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A Mathematical Model of Effect of Bacillus Calmette-Guerin Vaccine and Isoniazid Preventive Therapy in Controling the Spread of Tuberculosis in Nigeria

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Abstract: In this study, we modelled the effect of combining Immunization with latent tuberculosis treatment in controlling the spread of tuberculosis. The administration of BCG vaccines administered at birth protects children from early infection of the disease but the effect of these vaccines expires with time. Hence, detection and treatment of latent tuberculosis infections by administering isoniazid preventive therapy prevents the break down of latent infections into infectious cases this however, reduces greatly the rate of spread of the disease since, only members of the Infectious class can spread the disease to others. We established the existence of equilibrium states and analyse the disease free equilibrium state for stability using Routh-Hurwitz theorem. The disease free equilibrium state (i.e., the state of total eradication of tuberculosis) will be stable if effort is intensified in bringing down both the contraction rate β and the rate of break down to infectious tuberculosis τ.

Key words: BCG vaccines, latent TB treatment, equilibrium state, stability, administration, preventive therapy

INTRODUCTION

Tuberculosis progression from latent infection to active disease varies greatly. For instance, people with AIDS are more likely to develop to 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 5-10% chance of developing active disease each year thereafter. According to the World Health Organization (WHO), infants and young children infected with Mycobacterium tuberculosis are also more likely to develop active TB than older people since, their immune system are not yet well developed (Okyere, 2007).

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 (Dye, 2006).

Bacillus Calmette-Guerin (or Bacille Calmette-Guérin, BCG) is a vaccine against tuberculosis that is prepared from a strain of the attenuated (weakened) live bovine tuberculosis bacillus, *Mycobacterium bovis* that has lost its virulence in humans by being specially cultured in an artificial medium for years. The bacilli have retained enough strong antigenicity to become a somewhat effective vaccine for the prevention of human tuberculosis. At best, the BCG vaccine is 80% effective in preventing tuberculosis for duration of 15 years however, it is protective effect appears to vary according to geography (Colditz *et al*., 1994).

Mathematical models have played a key role in the formulation of TB control strategies and the establishment of interim goals for intervention programs. Most of these models are of the SEIR class in which the host population is categorized by infection status as susceptible, exposed (infected but not yet infectious), infectious and recovered. One of the principle attributes of these models is that the force of infection (the rate at which susceptibles leave the susceptible class and move into an infected category, i.e., become infected) is a function of the number of infectious hosts in the population at any time t and is thus, a nonlinear term. Other transitions such as the recovery of infectious individuals and death are modelled as linear terms with constant coefficients.

The co-pandemic nature of TB-HIV calls for more quantitative research on TB particularly because it has cure unlike HIV. It should then be no surprise that mathematical models and data mining techniques are now been deployed in the study of the disease epidemiology and the evaluation of some of the world TB control measures and strategy. Thus, if we are able to reduce (to barest minimum) the spread of TB via all the control measures and strategies, we will have succeeded in reducing the alarming TB death tools and increase the life expectancy of HIV patients by reducing their chances of

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contacting TB which may lead them to early grave. Tuberculosis (TB) and HIV are the leading causes of death from infectious diseases among adults (Corbett *et al*., 2003). Estimates for 2003 put the number of incident TB cases at 8.8 million up from an estimated 8.3 million in 2000 with HIV being the main driving force (WHO, 2003).

MATERIALS AND MEHODS

Model description: The population is partitioned into 5 compartments, immunized, susceptible, latent, infectious and recovered compartments. The immunized compartment changes due to the coming in of the immunized children into the population where we assumed that a proportion $\theta\rho$ of the incoming individuals are immunized against infection. This compartment reduces due to expiration of duration of vaccine efficacy at the rate α and also by natural death at the rate μ.

The susceptible population increases due to the coming of new births not immunized against infection into the population at the rate $(1 - \theta)\rho$ and the expiration of the efficacy of the vaccine at the rate α. The susceptible population also diminishes due to natural death at rate μ and infection with an incident rate of infection β. The population dynamic of the Latent class grows with the instantaneous incidence rate of infection β. This class also reduces by natural death rate μ, successful cure of infectious Latent TB patients at the rate σ and occasional break down of latent TB into infectious TB.

In the same way, the population dynamic of the infectious class grows with the occasional break down of latent TB into infectious TB. This class also reduces by natural death rate μ and successful cure of infectious TB patients at the rate γ and death caused as result of chronic TB infection at the rate δ. Lastly, the dynamics of the recovered class increases with successful cure of latent TB patients at the rate σ and that of infectious TB patients at the rate γ and decreases by natural death rate μ.

