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Tuberculosis Transmission Model with Extensive Drug Resistance Effects in Nigeria

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Abstract

In this paper, we proposed a mathematical model for the dynamics of Tuberculosis incorporating extensive drug resistance effect. Positivity of solutions of the model was determined and the effective reproduction number was obtained. A sensitively analysis (SA) of the effective reproduction number with respect to the model parameters is performed and the most sensitive parameters of the model are identified. The effective contact rate of individuals with tuberculosis has the highest sensitivity index followed by the treatment rate for individuals with tuberculosis which is enhanced by direct observation therapy strategy (DOTS). The parameters with the least SA are mortality rate of extensively drug resistance tuberculosis infected individuals undergoing treatment and the yearly recruitment rate due to birth. Furthermore, control programmes such as direct observation therapy strategy (DOTS) should be monitored in Nigeria to ensure compliance with treatment so as to reduce acquired drug resistance and transmission of drug-resistant strains.

Keywords: Tuberculosis, Extensively drug resistance tuberculosis, Effective reproduction number, Sensitivity Analysis.

1. Introduction

Tuberculosis is a bacterial infection caused by *mycobacterium tuberculosis* referred to as *tubercle bacilli* (TB). TB has caused many deaths globally in developing countries due to treatment failure or delayed intervention [14]. It is estimated that a third of the world's population is infected with *Mycobacterium tuberculosis*. Of the 1.7 billion people estimated to be infected with TB, 1.3 billion live in developing countries [15]. In 2012, 8.6 million people fell ill with *TB* and 1.3 million died from *TB* world-wide [13]. Africa and Asia have the highest burden of tuberculosis. The World Health Organization recommends vaccination with Bacille Calmette-Guerin vaccine at birth or first contact with health services as part of control measures to reduce the burden of tuberculosis especially among children in developing countries. Nigeria experienced an upsurge of tuberculosis (TB) cases over the past decade. The administration of BCG vaccine to children is essential in the control of tuberculosis [1]. Moreover, the emergence of the extensively drug resistant TB (XDR-TB) strains are making the existing intervention and prevention

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strategies less effective and posing a growing global health challenge to the underdeveloped and developing countries. XDR-TB is defined as TB with resistance to at least isoniazid (INH), rifampicin, any fluoroquinolone (FQ) and one of three second-line injectable drugs (amikacin, kanamycin or capreomycin) [2]. Tuberculosis remains a leading cause of death among infectious diseases, despite numerous strategies employed by various international organizations to eradicate the disease.

2. Materials and Methods

2.1. Model Development

This model incorporates extensive drug resistance effects in its dynamics with treatment and vaccination as control parameters to study the spread and control of tuberculosis using a non-linear system of ordinary differential equations. The total population (N) is divided into eight compartments namely; susceptible individuals (S), vaccinated individuals (V), latently infected individuals with TB (L), actively infected individuals with TB (I_1),actively infected individuals with TB undergoing treatment (T_1), actively infected individuals with extensively drug-resistant TB (I_2),actively infected individuals with extensively drug-resistant TB undergoing treatment (T_2) and recovered individuals (R), so that $N = S + V + L + \mathrm{I}_1 + T_1 + I_2 + T_2 + R$.

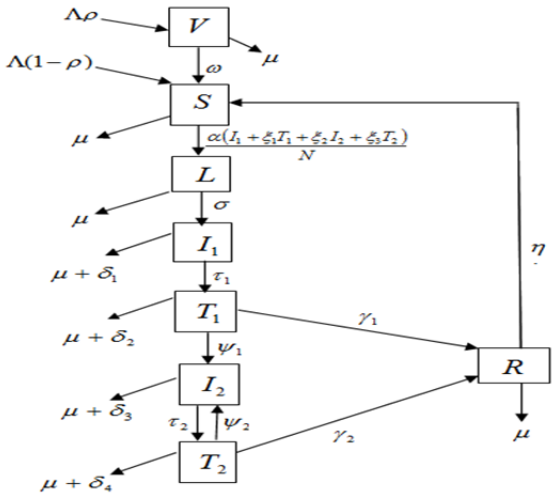

Figure 1: The schematic representation of the model.

The vaccinated class is generated from daily recruitment of new births successfully immunized against infection at a rate $\Lambda\rho$. It reduces due to the expiration of duration of vaccine efficacy at rate ω and also as a result of natural death at a rate μ.

The susceptible class increases due to the influx of new born babies not immunized against TB infection at a rate $\Lambda(1-\rho)$, the coming in of some recovered individuals due to the waning of temporal immunity of recovered individuals at a rate η and as a result of expiration of duration of vaccine efficacy at a rate ω. It decreases following interaction between susceptible, actively

infected with TB, actively infected with TB undergoing treatment, actively infected with XDR- TB, actively infected with XDR- TB undergoing treatment with the force of infection $\frac{\alpha(I_1+\xi_1T_1+\xi_2I_2+\xi_3T_2)}{N}$, where α is the effective contact rate of individuals with TB. ξ_1, ξ_2, ξ_3 are modification parameter associated with reduced contact rate by T_1, I_2, T_2 compartments respectively. It also decreases as a result of natural death at a rate μ.

