MODELING TUBERCULOSIS TRANSMISSION IN SOUTH-WEST NIGERIA

Adesupo A. Akinrefon [1], Olusola A. Adejumo [2]

[1] Dept. of Statistics & Operations Research, Modibbo Adama University of Technology, Yola, Adamawa State, Nigeria
[2] Dept. of Statistics, University of Ilorin, Kwara State, Nigeria

Corresponding Author: Adesupo A Akinrefon, akinrefonadesupo@yahoo.com

ABSTRACT: Tuberculosis has persisted over the years as a significant contributor to mortality and morbidity counts globally and in particular, Nigeria. This study formulated a continuous-time Markov process model for TB dynamics with the introduction of vaccination impact in the susceptible and exposed classes. Using the Gillespie's algorithm, we obtained stochastic realizations of the disease behavior using the Kolmogorov equations. Sensitivity analysis on impact of key parameters showed that intervention effort at 50% - 85% effectively reduced TB incidence despite reinfection of recovered individuals.
KEYWORDS: Continuous-Time Markov Chain, exogenous re-infection, Kolmogorov forward equations, Stochastic Simulation, Tuberculosis, Vaccination.

1. INTRODUCTION

Global rates of mortality have "Tuberculosis (TB)" to thank for its high values with almost one-third of the world's population infected ([ZA16]), a record 9.6 million new cases yearly and 1.8 million TB induced deaths ([ÉSK17]) and lots of attendant cure-limiting complications when treatment is either not given promptly or defaulted ([ZA16]).

Tuberculosis mainly can be either active or latent TB. Only about 10% - 15% of primary infections become active except with weak immune system, comorbidity or reinfection that raises the risk of progression. Latent TB, that is inactive in the body or showing no symptoms nor being transmissible, can last for decades ([SA18]).

Early discovery, conferment of permanent immunity and exogenous reinfection are prominent drivers of the disease continuity. Over the years, the government had made concerted efforts towards combating TB depending largely on voluntary case notification but this has been hampered as detection rate is still limited to 2 out of every 10 infections. The aim of this paper is to see how screening and vaccination of susceptible as well as latently infected individuals can mitigate current incidence rates in Nigeria in the presence of exogenous re-infection using data from the South-West geopolitical zone.

2. REVIEW OF RELATED LITERATURE

The past decade has witnessed a lot of contributions related to Tuberculosis modeling ranging from its dynamics to measures of control. ([T+16]) conducted a historical research on Tuberculosis assessing the current prevalence level while ([OCA08]) conducted a mathematical analysis of co-infection of HIV/AIDS and TB with intervention. ([JC09]) explored the advantages and disadvantages of homogeneous and heterogeneous mixing models in the transmission of tuberculosis, ([MDO16]) explored the stochastic differential equations methodology in modeling TB with and without stochasticity, from which similar trend was observed. The list cannot be exhausted, excellent reviews of mathematical and stochastic models of TB are found in ([CS04]). On vaccination, treatment or both, as control strategies for TB dynamics, the works of ([CF97], [All03], [All08], [Ade07], [Ade08]) are of great relevance.

3. METHODOLOGY

We consider the population growth dynamics of TB as a homogenous multivariate continuous-time stochastic birth-death process. The process {X(t): t} is a Markov process i.e. for any range $t_1 < t_2 < \cdots < t_n$, the conversion number from one state to another only depends on $(t, t + \Delta t)$. We look at the TB dynamics with five (5) states:

- infants born with "passive immunity, M",
- those who are "susceptible, S",
- those with "latent infection, E",
- the "infectious persons, I",
- and those who are "removed or recovered, R".

Those with passive immunity at birth but which wanes over time, also there is the possibility of being re-infected after treatment then moving into the latent state. We incorporate treatment of the susceptible and latently infected populations.

Model formulation:

The continuous-time Markov model we formulated assumes that the heterogeneous population can be grouped into compartments following their disease state per time. Also, the change in population size with time is probabilistic with natural birth as the means of entry and death either natural or TB related are the only means of exit. A fraction of neonates is given BCG at birth those who miss this enter in as susceptible infants and interaction within the population is homogenous. We further assume a constant birth and natural death rate.

