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Modeling the Dynamics of Tuberculosis Transmission in Children and Adults

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Abstract: Problem statement: The fight Against Tuberculosis (TB) has mainly focused on the adult population because children were perceived to pose a very low risk in TB transmission. This assumption ignores the potential risk children had as reservoirs of latent infections from which future cases evolve when they become adults. It was therefore important to investigate the dynamics of TB taking into consideration, children. **Approach:** We formulated a compartmental model for TB with two age classes, children and adults. Qualitative analysis of the model was done to investigate the stability of the model equilibria in terms of the model reproduction number R_0 Numerical simulations were also done to investigate the role played by some key epidemiological parameters in the dynamics of the disease. **Results:** The model had two equilibria: The disease free equilibrium which was globally stable for $R_0<1$ and the endemic equilibrium which was locally asymptotically stable for $R_0>1$, for R_0 near 1. The study showed increased latent infections in the adult population as a result of increased latently infected children who mature to adulthood with latent infections. **Conclusion/Recommendations:** Progression to active TB among adults is epidemiologically significant and interventions should focus on the adult population. Anti-tuberculosis, treatment of adults is crucial in controlling the epidemic and should interventions be proposed, they should target progression to active TB for those latently infected. The fight against TB should also take into consideration tuberculosis among children.

Key words: Tuberculosis (TB), pediatric tuberculosis, stability analysis, reproduction number, equilibria, latently infected

INTRODUCTION

Primary tuberculosis is the fountainhead of tuberculosis disease and when acquired during childhood, it may develop into serious tuberculosis disease within a short period of time or remain latent during childhood only to be reactivated in adulthood (Wood *et al*., 2010). Children usually progress to active disease within 12 months of primary infection because children have a high risk of progression to disease following infection (Brent *et al*., 2008; Sharomi *et al*., 2008). There has been limited interest in childhood tuberculosis because more than 95% of children with active disease are sputum smear negative and therefore not infectious. Infected children represent a pool from which a large proportion of future cases of adult TB will arise and thus perpetuating the TB epidemic (Bloch and Snider, 1985; Brent *et al*., 2008; Vynnycky *et al*., 2001). The burden of childhood tuberculosis is a clear indication of the TB severity in the adult population (Mairais *et al*., 2006; Warren *et al*., 2004). The contribution of children to TB caseload is not well documented in poor-resource settings with high disease burden, but research has shown that in high disease burdened areas, children less than 13 years of age, contribute about 13.7% of the total TB caseload in a particular community in South Africa (Murray and Salomon, 1998). The result compared well with that determined for low income countries for children less than 15 years of age, which was 15% (Schaaf *et al*., 2002). Children usually develop TB as a direct complication of the initial infection. Children with household or community exposure to TB are highly likely to be infected with the disease. Children acquire TB infection from an adult who is in their immediate environment (Schaaf *et al*., 2006; Wood *et al*., 2010).

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Lack of contagiousness is one of the reasons that public health programs on TB prevention have excluded children. They are regarded as the end of the transmission chain and therefore pose no threat to the evolution of the TB epidemic in the population. This view could have contributed significantly to early childhood TB.

Mathematical models for the dynamics of TB have been extensively developed and have been used in designing control programs and as predictive tools (Bhunu *et al*., 2008; Blower *et al*., 1995; Blower and Daley, 2002; Castillo-Chavez and Feng, 1997; Castillo-Chavez and Song, 2004; Gomes *et al*., 2004; Starke, 2003). Models that consider the potential impact of TB vaccines were studied in (Mairais *et al*., 2005). Recently, Bhunu *et al*. (2008) considered a model that studied the impact of treatment and chemoprophylaxis in combating TB.

Most of the studies reviewed concentrated on adult TB and ignored TB in children. It is upon this background that we propose a simple deterministic model for TB that incorporates children and adults, with the goal of investigating the dynamics of interaction of pediatric and adult TB epidemics. We develop a mathematical model with the object of quantifying the underlying factors that drive the epidemic in children.

This study aims to challenge public health policies regarding childhood TB. We endeavor to answer the following questions: What is the role of increased adult TB control on the growth of childhood TB? What is the proportion of adults that need to be targeted in order to control TB in children? To the best of our knowledge, there is a limited number of theoretical models of childhood TB.

MATERIALS AND METHODS

A two class age-structured model: The model considers a constant population N, subdivided into three different subgroups: susceptible (S) latently infected (L) and infected with active TB (I). Individuals move from one subgroup to the other as their status with respect to the disease changes. We again divide the population into two age classes, children and adults. Individuals below 5 years belong to the "children's" age class while those above 5 years belong to the "adult's" age-class. These age groups are separated primarily to distinguish between pediatric TB and adult TB. While the exact age demarcation is somewhat arbitrary, the main goal here is to divide the population into two reasonable age classes. Data from medical institutions also shows different phenomena in TB development for the two classes.

We use the following notation for individuals in the two age classes: we use the subscript c and a to represent children and adults respectively, so that S_c, LC, I_c and SA, L_a, I_a respectively represent susceptible, latently infected and infects with active TB in children and adults. The model is built on the following assumptions. All subgroups are subjected the natural mortality rateμ. The effective contact rate of infected adults is assumed to be higher with susceptible adults than children ($c_2 > c_1$). An effective contact is one that is sufficient to result in an infection if the contacted individual has never been infected (Walls and Shingadia, 2004). Susceptible children acquire TB infection from adults with active TB at a rate $B_1 = c_1\beta\frac{I_a}{N}$; while susceptible adults acquire TB infection from other adults with active TB at a rate $B_2 = c_2\beta\frac{I_a}{N}.\beta$ is the effective contact rate. The parameter c_2 accounts for the increased infectiousness among the adults due to several factors relating to mixing, bacteria propagation and environmental settings. A proportion p (q) of children (adults) develops active TB in the first year after primary infection and the remainder develops latent TB. Progression to active TB occurs at a rate $r_c(r_a)$ for children (adults). Recovery, naturally or with chemotherapy, results in an individual reverting back to the latent class at a rate σ_c (σ_a) for children (adults).