The latent class grows with the force of infection $\frac{\alpha(I_1+\xi_1T_1+\xi_2I_2+\xi_3T_2)}{N}$ and decreases due to natural death and activation of the mycobacterium residing inside the body at rates μ and σ respectively. The I_1 class grows due to activation of the mycobacterium residing inside the body at a rate σ and reduces due to treatment, natural death and disease induced death at rates τ_1, μ and δ_1.respectively.

The model equations describing the schematic diagram are;

$$\frac{dS}{dt}=\Lambda(1-\rho)-\frac{\alpha(I_1+\xi_1T_1+\xi_2I_2+\xi_3T_2)S}{N}+\omega V+\eta R-\mu S \quad (1)$$

$$\frac{dV}{dt}=\Lambda\rho-(\omega+\mu)V \quad (2)$$

$$\frac{dL}{dt}=\frac{\alpha(I_1+\xi_1T_1+\xi_2I_2+\xi_3T_2)S}{N}-(\sigma+\mu)L \quad (3)$$

$$\frac{dI_1}{dt}=\sigma L-(\tau_1+\mu+\delta_1)I_1 \quad (4)$$

The T_1 class grows due to treatment at a rate τ_1 and decreases due to recovery after treatment at a rate γ_1. It reduces as a result of progression to I_2 compartment due to treatment failure at a rate ψ_1 and diminishes due to natural death and disease induced death at rates μ and δ_2 respectively.

The I_2 class grows due to treatment failure in the T_1 class and also grows due to noncompliance with treatment in T_2 class at a rate ψ_1. It decreases as a result of treatment, natural death and disease induced death at rates τ_2, μ and δ_3 respectively. The T_2 class is generated through treatment at a rate τ_2 and decreases at rates γ_2, ψ_2, μ and δ_4 respectively. γ_2 is the recovery rate for actively infected individuals with XDR- TB, ψ_2 is the progression rate from T_2 to I_2 compartment, δ_4 is the disease induced death rate of actively infected individuals with XDR-TB undergoing treatment.

$$\frac{dT_1}{dt}=\tau_1I_1-(\gamma_1+\psi_1+\mu+\delta_2)T_1 \quad (5)$$

$$\frac{dI_2}{dt}=\psi_1T_1+\psi_2T_2-(\tau_2+\mu+\delta_3)I_2 \quad (6)$$

$$\frac{dT_2}{dt}=\tau_2I_2-(\gamma_2+\psi_2+\mu+\delta_4)T_2 \quad (7)$$

$$\frac{dR}{dt}=\gamma_1T_1+\gamma_2T_2-(\eta+\mu)R \quad (8)$$

where

$$N=S+V+L+\mathrm{I}_1+T_1+I_2+T_2+R \quad (9)$$

Let,

$$k_1 = \omega + \mu \quad (10)$$

$$k_2 = \sigma + \mu \quad (11)$$

$$k_3 = \tau_1 + \mu + \delta_1 \quad (12)$$

$$k_4 = \gamma_1 + \psi_1 + \mu + \delta_2 \quad (13)$$

$$k_5 = \tau_2 + \mu + \delta_3 \quad (14)$$

$$k_6 = \gamma_2 + \psi_2 + \mu + \delta_4 \quad (15)$$

$$k_7 = \eta + \mu \quad (16)$$

Thus, the equations (1) to (8) become

$$\frac{dS}{dt} = \Lambda(1-\rho) - \frac{\alpha(I_1 + \xi_1 T_1 + \xi_2 I_2 + \xi_3 T_2)S}{N} + \omega V + \eta R - \mu S \quad (17)$$

$$\frac{dV}{dt} = \Lambda\rho - k_1 V \quad (18)$$

$$\frac{dL}{dt} = \frac{\alpha(I_1 + \xi_1 T_1 + \xi_2 I_2 + \xi_3 T_2)S}{N} - k_2 L \quad (19)$$

$$\frac{dI_1}{dt} = \sigma L - k_3 I_1 \quad (20)$$

$$\frac{dT_1}{dt} = \tau_1 I_1 - k_4 T_1 \quad (21)$$

$$\frac{dI_2}{dt} = \psi_1 T_1 + \psi_2 T_2 - k_5 I_2 \quad (22)$$

$$\frac{dT_2}{dt} = \tau_2 I_2 - k_6 T_2 \quad (23)$$

$$\frac{dR}{dt} = \gamma_1 T_1 + \gamma_2 T_2 - k_7 R \quad (24)$$

Adding (1) - (8) gives

$$\frac{dN}{dt} = \Lambda - \mu N - (\delta_1 I_1 + \delta_2 T_1 + \delta_3 I_2 + \delta_4 T_2) \quad (25)$$

Let $\Omega = (S, V, L, I_1, T_1, I_2, T_2, R) \in \Re_+^8$ be any solution of the system with non-negative initial conditions. It can be shown that the feasible solution set of equation (1) – (8) enter and remain in the region;

$$\Omega = \left\{ (S, V, L, I_1, T_1, I_2, T_2, R) \in \Re_+^8 : N \le \frac{\Lambda}{\mu} \right\}$$

2.2. Positivity of Solutions

Lemma: All the solutions of the equations (17) to (24) are positive for all time $t \ge 0$ provided that the initial conditions are positive.

