A Study of Reinfection and Relapse in Tuberculosis disease using SIR Model

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Abstract

Many infectious diseases can relapse or re-infect the population with time. This study is based on the SIR epidemic model with three compartments susceptible S(t), infected I(t) and recovered R(t). The models with two different transmission rates defining relapse or recurrence infection and re-infection have been studied. The transmission rates from the recovered compartment to the infected compartment are defined as two distinct events: one dependent only on recovered population *R* while the other is dependent on both infected population *I* and recovered population *R*, called relapse and reinfection, respectively. Their corresponding basic reproduction numbers (R_0) from their respective characteristic polynomials are computed using the Jacobian Matrix method and stability discussed using the Lyapunov method. The disease-specific (TB model) is solved analytically and numerically, to study the growth of re-infection and relapse of the infection in the population.

1. Introduction

According to WHO, about one-quarter of the world's population is infected with tuberculosis (TB) bacteria. Only a small proportion of those infected will become sick with TB. In 2019, an estimated 10 million people fell ill with TB worldwide including 5.6 million men, 3.2 million women and 1.2 million children in all countries and age groups. TB causes 1.5 million deaths annually and it is estimated that 3 million cases go undiagnosed each year [20]. TB disease can be fatal if not adequately treated [3].

The detection of relapse, re-infection and mixed infections has major implications for the understanding of TB epidemiology to explore the available options for control and guiding the development of new interventional tools. These conclusions are not only relevant to TB but more generally applicable to diseases characterized by the recurrence of infection [5]. Social, environmental and biological determinants of health are attributed to high rates of infection [16].

Around one-third of the world's population is affected by latent tuberculosis infection (LTBI), identified as a condition of the persistent immune response to previously acquired Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB. Around 10% of people with LTBI will develop active TB disease in their lifetime, with the majority developing it in the first five years after initial infection [21]. Relapse of TB occurs due to the re-emergence of a strain of *M tuberculosis* that caused the original infection, indicating that during the primary disease episode, complete eradication of the bacteria was not achieved. When a patient is infected with an *M tuberculosis* strain that is distinct from the strain that caused the initial infection, re-infection occurs. In both primary and recurrent TB disease, mixed infections may emerge. It may during primary illness, whereby two genetically distinct strains are present during the initial infectious episode at the same time or latent infection or active disease may lead to infection with a second separate strain super-infection [15].

The simplest assumption is that the immune response to primary infection provides a solid immunity to subsequent infections or reinfections, and this gives rise to the susceptible–infected–recovered (SIR) and susceptible–exposed–infected–recovered (SEIR) frameworks [1]. Here, a simple SIR model [17, 18] is developed where the recovered are partially susceptible to reinfection and relapse. This paper aims to solve the TB disease model, considering that once a healthy person can be exposed to the same or different type of strain and after recovery is likely to experience serious health issues either through reinfection or relapse of the disease. In other words, a patient with TB cannot gain life-long immunity.

In this SIR model, the rate of transmission from the infected compartment to the recovered compartment is studied through two separate functions. The positivity of the solution for the considered models is discussed. The basic reproduction numbers are computed for each model. The stability of disease-free equilibrium and global stability is discussed using the Lyapunov method. In this dynamical model using Wolfram Mathematica, numerical solutions are obtained and analysed for both models predicting the disease spread with time to the extent of an epidemic.

The paper is organized in the following sections: Section 2, the SIR model for TB disease with two different functions is briefly described. Section 3, discusses the positivity of the solutions and Section 4, disease dynamics and stability analysis. In section 5, the numerical solutions are obtained. Finally, section 6 comprises the conclusions.

