Mathematical Modelling of Pulmonary and Extra-pulmonary Tuberculosis

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***Abstract*-- Tuberculosis (TB) is a big public health problem in India. As per WHO TB-report 2011, India accounts for one-fourth (approximately 26%) of the global TB incident cases. Each year nearly 20,00000 people in India develop TB, of which around 870000 are infectious cases. It is estimated that every day approximately 1000 Indians die due to TB. In this paper, a mathematical model is formulated for tuberculosis using ordinary differential equations which is similar to *SEIR* epidemic model. The entire population is divided into five compartments viz. susceptible (*S*), exposed (*E*), infectious with pulmonary tuberculosis (*I*) and extra-pulmonary tuberculosis (*X*) and treated (*T*). Basic reproduction number R_0 is defined and a relation is established for it. Steady state conditions are derived showing that when $R_0 > 1$ there is a disease free equilibrium which is locally asymptotically stable whereas for $R_0 > 1$ there exists an endemic equilibrium. Sensitivity of R_0 to each parameter is analysed.**

***Keywords*-- Extra-pulmonary, Pulmonary, Tuberculosis, Stability analysis.**

I. INTRODUCTION

TUBERCULOSIS or TB (short form for Tubercle Bacillus) is an infectious bacterial disease caused by Mycobacterium Tuberculosis. It is a huge health problem and a big cause of infectious mortality in India. Although TB cases are currently reducing in many developed countries but it is rising in Africa, Eastern parts of Europe and Asia. The introduction of MDR-TB (multi-drug resistant TB) and XDR-TB (extensively drug resistant TB) have created new challenges for the society and pushes the need of extensive work for deciding the right control strategies.

Many mathematical models are formulated and analysed using several techniques and mathematical tools. Most of these models are SEIR type.

Aparicio *et al*. discussed the re-emergence of tuberculosis using SEIR model [2]. In 2009, they presented a rather complex models using homogeneous mixing and heterogeneous mixing epidemic models [1]. Coljin *et al*. [6] reviewed and compared existing models showing that even small changes lead to some different types of useful interpretations. They presented their own model also using delay differential equations. Castillo-Chavez *et al*. [5] and Jung *et al*. [3] discussed models for a two-strain tuberculosis For the basics of epidemic modelling and stability analysis we referred [8] - [12]. References [7] and [13] - [14] provide the required data for India for sensitivity analysis.

Although these models of tuberculosis look similar in structure yet there are important (may not be apparent), differences in the way the population is classified and the transmission process is represented, leading to some other important conclusions. Here, we formulate the model with separating pulmonary and extra-pulmonary classes. And with the help of sensitivity analysis we try to trace the parameters which are most responsible for the spread of disease.

II. HISTORY/SYMPTOMS/TRANSMISSION OF TUBERCULOSIS

TB is caused by various strains of mycobacteria most commonly by mycobacterium tuberculosis. It most commonly affects the lungs (pulmonary) but can also affect other parts of the body (extra-pulmonary). It is transmitted from person to person through the air via droplets from the throat and lungs of people with active TB. These droplets come out when they cough or sneeze.

TB generally develops slowly. In cases when the bacteria infect the body and cause symptoms, it is called active TB otherwise it is called latent TB. Depending on the type of TB (i.e. pulmonary and extra-pulmonary), the symptoms are different.

The symptoms of active pulmonary TB are coughing, sometimes with sputum or blood, breathlessness, lack of appetite, weight loss, fever and night sweats.

Sometimes, TB occurs outside lungs, which is known as extra-pulmonary TB. It is more common in people with weak immune system particularly with an HIV infection. An extra-pulmonary infection site may be lymph nodes, bones and joints, digestive system, bladder and reproduction system, nervous system and any other part of the body. Out of these, all lymph nodes are the most common site for extra-pulmonary TB.

Once infected or infectious person may be cured with

medication or may die from TB. Recovered individuals may relapse to disease or be re-infected. In next section, we formulate mathematical model.

III. MATHEMATICAL MODEL

Here, we formulate a model based on SEIR model of infectious disease epidemiology. The entire population is divided into five compartments depending on disease status. These compartments are referred to as state variables. At time *t*, there are *S* susceptible, *E* exposed, *I* infectious (with pulmonary TB) and *X* with extra-pulmonary TB, and *T* treated.