The rate at which children join the adult classes is given by f. However, infected children are assumed not to graduate into adulthood being infective. We acknowledge here that the consideration of being constant is merely for mathematical convenience. We shall assume that f is less than or equal to the birth rate.

Figure 1 depicts the interaction of the two age-classes.

The model is thus described by the following set of ordinary differential Eq. 1:

$$\begin{aligned}
\frac{dS_c}{dt} &= \mu N - c_1\beta S_c\frac{I_a}{N} - (\mu + f)S_c\\
\frac{dL_c}{dt} &= (1-p)c_1\beta S_c\frac{I_a}{N} + \sigma_c I_c - (\mu + r_c + f)L_c,\\
\frac{dI_c}{dt} &= pc_1\beta S_c\frac{I_a}{N} + r_c L_c - (\mu + \sigma_c)I_c,\\
\frac{dS_a}{dt} &= fS_c - c_2\beta S_a\frac{I_a}{N} - \mu S_a\\
\frac{dL_a}{dt} &= fL_c + (1-q)c_2\beta S_a\frac{I_a}{N} + \sigma_a I_a - (\mu + r_a)L_a,\\
\frac{dI_a}{dt} &= qc_2\beta S_a\frac{I_a}{N} + r_a L_a - (\mu + \sigma_a)I_a
\end{aligned} \qquad (1)$$

By setting:

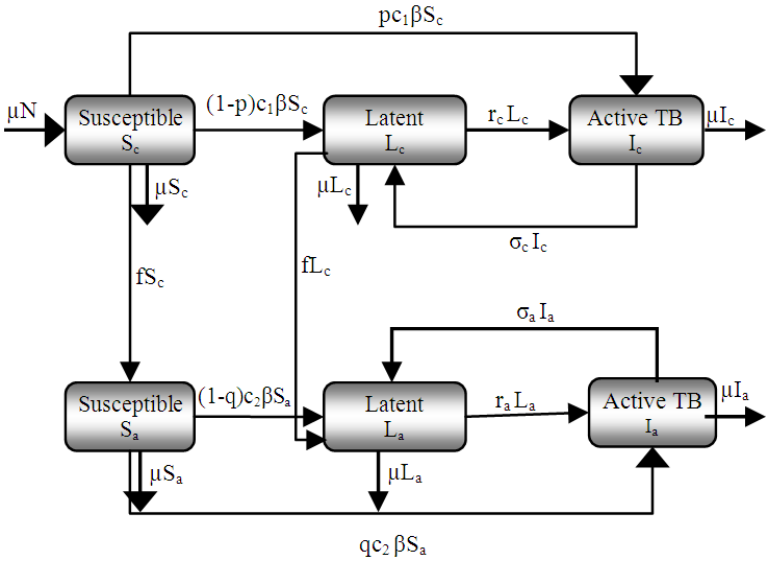


Fig. 1: Model diagram showing the transmission of TB between disease stages and age classes

$$x_1=\frac{S_c}{N}, x_2=\frac{L_c}{N}, x_3=\frac{I_c}{N}, x_4=\frac{S_a}{N}, x_5=\frac{L_a}{N} \text{ and } x_6=\frac{I_a}{N}$$

We can rewrite the system (1) as Eq. 2:

$$\begin{aligned}
\frac{dx_1}{dt}&=\mu-c_1\beta x_1x_6-(\mu+f)x_1,\\
\frac{dx_2}{dt}&=(1-p)c_1\beta x_1x_6+\sigma_c x_3-(\mu+r_c+f)x_2,\\
\frac{dx_3}{dt}&=pc_1\beta x_1x_6+r_c x_2-(\mu+\sigma_c)x_3, \frac{dx_4}{dt}=fx_1-c_2\beta x_4x_6-\mu x_4, \quad (2)\\
\frac{dx_5}{dt}&=fx_2+(1-q)c_2\beta x_4x_6+\sigma_a x_6-(\mu+r_a)x_5,\\
\frac{dx_6}{dt}&=qc_2\beta x_4x_6+r_a x_5-(\mu+\sigma_a)x_6.
\end{aligned}$$

The model has initial conditions given by $x_i(0)\geq 0$, = 1, 2,…, 6. Biological considerations entail that we study systematically (2) in the following region:

$$G=\{(x_1,x_2,x_3,x_4,x_5,x_6)\in R_+^6 \mid x_1+x_2+x_3+x_4+x_5+x_6\leq 1\}.$$

Proposition: Solutions of system (2) are positive for all $t \geq 0$ and are bounded. The region G is thus positively invariant and all solutions in G remain in G for all time.

Proof: For the given initial conditions, we prove by contradiction that if $x_1(t)$, $x_2(t)$, $x_3(t)$, $x_4(t)$, $x_5(t)$ and $x_6(t)$ are solutions of a system (2.2), then they are positive (see also Bhunu *et al*., 2008; Ziv *et al*., 2004).

Suppose there exists a first time t_1 such that $x_1(t_1) = 0$ and the derivative $\frac{dx_1}{dt}<0$ at $t = t_1$ and $x_i(t) >0$, (i = 1,…,6) for $0<t<t_1$. The first equation of the system (2) gives $\frac{dx_1}{dt}(t_1)=\mu>0,$ which is a contradiction? Thus $x_1(t)$ will remain positive for all t. Similar steps can be followed for the remaining variables. We conclude that all solutions of the system (2) are positive for all time. Our population is also bounded in G thus all solutions starting with G will remain in the G. Thus G is positively invariant and attracting and our model is thus epidemiologically well posed.

