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Assessing the Impact of Age – Vaccination Structure Models on the Dynamics of Tuberculosis Transmission

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Abstract

Vaccination has been the only preventive mechanism of tuberculosis (TB) yet due to inconsistencies in the efficacy of the mostly used vaccine, Baccille Calmette-Guerin (BCG), re-vaccination has been deemed to be ineffective. In this work, we sought to assess the impact of age-vaccination and re-vaccination on the transmission dynamics of TB. We developed an age-vaccination re- vaccination model to explore the disease transmission dynamics and the impact of re-vaccination on the disease transmission. By applying the vaccine within ten year intervals, we noticed that, there is no significant difference when the vaccine is administered once or many times for people less than 45 years of age. However, re-vaccination can prove to be effective when it is applied either before or immediately after the waning of the first vaccine.

Keywords: Vaccination • Tuberculosis • Acquired immuno deficiency syndrome

Introduction

Infectious diseases have been studied at large with various interventions such as vaccination and quarantine used as preventive strategies and drugs for therapeutics in combating the spread and to some extent eradication of these diseases [1]. Tuberculosis (TB) is an ancient infectious disease that has caused millions of deaths in humans and it is estimated to have infected about one - third of the world's population even though TB remains one of the first and most studied infectious diseases in history [2]. Vaccination is believed to be the main prevention strategy yet the inability of the vaccines to be 100% effective, some vaccines resulting in other diseases and some other side effects arising from the use of immuno-suppression drugs and the co-infection with some diseases such as the Human Immuno- deficiency Virus/ Acquired Immuno Deficiency Syndrome (HIV/AIDS) continues to make TB a deadly disease [1]. TB is caused by a strain of the bacteria species Mycobacterium Tuberculosis Complex (MTBC) [3]. In 2004, about 9 million people acquired the tuberculosis disease while 2 million of these died with or from the disease [4] and in 2014, an estimated 1.5 million people were killed dueto TB out of a possible 9.6 million people thought to have fallen ill with the disease [5]. According to a World Health Organisation (WHO) report on the disease, TB ranks alongside HIV/AIDS as the leading cause of deaths worldwide [5]. Tuberculosis affects young adults in their most productive years [4], however, childhood tuberculosis is also a major contributor to the high level of tuberculosis cases, due to the non-specific nature of symptoms in children, the high levels of poverty and malnutrition, the difficulty in collecting respiratory specimens for microbiological confirmation, and the fact that the nature of TB disease in children is made up of few bacilli which makes childhood tuberculosis difficult to detect [6]. A World Health Organisation report shows that, in 2015, tuberculosis prevalence reduced by 42% compared to the prevalence in 1990 with a sustained treatment success rate of 86% for newly diagnosed individuals since 2005 [5]. In Africa and most parts of the world, TB has regenerated by the emergence of HIV/AIDS and TB HIV/AIDS co-infection [4] and continues to thrive on the influence of poverty, immigration, prisons and in some cases control programmes as prison settings most especially provides the perfect environment for the successful growth of the bacteria [7]. The main preventions strategy of TB is vaccination with the most wildly used Bacille Calmette Guerin (BCG) vaccine. Reports by Barreto et al. suggest that, the efficacy of the vaccine is lowest in areas closer tothe equator as compared to areas further away from the equator. This assertion and many others, including; (a) the ability of the vaccine to have high protection when given at birth, and (b) variable protection when given at school-age and (c) its ability to have high protection against miliary and meningeal disease but variable protection against Pulmonary Tuberculosis (PTB), have been attributed to exposure to Non-tuberculous mycobacteria (NTM) which is deemed to affect BCG-specific immune response of the host through cross reactivity with BCG and a degree of variation in prevalence with latitude" [8]. In current studies, research has been geared towards the development of vaccines that can prevent those infected with TB from progressing to active tuberculosis disease and also protect individuals from initial infection with MTB or decrease the capacity of transmission by those with active disease. The common strategy employed in this research is the prime-boost strategy which combines the BCG vaccine with a novel vaccine candidate. In this regard, the effectiveness of the BCG vaccine can also be improved [9,10].

