On Mathematical Modeling of the Effect of Bi-Therapeutic Treatment of Tuberculosis Epidemic

Bassey B. Echeng and K.A. Lebedev
Federal State Educational Institution of Higher Professional Education,
Kuban State University, 149 Ctavrapolskaya Street, 350040 Krasnodar, Russia

Abstract: In this study, we provide a very accurate numerical and semi-analytical solution to a system of non-linear differential equations derived in modeling the effect of bi-therapeutic treatment of Tuberculosis (TB) in a homogeneous population consisting of different groups (six different groups). The model studied the outcome of simultaneous application of isoniazid preventive therapy-IPT and antiretroviral therapy-ART in the treatment of TB. The numerical analysis made use of MATHCAD Program and the result showed that accelerated control and eradication of TB is predominantly affected by a number of the model's input parameters such as: proportion of infectious individuals who use only IPT, the proportion of infectious individuals that use only ART, proportion of individuals who use both IPT and ART, the rate at which latently infected becomes infectious and the per capita rate of susceptible becoming latently infected. The model allowed us to evaluate the isolated performance of these treatment factors with ART indicating more active result. Our analysis show that effective eradication of TB can be achieved where a significant number of infected individual are exposed to free bi-therapeutic treatment and situation where this control measure is stipulated as a norm for the treatment and eradication of Tuberculosis (TB).

Key words: Bi-therapeutic isoniazid, antiretroviral, latently, vulnerable, chemotherapy, nosocomial, hypothetically, eradication

INTRODUCTION

Tuberculosis (TB) has it history as far back as the 17th century, when it was first identified as the major cause of death in Europe, particularly in England (Bloom and Murray, 1992). *Mycobacterium tuberculosis* is known to be the causative agent of Tuberculosis disease (TB) (Porco and Blower, 1998; Blower *et al.*, 1995). The disease is said to be causing more death worldwide than any other single infectious disease (Kochi, 1991; Bloom and Murray, 1992).

Following the increase in the reemergence of tuberculosis in the Sub-Saharan Africa Asia and Eastern Europe, consequent upon HIV pandemic in the second half of 1980s, World Health Organization (WHO), in 1993 declared tuberculosis, a global emergency with 2 billion people estimated to be infected by TB that year (Enarson *et al.*, 2000; Egbetade and Ibrahim, 2013). Other factors considered responsible for the growing TB spread is the high prevalence of multidrug-resistant strains which was estimated to account for third of the world population infected with TB. The alleged pandemic have no-doubt cause a substantial threat to socio-economic development and imposing a heavy burden on families, communities and the economy of the affected nations.

The progression rate of TB to its clinically active disease appear in two folds the "fast" develop TB which takes within 2 years to progress to clinically active TB and the "slow" TB which remain latent and gradually develop to clinically active TB in 20 years (Blower *et al.*, 1995; Egbetade *et al.*, 2012). The most vulnerable people are those living in poverty with 70% of the cases occurring among the age group of 15-59 years (the most productive age group) whereas in the developed countries, elderly people are more affected with nearly 60-65% of newly diagnosed cases being males. Tuberculosis transmission is by direct contact of the susceptible with aerosolized particles containing live tubercle bacilli released by individuals with infectious tuberculosis disease (I_i) (Philip and Barry, 1994).

Due to the emergence of drug-resistant TB strains and convergence of HIV and TB epidemic, the control of

Corresponding Author: Bassey B. Echeng, Federal State Educational Institution of Higher Professional Education, Kuban State University, 149 Ctavrapolskaya Street, 350040 Krasnodar, Russia

TB is of paramount importance. The main intervention and control measures comprises of BCG vaccination and the World Health Organization's "Directly Observed Treatment Short-course" (DOTS) chemotherapy which involves active case finding Isoniazid Prevention Therapy (IPT), Anti-Retroviral Therapy (ART) and treatment of patients with multidrug-resistant TB (Blower *et al.*, 1995; Egbetade *et al.*, 2012; Porco *et al.*, 2001; Cohen *et al.*, 2007).

