IOSR Journal of Mathematics (IOSR-JM)
e-ISSN: 2278-5728, p-ISSN: 2319-765X. Volume 16, Issue 2 Ser. II (Mar. – Apr. 2020), PP 41-49
www.iosrjournals.org

Deterministic Model of the Transmission Dynamics of Tuberculosis with Exogenous Re-Infection and Incomplete Treatment

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Abstract: *In this work, a deterministic Model is developed and investigated for the transmission dynamics of Tuberculosis with exogenous re-infection and incomplete treatment. We analyzed for the formulated model by considering the spread behavior and possible eradication of the disease versus persistence of tuberculosis. Our method includes: boundedness, existence of Equilibrium Points and basic reproduction number* (R_0).
From our model we obtained the basic reproduction number for determining whether the disease die out or not. The impact of different parameters of this model is studied. A sensitivity study of the model was carried out. A numerical simulation was also carried out to know further how the correct the model was
Keywords: *Deterministic Model, Basic reproduction number, Disease free equilibrium (DFE), Endemic equilibrium*

Date of Submission: 17-03-2020 Date of Acceptance: 02-04-2020

I. Introduction:

This section looks into the review of related works on tuberculosis using SEIS, SIR, SEIR and other deterministic models. Two decades have passed now with different people coming up with many mathematical models for TB. SIR models and variants like SEIR models were introduced in the 1990s and help to establish the foundation of much of the mathematical epidemiology.

The first mathematical model of TB was presented by Wattler et al. (1962) following this, there were several numerical studies, primarily focusing on cost effectiveness of different intervention model with one progression rate and various latent classes and argued that vaccination was cost-effective in countries with high TB burdens. Umana et al (2016) in his paper considered two models for tuberculosis. The first Model assumes constant recruitment with a fixed fraction entering each class, with consequences that TB never dies out and the stability analysis was done. Their second model concentrated on a general recruitment function whereby all recruitment is into the susceptible class. They concluded that the first model incorporates immigration of infectives at a constant rate, which makes it relevant and indicates that even with treatment in immigration of infectives, TB still remains endemic. Moreover they said that the differential equation system for the second Model with general recruitment has a Singularity at the origin when the total population size is zero. That concludes that in the absence of infective immigrants and then the second model of their paper predicts threshold conditions.

Okunghae et al (2010) studied differential equation and differential integral equations that describe the dynamics of disease transmission for TB in Nigeria. The main interest was to study these models to understand the long-time behavior of the dynamics of disease transmission thus, whether the disease would die out eventually or would persist. They looked at the effects of variable periods of latency on the dynamics of TB by considering an SEIS model with individual moving back to the susceptible (S) class from both the Exposed (E) and the Infectious (I) due to treatment. The findings their studies revealed that the addition of an arbitrarily distributed latency period to the basic TB model does not alter the quantitative dynamics of TB, the disease either dies or remains endemic regardless of the shape of the incubation/latent period distribution. Okuonghae et al (2008) formulated a two group model for one-strain and two-strain TB in order to determine possible mechanisms that may be useful for the survival and spread of naturally resistant strains of TB as well as antibiotics generated resistant strains of TB. They claimed that the analysis of their model will reveal that non-antibiotic co-existence is possible but rare for naturally resistant strains while co-existence is almost the rule for strains that results from the lack of compliance with antibiotic treatment by TB infected individuals. One of the possibilities is that such a person may develop active TB as a consequence of exogenous re-infection. Other papers that were consulted were Castilo-Chavez et al (1997), Cborgdoff (2004), Centre for Disease Control and Prevention (2011), Derrick et al (1976), Feng et al (2001), Ihejirika et al (2019), La Salle (1976), Omame et al (2015),Umana et al (2016), Van den Dnessche (2002).

