ORIGINAL PAPER

MATHEMATICAL ANALYSIS OF TB MODEL

ASGHAR ALI[1]*, MOHAMMAD MUNIR[2], RASHIDA HUSSAIN[1], SAJIDA AZIZ[1]

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Abstract. *The introduction of the SILR model in 1927 by W. O. Kermack and A. G. Mc Kendrick also led to the compartmental modeling of the transmission of the Tuberculosis (TB). We select two models describing the spread of the TB in the vaccinated and non-vaccinated populations. The main objective of this study is to understand the transmission of Tuberculosis specifically the impact of bacille Calmette-Guerin (BCG), a vaccine for tuberculosis (TB) disease. Most effective vaccination used against TB is BCG, and there is no consensus about its efficiency and the estimation of preservation dimension from 0 to 80%. For this we consider two models of transmission basic SILR model, this model is continued to incorporate vaccinations at birth to get a new model VI_VL_V so that we deeply analyze BCG vaccination impact. The models are analyzed by sensitivity analysis of parameters. We evaluated the sensitivities of all parameters in SILR and VI_VL_V models.*

Keywords: *Mathematical Model, Tuberculosis, Sensitivity Analysis.*

1. INTRODUCTION

Tuberculosis is an endemic disease which is caused by a bacterium called Mycobacterium tuberculosis. Tuberculosis have been known to the main kinds since ancient times. Earlier this disease has been called by numerous names. Tuberculosis bacterium which mostly affects lungs when the Mycobacterium enters the lungs, it is called the pulmonary TB. It also affects other parts of the body (e.g. the central nervous system, bones, joints, kidney and skin) [1]. Tuberculosis is caused by Mycobacterium Tuberculosis is a preventable and treatable disease that commonly affects the lungs. To date, TB confirms second biggest number of casualties because of solitary irresistible collaborator directly after Human Immune deficiency Infection and Immune Deficiency disorder (HIV/AIDS). There were right around 9.7 million orphan children in 2009 because of the TB passing among parents. In 2010, about 8.8 million people were corrupted counting 1.1 million cases among people with HIV and 1.4 million passed on from it, joining 350,000 people with HIV, equal to 3,800 passing's consistently [2]. Robert Koch gave his discovery of the causative organism of tuberculosis, Koch's bacillus or Mycobacterium Tuberculosis in Berlin on the 24th March 1882. Since then the 24th of the March has been seen as the World's tuberculosis day. In 1890, Koch made tuberculin, a purified Protein Derivative (PPD). In spite of the fact that it was inadequate methods for vaccination of TB. Charles Mantoux directed in 1908 that it is a compelling

[1] Mirpur University of Science and Technology (MUST), 10250 Mirpur, Pakistan.
E-mail: drali@must.edu.pk. , drrashida@must.edu.pk
[2] Government Postgraduate College No.1 Abbottabad, Department of Mathematics, Abbottabad, Pakistan.
E-mail: dr.mohammadmunir@gpgc1-atd.edu.pk.

method for diagnosing TB by intra-dermal technique (Mantoux test or tuberculin test) [3]. Roentegen revealed X- rays in 1895 which improved the diagnosis of TB.

The current vaccine for TB, Bacille Calmette Guerin (BCG), was first used in 1921 [4]. BCG was generally consumed until World War II. Pakistan presented it in 1949, advance responsible for TB instigation with the disclosure of Streptomycin in 1944, P-Amino-Salicylic corrosive (PAS) in 1946 and Isoniazid in 1951.

In 2009, about 9.4 million episode new instances of TB and a predominance of 137 instances of TB for each 100000 populace were accounted for globally. Most number of cases happened in Asia (55%) trailed by Africa (30%), Eastern Mediterranean district (7%) European region (4%) and the area of Americas (3%). The five nations with biggest number of cases were India, China, Afghanistan, Indonesia and Pakistan. India and China commonly represented 35% of these new cases. Roughly 1300,000 individuals kicked the bucked of TB in 2009.

