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DETERMINATION OF TB INDUCED DEATH RATE FOR HIV + AND HIV- PEOPLE

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ABSTRACT

In this study, TB induced death rate for HIV positive and HIV negative individuals has determined. We have also examined TB progression among HIV+ as well as in HIV – people.

Keywords: *Case fatality rate (c.f.r), Latent TB, HIV Positives, HIV Negatives and Rate of Self - cure.*

1. INTRODUCTION:

The Human Immunodeficiency Virus (HIV) epidemic in Kenya constitutes the most serious health problem and one that we do not fully understand. What makes the matter even more complex is the interaction with the parallel tuberculosis (TB) epidemic which affects both HIV-positive and HIV-negative people. TB and HIV are the leading causes of death from infectious diseases among adults globally and the number of TB cases has risen significantly since the start of the HIV epidemic, particularly in Sub-Saharan Africa where the HIV epidemic is most severe (Stephen D. Lawn, 2006). The World Health Organization (WHO) TB-control strategy, which is based on the directly observed treatment, short course (DOTS) strategy, has failed to contain the TB epidemic in Africa, largely due to the effects of the HIV epidemic in the region (Stephen D. Lawn, 2006).

Tuberculosis (TB) is a bacterial infection of the lungs (pulmonary tuberculosis) caused by bacterium Mycobacterium tuberculosis. It can also affect the central nervous system, the lymphatic system, the brain, spine and the kidneys. Only people who have pulmonary TB are infectious.

One-third of the world's population is currently infected with the TB bacillus and new infections are occurring at a rate of one per second (WHO, 2007).

Tuberculosis has a vaccine called BCG. Children are vaccinated with BCG at an early age. This has the effect of introducing the bacteria into the system making the child a latent slow rate case.

EXPOSURE TO TUBERCLE BACILLI:

Exposure is defined as a contact between two individuals in sufficient proximity to allow conversation between them, or, within confined spaces, where the air exchange (ventilation) of the space has been incomplete between the visits of the two people (Hans .L.R, 1999).

There are three major factors that determine the risk of becoming exposed to tubercle bacilli. They include:

(i) The number of incident infectious cases in the community,

(ii) The duration of infectiousness, and

(iii) The number and nature of interactions between a case and a susceptible contact per unit of time of infectiousness (Hans. L. R, 1999).

TB spreads from person to person through the air as a person with active tuberculosis coughs, sneezes, speaks, spits, kisses. Note that not everyone infected with Mycobacterium tuberculosis becomes sick. After a person becomes infected, the tuberculosis bacteria are controlled by the person's immune system. When this happens, the person moves

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from latent fast rate to latent slow rate. When the bacteria spread out of control, the infection becomes active. A person can have active or latent (inactive) TB. Both active and latent TB fast rate are treatable and curable. Active TB means the bacteria are active in the body and they weaken the immune system, making it impossible to stop them from causing illness. Only people with active TB can spread the disease. People with latent TB do not feel sick and do not have any symptoms.

In some people, Mycobacterium tuberculosis remains inactive for a lifetime without becoming active while others are likely to develop active TB if their immune system is compromised by some deadly disease such as HIV. The early symptoms of active tuberculosis include: coughing up blood, weight loss, fever, loss of appetite, and also shortness of breath indicates an advanced stage of active tuberculosis.

TB PROGRESSION:

TB progression from latent infection to active disease varies greatly. For instance, people with AIDS are more likely to develop active TB after infection. A patient with AIDS who becomes infected with Mycobacterium tuberculosis has a 50% chance of developing active tuberculosis within 2 months and a 5 to 10% chance of developing active disease each year thereafter (WHO 2007). According to the World Health Organization (WHO 2007), infants and young children infected with Mycobacterium tuberculosis are also more likely to develop active TB than older people since their immune system is not yet well developed.