The jump intensities are a represented below:

- entry into the Passively-immuned class, M, at rate $P\pi$
- entry into the Susceptible class, S, at a rate $(1-P)\pi$
- Linear migration:

i. From passively immuned class to Susceptible class (1 to 2) $K_{12}X_1$, $K_{12} = y$

ii. From susceptible to exposed class (2 to 3) at rate $K_{23}X_1$ where $K_{23} = \beta\frac{I}{N}\Delta t$

iii. From detected exposed (or Susceptible) to removed/treated via vaccination at rate $K_{35}X_3$, $K_{35} = \delta g$

iv. From Exposed to Infectious class (3 to 4) at rate $K_{34}X_3$ where $K_{34} = K + p\beta\frac{I}{N}$, p = proportion of those with a new TB infection

v. From Infectious to Removed/Treated class at rate $K_{45}X_4$, $K_{45} = r$

vi. From treated/removed class to exposed class $K_{53}X_5$ where $K_{53} = \sigma\beta\frac{I}{N}$

- Linear death in all compartments at rates $\mu_i X_i$, $i = 1,2,3,4,5$

Table 1: Parameters and variables of the model with passive immune and exogenous reinfection

Variables	Description
M(t)	Size of immunized infants at time *t*
S(t)	Count of susceptible persons at time *t*
E(t)	the count of latently infected individuals TB at time *t*
I(t)	the size of infectious individuals at time *t*
R(t)	the size of recovered individuals at time *t*
β	the effective TB transmission rate
π	the recruitment rate
g	vaccination parameter
P	proportion of new births that have been immunized through vaccination
y	the rate of expiration of vaccine efficacy
r	Recovery rate of infectious TB
μ	natural death rate
γ, σ	proportion with exogenous re-infection
μ_T	mortality rate due to TB
k	the rate of infectivity

For this model, the Kolmogorov equations thus will be obtained as the probability of an event taking place given the transition rates above which may be written as shown below.

$$
\begin{aligned}
P_{x_1x_2x_3x_4x_5}(t+\Delta t) =\; & P_{x_1-1,x_2,x_3,x_4x_5}(t)\, P\pi\Delta t + P_{x_1+1,x_2,x_3,x_4,x_5}(t)\,\mu(x_1+1)\Delta t \\
& + P_{x_1+1,x_2-1,x_3,x_4x_5}(t)\, K_{12}(x_1+1)\Delta t + P_{x_1,x_2-1,x_3x_4,x_5}(t)\,(1-P)\pi\Delta t \\
& + P_{x_1,x_2+1,x_3,x_4,x_5}(t)\,\mu(x_2+1)\Delta t + P_{x_1,x_2+1,x_3-1,x_4x_5}(t)\, K_{23}(x_2+1)\Delta t \\
& + P_{x_1,x_2+1,x_3,x_4x_5-1,}(t)\, K_{25}(x_2+1)\Delta t + P_{x_1,x_2,x_3+1x_4,x_5-1}(t)\, K_{35}(x_3+1)\Delta t \\
& + P_{x_1,x_2,x_3+1,x_4x_5}(t)\,\mu(x_3+1)\Delta t + P_{x_1,x_2,x_3+1,x_4-1,x_5}(t)\, K_{34}(x_3+1)\Delta t \\
& + P_{x_1,x_2,x_3,x_4+1x_5}(t)\,(\mu_T+\mu)(x_4+1)\Delta t + P_{x_1,x_2,x_3,x_4+1,x_5-1}(t)\, K_{45}(x_4+1)\Delta t \\
& + P_{x_1+1,x_2,x_3-1,x_4x_5+1}(t)\, K_{53}(x_5+1)\Delta t + P_{x_1,x_2,x_3,x_4x_5+1}(t)\,\mu(x_5+1)\Delta t \\
& + P_{x_1,x_2,x_3,x_4x_5}(t)\big(1 - P\pi - (1-P)\pi - (\mu+K_{12})(x_1+1) - (\mu+K_{23}+K_{25})(x_2+1) \\
& - (\mu+K_{34}+K_{35})(x_3+1) - (\mu+\mu_T+K_{45})(x_4+1) - (\mu+K_{53})(x_5+1) + o(\Delta t)\big) \qquad (1)
\end{aligned}
$$

