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DETERMINISTIC MODEL FOR TUBERCULOSIS AND HIV/AIDS

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ABSTRACT

In this study, a mathematical model that captures the role played by HIV/AIDS in accelerating the infection and hence spread of Tuberculosis is developed.

Keywords: *HIV/AIDS, TB, Modeling, Mackendrick-Von Foster equation.*

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1. INTRODUCTION:

The statistical analysis of infectious disease data usually requires the development of problem-specific methodology. There are a number of reasons for this but the main features that distinguish outbreak data are the high dependence that is inherently present and the fact that we can never observe the entire infection process. In many cases the data from the incidence of an infectious disease consist of only the final numbers of infected individuals. Thus, the analysis should take into account all the possible ways that these individuals could be infected. Moreover, even when the data contain the times that the symptoms occur, we cannot observe the actual infection times. These reasons suggest that in order to accurately analyse outbreak data, we need a model that describes a number of aspects of the underlying infection pathway. Hence, inference about the data generating process can provide us with an insight about the quantitative behavior of the most important features of the disease propagation. Additionally, the design of control measures against a disease can be improved through a quantitative analysis based on an epidemic model.

2. PRELIMINARIES:

The first model for the transmission dynamics of TB was built in 1962 by Waaler. He divided the population into three epidemiological classes: non-infected (susceptible), infected non-cases (latent TB), and infected cases (infectious). He formulated the infection rate as an unknown function of the number of infectious individuals. He used a particular linear function to model infection rates in the implementation of his model. The incidence (new cases of infections per unit time) was assumed to depend only on the number of infections. Furthermore, the equations for the latent and infectious classes were assumed to be uncoupled from the equation for the susceptible class. The central part of this model is given by the following linear system of difference equations:

$$\begin{aligned} E_{t+1} &= E_t + aI_t - eE_t - d_2E_t + gE_t \\ I_{t+1} &= I_t - gE_t - d_3I_t + eE_t \end{aligned} \qquad (1.1)$$

where the incidence rate aI_t is proportional to the number of infections; e is the per-capita progression rate from latent-TB to infectious-TB cases; g is the per-capita treatment rate (treated individuals will become members of latent-TB class again.); d_2 is the per-capita death rate of the latent-TB class; and d_3 is the per-capita death rate of the infectious-TB class.

Aparicio et al (2002) developed a basic generalized households (cluster) model, which took close and casual contacts into account. They focused on the active-TB cases within their social networks (family members, officemates, classmates, any persons who have prolonged contacts with an active case). Such a generalized household or epidemiologically active cluster was used to study transmission of TB outside and within their social networks. The study indicated that casual contact significantly increases the number of secondary active cases.

In this model the population was divided into two clusters. One of active TB (N_1), which have only one active case and another of inactive TB (N_2) which have no active cases. The clusters were further subdivided into a susceptible group

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(S_i), an exposed group (E_i) and an infectious group (I_i) according to the progression of TB, where it was assumed that when one person from an inactive cluster develops active TB, the whole cluster becomes an active-TB cluster and vice versa. It was also assumed that casual infection just occurs in N_2 and close infection depends on the life of the cluster (Aparicio et al, 2002). All assumptions lead to the basic household model:

$$\begin{aligned}
\frac{dS_1}{dt} &= -(\beta+\gamma)S_1 + \frac{S_2}{N_2}nkE_2 \\
\frac{dE_1}{dt} &= \beta S_1 - \gamma E_1 + \frac{E_2}{N_2}nkE_2 \\
\frac{dI}{dt} &= kE_2 - \gamma I \\
\frac{dS_2}{dt} &= \lambda - \mu S_2 + \gamma S_1 - \frac{S_2}{N_2}nkE_2 \\
\frac{dE_2}{dt} &= \gamma E_1 - (k+\mu)E_2 - \frac{E_2}{N_2}nkE_2
\end{aligned} \tag{1.2}$$

where β is transmission rate, n is the size of cluster, λ is the recruitment rate to S_2, μ is natural mortality of N_2, E_2 is the exposed in N_2, γ is the total per-capita removal rate from the I, k is the progression rate to active TB.
The basic reproductive number for the model is

$$R_0 = \left(\frac{n}{1+\frac{\gamma}{\beta}}\right)\left(\frac{1}{\frac{\mu}{k}+1}\right) \tag{1.3}$$

It can be seen that R_0 depends nonlinearly on the parameter β (risk of infection on an epidemiologically active cluster of size n) and linearly on the average generalized household size, n. If R_0>1 then there exist endemic equilibrium and disease persists.