II. Model Fomulation

2.1 FLOW DIAGRAM

We now formulate a model of the transmission dynamics and treatment of Tuberculosis with exogenous re-infection.We also divide the population into four compartments $S(t), L(t), I(t) and\ T(t)$ as susceptible, latent, infectous and Treated individuals where t represents time.

The flow diagram is given below:

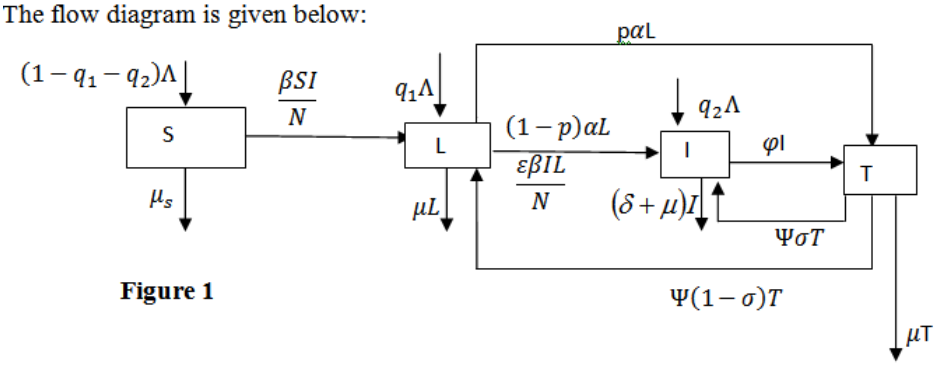

Figure 1

2.2 Symbols and Parameters

Below are the symbols and parameter used in formulating our model

Table 1: Symbols and Parameters

Symbols and Parameters	Description
$\boldsymbol{S(t)}$	Susceptible Individuals
$L(t)$	Latent Individuals
$I(t)$	Individual with active TB disease
$T(t)$	Treated Individuals
Λ	Recruitment rate
β	Contact rate
μ	Natural death rate
δ	TB Induced death rate
α	Rate of progression through the latent stage
P	Fraction of latent immigrants progressing to Treated Stage
Ψ	Treatment failure rate
ε	Exogenous re-infection rate
Type equation here.	Fraction of immigrants who fails treatment and progress to the active TB disease stage
φ	Rate of progression through the latent stage to treatment stage.
q_1	Fraction of immigrants who progress to latent stage
q_2	Fraction of immigrants who progresses to active TB disease stage
$\bar{N}$	Total population

2.3 Assumptions of the Model

Those in each class can die as a result of natural death

(i) All immigrants are assumed to be Susceptible
(ii) There is a tendency that those in the active TB disease stage can die as a result of TB disease.
(iii) Individuals treated of TB disease can fail treatment
(iv) Only those in active TB disease stage can transmit the disease.

2.4 Differential Equation for the Deterministic Model

We now formulate the Model equation from the flow diagram above

$$\left.\begin{aligned}
\frac{dS}{dt} &= (1-q_1-q_2)\Lambda - \frac{\beta SI}{N} - \mu S \\
\frac{dL}{dt} &= \frac{\beta SI}{N} + q_1\Lambda + \psi(1-\sigma)T - (\mu+\alpha)L - \frac{\varepsilon\beta IL}{N} \\
\frac{dI}{dt} &= (1-p)\alpha L + \frac{\varepsilon\beta IL}{N} + q_2\Lambda + \psi\sigma T - (\mu+\delta+\varphi)I \\
\frac{dT}{dt} &= \varphi I + p\alpha L - (\Psi+\mu)T
\end{aligned}\right\} \qquad (1)$$

2.4 BOUNDEDNESS

Theorem 2.1: The closed set $D = \left\{ \left(S(t), L(t), I(t), T(t)\right) \in \Re_+^4 : N \le \frac{\Lambda}{\mu} \right\}$ is positively invariant and attracts all positive solutions of the model.