In the context of TB disease, appreciable number of mathematical models has been widely used in various forms to study the transmission dynamics of TB epidemic. These include models (Basu and Galvani, 2008; Rodrigues *et al.*, 2007) that considered drug-resistant TB; (Sharomi *et al.*, 2008; Roeger *et al.*, 2009) that considered both co-epidemics of HIV and TB (Dye *et al.*, 1998) worked on the prospects for worldwide tuberculosis control under the World Health Organization, DOTS strategy and (Hirsch *et al.*, 1985) studied differential equation models of some parasitic infections.

The background of this present study alludes from the model (Porco and Blower, 1998). In that model, application of time-dependent sensitivity and uncertainty analysis were formulated to study tuberculosis model in order to quantitatively understand the transmission dynamics of untreated tuberculosis epidemics. Also, playing a vital role in this study is the study where the model was on sensitivity analysis of Multidrug-Resistant TB (MDR-TB). In this study, we account for the dynamics of the effect of the application of bi-therapeutic (Isoniazid Preventive Therapy-IPT and Antiretroviral Therapy-ART) treatment of TB infection using compatible mathematical parameters as a wholesome new novelty features. The model incorporate the biology of tuberculosis transmission as presented by each of the six compartments over time (Fig. 1).
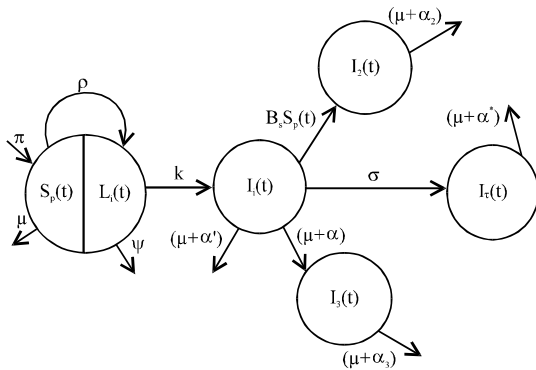

Fig. 1: A differential flow-chart for TB Bi-Therapy Treatment Model

In particular, we performed the simulation analysis using MATHCAD with in-built 'rkfixed' function to determine the most influential parameters. This is important in terms of both the application of chemotherapy and refinement of improved models in the context of TB control.

PARAMETERS AND MATHEMATICAL MODEL

In formulating this model, we consider the model (Porco and Blower, 1998) with which we construct a relatively simple model for a bi-therapeutic treatment of TB as seen in the differential flow-chart in Fig. 1: (the proportions highlighted are the new novelties of this present model). From Fig. 1 above, the parameters (functions) prescribed in the model are defined as follows:

- $S_p(t)$: susceptible population at time t
- $L_i(t)$: latently infected individuals at time t
- $I_i(t)$: infectious individuals at time t
- $I_2(t)$: infectious individuals who use only IPT at time t
- $I_3(t)$: infectious individuals who use only ART at time t
- $I_r(t)$: infectious individuals who use both IPT and ART at time t
- B_s: per capita rate of susceptible becoming latently infected
- K: the rate at which latently infected become infectious at time t
- N_p: total population understudy
- ρ: proportion of infectious individuals who use only IPT at time t
- ψ: proportion of infectious individuals who use only ART at time t
- σ: proportion of infectious individuals who use both IPT and ART at time t
- β_1: probability of transmission by L_i per unit time
- β_i: probability of transmission by I_i per unit time
- β_2: probability of transmission by I_2 per unit time
- β_3: probability of transmission by I_3 per unit time
- β^*: probability of transmission by I_r per unit time
- c_s: average number of contact by S_p with L_i
- c_l: average number of contact by L_i with I_i
- c_i: average number of contact by I_i with S_p
- Π: recruitment rate of susceptible, $\pi \geq 0$
- μ: natural death rate, $\mu \geq 0$
- α: TB-related death rate from I_i, $\alpha \geq 0$
- α_2: TB-related death rate from I_2, $\alpha_2 \geq 0$
- α_3: TB-related death rate from I_3, $\alpha_3 \geq 0$
- α^*: TB-related death rate from I_r, $\alpha^* \geq 0$
- α': death-related latent infected of TB is negligible (since, $L_i(t)$ are not infectious)