Determination of equilibria: We analyze the system (2) by finding the model equilibria and carrying out their stability analysis. At the steady state we set the right hand side of equations of the system (2) to zero and determine the state variables.

From the first five equations of a system (2), we have:

$$\begin{aligned}
x_1^*&=\frac{\mu}{(\mu+f)+c_1\beta x_6^*}, x_2^*=\frac{1}{(\mu+r_c+f)}\left[(1-p)c_1\beta x_1^*x_6^*+\sigma_c x_3^*\right],\\
x_3^*&=\frac{1}{(\mu+\sigma_c)}\left[pc_1\beta x_1^*x_6^*+r_c x_2^*\right], x_4^*=\frac{fx_1^*}{\mu+c_2\beta x_6^*},\\
x_5^*&=\frac{1}{(\mu+r_a)}\left[fx_2^*+\{(1-q)c_2\beta x_4^*+\sigma_a\}x_6^*\right].
\end{aligned}$$

Solving for x_2^* and x_3^* simultaneously, we have Eq. 4:

$$x_2^*=\omega_1 x_1^*x_6^* \quad (3)$$

$$x_3^* = \omega_2 x_1^* x_6^* \quad (4)$$

Where:

$$\omega_1 = \frac{[(1-p)\mu + \sigma_c]}{(\mu+\sigma_c)(\mu+f)+\mu r_c} c_1\beta .$$

And:

$$\omega_2 = \frac{p(\mu+f)+r_c}{(\mu+\sigma_c)(\mu+f)+\mu r_c} c_1\beta .$$

Substituting for x_1^* in x_4^*, we have Eq. 5:

$$x_4^* = \frac{\mu f}{(\mu + c_2\beta x_6^*)(\mu + f + c_1\beta x_6^*)} . \quad (5)$$

Substituting Eq. 3 into the expression for x_5^*, we have:

$$x_2^* = \frac{1}{(\mu + r_a)}\left[f\omega_1 x_1^* + \{(1-q)c_2\beta x_4^* + \sigma_a\} x_6^* \right] . \quad (6)$$

Substituting Eq. 6 into the last equation of system (2) we have the solutions, $x_6^* = 0$ and the solution of the quadratic polynomial:

$$P(x_6^*) = a_2 x_6^{*2} + a_1 x_6^* + a_0, \quad (7)$$

Where:

$$a_0 = \mu(\mu+f)(\mu+\sigma_a+r_a)[1-R_0],$$
$$a_1 = (\mu c_1 + (\mu+f)c_2)(\mu+\sigma_a+r_a) - r_a f\omega_1], a_2 = (\mu+\sigma_a+r_a)c_1c_2\beta^2$$

And:

$$R_0 = R_a + R_c \quad (8)$$

With:

$$R_a = \frac{c_2\beta f(\mu q + r_a)}{\mu(\mu+f)(\mu+\sigma_a+r_a)},$$
$$R_c = \left(\frac{[(1-p)\mu+\sigma_c]c_1\beta}{(\mu+\sigma_c)(\mu+f)+\mu r_c} \right)\left(\frac{r_a f}{(\mu+f)(\mu+\sigma_a+r_a)} \right) .$$

Here, R_a represents the contribution of adults to secondary infections while R_c is the contribution of children to secondary infection. The threshold parameter R_0 defines the mean number of secondary cases generated by introducing a single infected individual into a wholly susceptible population in which children are involved in the dynamics of the disease.

The case $x_6^* = 0$ gives the disease free equilibrium point:

$$E_0 = \left(\frac{\mu}{\mu+f}, 0, 0, \frac{f}{\mu+f}, 0, 0 \right)$$

The endemic equilibrium is thus determined from the solutions of (7). As regards the sign of a_1 in (7), we have the following proposition.

Corollary: If $R_0 < 1$ then $a_1 > 0$.

Proof: Consider:

$$a_1 = (\mu+\sigma_a+r_a)(\mu c_1 + (\mu+f)c_2) - r_a f\omega_1,$$
$$= (\mu+\sigma_a+r_a)(\mu c_1 + (\mu+f)c_2)[1-K]$$

Where:

$$K = \left(\frac{r_1}{\mu+\sigma_a+r_a} \right)\left(\frac{f}{\mu c_1 + (\mu+f)c_2} \right)\left(\frac{(1-p)\mu+\sigma_c}{(\mu+\sigma_c)(\mu+f)+\mu r_c} \right) c_1\beta$$

We note that if $R_0 < 1$ then $K \prec 1$ since:

$$\frac{f}{\mu c_1 + (\mu+f)c_2} < \frac{f}{\mu+f}.$$

This implies that $a_1 > 0$.

We thus have the following theorem on the existence of the endemic equilibrium.

Theorem 1: If $R_0 < 1$ then P (x_6) has no positive solution. However, if $R_0 > 1$, then P (x_6) has one positive solution. We therefore conclude that system (2) has a unique endemic equilibrium point E_1 whenever $R_0 > 1$.

Proof: The solution of (7) is given by:

$$x_6 = \frac{-a_1 \pm \sqrt{a_1^{\,2} - 4a_2a_0}}{2a_2} .$$

Here $a_2 > 0$ and $a_0 > 0$ if $R_0 < 1$ and $a_0 < 0$ if $R_0 > 1$and from (8), if $R_0 < 0$, then we have two negative solutions and for $R_0 > 1$, we have one positive solution for all a_1.