Model diagram: Schematic presentation of model three is shown in Fig. 1.

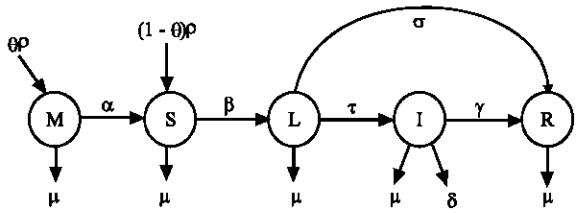

Fig. 1: Schematic presentation of model 3

Model equation:

$$\frac{dM}{dt} = \theta\rho - (\alpha + \mu)M \tag{1}$$

$$\frac{dS}{dt} = (1-\theta)\rho + \alpha M - \beta SI - \mu S \tag{2}$$

$$\frac{dL}{dt} = \beta SI - (\sigma + \tau + \mu)L \tag{3}$$

$$\frac{dI}{dt} = \tau L - (\gamma + \mu + \delta)I \tag{4}$$

$$\frac{dR}{dt} = \sigma L + \gamma I - \mu R \tag{5}$$

Equilibrium solutions: We now solve the model equations to obtain the equilibrium states as by Sirajo (2009). At the equilibrium state:

$$\frac{dM}{dt} = \frac{dS}{dt} = \frac{dL}{dt} = \frac{dI}{dt} = \frac{dR}{dt} = 0$$

Let:

$M(t) = v$, $S(t) = w$, $L(t) = x$, $I(t) = y$ and $R(t) = z$

Then the system of equations become:

$$\theta\rho - (\alpha + \mu)v = 0 \tag{6}$$

$$(1-\theta)\rho + \alpha v - w(\beta y + \mu) = 0 \tag{7}$$

$$\beta wy - (\sigma + \tau + \mu)x = 0 \tag{8}$$

$$\tau x - (\gamma + \mu + \delta)y = 0 \tag{9}$$

$$\sigma x + \gamma y - \mu z = 0 \tag{10}$$

The disease free equilibrium state. From Eq. 6:

$$\theta\rho - (\alpha + \mu)v = 0$$
$$v = \frac{\theta\rho}{(\alpha + \mu)} \tag{11}$$

From Eq. 9:

$$\tau x - (\gamma + \mu + \delta)y = 0$$
$$x = \frac{(\gamma + \mu + \delta)y}{\tau} \tag{12}$$

Substituting Eq. 12 for x in Eq. 8 gives:

$$\beta wy - (\sigma + \tau + \mu)\left[\frac{(\gamma + \mu + \delta)y}{\tau}\right] = 0$$

Either:

$$y = 0 \tag{13}$$

or:

$$\beta w - \frac{(\sigma + \tau + \mu)(\gamma + \mu + \delta)}{\tau} = 0 \tag{14}$$

Substituting Eq. 11 and Eq. 13 for v and y in Eq. 7 gives:

$$\begin{aligned}(1-\theta)\rho + \alpha\left[\frac{\theta\rho}{(\alpha+\mu)}\right] - w\mu = 0\\ w = \frac{\rho(\alpha + \mu - \theta\mu)}{\mu(\alpha+\mu)}\end{aligned} \tag{15}$$

Substituting Eq. 13 for y in Eq. 9 gives:

$$\tau x = 0$$

Hence:

$$x = 0 \tag{16}$$

Substituting Eq. 16 and 13 for x and y in Eq. 10 gives:

$$-\mu z = 0 \Rightarrow z = 0$$

Hence, the disease free equilibrium state is:

$$(v,w,x,y,z) = \left(\frac{\theta\rho}{(\alpha+\mu)}, \frac{(\alpha+\mu)(1-\theta)\rho + \alpha\theta\rho}{\mu(\alpha+\mu)}\, 0,0,0\right)$$

The endemic equilibrium state: From Eq. 14:

$$\Rightarrow \beta w - \frac{(\sigma + \tau + \mu)(\gamma + \mu + \delta)}{\tau} = 0$$

Hence:

$$w = \frac{(\sigma + \tau + \mu)(\gamma + \mu + \delta)}{\beta\tau} \tag{17}$$

Substituting Eq. 17 for w in Eq. 8 gives:

$$\begin{aligned}\beta\left[\frac{(\sigma+\tau+\mu)(\gamma+\mu+\delta)}{\beta\tau}\right]y - (\sigma+\tau+\mu)x = 0\\ x = \frac{(\gamma+\mu+\delta)y}{\tau}\end{aligned} \tag{18}$$