Thus, the Kolmogorov forward equation for the TB dynamics is:

$$
\begin{aligned}
\frac{\partial P_{x_1x_2x_3x_4x_5}(t)}{\partial t} =\; & P_{x_1-1,x_2,x_3,x_4x_5}(t)\, P\pi + P_{x_1+1,x_2,x_3,x_4,x_5}(t)\,\mu(x_1+1)\Delta t \\
& + P_{x_1+1,x_2-1,x_3,x_4x_5}(t)\, K_{12}(x_1+1) + P_{x_1,x_2-1,x_3x_4,x_5}(t)\,(1-P)\pi \\
& + P_{x_1,x_2+1,x_3,x_4,x_5}(t)\,\mu(x_2+1) + P_{x_1,x_2+1,x_3-1,x_4x_5}(t)\, K_{23}(x_2+1) \\
& + P_{x_1,x_2+1,x_3,x_4x_5-1,}(t)\, K_{25}(x_2+1) + P_{x_1,x_2,x_3+1x_4,x_5-1}(t)\, K_{35}(x_3+1) \\
& + P_{x_1,x_2,x_3+1,x_4x_5}(t)\,\mu(x_3+1) + P_{x_1,x_2,x_3+1,x_4-1,x_5}(t)\, K_{34}(x_3+1) \\
& + P_{x_1,x_2,x_3,x_4+1x_5}(t)\,(\mu_T+\mu)(x_4+1) + P_{x_1,x_2,x_3,x_4+1,x_5-1}(t)\, K_{45}(x_4+1) \\
& + P_{x_1+1,x_2,x_3-1,x_4x_5+1}(t)\, K_{53}(x_5+1) + P_{x_1,x_2,x_3,x_4x_5+1}(t)\,\mu(x_5+1) \\
& - P_{x_1,x_2,x_3,x_4x_5}(t)\big(P\pi + (1-P)\pi + (\mu+K_{12})(x_1+1) + (\mu+K_{23}+K_{25})(x_2+1) \\
& + (\mu+K_{34}+K_{35})(x_3+1) + (\mu+\mu_T+K_{45})(x_4+1) + (\mu+K_{53})(x_5+1)\big) \qquad (2)
\end{aligned}
$$

The partial differential equations (p.d.e) which satisfies the generating functions was obtained using the "Random Variable technique" developed by ([Bai64]) defined as:

$$\frac{\partial G}{\partial t} = \sum_{ijk\ldots l}\left(S_1^i S_2^j S_3^k \ldots S_5^l - 1\right) f_{ijk\ldots l}\left(S_1\frac{\partial}{\partial S_1}, S_2\frac{\partial}{\partial S_2}, S_3\frac{\partial}{\partial S_3}, \ldots, S_8\frac{\partial}{\partial S_5}\right) G(S_1, S_2, S_3, \ldots S_5, t) \quad (3)$$

$$\frac{\partial M}{\partial t} = \sum_{ijk\ldots l}\left(e^{i\theta_1 + j\theta_2 + k\theta_3 + \cdots + l\theta_5} - 1\right) f_{ijkl}\left(\frac{\partial}{\partial \theta_1}, \frac{\partial}{\partial \theta_2}, \frac{\partial}{\partial \theta_3}, \ldots \frac{\partial}{\partial \theta_5}\right) M(\theta_1, \theta_2, \theta_3, \ldots \theta_5, t) \quad (4)$$

Thus, we obtain the partial differential equation Probability generating function as

$$\frac{\partial G}{\partial t} = (S_1 - 1)P\pi G + (1 - S_1)\mu_1\frac{\partial G}{\partial S_1} + (S_2 - S_1)K_{12}\frac{\partial G}{\partial S_1} + (S_2 - 1)(1 - P)\pi G + (1 - S_2)\mu_2\frac{\partial G}{\partial S_2} + (S_5 - S_2)K_{25}\frac{\partial G}{\partial S_2} + (S_3 - S_2)K_{23}\frac{\partial G}{\partial S_2} + (1 - S_3)\mu_3\frac{\partial G}{\partial S_3} + (S_5 - S_3)K_{35}\frac{\partial G}{\partial S_3} + (S_4 - S_3)K_{34}\frac{\partial G}{\partial S_3} + (1 - S_4)\mu_4\frac{\partial G}{\partial S_4} + (S_5 - S_4)K_{45}\frac{\partial P}{\partial S_4} + (1 - S_5)\mu_5\frac{\partial P}{\partial S_5} + (S_3 - S_5)K_{53}\frac{\partial P}{\partial S_5} \quad (5)$$