RESULTS AND DISCUSSION

Qualitative results: Analysis of the Model Reproduction Number: We consider first, the effects of increasing the recovery rates σ_a and σ_c. We note that as $\sigma_a \to \infty$, $R_0 \to 0$ the implications of this result is that emphasis should be placed on preventing adult individuals from progressing to active TB. A high rate

of recovery of individuals with active TB plays a crucial role in decreasing the pool of infected individuals. However, as $\sigma_a \to \infty$, $R_0 \to R_0^{\sigma_a}$, where:

$$R_0^{\sigma_a} = \frac{c_2\beta f(\mu q + r_a)}{\mu(\mu+f)(\mu+\sigma_a+r_a)} + \frac{c_1\beta f}{\mu+f}\left(\frac{r_a}{(\mu+f)(\mu+\sigma_a+r_a)}\right).$$

This result shows that the recovery rate of children does not play a crucial role in the dynamic of TB as compared to that of adults. The contour plot in Fig. 2 shows the relationship between R_0, σ_a and σ_c.

Figure 2 represents a set of R_0 contours for which, for a chosen set of parameter values, changes in the values of σ_a and σ_a would give. We note that as the value of σ_a increases, the value of R_0 decreases. In fact, this result is similar to the one proven analytically, that as $\sigma_a \to \infty$, $R_0 \to 0$. Recovery in this case may be due to treatment or natural recovery. Since the fight against TB has been restricted to, vaccination, identifying infectious cases and treating them, one can consider this result to imply that the fight against TB must be directed mostly to the adult population since they are the source of infection. It is clear from Fig. 2 that increasing the recovery rate σ_c for children does not play any significant role in the transmission dynamics of the disease.

We now investigate the role of the progression rates r_a and r_c. As $r_a \to 0$, $R_0 \to R_0^{\sigma_a}$, where:

$$R_0^{r_a} = \frac{c_2\beta q f}{(\mu+f)(\mu+\sigma_a)}.$$

Note that $R_0^{r_a} < R_0$. Thus a reduction in the progression rates leads to a reduction in the number of secondary infections generated by an infected individual.

We also note that as $r_c \to 0$, we have $R_0 \to R_0^{r_c}$, where:

$$R_0^{r_c} = \frac{c_2\beta f(\mu q + r_a)}{\mu(\mu+f)(\mu+\sigma_a+r_a)} + \frac{c_1\beta f[(1-p)\mu+\sigma_c]}{(\mu+f)(\mu+\sigma_c)}\left(\frac{r_a}{(\mu+f)(\mu+\sigma_a+r_a)}\right).$$

That $R_0^{r_c} > R_0$. Reduction in the progression of latently infected children to active pediatric TB leads to increased secondary infections in the adult population. The implications of this scenario are that there are increased latent infections in the adult population as a result of increased latently infected children who mature to adulthood with latent infections.

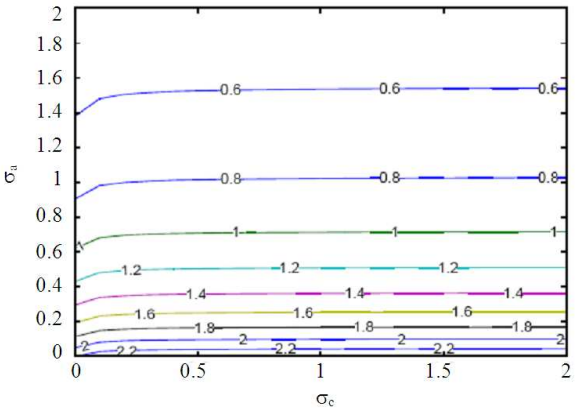


Fig. 2: Shows the relationship between the recovery rates and the reproduction number R_0 for the following set of parameter values; $\beta = 0.01$, $\mu = 0.017$, $p = q = 0.1$, $\sigma_c = 0.8$,$\sigma_a = 0.6$,c1 = 6,c2 = 10, f = 0.02

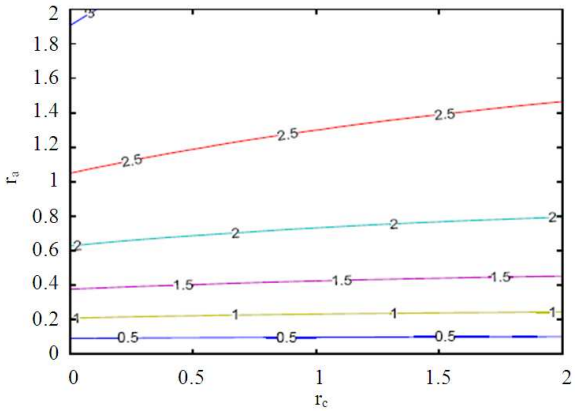


Fig. 3: Shows the relationship between the progression rates and the reproduction number R0 for the following parameter values; $\beta = 0.005$,p = 0.1,q0.1,rc = 0.08,ra = 0.5,c1 = 6,c2 = 20, f = 0.02.

Children become a reservoir of latent infections from which reactivation is highly likely to occur when they become adults. Figure 3 illustrates the theoretical results relating variations of progression r_a and r_c to secondary infections.

Global stability of E_0:

Theorem 2: The disease free equilibrium point E_0 is globally asymptotically stable in G whenever $R_0 < 1$.