Proof: For boundedness we add all the equation of our model, that is,

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dL}{dt} + \frac{dI}{dt} + \frac{dT}{dt}$$

$$\frac{dN}{dt} = (1-q_1-q_2)\Lambda - \frac{\beta SI}{N} - \mu S + \frac{\beta SI}{N} + q_1\Lambda + \psi(1-\sigma)T - (\mu+\alpha)L - \frac{\varepsilon\beta IL}{N} +$$

$$(1-p)\alpha L + \frac{\varepsilon\beta IL}{N} + q_2\Lambda + \psi\sigma T - (\mu+\delta+\varphi)I + \varphi I + p\alpha L - (\Psi+\mu)T$$

$$\frac{dN}{dt} = \Lambda - \mu(S+L+I+T) - (\mu+\delta)I = \Lambda - \mu N - (\mu+\delta)I > \Lambda - \mu N$$

$$\frac{dN}{dt} + \mu N \le \Lambda$$

Integrating both sides using an integrating factor $e^{\mu t}$ we have,

$$\frac{d}{dt}(e^{\mu}N) = \Lambda e^{\mu t}dt \Rightarrow e^{\mu}N \le \frac{\Lambda}{\mu}e^{\mu t} + c \Rightarrow N \le \frac{\Lambda}{\mu} + ce^{-\mu t}$$

Therefore the closed set $D = \left\{ \left(S(t), L(t), I(t), T(t)\right) \in \Re_+^4 : N \le \frac{\Lambda}{\mu} \right\}$ is positively invariant and attracts all positive solutions of the model.

2.5 Existence of Equilibrium Points

For there to exist equilibrium points, $\frac{dS}{dt} = \frac{dL}{dt} = \frac{dI}{dt} = \frac{dT}{dt} = 0$ which means that

$$(1-q_1-q_2)\Lambda - \frac{\beta SI}{N} - \mu S = 0 \qquad (i)$$

$$\frac{\beta SI}{N} + q_1\Lambda + \psi(1-\sigma)T - (\mu+\alpha)L - \frac{\varepsilon\beta IL}{N} = 0 \qquad (ii)$$

$$(1-p)\alpha L + \frac{\varepsilon\beta IL}{N} + q_2\Lambda + \psi\sigma T - (\mu+\delta+\varphi)I = 0 \qquad (iii)$$

$$\varphi I + p\alpha L - (\Psi+\mu)T = 0 \qquad (iv)$$

$$S^0 = \frac{(1-q_1-q_2)}{\mu}\Lambda$$

From (ii) we have,

$$q_1\Lambda + \psi(1-\sigma)T = (\mu+\alpha)L \Rightarrow L^0 = \frac{q_1\Lambda + \psi(1-\sigma)T^0}{(\mu+\alpha)}$$

From (iii) we have,

$$(1-p)\alpha L + \frac{\varepsilon\beta IL}{N} + q_2\Lambda + \psi\sigma T - (\mu+\delta+\varphi)I = 0 \Rightarrow (1-p)\alpha L + q_2\Lambda + \psi\sigma T = (\mu+\delta+\varphi)I$$

$$\Rightarrow I^0 = \frac{(1-p)\alpha L^0 + q_2\Lambda + \psi\sigma T^0}{(\mu+\delta+\varphi)}$$

From (iv) we have,

$$\varphi I + p\alpha L - (\Psi+\mu)T = 0 \Rightarrow \varphi I + p\alpha L = (\Psi+\mu)T \Rightarrow T^0 = \frac{\varphi I^0 + p\alpha L^0}{(\Psi+\mu)}$$

The equilibrium point is

$$\xi = \left(S^0, L, I^0, T^0\right) = \left(\frac{(1-q_1-q_2)}{\mu}\Lambda, \frac{q_1\Lambda + \psi(1-\sigma)T^0}{(\mu+\alpha)}, \frac{(1-p)\alpha L^0 + q_2\Lambda + \psi\sigma T^0}{(\mu+\delta+\varphi)}, \frac{\varphi I^0 + p\alpha L^0}{(\Psi+\mu)}\right)$$