Method

The population is divided into the following compartments, each at time t and age a: Susceptible $S(t, a)$ (individuals who are at risk of contracting the disease by making effective contacts with infectious individuals), Vaccinated $V(t, a)$ (individuals who have been vaccinated against the disease), Re-vaccinated $U(t, a)$ (individuals who have been vaccinated more than once against the disease), Latent $L(t, a)$ (individuals who have the disease but are not capable of transmitting it to others), Infectious $I(t, a)$ (individuals who have the disease and are capable oftransmitting it to others) and Recovered $R(t, a)$ (individuals who have been treated from the disease). All recruits (newborns) are deemed to be susceptible, vaccination is partially effective (i.e., vaccinated and re-vaccinated individuals can become infected again, but with reduced transmission rate), recovery is not a complete process due to some individuals not totally completing the therapy and also, the ability of the bacteria to go dormant in response to perturbations in its surroundings. This means recovered individuals go back into the state of latency and only susceptible individuals are vaccinated. We assume that mixing between individuals is proportional to their age-dependent activity level. We apply treatment only to the infectious compartment since people in this compartment can test positive and also show symptoms of

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the disease. Furthermore, there is a reduction δ in the transmission rate of vaccinated and re-vaccinated individuals due to the presence of the vaccine. The force of infection for this model is only in the infected compartment. That is, only infectious individuals are capable of transmitting the disease however, individuals from all the compartments can die from natural death that is not induced by the disease but infectious individual can die from the disease so the disease-induced death rate is only in the infectious compartment. Figures 1.1-1.3 shows the diagrammatic representation of the transmission model and it is mathematically represented by Equation (1.1.1).

Table 1.1. Description of model parameters.

Parameter	Description
$\mu_{TB}(a)$	An age dependent disease-induced death rate
$\mu(a)$	An age dependent natural death rate
$\gamma(a)$	Rate at which vaccinated individuals become susceptible due to wanning of vaccine.
$\Phi(a)$	Rate at which re-vaccinated individuals become susceptible due to wanning of vaccine.
$\sigma(a)$	Rate at which recovered individuals become susceptible due to lack of immunity.
$\psi(a)$	Rate of vaccination of susceptible individuals.
$\pi(a)$	Rate of re-vaccination of vaccinated individuals.
δ	Reduction in the transmission rate of vaccinated and revaccinated individuals ($0 \le \delta < 1$).
κ	Rate of leaving latent class to infectious class due to reinfection/ reactivation
r	Rate of recovery of infectious individuals
Λ	Birth/Recruitment rate

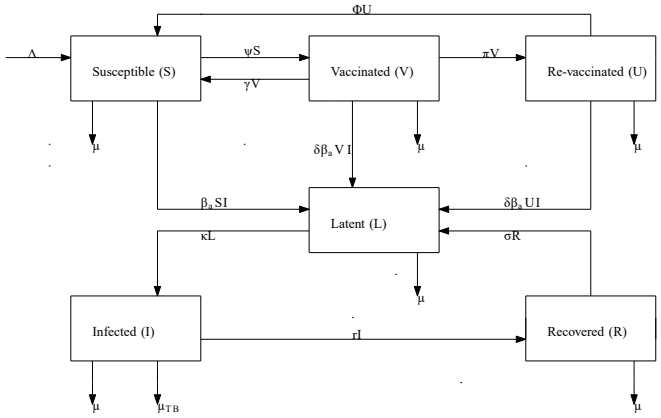


Figure 1.1. An age vaccination re-vaccination structure model for TB transmission.

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)S(t,a) = \Lambda+\gamma(a)V(t,a)+\Phi(a)U(t,a)-\psi(a)S(t,a)$$
$$-\big(\mu(a)+\beta(t,a)I(t,a)\big)S(t,a)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)V(t,a) = \psi(a)S(t,a)-\big(\pi(a)+\gamma(a)+\mu(a)\big)V(t,a)$$
$$-\delta(a)\beta(t,a)I(t,a)V(t,a)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)U(t,a) = \pi(a)V(t,a)-\delta\beta(t,a)I(t,a)U(t,a)$$
$$-(\mu(a)+\Phi(a))U(t,a) \qquad (1.1.1)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)L(t,a) = \beta(t,a)I(t,a)S(t,a)+\delta V(t,a)+\delta U(t,a)$$
$$+\sigma(a)R(t,a)-(\mu(a)+\kappa(a))L(t,a)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)I(t,a) = \kappa(a)L(t,a)-(\mu(a)+\mu_{TB}(a)+r)I(t,a)$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)R(t,a) = rI(t,a)-(\mu(a)+\sigma(a))R(t,a)$$