And the partial differential equation Moment Generating Function as:

$$\frac{\partial M}{\partial t} = (e^{\theta_1} - 1)P\pi + (e^{-\theta_1} - 1)\mu_1\frac{\partial M}{\partial \theta_1} + (e^{\theta_2 - \theta_1} - 1)K_{12}\frac{\partial M}{\partial \theta_1} + (e^{\theta_2} - 1)(1 - P)\pi + (e^{-\theta_2} - 1)\mu_2\frac{\partial M}{\partial \theta_2} + (e^{\theta_5 - \theta_2} - 1)K_{25}\frac{\partial M}{\partial \theta_2} + (e^{\theta_3 - \theta_2} - 1)K_{23}\frac{\partial M}{\partial \theta_2} + (e^{-\theta_3} - 1)\mu_3\frac{\partial M}{\partial \theta_3} + (e^{\theta_4 - \theta_3} - 1)K_{34}\frac{\partial M}{\partial \theta_3} + (e^{\theta_5 - \theta_3} - 1)K_{35}\frac{\partial M}{\partial \theta_3} + (e^{-\theta_4} - 1)\mu_4\frac{\partial M}{\partial \theta_4} + (e^{\theta_5 - \theta_4} - 1)K_{45}\frac{\partial M}{\partial \theta_4} + (e^{-\theta_5} - 1)\mu_5\frac{\partial M}{\partial \theta_5} + (e^{\theta_3 - \theta_5} - 1)K_{53}\frac{\partial M}{\partial \theta_5} \quad (6)$$

From (11) above the partial differential equation for the Cumulant Generating Function

$$\frac{\partial K}{\partial t} = [(e^{\theta_1} - 1)P\pi + (e^{-\theta_1} - 1)\mu_1\frac{\partial K}{\partial \theta_1} + (e^{\theta_2 - \theta_1} - 1)K_{12}]\frac{\partial K}{\partial \theta_1} + (e^{\theta_2} - 1)(1 - P)\pi + [(e^{-\theta_2} - 1)\mu_2 + (e^{\theta_3 - \theta_2} - 1)K_{23} + (e^{\theta_5 - \theta_2} - 1)K_{25}]\frac{\partial K}{\partial \theta_2} + [(e^{-\theta_3} - 1)\mu_3 + (e^{\theta_4 - \theta_3} - 1)K_{34} + (e^{\theta_5 - \theta_3} - 1)K_{35}]\frac{\partial K}{\partial \theta_3} + [(e^{-\theta_4} - 1)\mu_4 + (e^{\theta_5 - \theta_4} - 1)K_{45}]\frac{\partial K}{\partial \theta_4} + [(e^{-\theta_5} - 1)\mu_5 + (e^{\theta_3 - \theta_5} - 1)K_{53}]\frac{\partial K}{\partial \theta_5} \quad (7)$$

The initial conditions are as stated below:

$$X_i(0) = N_i(0) \qquad i = 1,2,3,4,5$$

Table 2: Parameters of the model with passive immunity, exogenous reinfection and vaccination

Variables	Values	Source
β	0.0290	Jung et al. (2002)
π	50	Assumed
r	0.05	Bhunu (2012)
g	0 to 1	Assumed
σ	0.07	Assumed
y	0.2	Bhunu (2012)
γ	0.3	Assumed
μ	0.02	Estimated
k	0.3	Assumed
μ_T	0.03	Bhunu (2012)
ρ	0.1	Bhunu (2012)

4. RESULT AND DISCUSSION

We carried out simulations for the formulated model using data on TB incidence counts obtained from the National Centre for Tuberculosis and Leprosy control, Abuja for 2012-2017 for South-west Nigeria. Simulations are performed using parameter values shown in the tables 2 to generate the sample paths of the model using the Stochastic Simulation Algorithm via the "*adaptivetavu*" package in R. The graphical simulation results for the model with passive immunity, exogenous re-infection and vaccination impact are as shown in the figures (1)-(11).