2. Basic Model Structure and Analysis

Mathematical modelling is an important method of understanding the nature of infectious diseases that can be useful in managing diseases, including their complete eradication. To analyse infectious diseases, various epidemiological models have been developed, including compartment models [2]. In this model, based on their epidemiological status, the population is divided into three different mutually exclusive compartments at any time t: susceptible *S(t)*, infectious *I(t)* and recovered *R(t)*. The transfer of population from one compartment to another depends on the rate of transmission [4]. Several forms of compartmental models [7,8,9] have been developed, for instance, SI (susceptible-infected), SIS (susceptible-infected-susceptible), SIR (susceptible-infected-recovered), SIRS (susceptible-infected-recovered-susceptible) and SEIR (susceptible-exposed-infected-recovered) [10,11,12].

Here, the SIR model of TB transmission is analysed by dividing the human population into three compartments, namely, suspected *S*, infected *I*, and Recovered *R*. The movement of the population is defined in ***Fig. 1***. The rate of birth, death is Λ and μ, respectively. The rate of movement from the susceptible to the infected compartment is β (contact rate) [19] and infected to the recovered compartment is γ. The treatment for tuberculosis (TB) symptoms can last anywhere from six months to a year, and sometimes more for drug-resistant tuberculosis. The recovered population moves back either to susceptible or infected. TB recurrence or relapse can be caused either by reactivation of the same strain (i.e. by relapse primarily due to unsuccessful or incomplete treatment) or by new strain reinfection, which means that a TB patient after recovering doesn't acquire any immunity [13]. So, the recovered population moves to susceptible again with a rate σ.

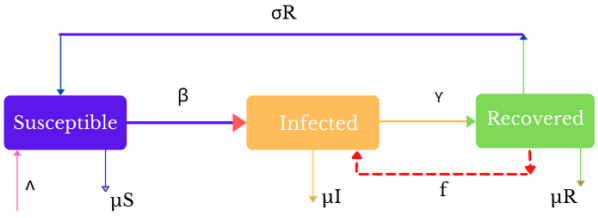


Fig. 1: SIR Model with Re-infection & Relapse

The governing differential equations of the above model **(*Fig.1*)** for:

$$\frac{dS}{dt} = \Lambda N - \frac{\beta\, S(t)I(t)}{N} - \mu\, S(t) + \sigma R(t), \qquad (1)$$

$$\frac{dI}{dt} = \frac{\beta\, S(t)I(t)}{N} - (\mu + \gamma)I(t) + f(I,R)R(t), \qquad (2)$$

$$\frac{dR}{dt} = \gamma I(t) - (\sigma + \mu)R(t) - f(I,R)R(t), \qquad (3)$$

$$\text{Where } N(t) = S(t) + I(t) + R(t), \qquad (4)$$

$$S(0)=S_0 > 0,\ I(0)=I_0 \geq 0 \text{ and } R(0)=R_0 \geq 0.$$

Model I: Reinfection function where $f(I,R) = \frac{\beta\, I(t)R(t)}{N}$, where the contact ratio is β.

Model II: Relapse or recurrence function where f(I, R) = δ (Constant) is:

The equations (1) - (4) are re-written using dimensionless variables as:

S' = S/N, I'=*I/N*, *R'=R/N*, and further omitting dashes, we obtain

Model I (Reinfection)

$$\frac{dS}{dt} = \Lambda - \beta S(t)I(t) - \mu S(t) + \sigma R(t), \quad (5)$$

$$\frac{dI}{dt} = \beta S(t)I(t) - (\mu + \gamma)I(t) + \beta I(t)R(t), \quad (6)$$

$$\frac{dR}{dt} = \gamma I(t) - (\sigma + \mu)R(t) - \beta I(t)R(t), \quad (7)$$

$$\text{Where } N(t) = S(t) + I(t) + R(t), \quad (8)$$

$S(0)=S_0 > 0$, $I(0)=I_0 \geq 0$ and $R(0)=R_0 \geq 0$.