Under the assumption that age depends on time (i.e., $a \equiv a(t)$), given any sufficiently smooth function $x(t, a(t)) \equiv x(t)$, so that, along the characteristic curve $\frac{da}{dt}=1$, we get;

$$\frac{dx}{dt}=\frac{\partial x}{\partial t}+\frac{\partial x}{\partial a}$$

Thus, for the system (1.1.1), the time dependent solution $(S^*(t),V^*(t),U^*(t),L^*(t),I^*(t),R^*(t))$ satisfies;

$$\dot{S}(t)=\Lambda+\gamma V(t)+\Phi U-\psi S(t)-\big(\mu+\beta_a(t)I(t)\big)S(t)$$
$$\dot{V}(t)=\psi S(t)-(\pi+\gamma+\mu)V(t)-\delta\beta_a(t)I(t)V(t)$$
$$\dot{U}(t)=\pi V(t)-\delta\beta_a(t)I(t)U(t)-(\mu+\Phi)U(t)$$
$$\dot{L}(t)=\beta_a(t)I(t)S(t)+\delta V(t)+\delta U(t)+\sigma R(t)-(\mu+\kappa)L(t) \qquad (1.1.2)$$
$$\dot{I}(t)=\kappa L(t)-(\mu+\mu_{TB}+r)I(t)$$
$$\dot{R}(t)=rI(t)-(\mu+\sigma)R(t)$$

with initial conditions given as;

$S(0) = S^0$, $V(0) = V^0$, $U(0) = U^0$ $L(0) = L^0$, $I(0) = I^0$, $R(0) = R^0$

Where $\dot{z}(t)$ represents $\frac{dz(t)}{dt}$.

$N(t) = S(t) + V(t) + U(t) + L(t) + I(t) + R(t)$

Notice that $\frac{dN(t)}{dt} < 0$ whenever $N(t) > \frac{\Lambda}{\mu}$. Also, since $\frac{dN(t)}{dt} \le \Lambda - \mu N$, whenever $N(0) \le \frac{\Lambda}{\mu}$,

$N(t) \le \frac{\Lambda}{\mu}$. This means that, for all $t > 0$, solutions of the model remains in the positively invariant set $D = \{(S(t), V(t), U(t), L(t), I(t), R(t)) \in R^6: N(t) \le \frac{\Lambda}{\mu}\}$

Equilibrium points and stability of equilibrium points

The disease-free equilibrium point obtained when $L(t) = I(t) = R(t) = 0$ and $\dot{V}(t) = \dot{U}(t) = 0$ is obtained by solving

$$\Lambda+\gamma V^*(t)+\Phi U^*(t)-(\psi+\mu)S^*(t)=0$$
$$\psi S^*(t)-(\pi+\gamma+\mu)V^*(t)=0$$
$$\pi V^*(t)-(\mu+\Phi)U^*(t)=0 \qquad (1.1.3)$$

Therefore the disease-free equilibrium is given as

$$E_0=(S^*(t),V^*(t),U^*(t),0,0,0) \qquad (1.1.4)$$

with $S^*(t), V^*(t)$ and $U^*(t)$, given as

$$S^*(t)=\frac{\Lambda(\Phi+\mu)(\pi+\mu+\gamma)}{(\Phi\mu+\mu^2)(\pi+\mu+\gamma+\psi)+\mu\pi\psi}$$
$$V^*(t)=\frac{\psi\Lambda(\Phi+\mu)}{(\Phi\mu+\mu^2)(\pi+\mu+\gamma+\psi)+\mu\pi\psi} \qquad (1.1.5)$$
$$U^*(t)=\frac{\pi\psi\Lambda}{(\Phi\mu+\mu^2)(\pi+\mu+\gamma+\psi)+\mu\pi\psi}$$

The endemic equilibrium is also obtained by solving

$$\frac{dS^*(t)}{dt}=\frac{dV^*(t)}{dt}=\frac{dU^*(t)}{dt}=\frac{dL^*(t)}{dt}=\frac{dI^*(t)}{dt}=\frac{dR^*(t)}{dt}=0$$

This implies that, we solve simultaneously the following system of equations:

$$\Lambda+\gamma V^*(t)+\Phi U^*-\psi S^*(t)-\big(\mu+\beta_a(t)I^*(t)\big)S^*(t)=0 \qquad (1.1.6)$$
$$\psi S^*(t)-(\pi+\gamma+\mu)V^*(t)-\delta\beta_a(t)I^*(t)V^*(t)=0 \qquad (1.1.7)$$
$$\pi V^*(t)-\delta\beta_a(t)I^*(t)U^*(t)-(\mu+\Phi)U^*(t)=0 \qquad (1.1.8)$$

$$\beta_a(t)I^*(t)S^*(t) + \delta V^*(t) + \delta U^*(t) + \sigma R^*(t) - (\mu+\kappa)L^*(t) = 0 \quad \textbf{(1.1.9)}$$

$$\kappa L^*(t) - (\mu + \mu_{TB} + r)I^*(t) = 0 \quad \textbf{(1.1.10)}$$

$$rI^*(t) - (\mu+\sigma)R^*(t) = 0 \quad \textbf{(1.1.11)}$$

This yields, after sets of lengthy calculations, the solutions;