The necessary assumptions of the model are as follows:

- The epidemiological population are either:
  - Susceptible (at risk of contracting the disease), S_p
  - Latently infected (but not infectious), L_i
  - Infective (capable of transmitting the disease), I_i
- Population understudy is heterogeneous
- Recovered individuals are naturally recruited into the susceptible population
- Latent infection related death rate is negligible
- Age structure is ignored
- Multidrug-resistant TB/HIV is ignored
- Reinfection does not occur (Porco and Blower, 1998)
- Nosocomial transmission (transmission from patients within hospital settings) is ignored
- Infection and death are not life-span dependent
- Population is homogeneous

Induced from Fig. 1 and the above assumptions, the model is governed by the following derivatives:

$$S_p^{'}(t) = \pi N_p - B_p S_p - \mu S_p \tag{1}$$

$$L_i^{'}(t) = B_p S_p - (k+\mu)L_i \tag{2}$$

$$I_i^{'}(t) = kL_i - (\rho+\psi+\mu+\alpha)I_i \tag{3}$$

$$I_2^{'}(t) = \rho I_i - (\mu+\alpha_2)I_2 \tag{4}$$

$$I_3^{'}(t) = \psi I_i - (\mu+\alpha_3)I_3 \tag{5}$$

$$I_\tau^{'}(t) = \sigma I_i - (\mu+\alpha^*)I_\tau \tag{6}$$

The population understudy is defined by the equation:

$$N_P = S_p(t) + L_i(t) + I_i(t) + I_2(t) + I_3(t) + I_\tau(t) \tag{7}$$

From Eq. 1 and 2, the per-capita rate of latent infection denoted by B_p is derived in relation to the individual fractions L_i/N_P, I_i/N_P, I_2/N_P, I_3/N_P, I_τ/N_P of TB-infected individuals (Hirsch *et al.*, 1985):

$$B_p = c_s\beta_i\frac{L_i}{N_p} + c_i\beta_i\frac{I_i}{N_p} + c_i\frac{(\beta_2I_2 + \beta_3I_3 + \beta^*I_\tau)}{N_p} \tag{8}$$

EQUATION TRANSFORMATION AND ANALYSIS

Equation transformation to dimensionless form reduces the number of equations for easy handling and initiates the biological meanings of the proportions of infected individual as well as defines the incidence and prevalence of infection. Suppose:

$$N_p(0) = N_p$$

Then, in terms of proportion:

$$s_p = \frac{S_p}{N_p} \tag{9}$$

$$l_i = \frac{L_i}{N_p} \tag{10}$$

$$u_i = \frac{I_i}{N_p} \tag{11}$$

$$w_i = \frac{I_2}{N_p} \tag{12}$$

$$x_i = \frac{I_3}{N_p} \tag{13}$$

$$y_i = \frac{I_\tau}{N_p} \tag{14}$$

Proportion-wise, let p(t) represent the effective population. Then we define as:

$$p(t) = \frac{N_p(t)}{N_p} = s_p + l_i + u_i + w_i + x_i + y_i \tag{15}$$

Applying similar transformation approach, Eq. 1-6 becomes:

$$s_p^{'} = \pi p(t) - B_p s_p - \mu s_p \tag{16}$$

$$l_i^{'} = B_p s_p - (k+\mu)l_i \tag{17}$$

$$u_i^{'} = kl_i - (\rho+\psi+\mu+\alpha)u_i \tag{18}$$

$$w_i^{'} = \rho u_i - (\mu+\alpha_2)w_i \tag{19}$$

$$x_i^{'} = \psi u_i - (\mu+\alpha_3)x_i \tag{20}$$

$$y'_i = \sigma u_i - (\mu + \alpha^*) y_i \qquad (21)$$

Further, we transform the coefficient of incidence of infection to dimensionless form (Anderson and May, 1991; Castillo-Chavez and Zhilan, 1997), i.e., Eq. 8 become:

$$B_p = c_s \beta_i \frac{l_i}{p(t)} + c_i \beta_i \frac{u_i}{p(t)} + c_i \frac{(\beta_2 w_i + \beta_3 x_i + \beta^* y_i)}{p(t)} \qquad (22)$$