Model II (Relapse)

S same as Model I with equations (7) and (8) will be replaced by the following equations:

$$\frac{dI}{dt} = \beta S(t)I(t) - (\mu + \gamma)I(t) + \delta R(t), \quad (9)$$

$$\frac{dR}{dt} = \gamma I(t) - (\sigma + \mu + \delta)R(t), \quad (10)$$

3. Conditions of Equilibrium

Positivity of the Solution: We show that the model equations (5-10) are biologically and epidemiologically meaningful and well-posed. It is appropriate to show that the solutions of all the stated variables are non-negative. The requirement is stated as theorems and is followed by its proof:

Theorem 1: If *S(0) > 0, I(0) > 0 and R(0) > 0* then the solution region *S(t), I(t) , R(t)* of the system of equations (5-10) is always non-negative.

Proof: Consider the system of the equations (5 - 10), each differential equation is discussed separately and shown that its solution is positive.

Theorem 2: *Positivity of infected human population*: Considering (6) and (9):

$$\frac{dI}{dt} = \beta S(t)I(t) - (\mu + \gamma)I(t) + \beta I(t)R(t) \geq -(\mu + \gamma)I(t).$$

$$\frac{dI}{dt} = \beta S(t)I(t) - (\mu + \gamma)I(t) + \delta R(t) \geq -(\mu + \gamma)I(t)$$

On, integrating the solution is $I = I_0 e^{-\int_0^t (\mu+\gamma)dt}$. It is clear from the solution that I(t) is positive since $I_0 > 0$ and the exponential function is always positive.

Theorem 3: Positivity of recovered: Considering the differential equation (9) and (10) of the system

$$\frac{dR}{dt} = \gamma I(t) - (\sigma + \mu)R(t) - \beta I(t)R(t) \geq -(\sigma + \mu)R(t) - \beta I(t)R(t)$$

$$\frac{dR}{dt} = \gamma I(t) - (\sigma + \mu + \delta)R(t),$$

I(t) is positive in time t. On, integrating, the solution is $R = R_0 e^{-\int_0^t (\sigma+\mu+I(t))dt}$ and $R = R_0 e^{-\int_0^t (\sigma+\mu+\delta)dt}$. It is clear from the solution that *R(t)* is positive since $R_0 > 0$ and the exponential function is always positive.

Theorem 4: Positivity of susceptible population: Finally, we consider the differential equation (6):

$$\frac{dS}{dt} = \Lambda - \beta S(t)I(t) - \mu S(t) + \sigma R(t) \geq - \beta S(t)I(t) - \mu S(t)$$

Λ is the rate of birth and *R(t)*, being positive, we can write as:

$$\frac{dS}{S(t)} = -(\beta I(t) + \mu)\, dt$$

On, integrating the solution is $S = S_0 e^{-\int_0^t (\beta I(t)+\mu)dt}$. It is clear from the solution that *S(t)* is positive since $S_0 > 0$ and the exponential function is also positive.

The model equations (6-10) are biologically and epidemiologically meaningful and well-posed as the solutions of all the state variables are bounded.

4. Disease Dynamics

From Equation (6) to (9), as

$$\frac{dS}{dt} + \frac{dE}{dt} + \frac{dR}{dt} = 0$$

$$\Lambda - \mu S(t) = 0$$

Therefore, the feasible region for the system is given by (S^*, I^*, R^*)

$$S^* = \frac{\Lambda}{\mu}, I^* = 0, R^* = 0$$

,

$$\omega = [(S^*, I^*, R^*) \in R^{3+} : S^* + I^* + R^* \leq \frac{\Lambda}{\mu}$$

Hence, it sufficient to consider solutions in the region ω. The solutions of the initial value problem starting in ω and defined by (6) - (10) exist and are unique on a maximal interval. Since the solution remains bounded in the positively invariant region ω, the maximal interval defined is [0, 1). So, the initial value problem is both well-posed and is positive. The above system always has a disease-free equilibrium:

$$\left(\frac{\Lambda}{\mu}, 0, 0, \right)$$

Model I:

Using the Jacobian Matrix method and differential equations (5)-(7), the Characteristic polynomial is obtained:

$$-\frac{(\lambda+\mu)(-\beta\Lambda + \mu(\gamma+\lambda+\mu))(\lambda+\mu+\sigma)}{\mu}$$

$$\lambda_1 = -\mu, \quad \lambda_2 = -\mu - \sigma$$

$$\lambda_3 = -\gamma + \frac{\beta\Lambda}{\mu} - \mu$$

As all the Eigen-values are real and negative for a system to be asymptotically stable, so, we have

$$\frac{\beta\Lambda}{\mu(\mu+\gamma)} < 1$$

So, we define, basic reproductive number R_0 as,

$$R_0 = \frac{\beta\Lambda}{\mu(\mu+\gamma)}$$

On solving equation (6) to (8), we obtain

$$S_0^* = \frac{\Lambda(R_0\mu+\sigma)}{R_0\mu((-1+R_0)\gamma+R_0\mu+\sigma)}$$

$$I_0^* = \frac{(-1+R_0)\Lambda}{R_0\mu}$$

$$R_0^* = \frac{(-1+R_0)\gamma\Lambda}{R_0\mu((-1+R_0)\gamma+R_0\mu+\sigma)}$$

Thus, DFE point (Λ/μ, 0, 0) of (5) - (8) is globally asymptotically stable in Ω if $R_0 \leq 1$ and is unstable if $R_0 > 1$.

Model II:

Using the Jacobian Matrix method and differential equations (5)-(9, 10), the Characteristic polynomial is obtained:

$$-\frac{(\lambda+\mu)(\gamma\mu(\lambda+\mu+\sigma)-\beta\Lambda(\delta+\lambda+\mu+\sigma)+\mu(\lambda+\mu)(\delta+\lambda+\mu+\sigma))}{\mu}$$

$$\lambda_1 = -\mu, \quad \lambda_2 = -\frac{A+\sqrt{B}}{2\mu}, \quad \lambda_3 - \frac{A-\sqrt{B}}{2\mu}$$

Where $A = -\beta\Lambda + \gamma\mu + \delta\mu + 2\mu^2 + \mu\sigma,$

$$B = [\beta\Lambda + \mu(-\gamma+\delta+\sigma)]^2 + 4\gamma\delta\mu^2.$$

As B>0, therefore the Eigenvalues λ_1 and λ_2 are real. As all the Eigen-values are real and negative for a system to be asymptotically stable, so, we define basic reproductive number R_0 as,

$$R_0 = \frac{\Lambda\beta(\delta+\mu+\sigma)}{\mu(\delta\mu+(\mu+\gamma)(\mu+\sigma))} < 1$$

On solving equation (5,9,10), we obtain

$$S_0^* = \frac{\Lambda}{R_0\mu}$$

$$I_0^* = \frac{(-1+R_0)\Lambda(\delta+\mu+\sigma)}{R_0\mu(\gamma+\delta+\mu+\sigma)}$$

$$R_0^* = \frac{(-1+R_0)\gamma\Lambda}{R_0\mu(\gamma+\delta+\mu+\sigma)}$$

Thus, DFE point (Λ/μ, 0, 0) of (6) - (10) is globally asymptotically stable in Ω if $R_0 \leq 1$ and is unstable if $R_0 > 1$ [6].

Now, we find the stability of the endemic equilibrium. We consider Model I i.e. (5), (6) and (7).