Figure (1)-(5) below shows the disease dynamics of the Passively immuned infants, the Susceptible, Latently Infected, Infectious and Recovered / Removed individuals respectively at the initial values stated in Table (2) above without vaccination impact. From figure (1), we observe that the population of passively immuned infants decreases exponentially and later stabilizes later on this is due largely to the waning of immunity in the infants. Figure (2) shows the behavior of the susceptible individuals. The incidence counts of the susceptible population rises steadily up to the 5th year then begins to steadily decline largely due to TB transmission and movement of infected susceptible individuals into the Latently Infected population. Figure (3) shows the Exposed or Latently Infected population declining fast up to the 10th year. From figure (4), incidence in the infectious population rises and peaks around the 7th or 8th year, then steadily declines as time progresses. The rise could be as a result of influx from the latently infected population driven by exogenous re-infection while figure (5) shows the recovered or removed population.

Figures (6)-(9) shows the effect of varying levels of vaccination intervention on the TB dynamics in the presence of exogenous re-infection. Figure (6) shows the effect on the susceptible population. At 25%, the incidence of susceptible persons drops fast around the 10th year and then becomes stable. A greater level of change is observed at 50% to 85% level of vaccination coverage. Literature suggest that the chances of moving into the active infectious class is higher between the 2nd to the 5th year of infection especially in the presence of exogenous re-infection. At about 75-85% vaccination compliance, the number of persons susceptible to infection is greatly reduced especially within this critical period. The disease spread will be greatly curbed given the impact of the intervention on the availability of susceptible persons.

Figure (7) shows the intervention impact on the latently infected population. These show a faster decline in the counts of latently infected in comparison to the dynamics in figure (3) largely due to the intervention effort introduced into both the susceptible and Latently Infected groups. Ample time that would have allowed the disease spread faster if left unchecked, is redeemed and the disease spread kept in check at least to a minimal level.

Figure (8) shows the intervention impact from 25% - 85% on the actively infectious population in the presence of exogenous re-infection. The peak level drops from about 1300(‘000) in figure (4) to below 900 (‘000) at 25% intervention compliance around the 5th – 6th year; at 50% - 85% intervention impact, the peak drops further to below 600 (‘000) at earlier period around the 2nd year of infection. This is attributive to the intervention efforts on the susceptible and latently infected population. The count of those infected continues to decline exponentially till it reaches a stable point as time progresses. It was observed from figure (9) that the population of recovered or removed individuals increase exponentially at 25% intervention level and peaks around the 10th year. At 50% - 85% vaccination compliance, we observe a sharp increase and the recovery rate peaks early around the 2nd year.

From figure (10)-(11), we observe the behavior of the latently infected and the infectious individuals at various re-infection levels when the vaccination impact level is at 50%. At the given level of intervention exogenous re-infection at 7% - 25% causes the latently infected individuals, which declines sharply, to move faster into the active class as seen in figure (10). There is slight variance among the infectious individuals, figure (11), at the various level of re-infection largely because the exposed individuals move faster into the infectious group.

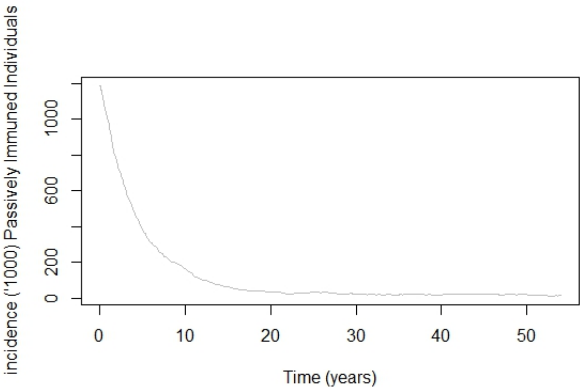

Figure 1: Plot showing sample path for Passively-immuned population (‘000)