The population move from one compartment to the other in the manner as shown in fig.1:

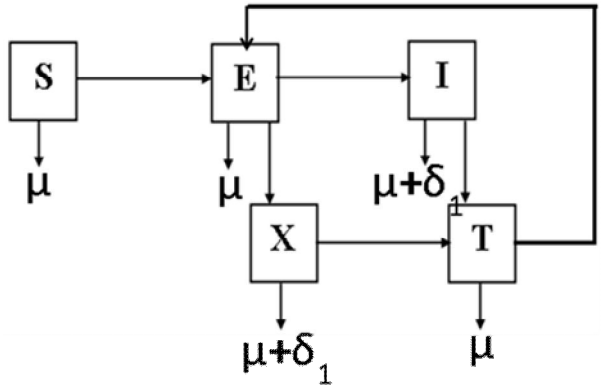

Fig.1: Flow of population from one compartment to the other

The state variables and parameters used are listed below:

- *S*: Number of susceptibles
- *E*: Number of exposed (latently infected)
- *I*: Number of infectious (pulmonary TB)
- *X*: Number of individuals with extra-pulmonary TB (non-infectious)
- *R*: Number of treated
- *B*: Recruitment as susceptible per unit time
- v_1: Rate of progression of individuals from the exposed class to the infectious (pulmonary) class
- v_2: Rate of progression of individuals from the exposed class to the non-infectious (extra-pulmonary) class
- γ_1: treatment rate of latent individuals
- γ_2: treatment rate of infectious (pulmonary) individuals
- γ_3: treatment rate of non-infectious (extra-pulmonary) individuals
- δ_1: Disease-induced death rate (pulmonary)
- δ_2: Disease-induced death rate (extra-pulmonary)
- μ: Natural death rate
- β: Probability that a susceptible becomes infected per contact per unit time
- β': Probability that a treated becomes infected per contact per unit time
- *c*: Contact rate

The model takes the form as follows:

$$\begin{aligned}
\frac{dS}{dt} &= B-\beta c\frac{SI}{N}-\mu S\\
\frac{dE}{dt} &= \beta c\frac{SI}{N}+\beta' c\frac{TI}{N}-(\gamma_1+\mu+\nu_1+\nu_2)E\\
\frac{dI}{dt} &= \nu_1 E-(\delta_1+\gamma_2+\mu)I \qquad (1)\\
\frac{dX}{dt} &= \nu_2 E-(\delta_2+\gamma_3+\mu)X\\
\frac{dT}{dt} &= \gamma_1 E+\gamma_2 I+\gamma_3 X-\beta' c\frac{TI}{N}-\mu T
\end{aligned}$$

Adding above equations, we have

$$\frac{d}{dt}(S+E+I+X+T)=B-\mu(S+E+I+X+T)-\delta_1 I-\delta_2 X$$

$$\Rightarrow (S+E+I+X+T)'\le B-\mu(S+E+I+X+T)$$

Then $\lim_{t\to\infty}\sup(S+E+I+X+T)\le\frac{B}{\mu}$

So, the feasible region for the system is

$$\Lambda=\left\{(S+E+I+X+T): S+E+I+X+T\le\frac{B}{\mu}, S>0, E\ge 0, I>0\right\}$$

Now the basic reproduction number R_0 will be calculated using the approach given in Drissche and Watmough [8].

The basic reproduction number, R_0, is defined as the expected number of secondary cases produced by a single (typical) infection in a completely susceptible population.

Let $\mathrm{E}(\bar{S},\bar{E},\bar{I},\bar{X},\bar{T})$ be the equilibrium point of the system (1). Since the recruitment term can never be zero and population can never extinct, therefore there is no trivial equilibrium point like $\mathrm{E}(\bar{S},\bar{E},\bar{I},\bar{X},\bar{T})=(0,0,0,0,0)$.

It is easy to see that the system has a disease free equilibrium at $\mathrm{E}_0(\bar{S},\bar{E},\bar{I},\bar{X},\bar{T})=\left(\frac{B}{\mu},0,0,0,0\right)$.

Let $\mathrm{E}'=(E,I,X,T,S)^T$

Therefore,

$$\mathrm{E}'=\frac{d\mathrm{E}}{dt}=F(\mathrm{E})-V(\mathrm{E})$$

where $F(\mathrm{E})$ gives the rate of appearance of new infections in a compartment and $V(\mathrm{E})$ gives the transfer of individuals, where

$$F(\mathrm{E}) = \begin{bmatrix} \beta c\frac{SI}{N} + \beta' c\frac{TI}{N} \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

$$V(\mathrm{E}) = \begin{bmatrix} (\gamma_1 + \nu_1 + \nu_2 + \mu)E \\ -\nu_1 E + (\gamma_2 + \mu + \delta_1)I \\ -\nu_2 E + (\gamma_3 + \mu + \delta_2)X \\ -\gamma_1 E - \gamma_2 I - \gamma_3 X + \mu T + \beta' c\frac{TI}{N} \\ -B + \beta c\frac{SI}{N} + \mu S \end{bmatrix}$$

Since E_0 is the disease free equilibrium therefore the derivatives $DF(\mathrm{E}_0)$ and $DV(\mathrm{E}_0)$ are partitioned as

$$DF(\mathrm{E}_0) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad DV(\mathrm{E}_0) = \begin{bmatrix} V & 0 \\ J_1 & J_2 \end{bmatrix}$$

where F and V are 3×3 matrices given by

$$F = \begin{bmatrix} 0 & \frac{\beta cB}{\mu N} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} (\gamma_1 + \nu_1 + \nu_2 + \mu) & 0 & 0 \\ -\nu_1 & (\delta_1 + \gamma_2 + \mu) & 0 \\ -\nu_2 & 0 & (\delta_2 + \gamma_3 + \mu) \end{bmatrix}$$

Respectively.