Substituting Eq. 18 for x in Eq. 10 gives:

$$\begin{aligned}\sigma\left[\frac{(\gamma+\mu+\delta)y}{\tau}\right] + \gamma y - \mu z = 0\\ z = \frac{[\sigma(\gamma+\mu+\delta) + \tau\gamma]y}{\mu\tau}\end{aligned} \tag{19}$$

Next, we add Eq. 6 and 7:

$$\begin{aligned}\theta\rho - (\alpha+\mu)v + (1-\theta)\rho + \alpha v - w(\beta y + \mu) = 0\\ \rho - \mu v - w\beta y - \mu w = 0\end{aligned} \tag{20}$$

Adding Eq. 20 in 8 give:

$$\rho - \mu v - (\sigma + \tau + \mu)x - \mu w = 0 \tag{21}$$

Adding Eq. 21 in 9 give:

$$\begin{aligned}\rho - \mu v - (\sigma+\tau+\mu)x - \mu w + \tau x - (\gamma+\mu+\delta)y = 0\\ \rho - \mu v - (\sigma+\mu)x - \mu w - (\gamma+\mu+\delta)y = 0\end{aligned} \tag{22}$$

Adding Eq. 22 in 10 give:

$$\begin{aligned}\rho - \mu v - (\sigma+\mu)x - \mu w -\\ (\gamma+\mu+\delta)y + \sigma x + \gamma y - \mu z = 0\\ \rho - \mu v - \mu w - \mu x - (\mu+\delta)y - \mu z = 0\end{aligned} \tag{23}$$

Next, we substitute Eq. 11, 17 18 and 19 for v, w, x and y in Eq. 23:

$$\begin{aligned}\rho - \mu\left[\frac{\theta\rho}{(\alpha+\mu)}\right] - \mu\left[\frac{(\sigma+\tau+\mu)(\gamma+\mu+\delta)}{\beta\tau}\right] -\\ \mu\left[\frac{(\gamma+\mu+\delta)y}{\tau}\right] - (\mu+\delta)y - \mu\left[\frac{[\sigma(\gamma+\mu+\delta)+\tau\gamma]y}{\mu\tau}\right] = 0\\ y = \frac{[\rho\beta\tau(\alpha+\mu) - \beta\tau\mu\theta\rho - \mu(\alpha+\mu)(\sigma+\tau+\mu)(\gamma+\mu+\delta)]\tau}{\beta\tau(\alpha+\mu)[\mu(\gamma+\mu+\delta) + \tau(\mu+\delta) + [\sigma(\gamma+\mu+\delta)+\tau\gamma]]}\end{aligned} \tag{24}$$

Substituting Eq. 24 for y in Eq. 18 and Eq. 19 give:

$$x = \frac{\left[\begin{matrix}\rho\beta\tau(\alpha+\mu) - \beta\tau\mu\theta\rho - \mu\\ (\alpha+\mu)(\sigma+\tau+\mu)(\gamma+\mu+\delta)\end{matrix}\right](\gamma+\mu+\delta)}{\beta\tau(\alpha+\mu)\left[\begin{matrix}\mu(\gamma+\mu+\delta) + \tau(\mu+\delta) +\\ [\sigma(\gamma+\mu+\delta)+\tau\gamma]\end{matrix}\right]} \tag{25}$$

and:

$$z = \frac{\left[\begin{matrix}\rho\beta\tau(\alpha+\mu) - \beta\tau\mu\theta\rho - \mu(\alpha+\mu)\\ (\sigma+\tau+\mu)(\gamma+\mu+\delta)\end{matrix}\right][\sigma(\gamma+\mu+\delta)+\tau\gamma]}{\mu\beta\tau(\alpha+\mu)\left[\begin{matrix}\mu(\gamma+\mu+\delta) + \tau(\mu+\delta) +\\ [\sigma(\gamma+\mu+\delta)+\tau\gamma]\end{matrix}\right]} \tag{26}$$

Hence, the endemic equilibrium state is given by:

$$v = \frac{\theta\rho}{(\alpha+\mu)}, \quad w = \frac{(\sigma+\tau+\mu)(\gamma+\mu+\delta)}{\beta\tau}$$

$$x = \frac{\left[\begin{matrix}\rho\beta\tau(\alpha+\mu)-\beta\tau\mu\theta\rho-\mu(\alpha+\\ \mu)(\sigma+\tau+\mu)(\gamma+\mu+\delta)\end{matrix}\right](\gamma+\mu+\delta)}{\beta\tau(\alpha+\mu)\left[\begin{matrix}\mu(\gamma+\mu+\delta)+\tau(\mu+\\ \delta)+\left[\sigma(\gamma+\mu+\delta)+\tau\gamma\right]\end{matrix}\right]}$$