The latently infected individuals (L_i), do not shed bacilli and are not infective to others. In some latently infected individuals, the infection remains latent and the infection may persist for life (Philip and Barry, 1994; Porco *et al.*, 2001). Therefore, at latently infected stage, if $\beta_i = 0$ then Eq. 16 become:

$$B_p = c_i \beta_i \frac{u_i}{p(t)} + c_i \frac{(\beta_2 w_i + \beta_3 x_i + \beta^* y_i)}{p(t)} \qquad (23)$$

Therefore, the model is governed by the 6 non-linear differential equations in 6 groups of the populations as highlighted in the summary of Table 1.

NUMERICAL SIMULATIONS AND RESULTS

Here, we set the 6 differential equations involving the populations (S_p, l_i, u_i, w_i, x_i, y_i) to a number of numerical simulations using a set of hypothetically generated data as highlighted in Table 2.

The characteristics of the proportions of the various population understudies are constant and are designated as follows:

$$P(t) = (Sp, l_i, u_i, w_i, x_i, y_i)$$
$$= [0.5, 0.1, 0.1, 0.1, 0.1, 0.1] \text{ and } T = 100; n \geq 0$$

In order for the parameters to be Runge-Kutter Method compactible, we transform the characteristics into vector quantities. Let:

$$H = \{H_1, ..., H_6\}^T = \{H_i\}_{i=1}^6 = \sum_{i=1}^6 H_i$$

Therefore, the systems of differential equations can be written as:

$$\frac{dH}{dt} = f(H), t \in [0, T]$$
$$H(0) = H_0$$

The computation is further enhanced by the use of MATHCAD grogram within-built "rkfixed" function.

In the analysis that follows, we focus on our set goal the dynamics of the effect of bi-therapy treatment of TB patients which is predominantly determined by ρ, ψ, σ, k, B_p. Other parameters were equally tested. Graphically, we represent the time by $Z^{<1>}$ and let $Z^{<2>}$, ..., $Z^{<7>}$ represent S_p, l_i, u_i, w_i, x_i, y_i, respectively with $\alpha^* = \alpha\tau$; $\beta^* = \beta\tau$ as seen in Fig. 2-5.

From Fig. 2, we investigate the zero variant factors (i.e., $\mu = 0$, $\alpha^* = 0$, $\sigma = 0$, $\beta^* = 0$). Here, with 20% rate of latently infected becoming infectious (i.e., $k = 0.2$) and in a situation where nobody uses the bi-therapeutic treatment as expressed in variant 1, we observed that the population experienced an initial rapid infection due to high average contact rate. The susceptible population is engulfed by infection after 20 years. Infection at various proportions decline but persisted steadily after 40 years due to overall transmission rate which stood at 14%.

Under Fig. 3, we study the performance of the bi-therapeutic treatment, allowing the parameters as in Fig. 2 with only variations in factors, i.e., $\mu = 0.04$, ρ, $\sigma = 0.1$, $\beta_3 = 0.1$, $\beta^* = 0.1$. It is seen that TB transmission was rapid, consuming the entire population within 30-50 years interval. This can be attributed to the fact that zero proportion uses the ART and only 10% were exposed to IPT and bi-therapeutic treatment.