Then

$$FV^{-1} = \begin{bmatrix} \frac{\beta cB\nu_1}{\mu N(\delta_1 + \gamma_2 + \mu)} & \frac{\beta cB}{\mu N(\delta_1 + \gamma_2 + \mu)} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Therefore, basic reproduction number

$R_0 = \rho\left(FV^{-1}\right)$ = spectral radius of FV^{-1}

$$\Rightarrow R_0 = \frac{B\beta c\nu_1}{N\mu(\delta_1 + \gamma_2 + \mu)(\gamma_1 + \nu_1 + \nu_2 + \mu)} \qquad (2)$$

IV. STABILITY OF DISEASE FREE EQUILIBRIUM

The disease free equilibrium is stable if all the eigen values of the Jacobian matrix of the given system have negative real parts. In order to check this, the Jacobian of the system (1) at $\mathrm{E}_0\left(\bar{S}, \bar{E}, \bar{I}, \bar{X}, \bar{T}\right) = \left(\frac{B}{\mu}, 0, 0, 0, 0\right)$ takes the form

$$J = \begin{bmatrix} -\mu & 0 & -\frac{B\beta c}{N\mu} & 0 & 0 \\ 0 & -(\gamma_1 + \nu_1 + \nu_2 + \mu) & \frac{B\beta c}{N\mu} & 0 & 0 \\ 0 & \nu_1 & -(\delta_1 + \gamma_2 + \mu) & 0 & 0 \\ 0 & \nu_2 & 0 & -(\delta_2 + \gamma_3 + \mu) & 0 \\ 0 & \gamma_1 & \gamma_2 & \gamma_3 & -\mu \end{bmatrix}$$

Here,

trace $(J) = -(\delta_1 + \delta_2 + \gamma_1 + \gamma_2 + \gamma_3 + \nu_1 + \nu_2 + 5\mu)$

Clearly, trace $(J) < 0$.

For det (J) to be > 0, we should have

$\frac{N\mu}{B} > \frac{\beta c\nu_1}{(\gamma_1 + \nu_1 + \nu_2 + \mu)(\delta_2 + \gamma_2 + \mu)}$ (on solving determinant of J)

or $\frac{B\beta c\nu_1}{N\mu(\gamma_1 + \nu_1 + \nu_2 + \mu)(\delta_2 + \gamma_2 + \mu)} < 1$

i.e. $R_0 < 1$.

This implies that the disease free equilibrium is locally asymptotically stable if $R_0 < 1$ otherwise unstable.

V. STABILITY OF ENDEMIC EQUILIBRIUM

Let the endemic equilibrium point be $\mathrm{E}_e\left(S^*, E^*, I^*, X^*, T^*\right) \neq (0,0,0,0,0)$.

Here, the Jacobian takes the form

$$JE=\begin{bmatrix} -\mu-\frac{I\beta c}{N} & 0 & -\frac{S\beta c}{N} & 0 & 0 \\ \frac{I\beta c}{N} & -(\gamma_1+\nu_1+\nu_2+\mu) & \frac{S\beta c}{N}+\frac{T\beta' c}{N} & 0 & \frac{I\beta' c}{N} \\ 0 & \nu_1 & -(\delta_1+\gamma_2+\mu) & 0 & 0 \\ 0 & \nu_2 & 0 & -(\delta_2+\gamma_3+\mu) & 0 \\ 0 & \gamma_1 & -\gamma_2-\frac{T\beta' c}{N} & \gamma_3 & -\mu-\frac{I\beta' c}{N} \end{bmatrix}$$

with

$$S^*=\frac{BN}{N\mu+I^*\beta c}, E^*=\left\{\frac{I^*S^*\beta c}{N}+\frac{I^*T^*\beta' c}{N}\right\}\frac{1}{(\gamma_1+\nu_1+\nu_2+\mu)},$$

$$I^*=\frac{E^*\nu_1}{(\delta_1+\gamma_2+\mu)}, X^*=\frac{E^*\nu_2}{(\delta_2+\gamma_3+\mu)}, T^*=\frac{E^*\gamma_1+I^*\gamma_2+X^*\gamma_2}{\left(\mu+\frac{I\beta' c}{N}\right)}$$

Here, $\text{trace}(JE)=-\begin{bmatrix} 2\mu+\frac{I\beta c}{N}+\frac{I\beta' c}{N}+(\gamma_1+\nu_1+\nu_2+\mu) \\ +(\delta_1+\gamma_2+\mu)+(\delta_2+\gamma_3+\mu) \end{bmatrix}$

Clearly, trace (JE) < 0.

