SIMULATION ON MATHEMATICAL MODELS ABOUT FUTURE PREDICTIONS ON TUBERCULOSIS DYNAMICS IN ALBANIA

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Abstract

Tuberculosis remains a major global health problem. It causes ill-health among millions of people each year and ranks as the second leading cause of death from infectious disease worldwide, after the human immunodeficiency virus (HIV). Tuberculosis has slow intrinsic dynamics. The incubation period, latent period and infectious period span long time intervals in order of years in average. The slow progression of tuberculosis on at the individual level leads to slow temporal dynamics and long – term outcomes of tuberculosis at the population level. Mathematical models are used to analyze dynamics of epidemic or endemic infections and create better insights into the measures that would be taken to prevent them in the future. Therefore, mathematical models are needed to estimate prolonged results and future trends of tuberculosis. The bacilli Calmette – Guérin (BCG) is the only vaccine in current use against tuberculosis. In this study we present a review of mathematical models that characterize various components of tuberculosis endemics. We assume that infection and vaccination induce an immune response that reduces susceptibility to subsequent infections but does not fully prevent it. This gives rise to the susceptible – infected – recovered (SIR) and susceptible – exposed – infected – recovered (SEIR) epidemiological models of transmission. The transmission dynamics and its long – term effects can often be better observed and predicted using simulations of those models. In this study we try to make a prediction about future developments of tuberculosis dynamics in Albania. The data for the simulations are taken from the World Health Organization reports. The results could guide future public health measures in Albania about tuberculosis control strategies.

Keywords**:** *tuberculosis endemics, transmission dynamics, partial immunity, re – infection.*

1. Introduction

Tuberculosis (TB) is an endemic bacterial disease present in humans since antiquity at the latest. The main cause of TB is the bacillus *Mycobacterium tuberculosis (Mtb)*, identified and described by Robert Koch on 24 March 1882 . He received the Nobel Prize in physiology or medicine in 1905 for his discovery [6].

Every year there are 8.8 million new active TB cases and nearly 2 million TB deaths worldwide – 5,000 every day – mostly in the poorest communities of the developing world. One third of the world's population has latent TB which may later develop into an active form of the disease [7]. TB typically attacks the lungs, but it can also affect other parts of the body. It is spread through the air, when people who have an active TB infection cough, sneeze, or otherwise transmit respiratory fluids through the air. TB has slow intrinsic dynamics. The incubation period, latent period and infection period span long time intervals, in the order of years on average. Six to nine months of therapy are required using a combination of several drugs to cure TB. In the case of drug-resistant disease, treatment is even longer. About 90% of those infected with *Mtb* have latent TB infections with only a 10% lifetime chance to progress active TB disease. If effective treatment is not given, the death rate for active TB cases is up to 66%.

TB incidence and prevalence have changed worldwide. Those two parameters are central to the rate of TB transmission. TB *incidence* is defined as the rate of appearance of new TB cases per unit time. TB *prevalence* is the proportion of infected individuals at one point or over a short time period. According to data, there is a general downward trend of prevalence and incidence in 1990 – 2011.

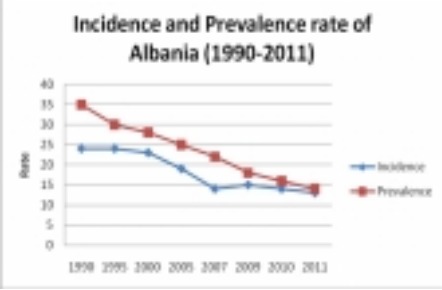

Fig. 1 Rates (per 100000 individuals) of TB in Albania between 1990 and 2011 shows a general downward trend. The plot is generated using data from [2]

To give some reference, the number of TB deaths in Albania has had a downward trend rate from 1.6 to 0.21 per 100,000 individuals for the period 1990 – 2011.

Despite predictions of a decline in global incidence, the number of new cases continues to grow in some countries. HIV infection increases susceptibility to TB infection and disease and has caused dramatic increases in TB rates in sub-Saharan Africa, even when TB control programmes are well established. The number of individuals which have TB and are HIV positive, in Albania is very slow, during the latest years, although there is a positive trend of this number. All factors associated with poverty, including malnutrition, crowding, poor air circulation and poor sanitation, increase the probability of a person becoming infected. TB as an endemic disease is present all the time in the population.