Schinazi (2000) introduced a spatial stochastic model for TB and HIV co-existence and showed that casual infection can induce an outbreak of TB independent of the active cluster. Song et al (2002) extended the basic cluster model (1.1) and investigated its global dynamics by using singular perturbation theory and multiple time scales techniques. The results supported the view that TB can be acquired from one or few contacts with an infectious individual. Generally, the probability that a susceptible individual, who does not belong to any active cluster, has a close contact with an active case is very low. Hence for those individuals who are only exposed to casual contacts the risk of infection is significantly smaller than that of individuals who are in active clusters. Nevertheless, the total number of secondary infections caused by casual contacts is greater than those produced by contacts in active clusters. This is so because the size of the subpopulation living in the active clusters is significantly smaller than the total population size. That is, it would not be surprising to find that the dynamics of tuberculosis at the population level in cities depends more on casual contacts than the close contacts. The modified model is given by the following nonlinear system:

$$\begin{aligned}
\frac{dS_1}{dt} &= -(p\beta(n)+\gamma)S_1 + \frac{S_2}{N_2}nkE_2 - (1-p)\beta^*\frac{I}{N-n}S_1, \\
\frac{dE_1}{dt} &= p\beta(n)S_1 - \gamma E_1 + \frac{E_2}{N_2}nkE_2 + (1-p)\beta*\frac{I}{N-n}S_1, \\
\frac{dI}{dt} &= kE_2 - \gamma I, \\
\frac{dS_2}{dt} &= \lambda - \mu S_2 + \gamma S_1 - \frac{S_2}{N_2}nkE_2 - (1-p)\beta^*\frac{I}{N-n}S_2, \\
\frac{dE_2}{dt} &= \gamma E_1 - (k+\mu)E_2 - \frac{E_2}{N_2}nkE_2 + (1-p)\beta^*\frac{I}{N-n}S_2
\end{aligned} \tag{1.4}$$

where β is the transmission rate within the cluster and assumed to depend on the average cluster size n, β^* is the casual transmission rate, p denotes the average fraction of time spent by the active case within his/her generalized

household and 1− p, the average fraction of time spent by this source-case outside the cluster. The rate of infection within clusters becomes pβ (n) S_1, while the rate of infection outside is given by (1−p) $\beta^* \frac{1}{N-n}$ (S_1+S_2), where N is the total population size, and (N − n) represents the average total number of individuals outside the cluster.

Hence, (1−p) $\beta^* \frac{1}{N-n} S_i, (i=1,2)$ gives the number of new infections per unit time in the N_1 population, that is, the incidence from S_1 to E_1 and the incidence from S_2 to E_2. There are no new cases of active TB within each epidemiologically active cluster, and consequently, the infection rate is pβ (n) S_1.

In the system of equations (2.2), when p = 1 and β(n)is a constant, the extended cluster model becomes the basic cluster model.

The basic reproductive number for the model in (1.2) is

$$R_0 = \left[\frac{p\beta(n)n}{p\beta(n)+\gamma} + (1-p)\frac{\beta^*}{\gamma}\frac{K}{K-n} \right] \left(\frac{1}{\frac{\mu}{k}+1} \right), \tag{1.5}$$

where, K = $\frac{\lambda}{\mu}$ is the asymptotic carrying capacity of the total population. Song and colleagues in 2002 discussed two special forms of $\beta(n)$ and concluded that casual infection indeed contributes to R_0 as well as close infection.

3. THE MODEL:

Blower and Castillo-Chavez in 2001 introduced a mathematical model that stresses the importance of treating individuals with latent TB where they added an early latent class and long-term latent class into the model. We borrow this to develop a model that explicitly represents two different latently infected classes: "fast progressors" denoted by E and "slow progressors" denoted by F. According to Williams et al (2006), active TB disease can be infectious or non-infectious. It is infectious if it infects the lungs i.e. pulmonary TB and non-infectious if it infects the spine, brain and the kidney. This approach is summarized in Figure 3.1 below. In this model, newly infected individuals are assigned to one of these two compartments and experience the corresponding rate of progression. Typically individuals can move from the slow group to the fast group (if a re-infection event occurs), and vice versa if there is treatment of latent TB as suggested by Blower and his colleagues. However, an individual fully treated or naturally recovered, cannot return to the susceptible class but moves to latent slow rate class. This is due to the fact that once vaccinated with BCG, which is a component of the childhood vaccination regimen in most African countries and typically administered at birth, an individual has the bacteria in his/her system. We assume that only people with active TB can transmit the disease to others.