$$y = \frac{\left[\begin{matrix}\rho\beta\tau(\alpha+\mu)-\beta\tau\mu\theta\rho-\mu(\alpha+\\ \mu)(\sigma+\tau+\mu)(\gamma+\mu+\delta)\end{matrix}\right]\tau}{\beta\tau(\alpha+\mu)\left[\begin{matrix}\mu(\gamma+\mu+\delta)+\tau(\mu+\\ \delta)+\left[\sigma(\gamma+\mu+\delta)+\tau\gamma\right]\end{matrix}\right]}$$

$$z = \frac{\left[\begin{matrix}\rho\beta\tau(\alpha+\mu)-\beta\tau\mu\theta\rho-\mu(\alpha+\\ \mu)(\sigma+\tau+\mu)(\gamma+\mu+\delta)\end{matrix}\right]\left[\sigma(\gamma+\mu+\delta)+\tau\gamma\right]}{\mu\beta\tau(\alpha+\mu)\left[\begin{matrix}\mu(\gamma+\mu+\delta)+\tau(\mu+\\ \delta)+\left[\sigma(\gamma+\mu+\delta)+\tau\gamma\right]\end{matrix}\right]}$$

Having established the equilibrium states. We now investigate the stability of the equilibrium states. To obtain this, we examine the behaviour of the model population near the equilibrium states.

RESULTS AND DUSCUSSION

Stability analysis of disease free equilibrium state

The characteristic equation: Recall that the system of equations in this model at equilibrium state is:

$$\begin{aligned}
&\theta\rho-(\alpha+\mu)v=0\\
&(1-\theta)\rho+\alpha v-w(\beta y+\mu)=0\\
&\beta wy-(\sigma+\tau+\mu)x=0\\
&\tau x-(\gamma+\mu+\delta)y=0\\
&\sigma x+\gamma y-\mu z=0
\end{aligned}$$

The Jacobian matrix of this system of equations is given by:

$$J_3=\begin{pmatrix}
-(\alpha+\mu) & 0 & 0 & 0 & 0\\
\alpha & -(\beta y+\mu) & 0 & -\beta w & 0\\
0 & \beta y & -(\sigma+\tau+\mu) & \beta w & 0\\
0 & 0 & \tau & -(\gamma+\mu+\delta) & 0\\
0 & 0 & \sigma & \gamma & -\mu
\end{pmatrix}$$

The characteristic equation is obtained from the Jacobian determinant with the eigenvalue λ:

$$\det(J_3-\lambda I)=\det\begin{pmatrix}
-(\alpha+\mu+\lambda) & 0 & 0 & 0 & 0\\
\alpha & -(\beta y+\mu+\lambda) & 0 & -\beta w & 0\\
0 & \beta y & -(\sigma+\tau+\mu+\lambda) & \beta w & 0\\
0 & 0 & \tau & -(\gamma+\mu+\delta+\lambda) & 0\\
0 & 0 & \sigma & \gamma & -(\mu+\lambda)
\end{pmatrix}=0$$

$$-(\alpha+\mu+\lambda)\begin{vmatrix}
-(\beta y+\mu+\lambda) & 0 & -\beta w & 0\\
\beta y & -(\sigma+\tau+\mu+\lambda) & \beta w & 0\\
0 & \tau & -(\gamma+\mu+\delta+\lambda) & 0\\
0 & \sigma & \gamma & -(\mu+\lambda)
\end{vmatrix}=0 \tag{27}$$

At the disease free equilibrium state:

$$(v,w,x,y,z)=\left(\frac{\theta\rho}{(\alpha+\mu)},\frac{(\alpha+\mu)(1-\theta)\rho+\alpha\theta\rho}{\mu(\alpha+\mu)},0,0,0\right)$$

Hence, substituting 0 for y in Eq. 27 give:

$$-(\alpha+\mu+\lambda)\begin{vmatrix}
-(\mu+\lambda) & 0 & -\beta w & 0\\
0 & -(\sigma+\tau+\mu+\lambda) & \beta w & 0\\
0 & \tau & -(\gamma+\mu+\delta+\lambda) & 0\\
0 & \sigma & \gamma & -(\mu+\lambda)
\end{vmatrix}=0$$

$$\Rightarrow(\alpha+\mu+\lambda)(\mu+\lambda)\begin{vmatrix}
-(\sigma+\tau+\mu+\lambda) & \beta w & 0\\
\tau & -(\gamma+\mu+\delta+\lambda) & 0\\
\sigma & \gamma & -(\mu+\lambda)
\end{vmatrix}=0$$