Pakistan stand 5^{th} among 22 countries with high burden of Tuberculosis. Estimated prevalence of TB in Pakistan is 350 cases per 100,000 populations. Total new cases reported were 258251 composed of 101887 smear positive cases, 112948 smear negative cases and 43416 cases of extra -pulmonary TB. Sixty thousand people died of TB in Pakistan in 2009 [5]. Tuberculosis is a contamination ailment caused by moderate developing microbes that develop best in areas of the body that have heaps of blood and oxygen. That is why it is regularly found in lungs this is called pulmonary tuberculosis. Mycobacterium tuberculosis is the main agent of tuberculosis which is a corrosive, quick, gram-positive, oxygen consuming, non-motile, rod-shaped organism. Its two shapes cause sickness in humans. Mycobacterium tuberculosis spread through air when an infected person coughs, sneezing, talks and spits, saliva droplets containing tuber bacilli are projected into the air and can be inhaled by a nearby person [6]. Tuberculosis also induced by interchange of environmental and genetic factors. The incubation period of a disease is defined as the time interval between initial infection and disease outbreak [7]. The incubation period of tuberculosis varies from 2 to 12 weeks. It was not clear how TB was transmitted until Robert Koch's awe inspiring exposure of the tubercle bacillus in 1882. Koch also recognized the purpose behind Bacillius anthracis. He broke down Mycobacterium tuberculosis as the causative expert of TB. The tubercle bacilli live in the lungs of tainted hosts. They spread recognizable all around when powerful individuals wheeze, hack, talk or sing. A powerless individual may wind up evidently debased with TB if he or she takes in bacilli from the air. The particles containing Mycobacterium tuberculosis are little to the point that standard air streams keep them airborne and transport them every single through room or structures [8]. TB was not only the first disease for which MTB was found. The innovative agent was identified, but also one of the first for which a vaccine was developed. The first discovery for the TB vaccine development was the use of Mycobacterium bovis bacillus Calmette Guerin commonly known as BCG, Doherty and Andersen [5]. This is a neonatal pre-presentation antibody that is generally utilized far and wide with around 350 billion people, that is, roughly 50 percent of the total populace having gotten it, for the most part in zones where TB is endemic [9].

The first direct model of Waaler's did not define the mechanics of TB transmission. He presented another model of 160 direct conditions in [5] taking a similar system, yet containing BCG inoculated and distinction recuperated classes for 20 different age classes. Revelle first present non-linear frameworks of ODEs Utilizing the model of Brogger and Waaler as a format that model TB elements. He clarified why the contamination estimate depends straightly on the commonness utilizing the probabilistic way that is regular today (homogeneous blending). He built up an improvement demonstrate and considered the insignificant cost procedure against TB. It justifies determining that Waaler besides in 1970 built a model that compel the worth of elective tuberculosis govern measures.

A mathematical analysis of a TB model without fast progression was developed by Chavez et al. [10]. After that, most publications have practical mathematical approach such as center manifold theory and Lyapunov functions, to examine transmission of tuberculosis [11].

The study of how the uncertainty in the output of a model (numerical or otherwise) can be apportioned to different sources of uncertainty in the model input [12]. Sensitivity analysis creates fundamental data for parameter estimation, enhancement, control, display simplification and test design. The sensitivity analysis introduce, the orderly investigation of the effects of parameter values on the estimation of scientific models is a fruitful apparatus for demonstrate assessment and approval and in addition for calculating the effect of parametric uncertainly and variability [13]. Sensitivity analysis is useful analysis of the impacts of parameter esteems on indicator of mathematical models which is a helpful weapon for model estimation, verification as well as assessment of the impact of parametric uncertainly and variability [14], [18-21].

2. MATERIALS AND METHODS

The well-studied model of TB transmission and the theory of the sensitivity functions are described in this section.

2.1. SILR MODEL

We take two transmission model of tuberculosis SILR (2.2) and vaccinated model VIL (2.3) [15].