Consider a Lyapunov function:

$$V = W_1\left(S - S^*\log\frac{S}{S^*}\right) + +W_2\left(I - I^*\log\frac{I}{I^*}\right) + W_3\left(R - R^*\log\frac{R}{R^*}\right) \qquad (10)$$

Substituting the value of $\dot{S}, \dot{I}$ and $\dot{R}$ from equation (5), (6) and (7),

$$\dot{V} = W_1(S-S^*)\left(\frac{\Lambda}{S} - \beta I - \mu - \frac{R}{S}\right) + W_2(I-I^*)\left(\beta S + \beta R - (\mu+\gamma)\right) + W_3(R-R^*)\left(\gamma\frac{I}{R} - (\sigma+\mu) - \beta I\right)$$

At equilibrium points

$$\mu = \frac{\Lambda}{S^*} - \beta I^* - \frac{R^*}{S^*}, \mu + \gamma = \beta(S^* + R^*), \quad \sigma + \mu = \gamma\frac{I^*}{R^*} - \beta I^*$$

Therefore,

$$\dot{V} = W_1(S-S^*)\left(\frac{\Lambda}{S} - \frac{\Lambda}{S^*} - \beta(I-I^*) - \left(\frac{R}{S} - \frac{R^*}{S^*}\right)\right) + W_2(I-I^*)(\beta(S-S^*) - \beta(R-R^*)) + W_3(R - R^*)\left(\gamma\left(\frac{I}{R} - \frac{I^*}{R^*}\right) - \beta(I-I^*)\right)$$

$$\leq -W_1\left(\Lambda\frac{(S-S^*)^2}{SS^*} + \beta(I-I^*)(S-S^*) + R^*\frac{(S-S^*)^2}{SS^*}\right) + W_2\left(\beta(S-S^*)(I-I^*) + \beta(I-I^*)(R-R^*)\right) - W_3\left(\gamma I^*\frac{(R-R^*)^2}{RR^*} + \beta(I-I^*)(R-R^*)\right) \qquad (11)$$

Substituting the value of $\dot{S}, \dot{L}$ and $\dot{I}$ from equation (5), (8) and (9) in (10)

$$\dot{V} = W_1(S-S^*)\left(\frac{\Lambda}{S} - \beta I - \mu - \frac{R}{S}\right) + W_2(I-I^*)\left(\beta S - (\mu+\gamma) + \frac{\delta R}{I}\right) + W_3(R-R^*)\left(\frac{\gamma I}{R} - (\sigma+\mu+\delta)\right)$$

At equilibrium points

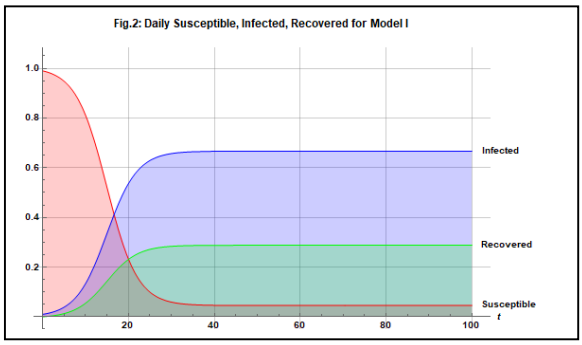
$$\mu = \frac{\Lambda}{S^*} - \beta I^* - \frac{R^*}{S^*}, \mu + \gamma = \beta S^* + \frac{\delta R^*}{I^*}, \quad \sigma + \mu + \delta = \gamma\frac{I^*}{R^*}$$

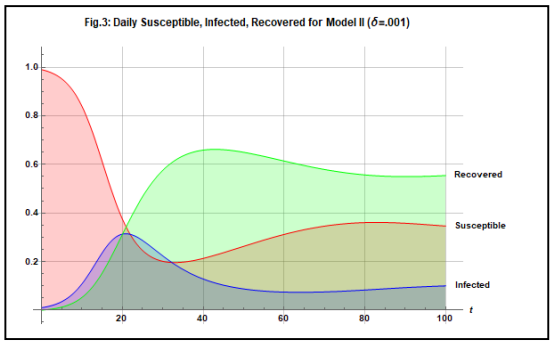
$$\leq -W_1\left(\Lambda\frac{(S-S^*)^2}{SS^*} + \beta(I-I^*)(S-S^*) + R^*\frac{(S-S^*)^2}{SS^*}\right) + W_2(\beta(S-S^*)(I-I^*) - \delta R^*(I-I^*)^2) - W_3\gamma I^*\frac{(R-R^*)^2}{RR^*} \qquad (12)$$