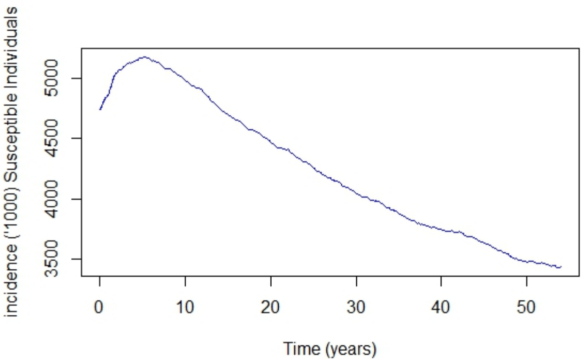

Figure 2: Plot showing sample path for Susceptible population (‘000)

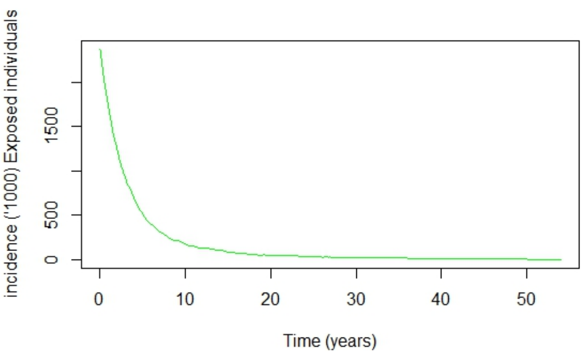

Figure 3: Plot showing sample path for Exposed population (‘000)

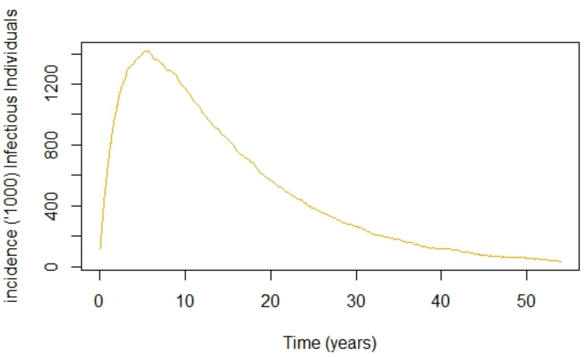

Figure 4: Plot showing sample path for Infectious population (‘000)

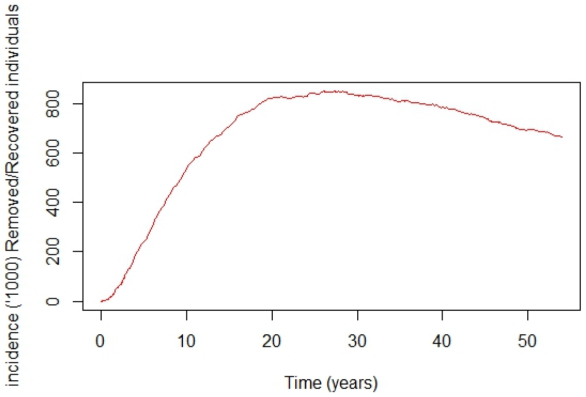

Figure 5: Plot showing sample path for Recovered/Removed population ('000)

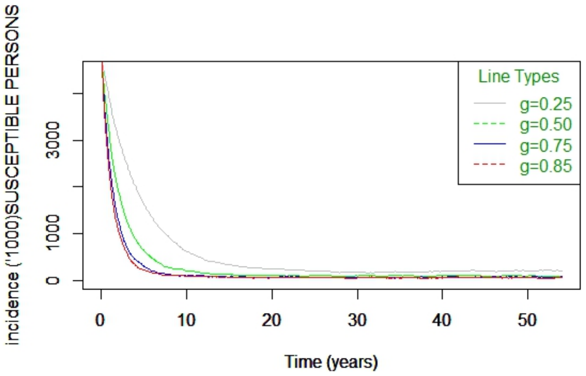

Figure 6: Plot showing sample path for Susceptible population at varying levels of vaccination ('000)