2.2. SILR MODEL EQUATIONS

$$\begin{aligned} \frac{dS}{dt} &= (1-v)\mu - \varepsilon\Lambda S - \mu S, \\ \frac{dI}{dt} &= \phi\Lambda(\varepsilon S + \sigma(R+L)) + \omega L - (\tau + \mu)\mathrm{I}, \\ \frac{dL}{dt} &= (1-\phi)\Lambda(\varepsilon S + \sigma R) - \phi\sigma\Lambda L - (\omega+\mu)L, \\ \frac{dR}{dt} &= \tau I - (\sigma\Lambda + \mu)R. \end{aligned} \tag{2.1}$$

These equations show the rates of change of individual class and determined in parameters terms as shown in (1). Extraneous notations are ε, the auxiliary parameters, that is 1 naturally and granted an age of sub-models, and Λ, the per capita rate of disease.

Basic reproduction number of SILR model

By using standard system Diekmann et.al. [16] the fundamental reproduction number is calculated as:

$$R_0 = \frac{(\omega+\phi\mu)\beta}{(\omega+\mu)(\tau+\mu)} \tag{2.2}$$

The SILR model is extended to incorporate vaccination at birth. This requires the further specification of three categories: V vaccinated individuals who are not infected; and vaccinated individuals who have been infected and are either infectious with active TB I_V or latent L_V. Transmission in the vaccinated population is described in (2.3) and, using the parameters in Table 1, this is formalized as:

2.3. VI_VL_V MODEL EQUATION

$$\begin{aligned}
\frac{dV}{dt} &= \nu\mu + \tau I_V - \sigma_V \Lambda V - \mu V \\
\frac{dI_V}{dt} &= \phi\sigma_V \Lambda(V + L_V) + \omega L_V - (\tau + \mu) I_V \\
\frac{dL_V}{dt} &= (1-\phi)\sigma_V \Lambda \mathrm{V} - \phi\sigma_V \Lambda L_V - (\omega + \mu) L_V
\end{aligned} \tag{2.3}$$

2.4. SENSITIVITY ANALYSIS

A multiple-output system with measureable outputs is given by:

$$\begin{aligned}
y(t,\theta) &= \big(f_1(t,\theta),\ldots,f_M(t,\theta)\big), \\
0 \le t \le T, \quad \theta \epsilon U,
\end{aligned} \tag{2.4}$$

where $T > 0$ is a fixed time instant and $U \subset R^P$ is an open set consisting of parameters θ which are to be estimated.

2.4.1. Sensitivity functions

For this model, the sensitivity or sensitivity functions of model output $f_i(t,\theta)$ with regard to the component of parameter θ_ϕ is defined as:

$$S_{\frac{f_i}{\theta_\phi}}(t) = \lim_{\delta\theta_\phi \to 0} \frac{\frac{\delta\, f_i(t,\theta)}{f_i(t,\theta)}}{\frac{\delta\theta_\phi}{\theta_\phi}}, \qquad \phi = 1,\ldots,p, \quad i = 1,\ldots M. \tag{2.5}$$

This can be written as:

$$S_{\frac{f_i}{\theta_\phi}}(t) = \frac{\delta\ f_i(t,\theta)}{\partial\theta_\phi}.\frac{\theta_\phi}{f_i(t,\theta)},\ i = 1,\ldots\ldots,M,\ \phi = 1,\ldots\ldots,p \tag{2.6}$$

Here both $f_i(t,\theta), i = 1,\ldots\ldots,M$ and $\theta_\phi,\quad \phi = 1,\ldots\ldots,p$ are assumed to be non-zero [17].

The sensitivity functions measures the effects of changes in parameters on model outputs. In order to illustrate which parameters, the outputs of model is least or most sensitive. The system sensitivity with respect to parameter vector component at any time instant t in $[0,T]$ combining individual sensitivities of all model outputs $f_i,\ i = 1,\ldots,M$ is defined by:

$$S_{\theta_\phi}(t) = \left(\sum_{i=1}^{M}\left(S_{\frac{f_i}{\theta_\phi}}(t)\right)^2\right)^{\frac{1}{2}},$$
$$\phi = 1,\ldots\ldots,p$$