$$S^*(t) = \frac{\alpha_1\alpha_2\Lambda\mu_{TB}}{\theta_1\mu_{TB} + \theta_2\beta_a(t)(\Lambda - N^*(t))}$$

$$V^*(t) = \frac{\alpha_2\psi\mu_{TB}^2\Lambda}{\theta_1\mu_{TB} + \theta_2\beta_a(t)(\Lambda - N^*(t))} \quad \textbf{(1.1.12)}$$

$$U^*(t) = \frac{\pi\psi\mu_{TB}^2\Lambda}{\theta_1\mu_{TB} + \theta_2\beta_a(t)(\Lambda - N^*(t))}$$

$$L^*(t) = \frac{(\Lambda - \mu N^*(t))(\mu + \mu_{TB} + r)}{\kappa\mu_{TB}}$$

$$I^*(t) = \frac{\Lambda - \mu N^*(t)}{\mu_{TB}}$$

$$R^*(t) = \frac{r(\Lambda - \mu N^*(t))}{\mu_{TB}(\sigma+\mu)}$$

where,

$$\theta_1 = \alpha_1\alpha_2\mu + \alpha_2\mu_{TB}\psi\mu + \mu_{TB}^2\pi\psi\mu$$

$$\theta_2 = \alpha_1\alpha_2 + \delta\alpha_2\mu_{TB}\psi + \delta\mu_{TB}^2\pi\psi$$

$$\alpha_1 = \mu_{TB}(\pi+\mu+\gamma) + \delta\beta_a(t)(\Lambda - \mu N^*(t))$$

$$\alpha_2 = \mu_{TB}(\Phi+\mu) + \delta\beta_a(t)(\Lambda - \mu N^*(t)$$

Thus the endemic equilibrium is given by

$$E^* = \left(S^*(t), V^*(t), U^*(t), L^*(t), R^*(t), I^*(t)\right) \quad \textbf{(1.1.13)}$$

Where $S^*(t), V^*(t), U^*(t), L^*(t), R^*(t)$ and $I^*(t)$ are given in equation **(1.1.12).**

By substituting the equilibrium points into equation **(1.1.9)**, $N^*(t)$ satisfies the equation

$$\left(\Lambda - \mu N^*(t)\right)F\left(N^*(t)\right) = 0 \quad \textbf{(1.1.14)}$$

With

$$F\left(N^*(t)\right) = \beta_a(t)\theta_2\eta_1\left(\Lambda - \mu N^*(t)\right) + \beta_a(t)\kappa\theta_2\Lambda\mu_{TB}(\sigma+\mu) + \theta_1\mu_{TB}\eta_1 \quad \textbf{(1.1.15)}$$

$$\eta_1 = \kappa\sigma r - (\mu + \mu_{TB} + r)(\kappa+\mu)(\sigma+\mu)$$

Lemma

The system given by equation **(1.1.2)** always has the positive endemic equilibrium given in equation in equation **(1.1.13)** in the interval $(0, \frac{\Lambda}{\mu})$

Proof We have

$$F(0) = \beta_a(t)\theta_2\eta_1\Lambda + \beta_a(t)\kappa\theta_2\Lambda\mu_{TB}(\sigma+\mu) + \theta_1\mu_{TB}\eta_1$$

$$F\left(\frac{\Lambda}{\mu}\right) = [\left(\frac{\beta_a(t)\kappa\Lambda\left((\Phi+\mu)(\pi+\gamma+\mu) + \delta\psi(\Phi+\pi+\mu)\right)}{\mu(\kappa+\mu)(\mu+\mu_{TB}+r)\left((\Phi+\mu)(\pi+\gamma+\mu+\psi)+\pi\psi\right)} - 1\right) + \left(\frac{\kappa\sigma r}{(\sigma+\mu)(\kappa+\mu)(\mu+\mu_{TB}+r)}\right)] \mu\mu_{TB}^2(\sigma + \mu)(\kappa+\mu)(\mu+\mu_{TB}+r)\left((\Phi+\mu)(\pi+\gamma+\mu+\psi)+\pi\psi\right)$$

$$F\left(\frac{\Lambda}{\mu}\right) = [(R_0 - 1) + \left(\frac{\kappa\sigma r}{(\sigma+\mu)(\kappa+\mu)(\mu+\mu_{TB}+r)}\right)] \mu\mu_{TB}^2(\sigma+\mu)(\kappa+\mu)(\mu+\mu_{TB}+r)\left((\Phi+\mu)(\pi+\gamma+\mu+\psi)+\pi\psi\right)$$

$$F\left(\frac{\Lambda}{\mu}\right) = [(R_0 - 1) + \left(\frac{\kappa\sigma r}{(\sigma+\mu)(\kappa+\mu)(\mu+\mu_{TB}+r)}\right)\eta_2$$