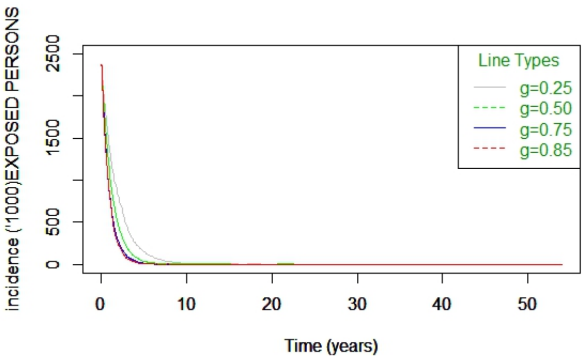

Figure 7: Plot showing sample path for Exposed population at varying levels of vaccination ('000)

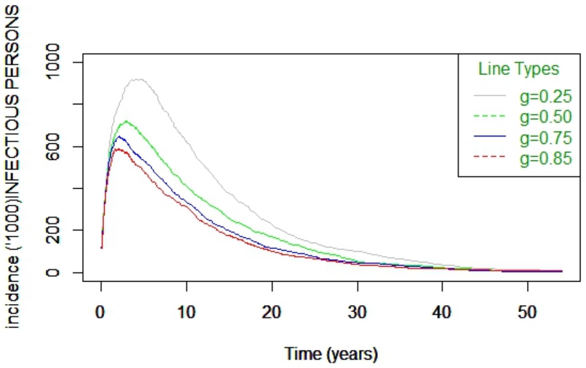

Figure 8: Plot showing sample path for Infectious population at varying levels of vaccination ('000)

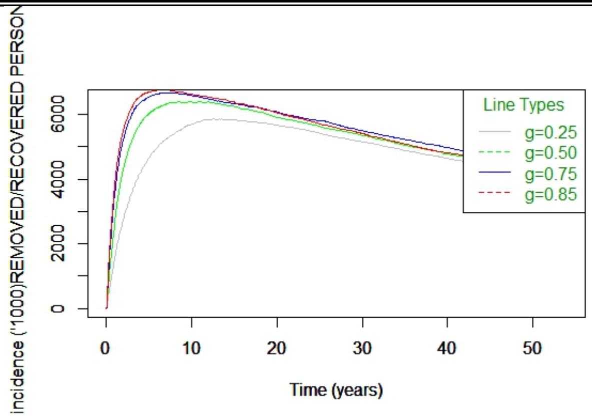

Figure 9: Plot showing sample path for Removed/Recovered population at varying levels of vaccination ('000)

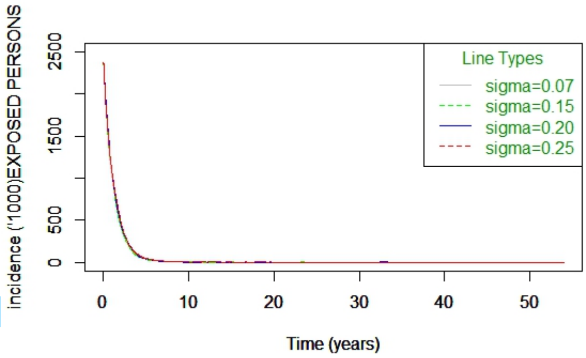

Figure 10: Plot showing sample path for Exposed population at varying levels of re-infection after treatment ('000) when g = 0.5

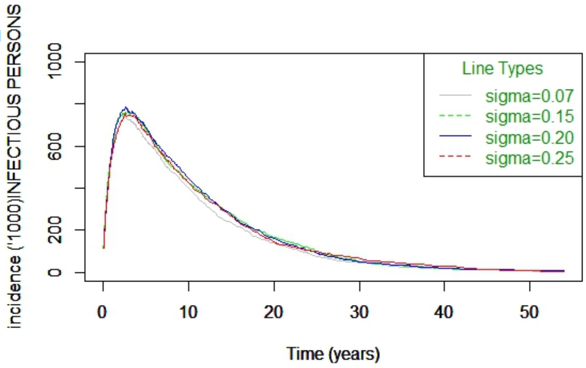

Figure 11: Plot showing sample path for infectious population at varying levels of re-infection after treatment ('000) when g = 0.5

CONCLUSION

In this study, a continuous-time Markov chain model was proposed and analyzed to study the dynamics of TB model in the presence of exogenous re-infection and vaccination intervention. The Kolmogorov equations were obtained and simulated using the stochastic simulation algorithm. A numerical study of the model was also conducted to see the impact of key parameters on the spread of TB. It is observed that intervention effort at 50% - 85% in the susceptible and exposed status classes is effective in reducing the scourge of TB spread early in its cycle. Furthermore, the intervention even at 50% will mitigate the impact of TB re-infection whether after treatment or as a second strain infection of exposed individuals.