3. NUMERICAL IMPLEMENTATION

We take the values of θ as shown in the Table (1) and the initial condition as S(0)= 529.6135, I(0)= 0.3092, L(0)= 0.0251 and R(0) = 0.2010 for the SILR model (2.2). The initial condition for the VIL (2.2) model as V(0) = 529.6135, I(0)= 0.3092, L(0)= 0.0251. Then we solve the system of sensitivity equation using Matlab ode solver *ode45* over the time interval [0,150] using the values of the parameter given in the table 1. We find the sensitivities of the state variables S, I, L and R and V, I_v and L_V with respect to the parameters $\theta = (\mu, \phi, \sigma, \sigma_v, \upsilon, \omega, \tau, \beta, \Lambda, \varepsilon)$ for the (2.2) and (2.3) models respectively.

4. RESULTS AND DISCUSSION

The results on the sensitivity studies of the Tb transmission model with and without vaccination are given in the following section:

4.1. SENSITIVITIES OF S, I, L AND R WITHOUT VACCINATION MODEL

The sensitivities model of the model outputs S, I, L and R, with respect to the parameters $\mu, \phi, \sigma, \sigma_v, \upsilon, \omega, \tau, \beta, \Lambda, \varepsilon$ are presented in Fig. 1(a-d).

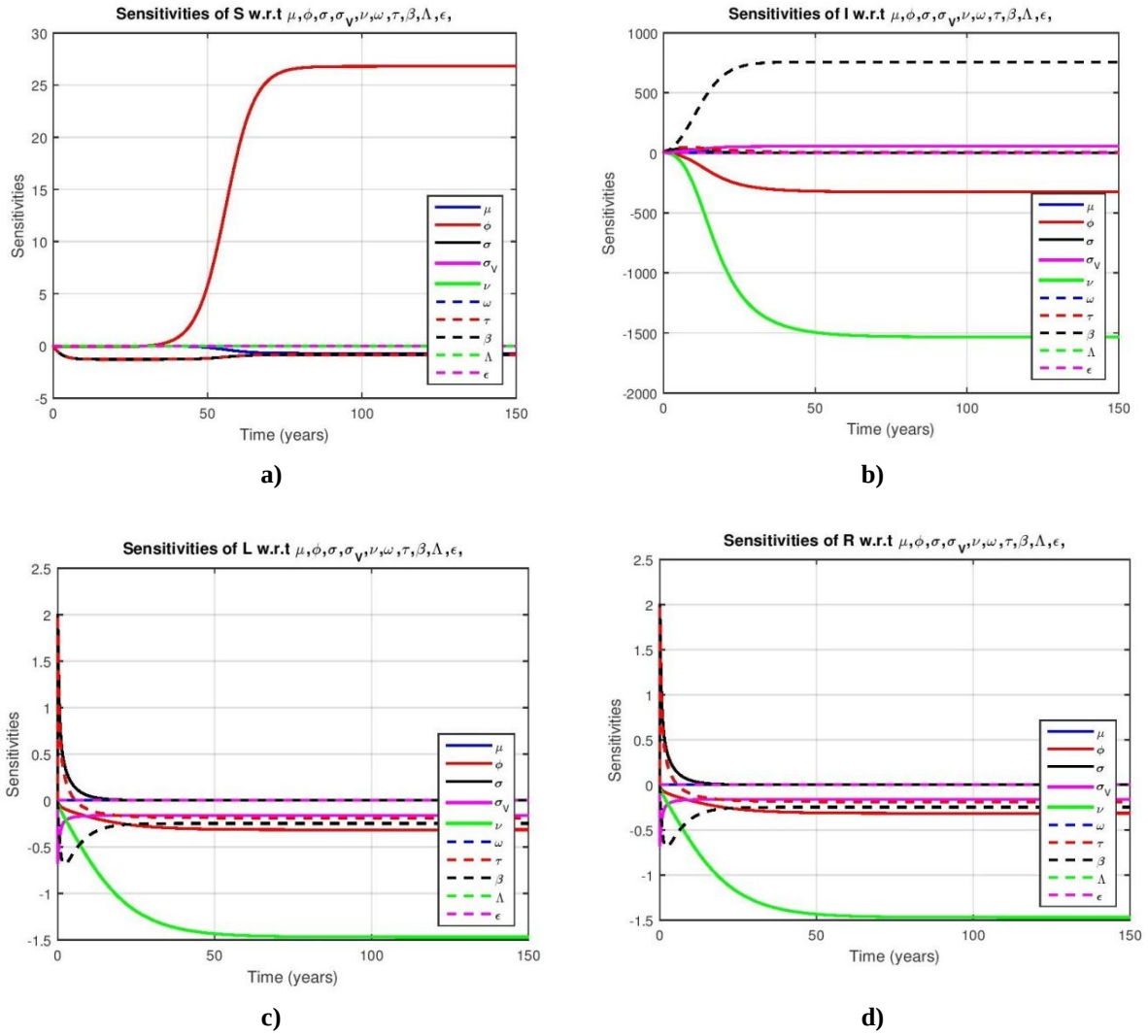

Figure 1. Sensitivity of: a) S w.r.t all parameters; b) I w.r.t all parameters; c) L w.r.t all parameters; d) R w.r.t all parameter.

Table 1. Parameters with their nominal values.

Symbol	Definition	Value
υ	vaccination coverage	95%
μ	death rate and birth rate	$1/70\ yr^{-1}$
ε	auxiliary parameter	0.1
ϕ	Proportion of individuals that are develop active TB The remaining $1-\phi$ have latent TB	0.1