The disease-free equilibrium is $\xi^0 = \left(S^0, 0, 0, 0\right) = \left(\frac{(1-q_1-q_2)}{\mu}\Lambda, 0, 0, 0\right)$ while the Endemic equilibrium is

$$\xi_E = \left(0, L, I^0, T^0\right) = \left(0, \frac{q_1\Lambda + \psi(1-\sigma)T^0}{(\mu+\alpha)}, \frac{(1-p)\alpha L^0 + q_2\Lambda + \psi\sigma T^0}{(\mu+\delta+\varphi)}, \frac{\varphi I^0 + p\alpha L^0}{(\Psi+\mu)}\right)$$

2.7 Basic Reproduction Number (R_0)

The basic reproduction number is the average number of secondary infection that occurs if a single infected individual is introduced into an entirely susceptible population. It is obtained by taking the largest eigenvalue. Note that $p(FV^{-1})$

Where, $F = \left(\frac{\delta f_i(P_0)}{\delta X_j}\right)$

And $V_i = \left(\frac{\partial V_i P_0}{\partial X_j}\right)$

Let $X = [E\ T]^T$

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

$$V(X) = V^- - V^+$$

Where

f_i is the rate of appearance of new infection in compartment I

V^- is the transfer of individual out of the disease compartment

V^+ is the rate of transfer of individuals into the disease compartment

F is the Jacobian of f_i evaluated at DFE. We have

V is the jacobian of V_i evaluated at DFE

$$f_i = \begin{pmatrix} \frac{\beta SI}{N} \\ 0 \end{pmatrix} V_i^- = \begin{pmatrix} (\mu+\alpha)L + \frac{\varepsilon\beta IL}{N} \\ (\mu+\delta+\varphi)I \end{pmatrix} V_i^+ = \begin{pmatrix} q_i\Lambda + \Psi(1-\sigma)T \\ (1-p)\alpha L + \frac{\varepsilon\beta IL}{N} + q_2\Lambda + \Psi\sigma T \end{pmatrix}$$

$$V_i = V_i^- - V_i^+$$

$$V_i = \begin{pmatrix} (\mu+\alpha)L + \dfrac{\varepsilon\beta IL}{N} - q_1\Lambda - \Psi(1-\sigma)T \\ (\mu+\delta+\varphi)I - (1-p)\alpha L - \dfrac{\varepsilon\beta IL}{N} + q_2\Lambda - \Psi\sigma T \end{pmatrix}$$

$$V_i = \begin{pmatrix} (\mu+\alpha)L + \frac{\varepsilon\beta IL}{N} - q_1\Lambda - \Psi(1-\sigma)T \\ (\mu+\delta+\varphi)I - (1-p)\alpha L - \frac{\varepsilon\beta IL}{N} - q_2\Lambda - \Psi\sigma T \end{pmatrix}$$

$$F = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix} V = \begin{pmatrix} (\mu+\alpha) & 0 \\ (p-1)\alpha & (\mu+\delta+\varphi) \end{pmatrix}$$

$$V^{-1} = \begin{pmatrix} \dfrac{1}{(\mu+\alpha)} & 0 \\ \dfrac{-(p-1)\alpha}{(\mu+\alpha)(\mu+\delta+\varphi)} & \dfrac{1}{(\mu+\delta+\varphi)} \end{pmatrix}$$

$$FV^{-1} = \begin{pmatrix} 0 & \beta \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \dfrac{1}{(\mu+\alpha)} & 0 \\ \dfrac{-(p-1)\alpha}{(\mu+\alpha)(\mu+\delta+\varphi)} & \dfrac{1}{(\mu+\delta+\varphi)} \end{pmatrix}$$