The bacilli Calmette – Guérin (BCG) is the only vaccine in current use against tuberculosis. It has existed for 80 years and is one of the most widely used of all current vaccines, reading >80% of neonates and infants in countries where it is part of the national childhood immunization programme. BCG vaccine has a documented protective effect against

meningitis and disseminated TB in children. It does not prevent primary infection and, more importantly, does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community. The impact of BCG vaccination on transmission of *Mtb* is therefore limited [11]. So we have not considered vaccination in our simulations. Immunity gained from vaccine or previous infection is temporary. Treatment of TB can be a long process. Quality antibiotics have to be taken during the treatment period. When a patient does not complete the treatment, a particularly dangerous form of drug-resistant TB called Multi-Drug Resistant Tuberculosis (MDR-TB) occurs. Albania is not so problematic related to MDR-TB.

2. Methods

(a) Literature review

The data set related TB was gathered by systematic literature review on TB reports from WHO. Published epidemiological studies were located through searches on the following terms: tuberculosis, recurrent, relapse, re – infection, epidemiological models, transmission, partial immunity.

(b) Mathematical formulation of models

There are two types of models used to study the infectious diseases at the population scale: stochastic and deterministic models. Stochastic models are used in small population size, were every individual plays an important role and heterogeneities are important. Deterministic models, also known as compartment models, attempt to describe and explain what happens on the average at the population scale. They fit well on large populations. The most known is SIR (Kermack – McKendrick, 1927) where the host population is divided into three compartments: *S(t)-susceptible, I(t)- infected* and *R(t)- recovered.* But this model is not very appropriate with the characteristics of TB. We have applied a model proposed by Blower *et al.* (1995). The compartments used for this detailed transmission model SEIR consist of :

- *S(t)-susceptible* is used to represent the number of individuals not yet infected with *Mtb* at time t,
- $E(t)$-*exposed (latent)* denotes the number of individuals at time t, who have been infected with *Mtb* but do not have the clinical illness and therefore are noninfectious,
- $I_i(t)$-*infected and infectious* denotes the number of individuals at time t, who have been infected with *Mtb*, and also they are infectious for others ,
- $I_n(t)$-*infected and non – infectious* denotes the number of individuals at time t, which are infected with *Mtb*, but they can't transmit the infection to others,
- $R(t)$-*recovered* denotes the number of individuals at time t which have been cured or completed a treatment and have a partial immunity.

$S(t) + E(t) + I_i(t) + I_n(t) + R(t) = N$ – total number of the host population.

Transmission of TB occurs because individuals with infectious TB (I_i) release aerosolized particles containing *Mtb*. This infectious particles may be inhaled by one of S susceptible individuals with *risk* $\lambda = \beta I_i$ of *infection*, were β is the *transmission coefficient*. The

incidence of infection is λS (Kermack and McKendrick, 1927). Here it is assumed that only a certain portion of cases are infectious (a fraction f of cases develop FAST TB due to primary progression, and a fraction q develop SLOW TB because of endogenous reactivation). A case may be cured without treatment at a rate c per person per year (Smith and Moss, 1994), and hence move into the non-infectious recovered category. Individuals with TB experience a death rate μ_t due to TB and mortality rate μ from other causes. An individual in the state of recovered may either relapse (and with equal probability develop either infectious (I_i) or non – infectious (I_n) TB at a rate w) or may die. So the relapse rate per person per year is given by $2w$. The system (1) of five nonlinear ordinary differential equations given below, one for each compartment describes the transmission of TB in SEIR.

$$\begin{cases} \frac{dS}{dt} = B - \lambda S - \mu S \\ \frac{dE}{dt} = (1-p)\lambda S - (v+\mu)E \\ \frac{dI_i}{dt} = pf\lambda S + qvE + \omega R - (\mu + \mu_t + c)I_i \\ \frac{dI_n}{dt} = p(1-f)\lambda S + (1-q)vE + \omega R - (\mu + \mu_t + c)I_n \\ \frac{dR}{dt} = c(I_i + I_n) - (2\omega + \mu)R \end{cases} \quad (1)$$

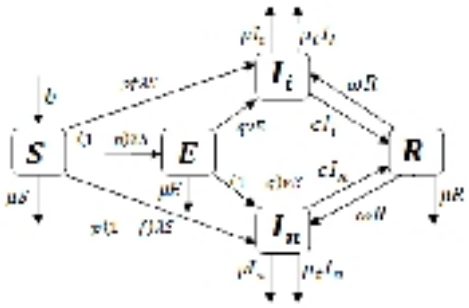

Fig. 2 SEIR model of *Blower et al. (1995)* with infectious and non – infectious infected individuals.