σ	factor that reduce infection risk as a result of acquired immunity to a previous infection.	0.25
σ_υ	factor reducing risk of infection as a result of vaccination	0.20
Λ	Per capita rate of infection	2
ω	rate of endogenous reactivation of latent TB	$0.0002\ yr^{-1}$
β	Transmission coefficient	2
τ	rate of treatment of active TB	$2\ yr^{-1}$

Fig. 1 (a-d) shows that the susceptible individuals are sensitive with respect to parameters ϕ and μ its sensitivity with respect to ϕ starts from 70 years to 95 years than remain constant and a little sensitive in low magnitude and μ is sensitive upto 45 years to 65

years than remain constant this implies that susceptible are infected by birth rate and proportional of individuals that develop active TB. Infected individuals are sensitive with respect to parameter β upto 40 years after that it remain constant and the parameter ϕ which is sensitive upto 60 years after that it remain constant and $,\upsilon$ which is most sensitive its sensitivity upto 60 years after that it remains constant it means infection rate affect on infected compartment L and B are also sensitive with respect to τ which is sensitive upto 47 years , β and σ are sensitive during initial years and parameter $,\upsilon$ which is most sensitive upto 95 years after that it remains constant this implies latent and recovered individuals are affected by the rate of treatment, transmission coefficient and mostly effected by vaccination coverage.

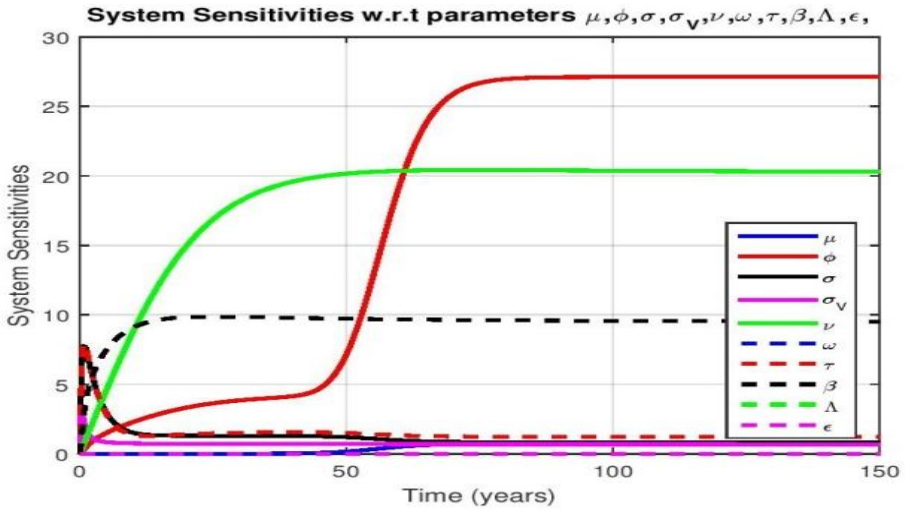

Figure 2. System Sensitivity w.r.t all parameters.