In Fig. 4, the effect of the bi-therapies was further analyzed by the enhancement of the parameters of Fig. 3,
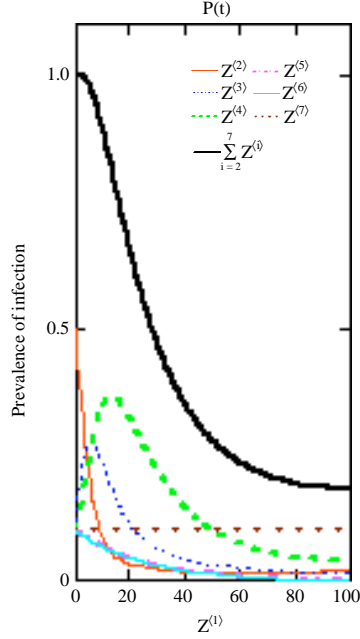
Table 1: Derivatives of proportions of TB bi-therapy control measures

Groups	Derivatives	Eq. No.
S_p	$S'_p = \pi p(t) - B_p S_p - \mu s_p$	16
L_i	$l'_i = B_p S_p - (k + \mu) l_i$	17
I_i	$u'_i = k l_i - (\rho + \psi + \mu + \alpha) u_i$	18
I_2	$w'_i = \rho u_i - (\mu + \alpha_2) w_i$	19
I_3	$x'_i = \psi u_i - (\mu + \alpha_3) x_i$	20
I_r	$y'_i = \sigma u_i - (\mu + \alpha^*) y_i$	21

Table 2: Table of parameter values for Fig. 1-4

Variants	π	μ	α	α_2	α_3	α^*	ρ	ψ	σ	k	c_i	c_i	β	β_2	β_3	β^*
1	0.02	0.00	0.10	0.04	0.04	0.00	0.0	0.0	0.0	0.2	5	5	0.2	0.14	0.14	0.00
2	0.02	0.04	0.10	0.14	0.14	0.10	0.1	0.0	0.1	0.2	5	5	0.2	0.14	0.10	0.10
3	0.02	0.04	0.10	0.14	0.14	0.00	0.0	0.1	0.1	0.2	5	5	0.2	0.10	0.14	0.00
4	0.02	0.01	0.04	0.14	0.14	0.04	0.1	0.1	0.4	0.2	5	5	0.2	0.10	0.14	0.04

Z_2-s_p-S_p, $s_p(0) = 0.5$; Z_3-l_i-L_i, $l_i(0) = 0.1$; Z_4-u_i-I_i, $u_i(0) = 0.1$; Z_5-w_i-I_i, $w_i(0) = 0.1$; Z_6-x_i-I_i, $x_i(0) = 0.1$; Z_7-y_i-I_r, $y_i(0) = 0.1$

Fig. 2: Graphical simulations of s_p, l_i, u_i, w_i, x_i, y_i from model (Eq. 16-21) against time with $Z^{(i)}$ the sum of proportions of various group populations, nobody used preventive measure. Parameter values are in variants (1 and 2) in Table 2
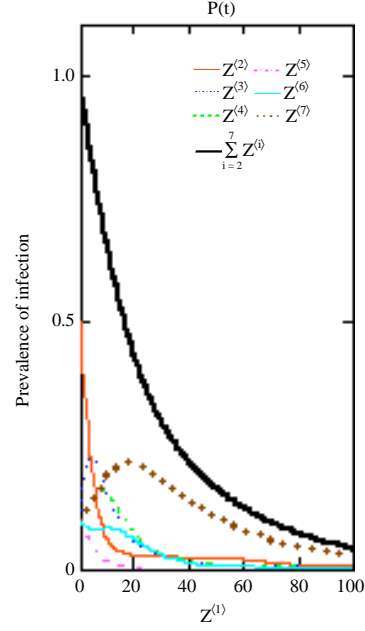