Hence:

$$\begin{aligned}
&(\alpha+\mu+\lambda)(\mu+\lambda)\{-(\sigma+\tau+\mu+\lambda)(\gamma+\mu+\\
&\delta+\lambda)(\mu+\lambda)+\beta w\tau(\mu+\lambda)\}=0\\
&(\alpha+\mu+\lambda)(\mu+\lambda)^2\{-(\sigma+\tau+\mu+\lambda)(\gamma+\mu+\\
&\delta+\lambda)+\beta w\tau\}=0\\
&(\alpha+\mu+\lambda)(\mu+\lambda)^2\{(\sigma+\tau+\mu+\lambda)(\gamma+\mu+\\
&\delta+\lambda)-\beta w\tau\}=0\\
&(\alpha+\mu+\lambda)(\mu+\lambda)^2\det\\
&\begin{pmatrix}-(\sigma+\tau+\mu+\lambda) & \beta w\\ \tau & -(\gamma+\mu+\delta+\lambda)\end{pmatrix}=0
\end{aligned} \tag{28}$$

From Eq. 28 either:

$$(\alpha+\mu+\lambda)(\mu+\lambda)^2=0 \tag{29}$$

Or:

$$\det\begin{pmatrix}-(\sigma+\tau+\mu+\lambda) & \beta w\\ \tau & -(\gamma+\mu+\delta+\lambda)\end{pmatrix}=0 \tag{30}$$

From Eq. 29:

$$\lambda_1=\lambda_2=-\mu$$

And:

$$\lambda_3=-(\alpha+\mu)$$

To determine the nature of eigen values in Eq. 30, we present the Routh-Hurwitz necessary and sufficient conditions for all roots of the characteristic polynomial to have negative parts thus, implying asymptotic stability as applied by Ssematimba *et al.* (2005) and Benyah (2008). Since:

$$(v,w,x,y,z)=\left(\frac{\theta\rho}{(\alpha+\mu)},\frac{(\alpha+\mu)(1-\theta)\rho+\alpha\theta\rho}{\mu(\alpha+\mu)}0,0,0\right)$$

At the disease free equilibrium state, we now substitute:

$$\frac{(\alpha+\mu)(1-\theta)\rho+\alpha\theta\rho}{\mu(\alpha+\mu)}$$

For w in Eq. 30 to obtain:

$$\det\begin{pmatrix}-(\sigma+\tau+\mu+\lambda) & \frac{\beta[(\alpha+\mu)(1-\theta)\rho+\alpha\theta\rho]}{\mu(\alpha+\mu)}\\ \tau & -(\gamma+\mu+\delta+\lambda)\end{pmatrix}=0 \quad (31)$$

$$\text{Let } A=\begin{pmatrix}-(\sigma+\tau+\mu) & \frac{\beta[(\alpha+\mu)(1-\theta)\rho+\alpha\theta\rho]}{\mu(\alpha+\mu)}\\ \tau & -(\gamma+\mu+\delta)\end{pmatrix}$$

Then from matrix A, we have:

$$\text{dot}\,A=(\sigma+\tau+\mu)(\gamma+\mu+\delta)-\tau\beta\left[\frac{[(\alpha+\mu)(1-\theta)\rho+\alpha\theta\rho]}{\mu(\alpha+\mu)}\right]$$

And trace:

$$A=-(\sigma+\tau+\mu)-(\gamma+\mu+\delta)$$

Clearly trace (A)<0 since, all the parameters are positive. For the determinant of A to be >0, we should have:

$$(\sigma+\tau+\mu)(\gamma+\mu+\delta)-\tau\beta\left[\frac{[(\alpha+\mu)(1-\theta)\rho+\alpha\theta\rho]}{\mu(\alpha+\mu)}\right]>0$$

$$(\sigma+\tau+\mu)(\gamma+\mu+\delta)>\tau\beta\left[\frac{[(\alpha+\mu)(1-\theta)\rho+\alpha\theta\rho]}{\mu(\alpha+\mu)}\right]$$

From the stability analysis, the first 3 eigen values are all negative. We then established the necessary and sufficient conditions for all the roots of Eq. 30 to be negative using the Routh-Hurwitz theorem. The condition for the disease free equilibrium state to be stable is that:

$$(\sigma+\tau+\mu)(\gamma+\mu+\delta)>\tau\beta\left[\frac{[(\alpha+\mu)(1-\theta)\rho+\alpha\theta\rho]}{\mu(\alpha+\mu)}\right]$$

which implies that the product of total contraction and total break down of Latent class should be less than the total removal rate from both Latent and Infectious classes.

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