MDR-TB AND XDR-TB:

Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis that is resistant to at least isoniazid and rifampicin, the two most powerful first-line anti-TB drugs. The World Health Organization (WHO) defines extensively drug resistant TB (XDR-TB) as MDR-TB plus resistance to any fluoroquinolone and at least 1 of 3 injectable second-line drugs capreomycin, kanamycin and alizarin. People who have active TB usually develop MDR-TB or XDR-TB when they fail to fulfill their prescription of TB medicine as ordered by the Doctor. MDR-TB is dangerous and very difficult to treat. The most important factor in preventing drug resistant TB is to ensure full compliance with anti-TB treatment. As recommended by the WHO, directly observed therapy (DOT) is an effective treatment measure.Anyone can get TB, but some people are highly susceptible. Those that are at high risk include: people with HIV, people in close contact with infectious individuals, people who are malnourished, health care workers, prison guards, alcoholics, intravenous drug users and the homeless.

TB SKIN TEST AND TREATMENT:

The tuberculin skin testing is the major method of diagnosing the tuberculosis infection. When the test result is positive it implies there is tubercle bacilli. It is normally used to distinguish infected individual from the exposed individual without infection. The infected individuals will then be put on the DOT strategy in order to reduce infections and also treat the disease. An active TB patient can be treated by a combination of anti-tuberculosis therapies such as the ones mentioned in subsection 1.1.3 above. Latent TB fast rate can be treated with isoniazid. The treatment is very effective provided the patients take it for at least six months as prescribed.

HIV/AIDS:

AIDS is a life threatening disease caused by HIV which is a sexually transmitted disease. One can become infected with the virus through unprotected sex and sharing of hypodermic needles as well as through blood transfusion. The virus is not transmitted through saliva, spit, sweat, tears, air or insects. HIV in humans is now pandemic. As of January 2006, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that AIDS had killed more than 25 million people since it was first recognized on December 1, 1981, making it one of the most destructive pandemics in recorded history. In 2005 alone, AIDS claimed an estimated 2.4 to 3.3 million lives, of which more than 570,000 were children. It is estimated that about 0.6% of the world's living population is infected with HIV. A third of these deaths are occurring in sub-Saharan Africa, retarding economic growth and increasing poverty.

STAGES OF HIV INFECTION:

Generally there are four stages of HIV infection. They are briefly described as follows;

Stage: 1 Primary HIV infection: The first stage of infection is extremely infectious. It normally lasts for a few weeks and is often accompanied by a short flu-like illness

Stage: 2 Asymptomatic stage: This stage lasts for an average of ten years and the infected person does not show any symptoms of the disease

Stage: 3 Symptomatic HIV infection: This is the stage where a lot of symptoms (diarrhoea, heavy weight loss, fever, cough and shortness of breath) begin to manifest because the immune system is severely damaged by the virus. It is at this stage that pulmonary TB manifests itself.

Stage: 4 Progression from HIV to AIDS: The final stage occurs when the immune system is extremely weakened. As a result, certain infections called "opportunistic" (infections which cannot attack people with a healthy immune system) take the opportunity to infect the HIV-patients. This is where the patients develop full blown AIDS.

HOW TB AND HIV AFFECT EACH OTHER:

Each disease acts as a catalyst in the progression of the other. TB significantly reduces the survival time for people with HIV/AIDS. HIV infection is the largest risk factor for the progression of inactive TB to active TB, and Mycobacterium tuberculosis can speed up the progression of HIV. It is clear that each of these diseases can have a profound impact on the other. First, there is an increasing interaction between those individuals at high risk for TB and those at high risk for HIV: Second, TB is the most common HIV-related complication world-wide (Narain et al., 1992). Third, HIV infected individuals are not only at a greater risk for acquiring TB, but reactivation of latent TB infection is greatly increased due to the fact that the very cells that hold the latent TB in check (the CD4+ T lymphocytes) are precisely the cells that are rendered dysfunctional in HIV-infected individuals (Bryt et al., 1994).

Fourth, TB decreases the number of CD4+ T cells thereby interfering with the best predictor of AIDS survivability (Bryt et al., 1994). This is important, because the CD4+ T cells are the cells that not only become infected with HIV, but orchestrate the immune response against both TB and HIV, as well as other pathogens.

2. MATERIALS AND METHODS/DEFINITIONS AND PRELIMINARIES:

In this section we present an overview of the Mackendrick-Von Foster equation, which we will apply in formulation of the model equations. We hence develop our models for TB in the presence of HIV as well as for TB in the absence of HIV and give an explanation of the model.