The basic reproduction number R_0 (threshold value) is the average number of secondary infections that would be produced by an infective in a wholly susceptible population of size S_0. It is derived from the model parameters in Table. 1. The derivation of an analytic expression for R_0 depends on the epidemiological model. Endemic infections (like TB is) show short or long periods with little fluctuations in prevalence, while epidemic infections show rapid changes in prevalence of infections. The tuberculosis endemic can be viewed as a series of linked sub – endemics. The value of R_0 modeled by system (1) is $R_0 = R_0^{FAST} + R_0^{SLOW} + R_0^{RELAPSE}$ where $R_0^{FAST}, R_0^{SLOW}, R_0^{RELAPSE}$ the basic reproductive numbers of the FAST, SLOW and RELAPSE tuberculosis sub – endemics respectively are:

$$\begin{cases} R_0^{FAST} = \left(\frac{\beta b}{\mu}\right)\left(\frac{1}{\mu+\mu_t+c}\right)pf \\ R_0^{SLOW} = \left(\frac{\beta b}{\mu}\right)\left(\frac{1}{\mu+\mu_t+c}\right)\left(\frac{q(1-p)v}{v+\mu}\right) \\ R_0^{RELAPSE} = \left(\frac{\beta b}{\mu}\right)\left(\frac{1}{(\mu+\mu_t+c)\left((\mu+\mu_t+c)-\frac{2\omega c}{2\omega+\mu}\right)}\right)\left(\frac{p+(1-p)v}{v+\mu}\right)\left(\frac{\omega c}{2\omega+\mu}\right) \end{cases}$$

Table 1. Parameter notation and values

Symbol	*Description*	*Values*			*Units*	*Notes and references*
		Lower	*Mode*	*Upper*		
β	Transmission coefficient				*/person/ year*	Derived from $\beta b/\mu$
b	Recruitment rate/birth rate				*person/year*	Derived from $\beta b/\mu$
p	Proportion of new infections that develop TB within a year	*0.0*	*0.05*	0.30	-	Styblo(1986), Comstock (1982)
f	Probability of developing FAST infectious TB	*0.50*	*0.70*	0.85	-	Styblo(1986), Comstock(1982)
q	Probability of developing SLOW infectious TB	*0.50*	*0.85*	1.0	-	Styblo(1986), Comstock(1982)
ν	Progression rate to TB	*0.00256*	-	0.00527	*/year*	5-10% progression in 20 years (Comstock and Cauthen(1993))
$1/\mu$	Average life expectancy	*65.0*[*]	-	77.0[*]	*years*	([*]WHO report for Albania (1990-2011))
μ_1	Mortality rate due TB	*0.21*	-	1.6	*/year*	([*]WHO report for Albania (1990-2011))
2ω	Rate of relapse to active TB	*0.0*	*0.01*	0.03	*/year*	Styblo(1986)
c	Natural cure rate	*0.021*	*0.058*	0.086	*/year*	(Grzybowski and Enarson (1978))
$\beta b/\mu$	Average number of infections caused by one case	*3*	*7*	13	*/year*	Styblo(1986)

(c) Simulation

According to WHO report [3] the data related to Albania (2009) are given from Table. 2.

Table. 2 TB Albania data (2009).