Fig. 4: Graphical simulations of s_p, l_i, u_i, w_i, x_i, y_i from model (Eq. 16-21) against time with $Z^{(i)}$ the sum of proportions of various group populations, only ART and bi-therapy were used. Parameter values are in variants (3 and 4) in Table 2
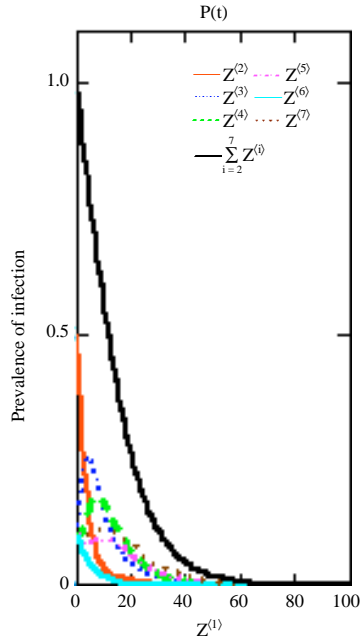

Fig. 3: Graphical simulations of s_p, l_i, u_i, w_i, x_i, y_i from model (Eq. 16-21) against time with $Z^{(i)}$ the sum of proportions of various group populations, only IPT and bi-therapy were used. Parameter values are in variants (1 and 2) in Table 2

increasing the proportion of infectious individuals that use the ART by 10% while the proportion that uses the IPT was allow to remain at zero. With 10% proportion of the individuals that use the bi-therapies (both IPT and ART) and zero transmission by this group, simulation indicates low and slow transmission of infection, compared to Fig. 3. It is arguably noticed that the ART is more effective compared to the IPT as shown by $Z^{(6)}$ against $Z^{(5)}$. The entire population were consumed by the infection but sustained by the introduction of bi-therapeutic treatment.

Finally, as in Fig. 5, we attempt and visibly analyze the effect of the bi-therapeutic treatment by absorbing the parameters as in Fig. 4 but with an enhancement of the proportion of the individuals who use both IPT and ART simultaneously by 40% (i.e., σ = 0.4), accounting for low transmission rate as well as related death rate of 4%. We observed initial rapid infection in the early 30 years but were curtailed by the application of IPT and ART, respectively. Figure 5 indicates that with the combination of both IPT and ART simultaneously, infected population generally have greater chances of surviving and living longer live even after 100 years with lesser probability of transmitting the disease.
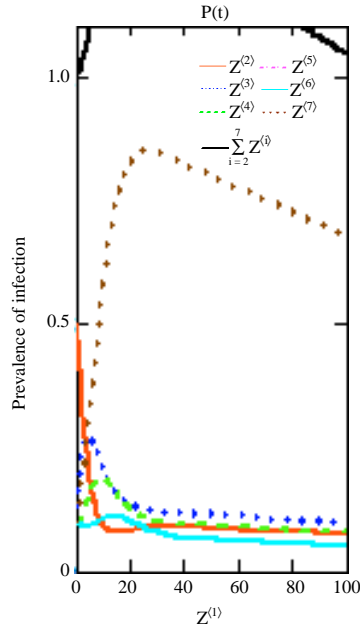
Fig. 5: Graphical simulations of s_p, l_i, u_i, w_i, x_i, y_i from model (Eq. 16-21) against time with $Z^{(i)}$ the sum of proportions of various group populations, all in propotions uses IPT, ART and bi-therapy. Parameter values are in variants (3 and 4) in Table 2

DISCUSSION

In the study, we present the dynamics of the effect of bi-therapeutic treatment of TB epidemic, an investigation informed by the research by Porco and Blower (1998). That study was basically on the understanding of the historical epidemiology of tuberculosis in developing countries where treatment is not a norm. Therefore, this present work which account for the effect of treatment of TB infection, justify its relevance. The model was instrumentally constructed using 6 groups of the population which leads to 6 non-linear differential equations. It also took onto account, natural birth rate which include recruitment of recovered individuals and related death rate from the considered groups of infected population.

Our model allows incisive comparison of the independent performance of treatment factors (i.e., IPT and ART) and as well the combination of both factors simultaneously in the fight to reduce and possibly eradicate the spread of TB disease. From the studies, we observed that the general behavior of these treatments depends predominantly on parameters such as ρ, ψ, σ, K, B_p.