Population Model with Age Structure, Time dependent

This is the type of structured population model whereby the birth and death rate depend on both age and time. This occurs, when the environment changes over time. The model is often called Mackendrick-Von Foster equation. It is a first order partial differential given by

$$\frac{\partial n(a,t)}{\partial t} = -\frac{\partial n(a,t)}{\partial a} - \mu(a,t)n(a,t) \qquad a,t \geq 0 \tag{3.1}$$

where n(a,t) is the age distribution of the population at time t and $\mu(a,t)$ is the age and time dependant natural mortality rate.

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.

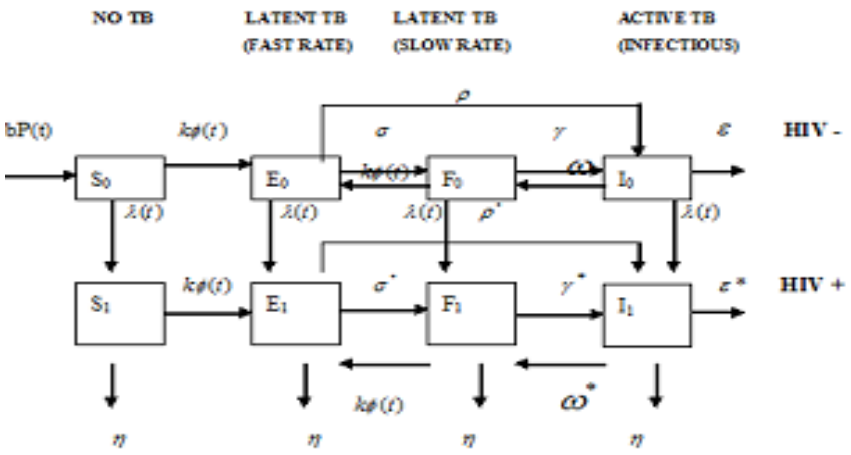

Figure 1.1: Compartmental age-structured model for HIV and TB with natural mortality μ in every compartment.

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

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

Model equation for TB/HIV+

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

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.

3. RESULTS AND DISCUSSION:

According to Corbett et al (2006), the duration of illness for untreated TB is 2.0 years if HIV-negative and 1 year if HIV-positive. The average fatality rates for HIV-negative and HIV-positive people are 43% and 78% respectively. We assume that TB can be ended by either death or self cure in the absence of treatment.

Let i be the duration of untreated TB i.e. $i=\frac{1}{r+\varepsilon}$,

then the proportion of TB patients who die from TB for HIV negative individuals i.e. case fatality rate (cfr) is given by $\frac{\varepsilon}{r+\varepsilon}$

Where r refers to the rate of self cure in for TB in HIV negative individuals, r^* is the rate of self cure in HIV positive individuals, ε is the death rate from TB in HIV negative people and ε^* represent TB death rate in HIV positive people.

This is translated within the model to obtain the following equations:

$$\frac{1}{r+\varepsilon}=2.0 \text{ Years},$$
$$\frac{\varepsilon}{r+\varepsilon}=\frac{43}{100}$$
$$\frac{1}{r^*+\varepsilon^*}=1 \text{ Year},$$
$$\frac{\varepsilon^*}{r^*+\varepsilon^*}=\frac{78}{100}$$

Solving we obtain r = 0.29, ε = 0.22, r^* = 0.22 and ε^* = 0.78.

4. CONCLUSIONS:

We have obtained in section 3.1 above the rates of self cure for TB in HIV negative and positive individuals as $r = 0.29 > r^{*} = 0.22$. The rate of self cure for TB in HIV negative individuals is higher than the rate in HIV positive individuals. This is so because People living with HIV/AIDS have their immune system compromised such that they cannot effectively fight the disease.

TB induced death rate among HIV – population (ε) = 0.22 while TB induced death rate among HIV+ population (ε^{*}) = 0.78. We observe that the rate is higher for the HIV + population due to the fact that HIV/AIDS seriously compromise their immune system such that they cannot effectively fight the bacterium.

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