Population estimate by UN Statistical database (N)	3,155,271	Pulmonary cases which are smear – negative and culture – negative or unknown	70
		Extrapulmonary (I_n)	137
Pulmonary cases which are smear – positive and culture – positive (I_i)	140	No reported	5
		Total number of new TB	416
Pulmonary cases which are smear – positive and culture – negative or unknown	31	Previously treated	21
Pulmonary cases which are smear – negative and culture – positive	33	Unknown previous TB history	10
		Total number of TB cases	447

The results after the simulation using R, in a time period (2009 - 2225) are given from the graphics on Fig. 3. The script of this simulation is given in the appendix. The model that we have applied does not take in consideration vaccination. We have considered a lower natural

cure rate of the infected individual with *c=0.021*. In this case, the basic reproductive numbers are respectively: $R_E^{Fast} = 0.7274314;\ R_E^{Slow} = 2.7635;\ R_E^{Relapse} = 0.985581;\ R_E = 4.47652.$

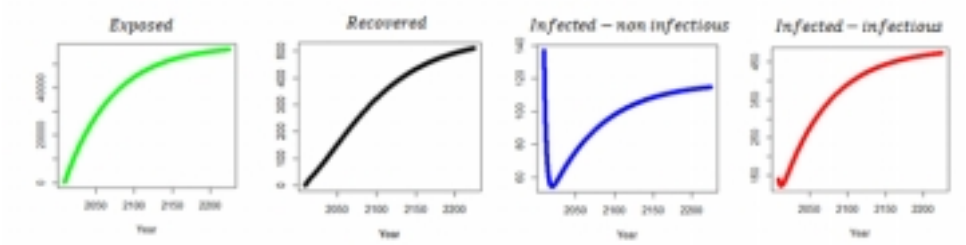

Fig. 3 A numerical simulation on SEIR model of *Blower et al. (1995)* in a time period (2009 - 2225). The endemic were initiated by introducing $S(2009) = 3154824;\ I_i(2009) = 140;\ I_n(2009) = 137;\ E(2009) = 170;\ R(2009) = 0,\ N = 3155271;\ p = 0.05;$ $q = 0.85;\ f = 0.70;\ v = 0.00256;\ c = 0.021;\ \beta = 0.0000022;\ \mu = \frac{1}{77};\ \mu_{TB(2009)} = 0.3;\ \omega = 0.005.$

We have applied this model with cure rate *c=2* of the individuals that are in the compartments $I_i(t)$ and $I_n(t)$, that is if we take in consideration a minimal period of six months that needs an infected individual to end a complete treatment without vaccination. In this case, the basic reproductive numbers are respectively: $R_E^{Fast} = 0.1050385;$ $R_E^{Slow} = 0.3990395;\ R_E^{Relapse} = 3.051419;\ R_E = 1.555497.$ The results of simulation are given in Fig. 4.

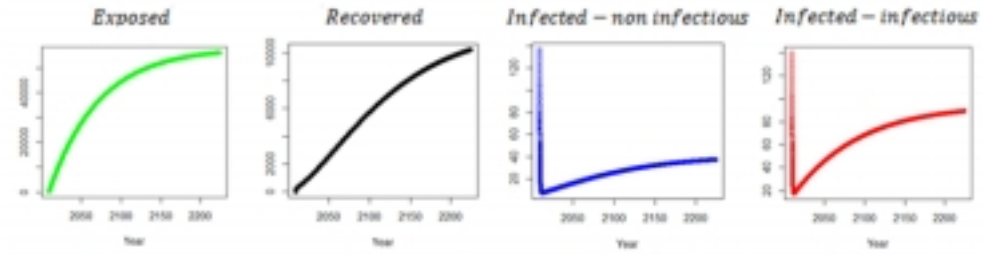

Fig. 4 A numerical simulation on SEIR model of *Blower et al. (1995)* in a time period (2009 - 2225). The endemic were initiated by introducing $S(2009) = 3154824;\ I_i(2009) = 140;\ I_n(2009) = 137;\ E(2009) = 170;\ R(2009) = 0,\ N = 3155271;\ p = 0.05;$ $q = 0.85;\ f = 0.70;\ v = 0.00256;\ c = 2;\ \beta = 0.0000022;\ \mu = \frac{1}{77};\ \mu_{TB(2009)} = 0.3;\ \omega = 0.005.$