4.1.1. System Sensitivity of the SILR Model

System sensitivities of all parameters are presented in Fig. 2. Information acquired by the time courses of the system sensitivities are more or less similar to the information given by their individual sensitivities. The sensitivities signpost that the model outputs of X=(SILR) is more sensitive with respect to parameter β, then with respect to parameter ϕ, then with respect to υ, then τ and then σ_v respectively. Model output is least sensitive with respect to μ and some parameters are insensitive in the model.

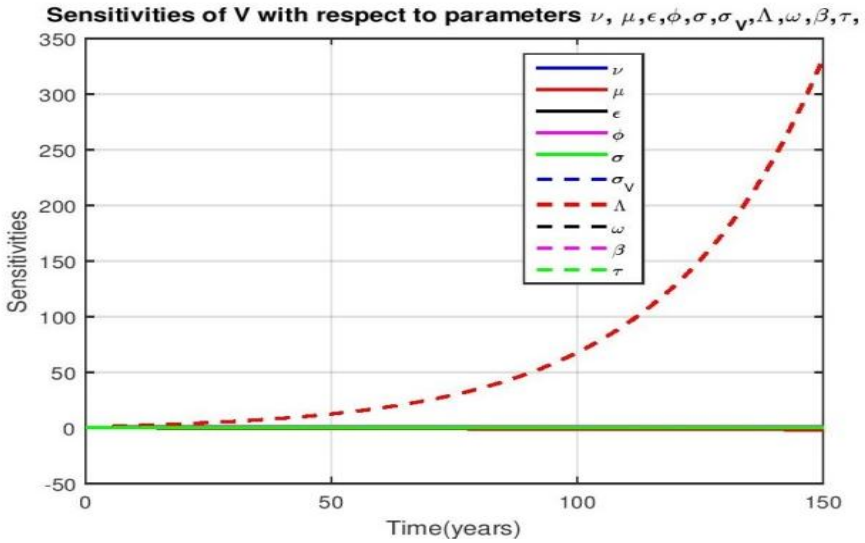

Figure 3(a). Sensitivity of V (Tb transmission model) with Vaccination Model.

4.1.2. Sensitivities of VI_vL_V with respect to $\mu, \phi, \sigma, \sigma_v, \upsilon, \omega, \tau, \beta, \Lambda, \varepsilon$

Fig. 3 represents the Sensitivity of VI_vL_V model with respect to all the parameters. Λ is the most sensitive parameter in vaccinated model.

4.1.3. System Sensitivity of VI_vL_V Model

System Sensitivities of the parameters combine the effects of sensitivities of all outputs of the VI_vL_V model. They also depend on the number of measurements points. By taking the mesh points as the measurement points the system sensitivity of the model are presented in Fig. 3.

The information given by the time courses of the system sensitivities are more or less similar to the information given by their individual sensitivities. The system sensitivities indicate that the model outputs X= (VI_vL_V) is sensitive only with respect to parameter Λ, all other parameters are insensitive for vaccinated model.