Where

$$\eta_2 = \mu\mu_{TB}^2(\sigma+\mu)(\kappa+\mu)(\mu+\mu_{TB}+r)\left((\Phi+\mu)(\pi+\gamma+\mu+\psi)+\pi\psi\right)$$

and

$$R_0 = \frac{\beta_a(t)\kappa\Lambda\left((\Phi+\mu)(\pi+\gamma+\mu) + \delta\psi(\Phi+\pi+\mu)\right)}{\mu(\kappa+\mu)(\mu+\mu_{TB}+r)\left((\Phi+\mu)(\pi+\gamma+\mu+\psi)+\pi\psi\right)}$$

c endemic equilibrium given in equation in equation (1.1.13).

The basic reproduction number

The basic reproduction number (R_0) serves as means for analyzing epidemic models and determining whether the disease will die out within a short period of time or become a pandemic. Quantitatively, R_0 has a threshold value of one. Mathematically, R_0 is derived as the spectral radius (largest eigenvalue) of the next generation matrix

Consider a disease transmission model with n compartments. We let $x(t) \in R_+^n$, where $x_i(t)$ is

the number of individuals in compartment *i* at time *t* and R_+^n corresponds to the non-negative

part of R^n. Also, we let *K* be a set of compartments corresponding to the states with infections and,

$$X = \{x(t) \in R_+^n : x_i(t) = 0 \; for \; i \in K\}$$

be the set of compartments corresponding to the disease-free states. Then, the transmission model given by:

$$\frac{dx_i(t)}{dt} = f_i(x)$$

Can be re-written as :

$$\frac{dx_i(t)}{dt} = \mathcal{F}_i(x) - \mathcal{M}_i(x)$$

Where $\mathcal{F}_i(x)$ represents the rate of occurrence of new infections in compartment i and

$$\mathcal{M}_i(x) = \mathcal{M}_i^-(x) - \mathcal{M}_i^+(x)$$

represent the transition of individuals in compartment i. Where $\mathcal{M}_i^-(x)$ is the transfer of individuals out of compartment i and $\mathcal{M}_i^+(x)$ is the transfer of individuals into compartment i. Let E_0be the disease free equilibrium point of the model and define $m \times m$ matrices F and V respectively as the Jacobian of $\mathcal{F}$ and $\mathcal{M}$ eavaluated at the equilibrium E_0. The system (1.1.2) is therefore given by the equation;

$$\frac{\partial E}{\partial t} = \mathcal{F}(E) - \mathcal{M}(E)$$

Which after linearizing at the disease free equilibrium gives the derivatives $D\mathcal{F}(E_0)$ and $D\mathcal{M}(E_0)$ from which we obtain the 2×2 matrices F and V defined as

$$F = \begin{pmatrix} 0 & \beta_a(t)(S^*(t,a) + \delta V^*(t,a) + \delta U^*(t)) \\ 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \kappa+\mu & 0 \\ -\kappa & \mu+\mu_{TB}+r \end{pmatrix}$$

With $S^*(t), V^*(t)$ and $U^*(t)$ given in Equation (1.1.5). The next generation matrix is thus given by

$$FV^{-1} = \begin{pmatrix} \frac{\kappa(P_1+P_2+P_3)}{(\kappa+\mu)(\mu+\mu_{TB}+r)} & \frac{P_1+P_2+P_3}{\mu+\mu_{TB}+r} \\ 0 & 0 \end{pmatrix} \quad (1.1.16)$$

Where

$$P_1 = \frac{\beta_a(t)\Lambda(\Phi+\mu)(\pi+\mu+\gamma)}{(\Phi\mu+\mu^2)(\pi+\mu+\gamma+\psi)+\mu\pi\psi}$$

$$P_1 = \frac{\beta_a(t)\Lambda\psi\delta(\Phi+\mu)}{(\Phi\mu+\mu^2)(\pi+\mu+\gamma+\psi)+\mu\pi\psi}$$

$$P_1 = \frac{\beta_a(t)\Lambda\pi\psi\delta}{(\Phi\mu+\mu^2)(\pi+\mu+\gamma+\psi)+\mu\pi\psi}$$

The largest eigenvalues of Equation (1.1.16) is thus, the basic reproduction number and it is given as:

$$R_0 = \frac{\kappa(P_1+P_2+P_3)}{(\kappa+\mu)(\mu+\mu_{TB}+r)} \quad (1.1.17)$$