For $S = S^*, I = I^*, R = R^*, V = 0$ and $\dot{V} \leq 0$ for $S < S^*, I < I^*, R < R^*, W_1 = W_2 = W_3 = 1$. Therefore, by La Salle's Invariance principle [6], both endemic systems (11, 12) are globally asymptotically stable [14].

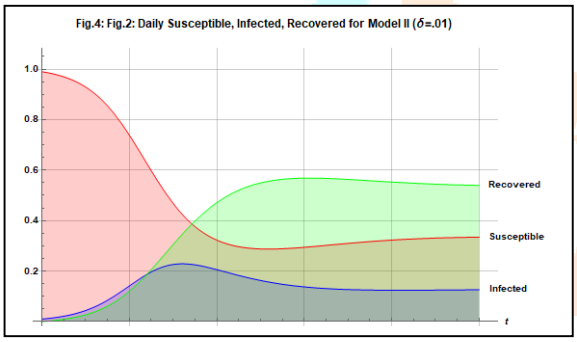
5. Numerical Simulations

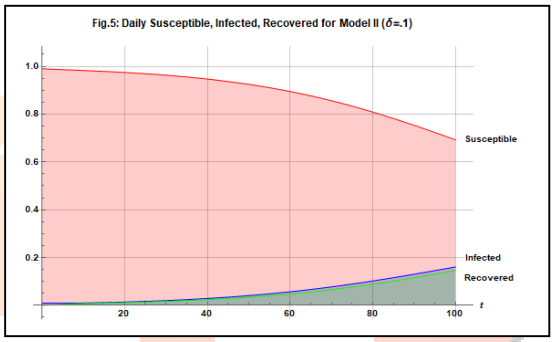
The dimensionless differential equations (5) to (8) are solved numerically using the *NDSolve* function of Wolfram Mathematica. The numerical solutions of *S*, *I* and *R*, are plotted for different values of parameters. A typical view of the solutions of *S(t)*, *I(t)* and *R(t)* for the parameters: $t=100$, $\Lambda=\mu=.01$, $R_0=3$, $\gamma=.13, \sigma=0.011$ (***Fig.2***). It is evident that in Model I (Re-infection), where the rate of movement of population from recovered compartment to the infected compartment depends on the contact rate β and infected population *I*, the susceptible population reduces quickly as the graph of the infected population rises to 0.62 and becomes saturated. Also, the graph of the recovered population saturates with time.





In Model II (Relapse or recurrence), the constant δ, coefficient of $R(t)$ plays an important role in the growth of susceptible, infected and recovered population ***(Fig.3-5)***. As δ increases, δ=0.001, 0.01 and 0.1, the rate of transmission from recovered to infected population also increases, so the average relapse days decrease. When the average number of days for relapse of disease is decreased and the disease will remain longer in the population with a reduced peak of infected and recovered. Thus, relapse of disease due to constant parameter δ spreads the infection longer for a period after achieving a higher peak value as compared to reinfection which saturates.





6. Conclusions

A mathematical model has been developed to study the behaviour of Tuberculosis disease due to either reinfection or relapse. The transmission rates from the recovered compartment to the infected compartment are defined as two distinct functions: one is a constant function so that the movement of recovered population to infected depends only on recovered population R, while in the re-infection the function is dependent both on infected I and recovered population R. It has been found that the re-infection saturates with time as it depends on the contact ratio and infected population. The relapse of the disease depends on the δ, as the constant is increased, the infected population I grows and is spread over time, recovered R population decreases leading to a serious issue in the population of Tuberculosis patients (R_0, in this case, depends on δ).

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