Proof: We consider the following Lyapunov function:

$$V = \alpha_1 x_2 + \alpha_2 x_3 + \alpha_3 x_5 + \alpha_4 x_6$$

Where:

$\alpha_1 = fr_a(\mu+\sigma_c), \alpha_2 = fr_a\sigma_c, \alpha_1 = r_a[(\mu+f)(\mu+\sigma_c)+\mu r_c]$
and $\alpha_4 = (\mu+r_a)[(\mu+f)(\mu+\sigma_c)+\mu r_c]$

The derivative of V with respect to time is given by:

$$\frac{dV}{dt} = \alpha_1\frac{dx_2}{dt} + \alpha_2\frac{dx_3}{dt} + \alpha_3\frac{dx_5}{dt} + \alpha_4\frac{dx_6}{dt},$$
$$\leq [(\mu+f)(\mu+\sigma_c)+\mu r_c][\mu(\mu+r_a)+\mu\sigma_a](R_0-1)x_6, \leq 0 \text{ for } R_0 < 1$$

It follows that $\frac{dV}{dt} \leq 0$ for $R_0 < 1$, since the model parameters are assumed to be positive. The derivative $\frac{dV}{dt} = 0$, if and only if $R_0 = 1$. Hence V is a Lyapunov function on G. The largest compact set that is invariant in $\{(x_1, x_2, x_3, x_4, x_5, x_6) \in G \mid \frac{dV}{dt} = 0\}$ is the singleton $\{E_0\}$. It follows from the lasalle's invariance Principle (Lietman and Blower, 2000), that every solution of (2) with initial conditions in G approaches E_0 as $t \to \infty$ whenever $R_0 < 1$.

Local stability of the endemic equilibrium: The size and nature of the matrix resulting from standard linearization of the system (2) makes the determination of eigenvalues and their nature a difficult and tedious exercise. We resort to the center manifold theory described in (Feng *et al*., 2001) and used in (Song *et al*., 2002) to determine the stability of the endemic equilibrium point. We note that our system is of the form:

$$\frac{dX}{dt} = F(X)$$

Where:

$X = (x_1, x_2, x_3, x_4, x_5, x_6)^T$

and $F (f_1, f_2, f_3, f_4, f_5, f_6)^T$ where $(.)^T$ denotes a matrix transpose. System (2) becomes Eq. 7:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \mu - c_1\beta x_1 x_6 - (\mu+f)x_1\\
\frac{dx_2}{dt} &= f_2 = (1-p)c_1\beta x_1 x_6 + \sigma_c x_3 - (\mu + r_c + f)x_2,\\
\frac{dx_3}{dt} &= f_3 = pc_1\beta x_1 x_6 + r_c x_2 - (\mu+\sigma_c)x_3,\\
\frac{dx_4}{dt} &= f_4 = fx_1 - c_2\beta x_4 x_6 - \mu x_4,\\
\frac{dx_5}{dt} &= f_5 = fx_2 + (1-q)c_2\beta x_4 x_6 + \sigma_a x_6 - (\mu + r_a)x_5,\\
\frac{dx_6}{dt} &= f_6 = qc_2\beta x_4 x_6 + r_a x_5 - (\mu+\sigma_a)x_6
\end{aligned} \tag{9}$$

Suppose β is the bifurcation parameter. When $R_0 = 1$ we have:

$$\beta^* = \frac{(\mu+f)[\mu(\mu+\sigma_a+r_a)][(\mu+\sigma_c)(\mu+f)+\mu r_c]}{fc_2(\mu q + r_a)[(\mu+\sigma_c)(\mu+f)+\mu r_c] + \mu r_a f c_1[(1-p)\mu+\sigma_c]}$$

The Jacobian matrix of the system (7) at E_0 for $\beta = \beta^*$ is given by:

$$J_{\beta^*} = \begin{pmatrix} A & B \\ C & D \end{pmatrix}$$

where, A,B,C and D are 3×3 matrices given by:

$$A = \begin{pmatrix} -(\mu+f) & 0 & 0 \\ 0 & -(\mu+r_c+f) & \sigma_c \\ 0 & r_c & -(\mu+\sigma_c) \end{pmatrix}$$

$$B = \begin{pmatrix} 0 & 0 & -c_1\beta^* x_1^* \\ 0 & 0 & (1-p)c_1\beta^* x_1^* \\ 0 & 0 & pc_1\beta^* x_1^* \end{pmatrix}, C = \begin{pmatrix} f & 0 & 0 \\ 0 & f & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

$$D = \begin{pmatrix} -\mu & 0 & -c_2\beta^* x_4^* \\ 0 & -(\mu+r_a) & (1-q)c_2\beta^* x_4^* + \sigma_a \\ 0 & r_a & qc_2\beta^* x_4^* - (\mu+\sigma_a) \end{pmatrix}$$

J_{β^*} has a zero simple eigenvalue and the corresponding right eigenvector associated with this simple eigenvalues is given by $y = (y_1, y_2, y_3, y_4, y_5, y_6)^T$ where:

$$y_1 = \frac{-\mu^2 c_1(\mu+\sigma_a+r_a)[(\mu+\sigma_c)(\mu+f)+\mu r_c]}{f(\mu+f)\{c_2(\mu q+r_a)[(\mu+\sigma_c)(\mu+f)+\mu r_c] + \mu r_a c_1[(1-p)\mu+\sigma_c]\}}$$

$$y_2 = \frac{\mu^2 c_1(\mu+\sigma_a+r_a)[(1-p)\mu+\sigma_c]}{f\{c_2(\mu q+r_a)[(\mu+\sigma_c)(\mu+f)+\mu r_c] + \mu r_a c_1[(1-p)\mu+\sigma_c]\}}$$

$$y_3 = \frac{\mu^2 c_1[p(\mu+f)+r_c][(\mu+\sigma_c)(\mu+f)+\mu r_c]}{f\{c_2(\mu q+r_a)[(\mu+\sigma_c)(\mu+f)+\mu r_c] + \mu r_a c_1[(1-p)\mu+\sigma_c]\}}$$

$$y_4 = \frac{-(c_1\mu + c_2(\mu+f))(\mu+\sigma_a+r_a)[(\mu+\sigma_c)(\mu+f)+\mu r_c]}{(\mu+f)\{c_2(\mu q+r_a)[(\mu+\sigma_c)(\mu+f)+\mu r_c] + \mu r_a c_1[(1-p)\mu+\sigma_c]\}}$$

$$y_5 = \frac{\mu\, c_1(\sigma_a+r_a)[(1-p)\mu+\sigma_c] + c_c[(\mu+\sigma_c)(\mu+f)+\mu r_c][\mu(1-q)+\sigma_a]}{\{c_2(\mu q+r_a)[(\mu+\sigma_c)(\mu+f)+\mu r_c] + \mu r_a c_1[(1-p)\mu+\sigma_c]\}}, y_6 = 1$$