Estimation of model parameters

Let's write our model (1.1.2) in theform

$$\begin{cases} \frac{d}{dt}y(t,\theta) = f(t,y,\theta) \\ y(0,\theta) = y_0 \end{cases}$$

where $y(t,\theta) = \left(S(t,\theta), V(t,\theta), U(t,\theta), L(t,\theta), R(t,\theta), I(t,\theta)\right) \in \mathbb{R}^6$ is a vector of the state

variables and $\theta = (\Lambda, \gamma, \Phi, \sigma, \psi, \pi, \beta, r, \delta, \kappa, \mu, \mu_{TB}) \in \mathbb{R}^{12}$ represents a vector of the parameters that are to be estimated. The parameter estimation procedure seeks to find values for each of the parameters of the system for which the sum of square errors between the observed data points and the solution of the system is minimized. That is, given m data points $(t_i, y_i), i = 1,23, \ldots m$, we seek to minimize the objective function given by;

$$F(\theta) = \sum_{i=1}^{m} [y(t_i) - \hat{y}(t_i, \theta)]^2$$

where $\hat{y}(t_i, \theta)$ is the solution of the system (1.1.2) associated with the model parameters θ.

Finding the parameter vector θ that fits best the model corresponds to solving the following optimization problem:

$$\min_{\theta \in \mathbb{R}^{12}} F(\theta) \text{ subject to } \theta_{min} \leq \theta_i \leq \theta_{max}$$

for i = 1, . . . , 12. We implement our model using the deSolve package in RStudio which is a general solver for initial valued ordinary differential equations [11] and then fit the model to real data using optim in R software [12]. This criterion is based on the Nelder-Mead method for optimization [13].

We obtained age-specific tuberculosis notification data of Ghana from the WHO website [14]. In fitting the model to the age-specific data, we fix the natural death rate as the inverse of thelife expectancy at birth. Given the life expectancy of Ghana to be 65.7, the natural death rate was given as μ=0.0152207. The disease induced death rate was taken to be the average of the estimated TB death rate (upper bound) per 100000 population from 1995 to 2012 [15] given as 28.883333333. Therefore, the disease induced death rate was chosen to be μ_{TB} = 0.0002888. We assumed recruitment is only by birth, as such, the recruitment rate was taken to be zerofor all age groups aside age $0 - 14$. All other parameters were estimated using optim in R software. The age-specific TB notification data is presented in Table 1.1.

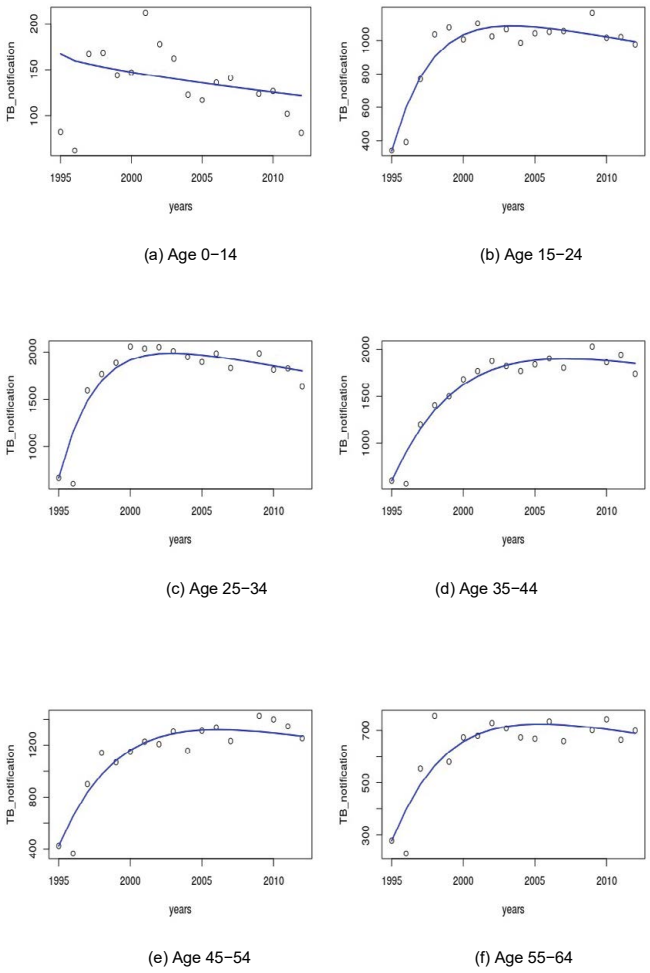
Results

For each of the age groups, we fit the model to the TB notification data presented in Tables 1.2 and 1.3. The following results were obtained after the fitting.

Table 1.2. Age specific TB notification in Ghana.