3. Conclusion

In this study we have made a simulation of SEIR model of *Blower et al. (1995)* with data that belong to Albania in 2009. The period of simulation is taken 1999 – 2225. We have not include the process of vaccination in our model assuming that the impact of BCG is limited. We have noted that the number of individuals with characteristic *infected – infectious* ($I_i(t)$)and *infected – non infectious* ($I_n(t)$) tend to decrease at the first years, but after that they increase again. The number of $I_i(t)$ and $I_n(t)$ is greater when *c=0.021* compared to that when *c=2*. In both simulation, the number of *exposed* ($E(t)$) is at the same level, but the number of *recovered* ($R(t)$) is greater when *c=2* compared to *c=0.021*. In our study we haven't take in consideration the parameter "age" of individuals. The number of individuals with HIV+TB doesn't affect to much increasing the spread of TB, because it is to slow in Albania. We have assumed that only infected individuals ($I_i(t)$ and $I_n(t)$) can have a natural cure or a treatment cure. It would be interesting to see what happens when we take in consideration treatment also in the *exposed* compartment. The prevention of active TB through the treatment of *exposed* TB infection would be a major element of the strategy for eleminating TB in Albania.

4. Appendix

A. The code to generate plots in Fig.3 and Fig.4 with R – software using SEIR model of *Blower et al. (1995)*.

```
library(deSolve)
Year<-seq(2009,2225,0.01)
 parms<-c(
p=0.05,#proportion of new infections that develop TB within a year
q=0.85,#probability of developing slow TB
f=0.70,#probability of developing fast TB
v=0.00256,#lower progression rate of TB
c=0.021,#lower natural cure rate, or try treatment cure rate c=2
landa=0.0000022*140,#=beta*(Ii)  infection rate where beta is derived from
((beta*b/mju)=7)
mju=1/77,#Albania birth rate WHO 2009
mjut=0.3,#mortality rate due to TB WHO 2009
b=40977,#mju*N
w=0.005 #2*W=0.01 rate of relapse
 )
 xstart<-c(S=(3155271-447),E=170,Ii=140,In=137,R=0,N=3155271)
 model<-function(t,x,parms){
 S <-x[1]
 E <-x[2]
 Ii <-x[3]
In<-x[4]
 R <-x[5]
 N <-x[6]
 with(as.list(parms),{
 dS=b-landa*S-mju*S
dE=(1-p)*landa*S-(v+mju)*E
dIi=p*f*landa*S+q*v*E+w*R-(mju+mjut+c)*Ii
dIn=p*(1-f)*landa*S+(1-q)*v*E+w*R-(mju+mjut+c)*In
dR=c*(Ii+In)-(2*w+mju)*R
 dN<-dS+dE+dIi+dIn+dR
 list(c(dS,dE,dIi,dIn,dR,dN))
 })
 }
 outNr<-as.data.frame(lsoda(xstart,Year,model,parms))
#Infected - infectious plot
plot(Year,outNr$Ii,col="red")
#Infected - non infectious plot
 plot(Year,outNr$In,col="blue")
# Recovered plot
 plot(Year,outNr$R,col="black")
# Exposed plot
 plot(Year,outNr$E,col="green")
```

B. The code to display K_0^{FAST}, K_0^{SLOW}, $K_0^{RELAPSE}$ and K_0 with R – software using SEIR model of *Blower et al. (1995).*

```
p=0.05#proportion of new infections that develop TB within a year
q=0.85#probability of developing slow TB
f=0.70#probability of developing fast TB
v=0.00256#lower progression rate of TB
c=0.021#lower natural cure rate or  try treatment cure rate c=2
beta=0.0000022 #transmission coefficient
mju=1/77#Albania birth rate WHO 2009
mjut=0.3#mortality rate due to TB WHO 2009
b=40977#mju*N
w=0.005 #2*W=0.01 rate of relapse
R0Fast=((beta*b)/mju)*(1/(mju+mjut+c))*p*f
R0Slow=((beta*b)/mju)*(1/(mju+mjut+c))*((q*(1-p)*v)/(v+mju))
R0Relapse=((beta*b)/mju)*(1/((mju+mjut+c)*((mju+mjut+c)-
((2*w*c)/(2*w+mju))))*((p+(1-p)*v)/(v+mju))*((w*c)/(2*w+mju)))
R0=R0Fast+R0Slow+R0Relapse
#Display the result of R0Fast
R0Fast
#Display the result of R0Slow
R0Slow
#Display the result of R0Relapse
R0Relapse
##Display the result of R0
R0
```

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