REFERENCE

[Ade07] **I. A. Adetunde** – *Mathematical models of the dynamical behavior of tuberculosis disease in the Upper East Region of the Northern Part of Ghana: A case study of Bawku*. Research Journal of Appl. Sci. 2(9): 943-946. 2007.

[Ade08] **I. A. Adetunde** – *On the control and eradication strategies of mathematical models of the tuberculosis in a community*. Environmental Research Journal 2(4): 155-158. 2008.

[All03] **L. J. S. Allen** – *An Introduction to Stochastic Processes with Applications to Biology*. Prentice Hall, Upper Saddle River, NJ. 2003.

[All08] **L. J. S. Allen** – *An Introduction to Stochastic Epidemic Models*. Mathematical Epidemiology, Lecture Notes in Mathematics. Vol. 1945. pp. 81-130, F. Brauer, P. van den Driessche, and J. Wu (Eds.) Springer. 2008.

[Bai64] **N. T. J. Bailey** – *The Elements of Stochastic Processes with applications to the natural sciences*. John Wiley & Sons, Inc., New York. 1964.

[B+12] **C. P. Bhunu, W. Garira, Z. Mukandavire, M. Zimba** – *Tuberculosis Transmission Model with Chemoprophylaxis and Treatment*. Bulletin of Mathematical Biology, 70, 1163-1191. 2012.

[CS04] **C. Castillo-Chavez, B. Song** – *Dynamical models of tuberculosis and their applications*, Mathematical Biosciences and Engineering 1(2): 361-404. 2004.

[CF97] **C. Castillo-Chavez, C. Feng** – *To treat or not to treat: The case of tuberculosis*. J.Math. Biol., 35:629-656. 1997.

[ÉSK15] **L. Évora, J. M. Seixas, A. L. Kritski** – *Artificial Neural Network Models for Diagnosis Support of Drug and Multidrug Resistant Tuberculosis*. IEEE, 2015.

[JC09] **P. A. Juan, C. Carlos** – *Mathematical modeling of tuberculosis epidemics*. Mathematical biosciences and engineering. Volume 6, Number 2, pp. 209-237, 2009.

[JLF02] **E. Jung, S. Lenhart, Z. Feng** – *Optimal Control of Treatments in a Two-strain Tuberculosis Model*. Discrete and Continuous Dynamics System-Series B, 2(4), 473-482. 2002.

[MDO16] **T. Mbaya, J. L. Dimi, B. Ondami** – *Mathematical Analysis of Deterministic and Stochastic Model of Tuberculosis*. International Journal of Scientific and Innovative Mathematical Research (IJSIMR) Volume 4, Issue 1, January 2016, PP 8-20 ISSN 2347-307X (Print) & ISSN 2347-3142 (Online) www.arcjournals.org, 2016.

[OCA08] **S. Oluwaseun, N. P. Chandra, B. G. Abba** – *Mathematical analysis of the transmission dynamics of HIV/TB co-infection in the presence of treatment*. Journal of mathematical biosciences and engineering. Volume 5, Number 1, pp. 145-174. 2008. Retrieved online from http://www.mbejournal.org/

[SA18] **N. Suresh, K. Arulanandam** – *A Study On Tuberculosis Analysis Using Data Mining Techniques*. International Journal of Advanced Research in Computer and Communication Engineering 7(3), pp 458-473, DOI:10.17148/IJARCCE.2018.7387. 2018.

[T+16] **M. H. Taghizade, M. Z. Emami, B.A. Khademi, M. Saeidi** – *Tuberculosis: Past, Present and Future*. International Journal of Pediatrics. 4(1): 1243-54. 2016.

[ZA16] **R. Zakhmi, J. Arora** – *Review on Tuberculosis Detection Using Various Data Mining Techniques*. International Research Journal of Engineering and Technology 3 (issue no), pp840-843. 2016.