$$FV^{-1} = \begin{pmatrix} \dfrac{(1-p)\alpha\beta}{(\mu+\alpha)(\mu+\delta+\varphi)} & \dfrac{\beta}{\mu+\delta+\varphi} \\ 0 & 0 \end{pmatrix}$$

$$R_0 = |FV^{-1}\text{-I}\lambda| = 0$$

$$R_0 = \begin{vmatrix} \dfrac{\beta(1-p)\alpha - \lambda}{((\mu+\alpha)(\mu+\delta+\varphi))} & \dfrac{\beta}{\mu+\delta+\varphi} \\ 0 & -\lambda \end{vmatrix} = 0$$

$$R_0 = \frac{(1-p)\alpha\beta}{(\mu+\alpha)(\mu+\delta+\varphi)}$$

III. Sensitivity Analysis

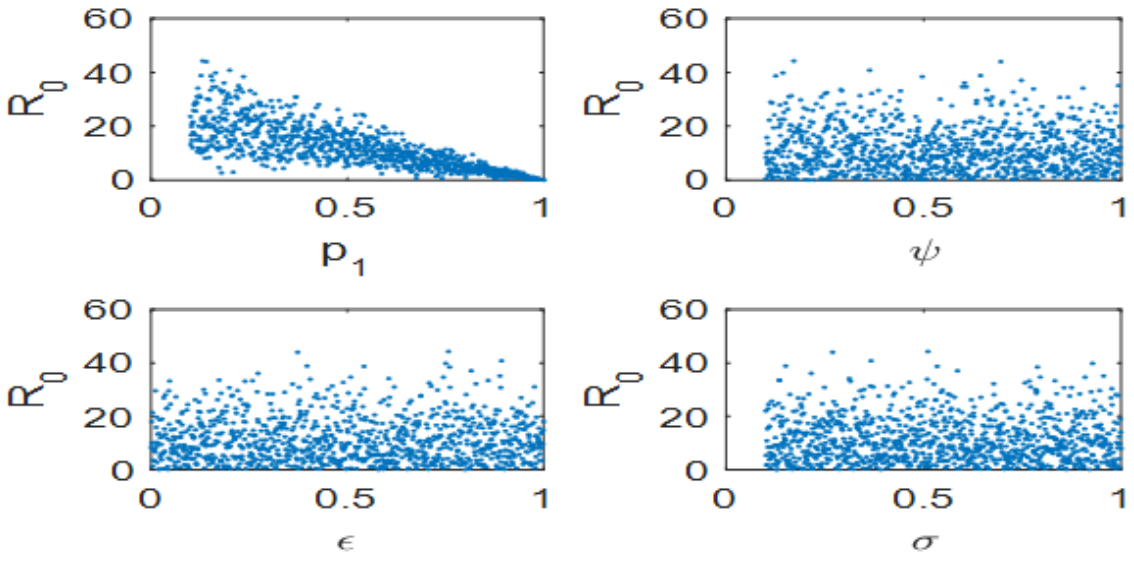

Figure 2

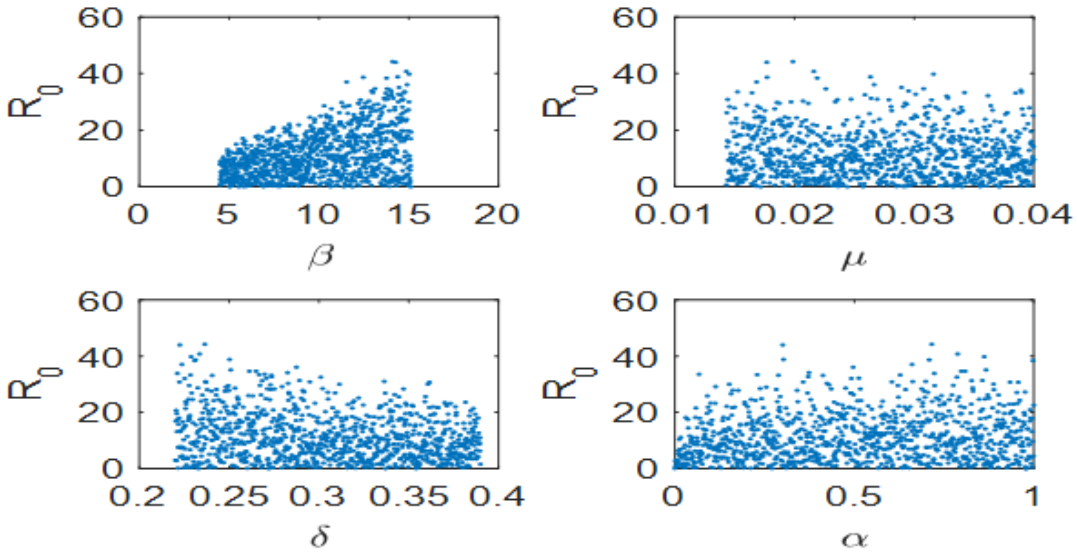

Figure 3

3.1 Numerical Simulation

Many phenomena of interest in biology that can be modelled by the use of diffusion processes satisfying a nonlinear stochastic differential equation are not easy to solve analytically, it is advantageous to proceed via computer simulations. There will be time when the physical system is too complicated for analytical modeling; in such a case, simulation would be an appropriate tool (Feldan and Valdez-Flores, 2010). We therefore solve the model numerically using the MATLAB software (see appendix).
The parameters information is given below:

Table 2: Parameters and values

Parameters	Description	Values	Sample range	References
Λ	Recruitment rate	2041	----	*Song et al* (2002)
β	Contact rat	8.557	[4.4769, 15.1347]	Okuonghae and Aihie(2008)
μ	Natural death rate	0.02041	[0.0143,0.04]	UNAIDS-WHO (2004)
δ	TB Induced death rate	0.365	[0.22,0.39]	Borgdoff (2004), Cohen *et al.* (2007), *Dye et al*(1998), Styblo(1991)
α	Rate of progression through the latent stage	1.5	[0,1]	Hongbin Guo *et al.* (2011)
P	Fraction of latent immigrants progressing to Treated Stage	0.5	[0.1,1.0]	Assumed
Ψ	Treatment failure rate	0.2	[0.1,1.0]	Assumed
ε	Exogenous re-infection rate	0.2	[0.1,1.0]	Assumed
σ	Fraction of immigrants who fails treatment and progress to the active TB disease stage.	0.4	[0.1,1.0]	Assumed
φ	Rate of progression through the latent stage to treatment stage.	0.05	[0.005,0.05]	Blower *et al.* (1995),Cohen *et al.* (2007)
q_1	Fraction of immigrants who progress to latent stage	0.3	[0.1,1.0]	Assumed
q_2	Fraction of immigrants who progresses to active TB disease stage	0.13	[0.1,1.0]	Assumed
$\bar{N}$	Total population	1000	----	Assumed