In our program, we use MATHCAD with rkfixed in-built Runge-Kutter function. Results obtained from the numerical simulations of the model equations indicate that both therapies are vital in the treatment of TB infection. However as a single treatment, ART have shown to be more active compared with IPT. The investigation further reveal that prolonging the lives of the infected individuals and eradicating the spread of the disease is best control with through simultaneous application of both IPT and ART to affected patients. Figure 4 clearly vindicate this situation.

CONCLUSION

Investigation on the individual performance of IPT and ART and as a combined factor for the treatment of TB has been successfully conducted. The numerical analysis suggests that despite the individual effect of IPT and ART, respectively on the control and treatment of TB, the study have recommended the use of bi-therapeutic treatment as a norm for accelerated control and eradication of the spread of TB among infected individuals and the society. The result shows that for effective eradication of TB disease, adequate provision of medication should be made available and free to infected individuals. An environment of highly significant application and adherent to treatment will enhance the set goal of complete eradication of TB. The study also recommends continuous awareness campaign and education of the public, especially the developing countries on this best treatment measures.

REFERENCES

Anderson, R. and R. May, 1991. Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford.

Basu, S. and A.P. Galvani, 2008. The transmission and control of XDR TB in South Africa: An operations research and mathematical modelling approach. Epidemiol. Infect., 136: 1585-1598.

Bloom, B.R. and C.T.L. Murray, 1992. Tuberculosis commentary on a recent killer. science, 257: 1055-1064.

Blower, S.M., A.R. Mclean, T.C. Porco, P.M. Small and P.C. Hopewell *et al.*, 1995. The intrinsic transmission dynamics of tuberculosis epidemics. Nat. Med., 1: 815-821.

Castillo-Chavez, C. and F. Zhilan, 1997. To treat or not to treat: The case of tuberculosis. J. Math. Biol., 35: 629-656.

Cohen, T., C. Colijn, B. Finklea and M. Murray, 2007. Exogenous re-infection and the dynamics of tuberculosis epidemics: Local effects in a network model of transmission. J. R. Soc. Interface, 4: 523-531.

Dye, C., G.P. Garnett, K. Sleeman and B.G. Williams, 1998. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Lancet, 352: 1886-1891.

Egbetade, S.A. and M.O. Ibrahim, 2013. Stability analysis of equilibrium states of an SEIR tuberculosis model. J. Niger. Assoc. Math. Phys., 20: 119-124.

Egbetade, S.A., M.O. Ibrahim and A.O. Babatunde, 2012. Mathematical analysis of a tuberculosis epidemic model. Int. Refereed J. Eng. Sci., 1: 23-26.

Hirsch, W.M., H. Hanisch and J.P. Gabriel, 1985. Differential equation models of some parasitic infections: Methods for the study of asymptotic behavior. Commun. Pure Appl. Math., 38: 733-753.

Kochi, A., 1991. The global tuberculosis situation and the new control strategy of the world health organization. Tubercle, 72: 1-6.

Philip, C.H. and R. Barry, 1994. Tuberculosis and Other Mycobacterial Disease. W.B. Saunders Co., Philadelphia, PA.

Porco, T.C. and S.M. Blower, 1998. Quantifying the intrinsic transmission dynamics of tuberculosis. Theor. Popul. Biol., 54: 117-132.

Porco, T.C., P.M. Small and S.M. Blower, 2001. Amplification dynamics: Predicting the effect of HIV on tuberculosis outbreaks. J. Acquir Immune Defic Syndr., 28: 437-444.

Rodrigues, P., M.G.M. Gomes and C. Rebelo, 2007. Drug resistance in tuberculosis: A reinfection model. Theor. Popul. Biol., 71: 196-212.

Roeger, L.I.W., Z. Feng and C. Castillo-Chavez, 2009. Modeling TB and HIV co-infections. Math. Biosci. Eng., 6: 815-837.

Sharomi, O., C. Podder, A. Gumel and B. Song, 2008. Mathematical analysis of the transmission dynamics of HIV/TB coinfection in the presence of treatment. Math. Biosci. Eng., 5: 145-174.