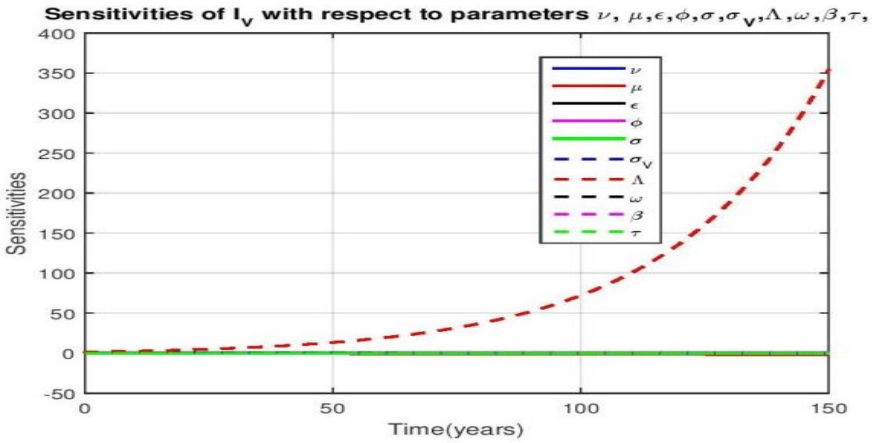

Figure 3(b). Sensitivity of I_V (Tb transmission model) with Vaccination Model.

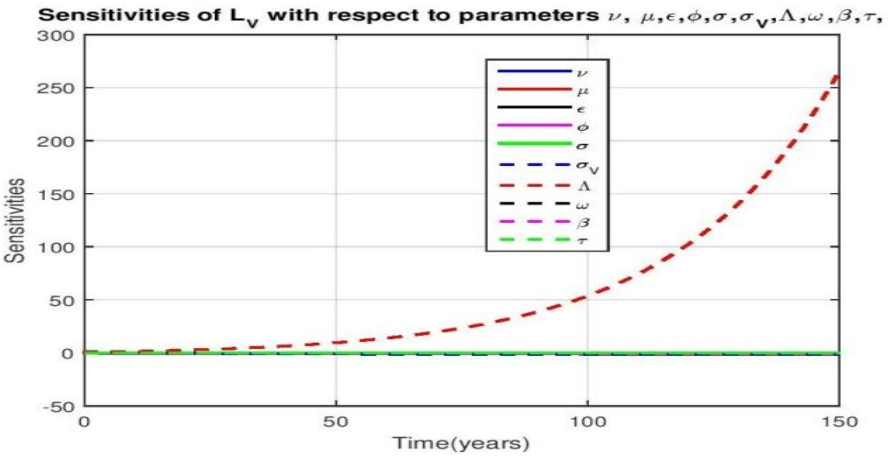

Figure 3(c). Sensitivity of L_V Tb transmission model with Vaccination Model.

4. CONCLUSIONS

We have analyzed the tuberculosis model for the non-vaccinated and vaccinated populations by the sensitivity analysis:

(1) We have found the sensitivities of all parameters in SILR and VI_vL_V models. The model output S is more Sensitive w. r. t parameter Λ during time interval of [25 150]. Whereas all other parameters are sensitive but with less magnitude. The parameter Λ is sensitive for all the models outputs in the VI_vL_V model for whole of epidemic period.

(2) The parameter ω, Λ and ε are sensitive for all model output in the SILR model. ω remain sensitive to all outputs in VI_vL_V model upto 20 years. Whereas ε and β are insensitive in VI_vL_V model. Λ is sensitive for whole epidemic period.

(3) β is insensitive for all outputs in the VI_vL_V where as it is sensitive for the outputs I, L and R for almost 25 years, only S is insensitive.

(4) The sensitivity of the parameters ϕ and σ shows that these two parameters are sensitive for all model outputs of SILR and VI_vL_V.

(5) The sensitivity studies of the SILR model indicate that the parameter σ_v is less sensitive as compared to VI_vL_V.

(6) The qualitative and the quantitative sensitivity studies of the non vaccinated and vaccinated reaffirm each other.

REFERENCES

[1] Smith, I., Mycobacterium tuberculosis Pathogenesis and Molecular Determinants of Virulence, *CLINICAL MICROBIOLOGY REVIEWS*, **16**(3), 463-496, 2003.

[2] Kochi, A., The Global Tuberculosis Situation and the New Control Strategy of the *World Health Organization*, **79**(1) , 71-75, 2001.

[3] Rustum, I., Aminov, A Brief History of the Antibiotic Era: Lessons Learned and Challenges for the future, *Frontiers in microbiology*, **1**(134), 1-7, 2010.

[4] Kaufmann, S.H., Tuberculosis: Deadly Combination. *Nature*, **453**(7193), 295, 2008.