For det (JE) > 0, after a long cumbersome calculation and assuming $\beta=\beta'$, we finally get that

$$R_0>1$$

Thus the endemic equilibrium is stable if $R_0>1$.

VI. SENSITIVITY ANALYSIS

Here, we evaluate the sensitivity indices of R_0 to all the different parameters it depends on. These indices tell us how crucial each parameter is to disease spread and guide us to find the right parameter to be taken care of.

TABLE I
VALUES OF PARAMETERS FOR TB (IN INDIA)

Parameter	Value
μ	0.008
δ_1	0.24
β	2
γ_1	2
γ_2	1.5
ν_1	0.0057
ν_2	0.009
c	100
B	800
N	100000

TABLE II
SENSITIVITY INDICES OF R_0 TO THE PARAMETERS FOR TB

Paramete r	Sign	Value
μ	-	1.0085
δ_1	-	0.1373
β	+	1
γ_1	-	0.9888
γ_2	-	0.8581
ν_1	+	0.9972
ν_2	-	0.0045
c	+	1
B	+	1
N	-	1

VII. RESULT AND DISCUSSION

In this study, we formulate a mathematical model for understanding the population dynamics of tuberculosis considering the pulmonary and extra-pulmonary separately. For starting the qualitative analysis of the model, a relation for basic reproduction number R_0 is established. Then the existence of steady states and their stabilities is analysed. The analysis shows that the disease free equilibrium is globally asymptotically stable if $R_0<1$. Also the endemic equilibrium is found to be globally asymptotically stable if $R_0>1$ provided it exists.

Sensitivity analysis of the model is carried out using the data for India. Here, we use the normalised forward sensitivity index of a variable, u (say), which depends continuously on a parameter, p (say). The results of sensitivity analysis shows that overcrowding un sanitary conditions were the major causes in for the prevalence of the disease in India

as it increases the contact rate and provides the bacteria the environment to survive longer.

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VIII. REFERENCES

[1] J.P. Aparicio and C. Castillo-Chavez, "Mathematical Modelling of Tuberculosis Epidemics". *Mathematical Biosciences and engineering*, vol. 6, pp. 209-237, April 2009.

[2] J.P. Aparicio, A.F. Capurro and C. Castillo-Chavez, "Long-term Dynamics and Re-emergence of Tuberculosis". *Workshop on Wmerging and Re-emerging Diseases*, Institute of Mathematics and applications, University of Minnesota, May 17-21, 1999.

[3] E. Jung, S. Lenhart and Z. Feng, "Optimal control of Treatment in a Two-Strain Tuberculosis Model". *Discrete and Continuous Dynamical Systems-Series B*. vol. 2, pp. 473-482, November 2002.

[4] H.S. Joshi and M.N. Bates, "Comparision of pulmonary and extrapulmonary tuberculosis in Nepal-a hospital-based retrospective study". *BMC infectious disease*, 2008, 8:8. doi: 10.1186/1471-2334-8-8.

[5] C. Castillo-Chavez and Z. Feng, "To treat or not to treat: the case of tuberculosis". *Journal of Mathematical Biology*, Springer-Verlag, 35: pp 629-656, 1997.

[6] C. Coljin, T. Cohen and M. Murray, "Mathematical Models of Tuberculosis: Accomplishments and future challenges". *BIOMAT- 2006, International Symposium on Mathematical and Computational Biology*, doi: 10.1142/9789812708779_0008.

[7] C.J.L. Murray and J. A. Salomon, "Using mathematical models to evaluate global tuberculosis control strategies". *Harward Centre for Population and Development Studies*, Harvard University, Cambridge MA.

[8] O. Diekmann, J. A. P. Heesterbeek, Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation, Wiley, 1999.

[9] Sarah A. Al-Sheikh: "Modeling and analysis of an SEIR Epidemic Model with a Limited Resource for Treatment". *Global Journal of Sceience Frontier Research: Mathematics and Decision Sciences*, vol 12, pp. 57 – 66, 2012.

[10] P. van den Driessche and J. Watmough.: "Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission". *Mathematics Biosciences*, 180, pp. 29-48, 2002.

[11] S.A. Egbetade and M.O. Ibrahim,"Global Stability Result for a Tuberculosis Epidemic Model". *Research Journal of mathematics and Statistics*, 4(1): pp. 14-20, 2012.

[12] J. H. Jones: Notes on R_0. Standford University, 2007.

[13] www.who.int/tb/data/

[14] www.tbcindia.nic.in/

[15] http://www.cdc.gov/