; 183 per 100,000). Hence the study concluded that the risk of active TB among symptomatic household contacts of active case subjects in the community is very high and results suggested that contact tracing in such setting may be a powerful tool in improving case detection rates for active tuberculosis disease. The estimations used for the computer simulations of the general model suggests that while there have been improvement in tuberculosis treatment success rate under DOTS in Nigeria, the small number of cases detected under DOTS and treated (or re-treated) remains an obstacle to the long-term success of DOTS on TB control in Nigeria. Hence, if DOTS is expanded, this should include screening of close contacts of the treated infectious individual. For now, we can say that DOTS is not having much impact on efforts to reduce the incidence of tuberculosis in Nigeria as only a little fraction of the infectious individuals are actually treated under DOTS while the vast majority of undetected cases are actually leading to an increase on the number of new infectious cases in the country and a huge pool of latent individuals, and by extension the prevalence rate.

We also suggest that reaching the rural areas will have to include providing transportation for the sick to receive their medication and if possible seeking the attention of the families of these patients for screening. Medical personnel can be paid to go to these areas to provide medications for the patients as well as simultaneously conduct screening for close contacts of the patients. In this regards, we suggest dedicated vehicle from the government or other health agencies to carry out these tasks.

DOTS, as a strategy adopted by WHO, is to help reduce the number of active tuberculosis cases as well as effect proper treatment of patients. The insights gained from the mathematical model treated in this article can be useful in the study of the impact of DOTS on the dynamics of tuberculosis in Nigeria. This may assist health and government officials plan on improving the case detection rate which will help in bringing down the incidence and prevalence of TB in the country. This can be achieved if the current DOTS service in Nigeria is greatly improved upon and the fraction of infectious individuals undergoing treatment (or re-treatment) is significantly increased.

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