[5] Doherty T. M and Andersen, P.J, Vaccines for Tuberculosis: Novel Concepts and Recent Progress. *Clinical Microbiology Review*, **18**(4), 687-702, 2005.

[6] Banuls, A.L, Sanou, A., Van Anh, N.T. and Godreuil, S., Mycobacterium Tuberculosis: Ecology and Evolution of a Human Bacterium. *Journal of Medical Microbiology*, **64**(11), 1261-1269, 2015.

[7] Wells, W. F., Airborne Contagion and Air Hygiene, An Ecological Study of Droplet Infections, Airborne Contagion and Air Hygiene, An Ecological Study of Droplet Infections, *Cambridge : Harvard University Press (for The Commonwealth Fund), Mass., U.S.A. London : Geoffrey Cumberlege, Oxford University Press.*,1955, 423.

[8] Waaler, H. T., The Economics of Tuberculosis Control. *Tubercle*, **49**, 2-4, 1968.

[9] Gomes, M Gabriela M and Franco, Ana O and Gomes, Manuel C and Medley, Graham F, The Reinfection Threshold Promotes Variability in Tuberculosis Epidemiology and Vaccine Efficacy, *Proceedings of the Royal Society of London B: Biology Sciences. The Royal Society*, **1539**(271), 617-623, 2004.

[10] Castillo-Chavez, C. and Feng Z., To Treat or not to Treat: the Case of Tuberculosis. *Journal of Mathematical Biology*, **35**(6), 629-656, 1997.

[11] Vynnycky, E. and Fine, P.E.M., The Annual Risk of Infection with Mycobacterium Tuberculosis in England and Wales since 1901. The International Journal of Tuberculosis and Lungs Disease, **1**(5), 389-396, 1997.

[12] Taufik, M. R., Lestari, D. and Septiarini, T.W., Mathematical Model for Vaccinated Tuberculosis Disease with VEIT Model. *International Journal of Modeling and Optimization*, **5**(3), 192, 2015.

[13] Munir, M., Sensitivity and Generalized Sensitivity studies of the SIR and SEIR Models of Computer Virus, *J PPAS* **54**(2)167-178, 2017.
[14] Kumar, A., Jain, D.C., Gupta, D., Satyanarayana, S., Zachariah, R. and Harries, A.D., Screening of Patients with tuberculosis for diabetes mellitus in India. *Tropical medicine and international health,* 2013.
[15] Hilderbrandt, S., Bagheri, N., Gunawan, R., Mirsky, H., Shoemaker, J., Taylor, S., Vynnycky, E. and Fine, P.E.M., The Annual Risk of Infection with Mycobacterium Tuberculosis in England and Wales since 1901. The International Journal of Tuberculosis and Lungs Disease, **1**(5), 389-396, 1997.
[16] Diekmann, Odo and Heesterbeek, Johan Andre Peter and Metz, Johan AJ, On the Definition and the Computation of the Basis Reproduction Ratio R_0 in Models for Infectious Diseases in Heterogeneous Populations. *Journal of Mathematical Biology, Springer*, **4**(28), 365-382, 1990.
[17] Saltelli, A., Chan, K and Scott, E.M. Eds., Sensitivity Analysis. New York: *Wiley*, 1, 2000.
[18] Garba, S. M., Gumel, A. B. and Bakar, M. A., Backward Bifurcations in Dengue Transmission Dynamics. *Mathematical Biosciences*, **215**(1), 11-25, 2008.
[19] Petzold, L. and Doyle, F.J., Systems Analysis for system Biology. *In Systems Biomedicine*, 249-272, 2009.
[20] Karmer, M.A., Rabitz, H. and Calo, J.M., Sensitivity Analysis of Oscillatory Systems. *Applied Mathematical modelling*, **8**(5), 328-340, 1984.
[21] Tewa, J.J., Dimi, J. L. and Bowong, S., Lyapunov Functions for a Dengue Disease Transmission Model, Chaos, Solutions and Fractals. **39**(2), 936-941, 2009.