Table 1.1: The variables t and a represent time

	No TB	**Latent TB (fast rate)**	**Latent(slow rate) or Active TB non-infectious**	**Active TB (Infectious)**
HIV-	$S_0(t)$	$E_0(t)$	$F_0(t)$	$I_0(t)$
HIV+	$S_1(t)$	$E_1(t)$	$F_1(t)$	$I_1(t)$

We let $P(t)$ denote the total population with $\phi(t)$ representing the fraction of the total population that transmit TB, $\phi(t) = \sum_{n=0}^{1} I_n(t)/P(t)$, where $I_n(t)$ is the number of infective individuals at time t.

Let the force of infection by HIV for people aged a at time t is given by;
$\lambda(t) = \frac{I(t)}{N(t)}\beta(t)C$, Where $\frac{I(t)}{N(t)}$ measures the risk of getting HIV, $\beta(t)$ is the net rate of recruitment into the susceptible class and we take it to be 0.02 (Diego C.P et al, 2007) and C is the number of partners per unit time.

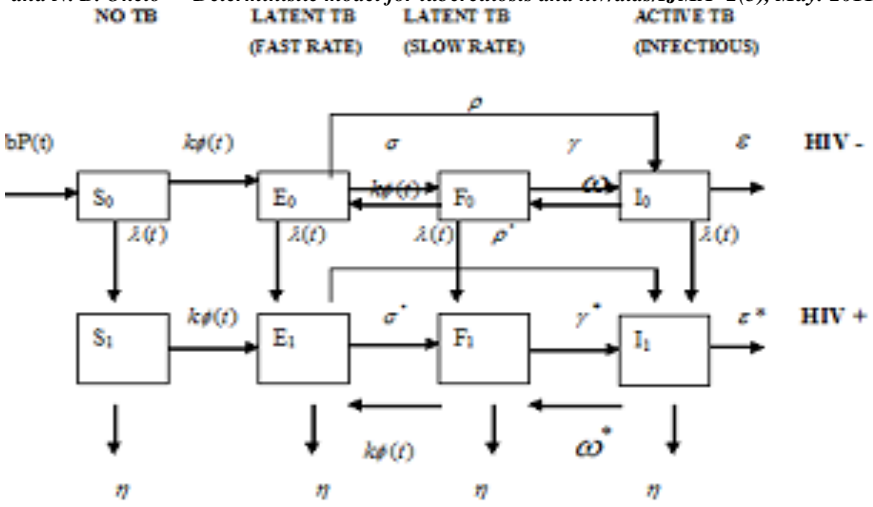

Figure 1.1: Compartmental age-structured model for HIV and TB with natural mortality μ in every compartment.

The absence of birth inflows into the S_0 compartment is due to our assumption that mother-to-child transmission of HIV is neglected. People who get infected by M.Tuberculosis move from an S-compartment to an E-compartment where they have a relatively high risk of progressing to active infectious TB (disease stage). If After a few years they haven't developed the disease, then they move to compartment F where progression to the active infectious disease is still possible but at a slow rate. But a re-infection may bring them back to the E-compartment. Successfully treated or naturally recovered people return from compartment I to the low risk compartment F. People who get infected by HIV move from a compartment with subscript 0 to the corresponding compartment with subscript 1 (HIV stage).

Where $P = S_0 + S_1 + E_0 + E_1 + F_0 + F_1 + I_0 + I_1$

Model equation for TB/HIV

$$\begin{aligned}
&\frac{\partial S_0}{\partial t}+\frac{\partial S_0}{\partial a}=bP(t)-\left(\mu(a)+k\phi(t)+\lambda(t,)\right)S_0(t,a)\\
&\frac{\partial E_0}{\partial t}+\frac{\partial E_0}{\partial a}=-\left(\mu(a)+\rho+\sigma+\lambda(t)\right)E_0(t,a)+k\phi(t)\left(S_0(t,a)+F_0(t,a)\right)\\
&\frac{\partial F_0}{\partial t}+\frac{\partial F_0}{\partial a}=-\left(\mu(a)+\gamma+k\phi(t)+\lambda(t)\right)F_0(t,a)+\sigma E_0(t,a)+\omega I_0(t,a)\\
&\frac{\partial I_0}{\partial t}+\frac{\partial I_0}{\partial a}=-\left(\mu(a)+\omega+\varepsilon+\lambda(t)\right)I_0(t,a)+\rho E_0(t,a)+\gamma F_0(t,a)
\end{aligned} \tag{1.6}$$