The left eigenvector of the transpose of J_{β^*} that is, the left eigenvector of J_{β^*} is given by:

$$Z = (z_1, z_2, z_3, z_4, z_5, z_6)^T$$

Where:

$$z_1 = 0, z_2 = \eta f r_a(\mu + \sigma_c), z_3 = \eta f r_a \sigma_c, z_4 = 0,$$
$$z_5 = \eta r_a[(\mu + \sigma_c)(\mu + f) + \mu r_c], z_6 = \eta(\mu + r_a)[(\mu + \sigma_c)(\mu + f) + \mu r_c]$$

And $\eta>0$ is chosen so that the condition $y \bullet z=1$ is satisfied.

Following Theorem 4.1 in (Feng *et al*., 2001), we thus compute a and b to determine the stability of E_1 around $R_0 = 0$, where:

$$a = \sum_{kij=1} z_k y_i y_j \frac{\partial^2 f_k}{\partial x_i \partial x_j} b = \sum_{ki=1} z_k y_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*} \quad (10)$$

And β^* the bifurcation parameter.

The non-zero partial derivatives of F at the disease free equilibrium point are given by:

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_6} = (1-p)c_1\beta^*, \frac{\partial^2 f_3}{\partial x_1 \partial x_6} = pc_1\beta^*, \frac{\partial^2 f_5}{\partial x_4 \partial x_6} = (1-q)c_2\beta^*, \frac{\partial^2 f_6}{\partial x_4 \partial x_6} = qc_2\beta^*$$

To determine a we substitute the above expressions of the partial derivatives into Eq. 10. We thus have:

$$a = y_1 y_6 \beta^*[(1-p)z_2 + pz_3] + y_4 y_6 \beta^*[(1-q)z_5 + qz_6] < 0$$

Since $y_1<0$ and $y_4<0$, the right hand side of a is always negative. For the sign of b the following are the non-zero partial derivatives of F:

$$\frac{\partial^2 f_2}{\partial x_6 \partial \beta^*} = (1-p)c_1 x_1^*, \frac{\partial^2 f_3}{\partial x_6 \partial \beta^*} = pc_1 x_1^*, \frac{\partial^2 f_5}{\partial x_6 \partial \beta^*} = (1-q)c_2 x_4^*, \frac{\partial^2 f_6}{\partial x_6 \partial \beta^*} = qc_2 x_4^*$$

An evaluation of b shows that b is always greater than 0. We thus have the following results based on Theorem 4.1 in (Feng *et al*., 2001).

Theorem 3: The endemic equilibrium point E_1 is locally asymptotically stable for $R_0>1$ but with R_0 near 1.

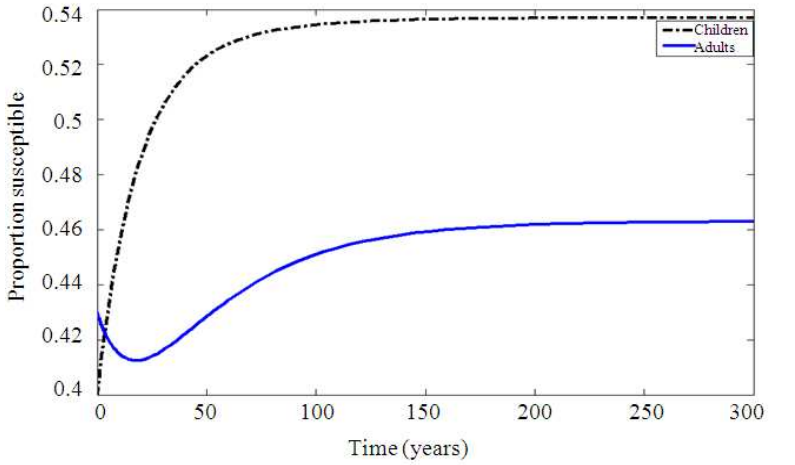
Numerical results: We now give a discussion of the numerical solutions of systems (2), the parameter values and interpretations of the cases that arise thereof. The dynamics of the system (2) are studied numerically using the fourth order Runge-Kutta numerical scheme in MATLAB.

Parameter values: Some of the model parameters were decided upon based on the following assumptions:

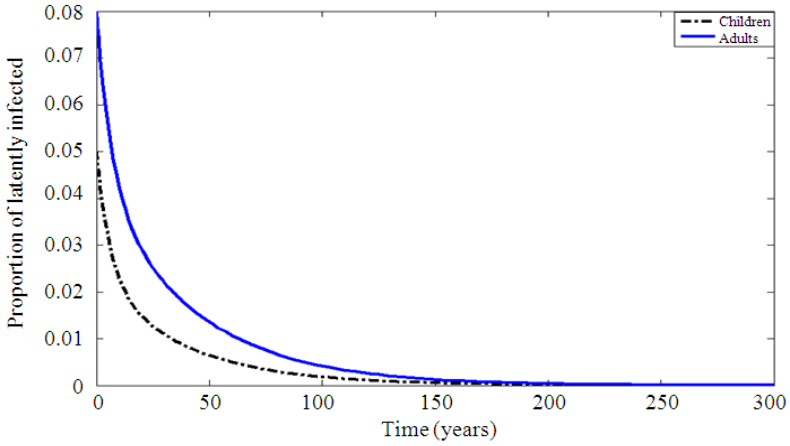
- Since the birth and death rates are taken to be the same, we assume that the average lifespans of human beings are between 40 and 80 years. We use the natural mortality rate in the range $0.0125 \leq \mu \leq$
- The rate at which children join the adult class f is assumed to be less than or equal to the birth rate. We try to accommodate, the fact that not every child survives to adulthood. So we set $f \leq \mu$
- Susceptible children and adults are infected with probability β upon contact. Contact patterns that can result in infection can be random, associative, age-specific and sex-specific and so on, but in this study we assume random mixing. This means that every susceptible is equally likely to be infected by an infective should contact occur
- While the probability of infection is taken to be the same for children and adults, we assume that adults have increased chances of mixing. We thus consider different contact rates
- Estimates have shown that 10% (proportions p, q) of TB infection progression fast to active TB (Jung *et al*., 2002). The risk for young children to develop active TB if the infection is not treated is up to 43% in children less than a year old, approximately 24% for children between 1 and 5 years of age and much lower for those between 6 and 13 years (Schaaf *et al*., 2003). The proportion of children that develop active TB fast can thus be assumed reasonably to be higher than 10%
- Active TB has always been taken as a continued development of the primary infection first acquired or due to endogenous reactivation or exogenous re-infection with a second or the same strain. Separation and quantification of these mechanisms especially (endogenous reactivation and exogenous re-infection) requires technology that can differentiate between strains (Zhang *et al*., 2007). We crudely lump the two processes (Jung *et al*., 2002) in this study to represent a progression to active TB, denoted by r_a and r_c
- Recovery, may be due to treatment or natural recovery In which case individuals revert back to the exposed class at rates σ_c and σ_a. The rate at which individuals recover usually depends on the immune status of the individual, types of drugs, genetic and socioeconomic factors. We acknowledge that quantification of these rates of recovery is difficult as evidenced by variations in the parameter values in research publications

The estimated parameter values used are given in Table 1.

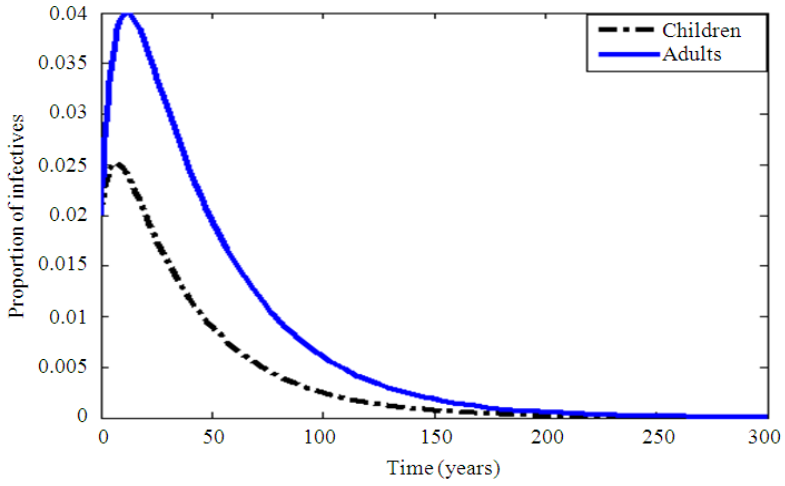
Numerical plots: Figure 4a shows the changes in the proportion of the susceptible populations for children and adults, with increasing time.



(a)

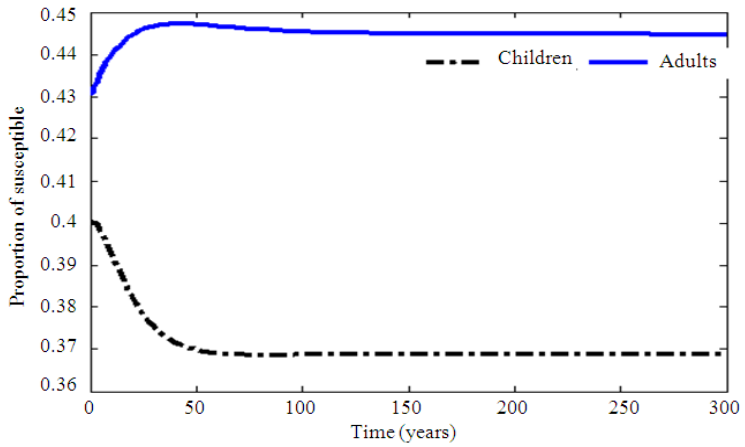


(b)

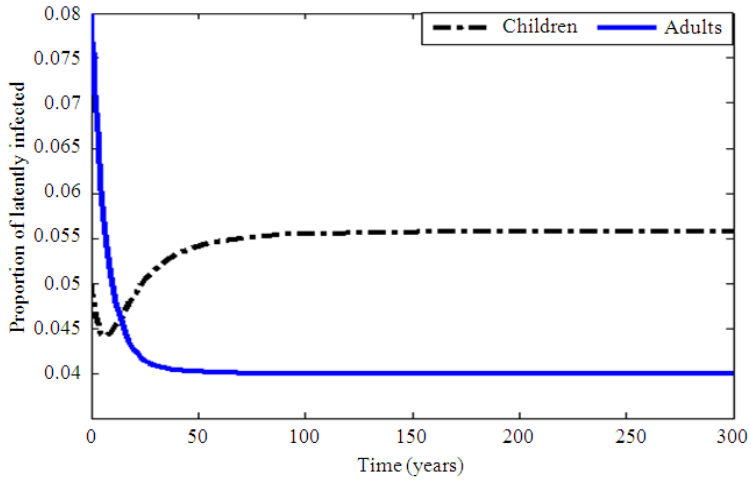


(c)