Years	Age-specific TB notifications						
	0–14	15–24	25–34	35–44	45–54	55–64	≥65
1995	82	342	669	603	424	278	160
1996	62	393	605	568	365	229	200
1997	167	769	1592	1199	899	555	415
1998	168	1036	1767	1406	1141	757	730
1999	144	1077	1885	1500	1069	581	569
2000	147	1006	2057	1681	1149	674	602
2001	212	1102	2037	1767	1227	680	687
2002	178	1024	2051	1874	1208	730	667
2003	162	1066	2009	1820	1304	709	644
2004	123	986	1947	1768	1157	674	604
2005	117	1042	1894	1838	1310	669	635
2006	136	1051	1984	1903	1337	736	672
2007	141	1055	1831	1803	1232	660	713
2009	124	1165	1986	2028	1426	702	824
2010	127	1016	1813	1861	1399	744	696
2011	102	1020	1826	1942	1345	665	716
2012	81	977	1634	1739	1253	700	733

Source: [52]



(a) Age 0–14 (b) Age 15–24

(c) Age 25–34 (d) Age 35–44

(e) Age 45–54 (f) Age 55–64

Figure 1.2. A plot of fitted model to notification data for various age intervals.

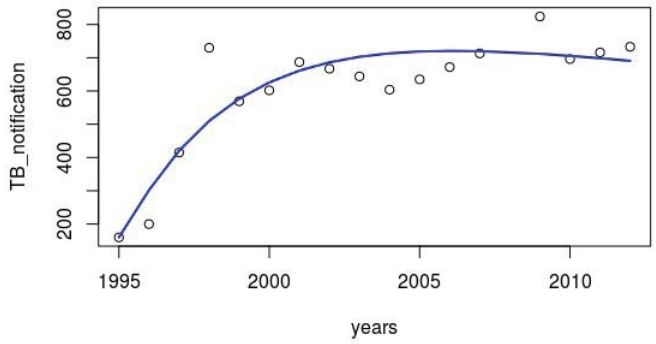


Figure 1.3. A plot of fitted model to notification data for age 65 and above.

In order to know how the vaccine impacts the model, consider a sufficiently smooth function $F(t, a)$, our aim is to approximate the solution of the partial derivatives of the function with respect to time t and age "a". For "a" close to a_0 $(a - a_0 = h, for\ h > 0)$ and t *close* to t_0, $(t - t_0 = k, for\ k > 0)$, the Taylor series expansions of $F(t, a)$ around a_0 for a fixed time t and t_0 for fixed age "a" are given by

$$F(t,a) = F(t,a_0) + h\frac{\partial F(t,a)}{\partial a} + \frac{h^2}{2}\frac{\partial^2 F(t,a)}{\partial a^2} + \frac{h^3}{6}\frac{\partial^3 F(t,a)}{\partial a^3} + \cdots$$

And

$$F(t,a) = F(t_0,a) + k\frac{\partial F(t,a)}{\partial t} + \frac{k^2}{2}\frac{\partial^2 F(t,a)}{\partial t^2} + \frac{k^3}{6}\frac{\partial^3 F(t,a)}{\partial t^3} + \cdots$$

Neglecting second and higher order terms, the change of $F(t,a)$ with

Table 1.3. Estimated and fixed parameter values.

Parameters	Ages						
	0–14	15–24	25–34	35–44	45–54	55–64	≥65
Λ	0.04584792	0	0	0	0	0	0
γ	0.02578672	0.0084566454	0.0409598998	0.5363334832	0.0494866724	0.0656823672	0.0655698455
Φ	0.02593773	0.0403558143	0.0475632553	0.0801306457	0.0100683365	0.0366654524	0.0290069461
σ	0.006368926	0.0126930066	0.1178164030	0.1112911616	0.0635126726	0.0522716863	0.0515740811
ψ	0.05576680	0.0102027336	0.0629562724	0.0242924780	0.1200642761	0.1361610979	0.1348354914
β	0.1048308	0.1223517566	0.1216519908	0.0533610705	0.0951178470	0.0911574759	0.0920698815
π	0.03577666	0.1718165953	0.158923744	0.2251141523	0.1099700959	0.1261517818	0.0571354697
r	0.3057508	0.3420294651	0.3671863857	0.1938807747	0.2198634213	0.2363816226	0.2368510920
κ	0.000008752815	0.0001530398	0.0003944183	0.0003141603	0.0003562288	0.0003674053	0.0003162655
δ	0.2058276	0.1643754451	0.5973437544	0.4127109839	0.6191274089	0.5619692944	0.6323246560
μ	0.0152207	0.0152207	0.0152207	0.0152207	0.0152207	0.0152207	0.0152207
μTB	0.0002888	0.0002888	0.0002888	0.0002888	0.0002888	0.0002888	0.0002888

respect to a is approximated to be;

$$\frac{\partial F(t,a)}{\partial a} \approx \frac{F(t,a)-F(t,a-h)}{h}$$

In a similar way, the change of $F(t, a)$ with respect to t is also approximated as;

$$\frac{\partial F(t,a)}{\partial t} \approx \frac{F(t,a)-F(t-k,a)}{k}$$

Assuming $h = k$, we have;