Model equation for TB/HIV+

$$\begin{aligned}
&\frac{\partial S_1}{\partial t}+\frac{\partial S_1}{\partial a}=-\left(\mu(a)+k\phi(t)+\eta\right)S_1(t,a)+\lambda(t)S_0(t,a)\\
&\frac{\partial E_1}{\partial t}+\frac{\partial E_1}{\partial a}=-\left(\mu(a)+\rho^*+\sigma^*+\eta\right)E_1(t,a)+k\phi(t)\left(S_1(t,a)+F_1(t,a)\right)+\lambda(t)E_0(t,a)\\
&\frac{\partial F_1}{\partial t}+\frac{\partial F_1}{\partial a}=-\left(\mu(a)+\gamma^*+k\phi(t)+\eta\right)F_1(t,a)+\sigma^*E_1(t,a)+\omega^*I_1(t,a)+\lambda(t)F_0(t,a)\\
&\frac{\partial I_1}{\partial t}+\frac{\partial I_1}{\partial a}=-\left(\mu(a)+\omega^*+\varepsilon+\eta\right)I_1(t,a)+\rho^*E_1(t,a)+\gamma^*F_1(t,a)+\lambda(t)I_0(t,a)
\end{aligned} \tag{1.7}$$

4. MODEL EQUATIONS DESCRIPTION:

We briefly discuss an intuitive interpretation of the first-four model equations (1.6). Since they are all age-structured models, the descriptions will be similar for the other equations (1.7). The first equation implies that $S_0(t, a)$ (which represents the number of susceptible individuals, of age a, at time t) at a given point in time may change with age

$\frac{\partial S_0}{\partial a}$ and likewise the number at a given age may change over time $\frac{\partial S_0}{\partial t}$, as susceptibles are recruited at the rate bP(t) and as susceptibles are lost by natural death at a rate μ(a) or as they transferred to the latent TB class, $E_0(t, a)$ at a rate $k\phi(t)$ or as they are transferred to HIV+ class at the rate $\lambda(t)$. The left-hand side of the other three equations will follow the same explanation as the first, so we will rather explain the right-hand side. The second equation means that the $E_0(t, a)$ population are lost by natural mortality of rate μ(a) or as they are transferred to the $F_0(t, a)$ and $I_0(t, a)$ classes at the rates σ and ρ respectively and as they are transferred to E_1 at the rate $\lambda(t)$. $E_0(t, a)$ increases their population through the outflows from the $S_0(t, a)$ and $F_0(t, a)$ compartments with the equal rates as $k\phi(t)$ as shown in the model diagram. The rest of the equations will follow the same explanation.

We are neglecting here both mother-to-child transmission of HIV and the impact of HIV/TB on the number of births.

5. RESULTS AND DISCUSSION:

According to Hughes and others (2006), progression to active TB is said to be rapid if it occurs within 5 years after infection. According to the same paper, the proportion of HIV-negative people or early HIV-positive people who develop active TB within these five years is 0.14. After that, the progression is slow which 0.001/year is. In addition, the proportion of people in their late stage of HIV who develop Active TB within 5 year is 0.67, after that the progression rate is slow, 0.1/year. According to Cohen, T et al, 2006, in 2.5 above, the rate of movement from latent TB fast rate to latent TB slow rate is 0.2. We assume that this rate is the same for both HIV-infected and HIV-uninfected i.e. $\sigma = \sigma^* = 0.2$/year. With this information, we evaluate the following parameters ρ and ρ^* as follows. We translate this information within the model by equations;

$$\frac{\rho}{\rho+\sigma} = \frac{14}{100} \tag{2.1}$$

$$\frac{\rho^*}{\rho^*+\sigma^*} = \frac{67}{100} \tag{2.2}$$

$\gamma = 0.001$/year and $\gamma^* = 0.1$/year. From equations 2.2 and 2.3, we obtain $\rho = 0.033$/year and $\rho^* = 0.41$/year.

The reason why $\rho^* > \rho$ is due to the fact that, people who are HIV positive develop TB at a faster rate than those who are HIV-negative.

6. CONCLUSIONS:

Our findings are consistent with reality that those with HIV develop TB at a faster rate of 0.41/year compared to the rate 0.033/year for those who are HIV negative.

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