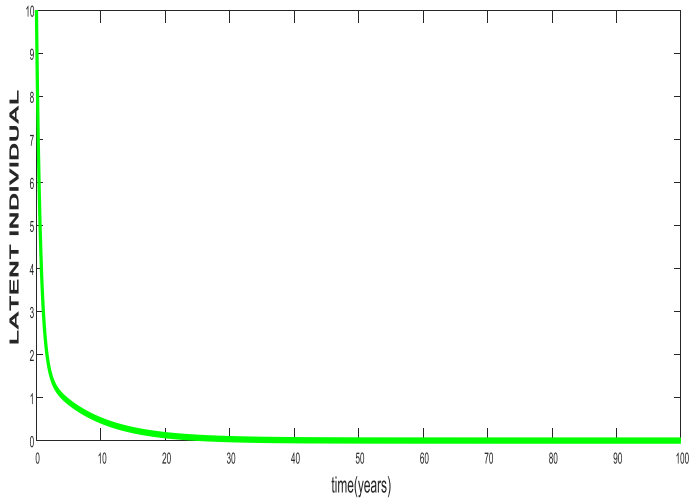

Figure 4: Plot of the latent individuals against time years

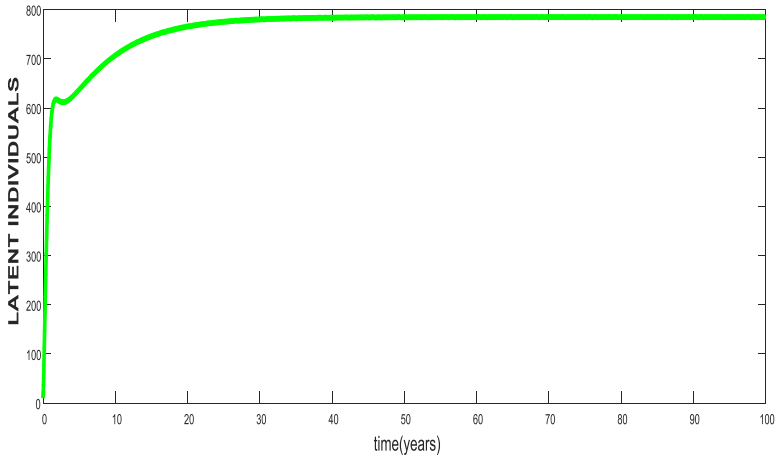

Figure 5: Plot of latent individuals against time in years

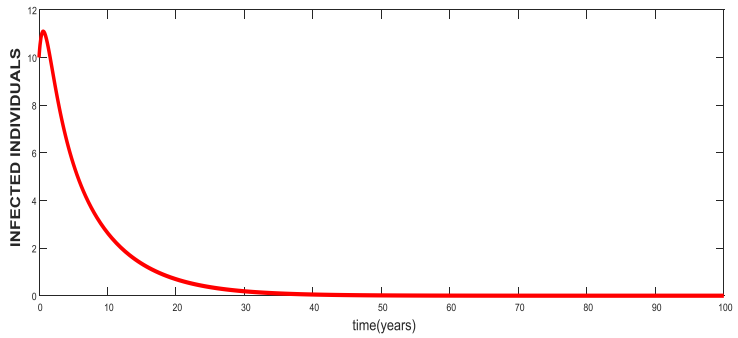

Figure 6: Plot of Infected Individuals against time in years

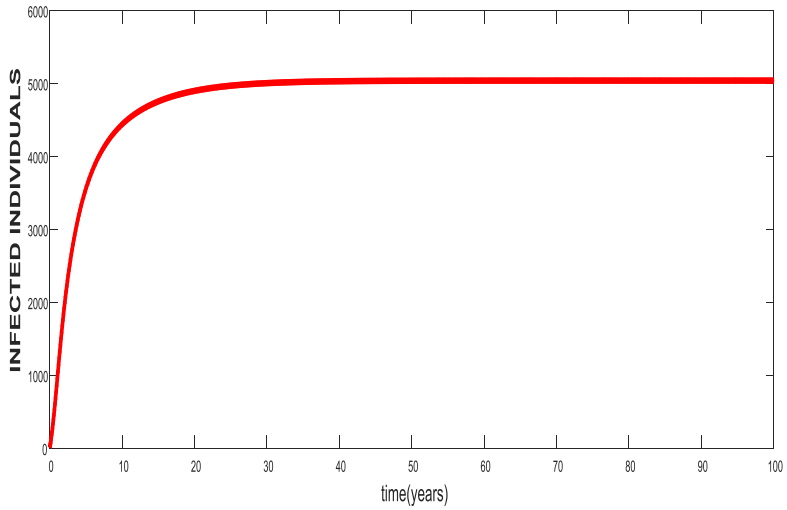

Figure 7: Plot of Infected individuals against time in years

IV. Discussion of Results

The model has eleven parameters and uncertainties are expected to arise in estimates of the values used in the numerical simulations. In order to assess the effect of these uncertainties and to determine the parameters that have the greatest impact on the transmission dynamics of tuberculosis, we perform uncertainty and sensitivity analysis. We perform Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC) on the model.