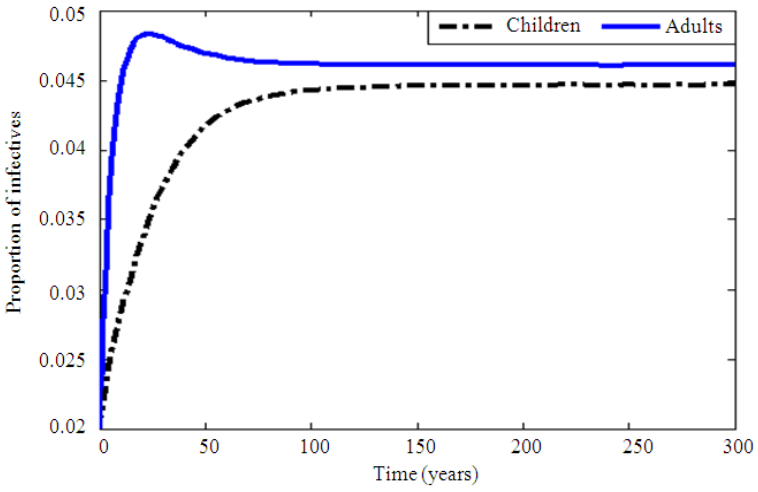
Fig. 4: Shows the changes in the proportion for each population with time. The value of the model reproduction number is 0.0792 in this case



(a)



(b)



(c)

Fig. 5: Shows the changes in the proportion for each population with time. The value of the model reproduction number is 1.1426

Table 1: Table of parameters and numerical values

Parameter	Value(s)	Reference
μ	0.0125-0.025	(Song *et al*., 2002)
β	(0, 1)	Variable
p, q	(0, 1)	Variable
σ_c, σ_a	(0.5, 1)	(Bhunu *et al*., 2008; LaSalle, 1976; Nelson and Wells, 2004)
r_c	0.03	(Nelson and Wells, 2004)
c_1, c_2	(1, 100)	Estimated
F	$f \leq \mu$	Estimated
r_a	(0.5,1)	(LaSalle, 1976)

The susceptible population of adults initially falls as the infective among adults increase, but later increases to a steady state value over time. The susceptible children increase to a steady state. This is reasonable since in most population structures, the proportion of children is higher than that of adults. In Fig. 4b the latently infected population for the two subgroups decreases over time to zero. In Fig. 4c the graphs for the two sub-populations show a similar trend in which their proportions fall over time to zero We observe that infection in the adult population clear later than that of children mainly because of the latent reservoir of infection from children. Overall, the Fig. 4a-c, represent the disease free equilibrium point E_0 over a longer period of time than the one presented in the simulations.

In Fig. 5a shows the changes in the proportion of the susceptible populations for children and adults, with increasing time. Both sub-populations decrease to a steady state over time and again we have the proportion of children being higher than that of adults as the epidemic evolves. In Fig. 5b, the latently infected population for the two subgroups initially decreases and then rises to a steady state over time. Figure 5c shows the graphs for the proportions of infectives. The adult infects increased rapidly and settled in an endemic steady state over time. This scenario represents the endemic steady state E_1, which we deduced analytically to be asymptotically stable for $R_0 > 1$.

CONCLUSION

The study presented in this study is a very simple model showing the dynamics of TB in children and adults in the absence of any intervention. Many deterministic models of TB have been developed but a few, to the best of our knowledge, have been developed this way without using the age structures. We presented a model in which there are no interventions. A more realistic approach would be to include the current intervention strategies. This forms our research that is in progress. Although some of the model assumptions are realistic, many of them over simplifies the natural evolution of TB. In particular, the ageing function f, was chosen so that it does not exceed the birth rate of the population based on the assumption that the individuals that graduate into adulthood survive with some probability less than or equal to one. We acknowledge that it is difficult to estimate and an age-structured model would have eliminated such a difficulty. The lumping up of progression to active TB to include reinfection and reactivation and recovery to include both natural recovery and recovery due to the treatment represent significant short comings to the model. The agreement between the model output and epidemiological data has been restricted to very broad TB epidemiological trends. Despite these inadequacies, this study provides some unique insights in the way progression and recovery parameters influence the dynamics of the disease. Any form of intervention implemented should influence these parameters and quantify their changes and influence on the reproduction number.

Our analysis shows that progression to active TB among adults is epidemiologically significant and interventions should focus on the adult population. This perhaps explains why TB among children has not been a major subject for research. Similar trends can be observed in the recovery rates r_c and r_a. The relationship between the progression rates to active TB for children and adults and the model reproduction number draws out important information that can help in prophylactic treatment such as the use of Isoniazid in preventing progression to active TB. Figure 3, also shows that change in the progression rate for adults, results in significant changes in the model reproduction number. Attempts to use chemoprophylaxis for active TB prevention should be targeted to adults.

The global stability of the model shows that if $R_0 < 1$ then every solution tends to the disease free equilibrium and the disease clears from the population. We showed that there exists a unique endemic equilibrium point whenever $R_0 > 1$. If the TB is present in a population then, as long as $R_0 > 1$, it will always persist.

In conclusion, despite all our results pointing out the need to focus interventions on adults, pediatric TB forms an important indicator of how the TB epidemic is evolving in adults. Infected children act as a reservoir of latent infections that can reactivate into active TB when they become adults. One of the most important factors to consider with regards to pediatric TB is that, it is possible to clearly distinguish between disease progression stages, exposure, infection and disease. This is particularly important to public health policy formulation, designing interventions and modeling in general.

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