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)F(t,a) = \frac{2F(t,a)-F(t-k,a)-F(t,a-k)}{k} \quad (1.2.3)$$

For numerical evaluation, consider the intervals $[a_0, a_n]$ and $[t_0, t_m]$ where $a_0 < a_1 < \cdots < a_i < \cdots < a_n$ and $t_0 < t_1 < \cdots < t_j < \cdots < t_m$ with $a_i = a_{i-1} + k$ and $t_j = t_{j-1} + k$ Equation **(1.2.3)** can be re-written as

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)F(t_j,a_i) = \frac{2F(t_j,a_i)-F(t_{j-1},a_i)-F(t_j,a_{i-1})}{k} \quad (1.2.4)$$

Using the index notation, we let $F(t_j, a_i) = F_{j,i}$. For $i = 1,2,\ldots,n$ and $j = 1,2,\ldots,m$. For clarity of notation, we denote the disease induced death rate by d. The numerical solutions of system (1.1.1) is obtained by solving the following set of equations;

$$\begin{aligned}
S_{j-1,i} + S_{j,i-1} &= (2 + k\psi_i + k\mu_i + k\beta_{ji}I_{ji})S_{ji} - k(\Lambda + \gamma_i V_{ji} + \Phi_i U_{ji} + \sigma_i R_{ji}) \\
V_{j-1,i} + V_{j,i-1} &= (2 + k\pi_i + k\gamma_i + k\mu_i + k\delta\beta_{ji}I_{ji})V_{ji} - k\psi_i S_{ji} \\
U_{j-1,i} + U_{j,i-1} &= (2 + k\Phi_i + k\mu_i + k\delta\beta_{ji}I_{ji})U_{ji} - k\pi_i V_{ji} \\
L_{j-1,i} + L_{j,i-1} &= (2 + k\kappa_i + k\mu_i)L_{ji} - k\beta_{ji}I_{ji}(S_{ji} + \delta V_{ji} + \delta U_{ji}) \\
I_{j-1,i} + I_{j,i-1} &= (2 + kd_i + k\mu_i + kr_i)I_{ji} - k\kappa_i L_{ji} \\
R_{j-1,i} + R_{j,i-1} &= (2 + k\mu_i + k\sigma_i)R_{ji} - kr_i I_{ji}
\end{aligned} \quad (1.2.5)$$

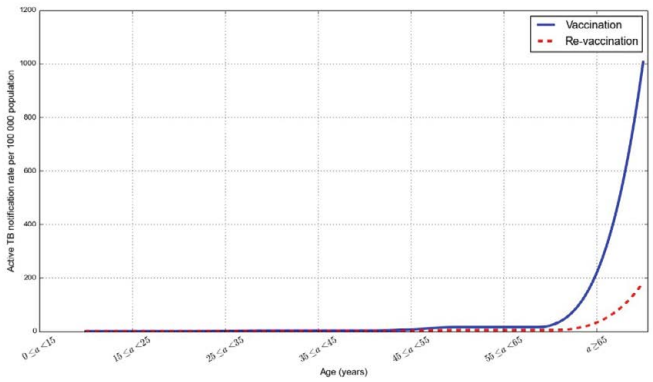


Figure 1.4. Assessing the impact of vaccination and re-vaccination on the model.

Based on the assumption that, the vaccine takes 10 years to lose its potency, we assume for this model that the vaccine at the beginning of each age group. There is no significant difference among the two trends from age $0-44$ as can be observed from Figure 1.4. However, both trends turn to rise after 45 years even though when vaccination is applied once, notified infection cases tend to be higher after compared to when re-vaccination is applied. The difference in the number of active TB infections for people aged 45 and above for the two trends suggests that, both one-time vaccination and re-vaccination proves less effective in people aged 45 andabove.

Conclusion

Vaccination has been the major means of preventing tuberculosis infection but due to inconsistency of vaccine to provide protective immunity and also high cost of mass vaccination, there has been no clear cut as to whether vaccination should be applied once or many times. In this work, we divided the population into eight different ten year age groups and analysed the impact of both one time vaccination and re-vaccination. Our work has shown that, there is no significant difference as to whether vaccination is applied once or twice for people aged less than 45 years. However, even though both strategies prove less effective in people above 45 years of age, the trend when vaccination is administered once is higher compared to when it is administered twice. This trends were however obtained by administering the vaccine at ten yearintervals.

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