Using the reproduction number as the response function, the top ranked parameters are shown in Table 4.1 below.

Table 3: PRCC values for the parameters of the model using the reproduction number ($\boldsymbol{R_o}$) as response function.

Parameters	**PRCC (R_o)**
β	0.7576
μ	0.1721
δ	-0.5001
α	-0.5010
P_1	-0.9324
Ψ	0.0602
ε	-0.0080
σ	0.0422
ϕ	-0.0786
q_1	-0.0015
q_2	-0.0534

A parameter is said to be significant if its PRCC values $|P| \geq 0.5$ from the table 4.1 the most significant parameters are$\beta, \delta, \alpha \; and \; P_1$. β is positively correlated. This means if there is an increase in β it will also result in an increase in disease burden in the population. $\delta, \alpha \; and \; P_1$ **are** negatively correlated this mean that if there is an increase in $\delta, \alpha \; and \; P_1$ it will also result in an increase in disease burden in the population.

4.1 Deterministic analysis

The above graph Figure 3.4 under deterministic shows the behavior of the disease of the Latent compartment when the reproduction number $R_0 = 0.00566 < 1$. We observed that the disease will die out. Figure 3.5 shows the behavior of the disease in the Latent compartment when the reproduction number $R_0 = 9.6944 > 1$. We observed that the disease will produce an endemic. Figure 3.6 under Deterministic shows the behavior of the disease in the infected compartment when the reproduction number. This means the disease will eventually die out. Figure3.7 under Deterministic shows the behavior of the disease when the reproduction number $R_0 = 9.6944 > 1$. This means there will be more and high occurrence of the disease within the population.

V. Summary, Conclusion and Recommendations

5.1 Summary

In this work, we formulated a deterministic and stochastic model for the transmission dynamics of tuberculosis with exogenous re-infection and incomplete treatment. We observed the behavior of the disease compartment when the reproduction number is less than and greater than one. We also showed disease free equilibrium and carried out sensitivity analysis to know the effect of each parameter in the population. Our work includes simulation.

5.2 Conclusion

In this work a Stochastic differential equation model is developed and investigated for the transmission dynamics of Tuberculosis with exogenous re-infection and incomplete treatment. The model strongly indicated that the spread of a disease largely depend on the contact rate with infected individuals within a population. In this work we carried out three different analyses which are Deterministic, Stochastic as Sensitivity analysis. We formulated the Mathematical Model and showed that the population classes are non-negative and we obtain the reproduction number using the next generation matrix. With the aid of the reproduction number, we proved the condition for stability of disease free equilibrium. When the reproduction number is less than one, our model has only a disease free equilibrium, which implies that disease die out eventually when the reproduction number is larger than one, our model has a unique endemic equilibrium which implies that the disease persists in the whole population and tends to a steady state. Finally Simulation results are given to verify our conclusion.

5.3 Recommendations

As tuberculosis continues to claim more lives, it is imperative to have comprehensive researches done in order to explore possible new control strategies of the infection as well as assessing the impact of the existing control strategies. From the results of this project the following control strategies are recommended:

(1) Carrying out a cost-effectiveness analysis of the control strategies of TB in the model

(2) Expanding the model to incorporate vaccination of susceptible population, immigrants and newborns, thus assess its role on the dynamics of TB.

(3) An investigation on the efficacy of TB treatments and up take in educational programs

(4) Since the model shows that the spread of the disease largely depend on the contact rate, therefore efforts should be made to minimize unnecessary Contact with TB infected individuals, this will reduce risk of an outbreak.

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