Proof

As applied in [23]

Let,

$$\{(S(0), V(0), L(0), I_1(0), T_1(0), I_2(0), T_2(0), R(0)) \ge 0\} \in \Re_+^8$$

From (17),

$$S' = \Lambda(1-\rho) - \left(\frac{\alpha(I_1 + \xi_1 T_1 + \xi_2 I_2 + \xi_3 T_2)}{N} + \mu \right) S + \omega V + \eta R \quad (26)$$

$$S' \ge -\left(\frac{\alpha(I_1 + \xi_1 T_1 + \xi_2 I_2 + \xi_3 T_2)}{N} + \mu \right) S \quad (27)$$

$$\frac{S'}{S} \ge -\left(\frac{\alpha(I_1 + \xi_1 T_1 + \xi_2 I_2 + \xi_3 T_2)}{N} + \mu \right) \quad (28)$$

$$S(t) \ge S(0) e^{\int_0^t -\left(\frac{\alpha(I_1 + \xi_1 T_1 + \xi_2 I_2 + \xi_3 T_2)}{N} \right) dt - \mu t} \ge 0 \quad (29)$$

Since

$$\frac{\alpha\left(I_1+\xi_1 T_1+\xi_2 I_2+\xi_3 T_2\right)}{N}\geq 0$$

and

$$\mu \geq 0$$

From (18),

$$V' = \Lambda\rho - k_1 V \geq -k_1 V \qquad (30)$$

$$\frac{V'}{V} \geq -k_1 \qquad (31)$$

$$V(t) \geq V(0)e^{-k_1 t} \geq 0 \qquad (32)$$

since

$$k_1 \geq 0$$

Similarly, from (19) - (24), it can be shown that
$\{L(0), I_1(0), T_1(0), I_2(0), T_2(0), R(0)) \geq 0\}$

2.3. Existence of Disease Free Equilibrium State, E_0

Disease free equilibrium states are steady state solutions where there is no infection. Setting the derivatives to zero in (17) – (24), the disease free equilibrium state is obtained and is given by

$$E_0 = \begin{pmatrix} S^0 \\ V^0 \\ L^0 \\ I_1^{\,0} \\ T_1^{\,0} \\ I_2^{\,0} \\ T_2^{\,0} \\ R^0 \end{pmatrix} = \begin{pmatrix} \frac{k_1\Lambda(1-\rho)+\omega\Lambda\rho}{\mu k_1} \\ \frac{\Lambda\rho}{k_1} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \qquad (33)$$

2.4. Effective Reproduction Number, R_c

Using the approach described in [21], we obtained the effective reproduction number R_c which is the largest eigenvalue (spectral radius ρ) of the next generation matrix, FV^{-1} i.e. $R_c = \rho FV^{-1}$ as follows;

$$F = \begin{pmatrix} 0 & \frac{\alpha S^0}{N^0} & \frac{\alpha\xi_1 S^0}{N^0} & \frac{\alpha\xi_2 S^0}{N^0} & \frac{\alpha\xi_3 S^0}{N^0} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \qquad (34)$$

and

$$V = \begin{pmatrix} k_2 & 0 & 0 & 0 & 0 \\ -\sigma_1 & k_3 & 0 & 0 & 0 \\ 0 & -\tau_1 & k_4 & 0 & 0 \\ 0 & 0 & -\psi_1 & k_5 & -\psi_2 \\ 0 & 0 & 0 & -\tau_2 & k_6 \end{pmatrix} \qquad (35)$$

Thus, the spectral radius of FV^{-1} is given as

$$R_c = \frac{\left(\alpha\sigma k_4 D + \alpha\xi_1\tau_1\sigma D + \alpha\xi_2\psi_1\tau_1\sigma k_6 + \alpha\xi_3\tau_2\psi_1\tau_1\sigma\right)\left(k_1\Lambda(1-\rho)+\omega\Lambda\rho\right)}{N^0 k_2 k_3 k_4 D\mu k_1} \qquad (36)$$

$$D = (k_5 k_6 - \psi_2\tau_2)$$

R_c is the average number of secondary infectious cases that an actively infected individual with typical TB would produce in a totally susceptible population when vaccination is administered at birth.

2.5. Sensitivity Analysis

For infectious disease models in particular, the sensitivity analysis of the effective

reproduction number R_c with respect to the model parameters has been performed to determine the importance of the epidemic model parameters [19]. The sensitivity analysis of the magnitude of R_c will be computed with respect to the model parameter values to determine the relative influence of each parameter on the transmission and control of the disease. The normalised sensitivity index of the effective reproduction number R_c with respect to a parameter value Q is given by $S_Q^{R_c} = \frac{\partial R_c}{Q} \times \frac{Q}{R_c}$

Table 1 Baseline values for population-independent parameters of the model (yr^{-1})

S/No	Parameter	Value	Source	S/No	Parameter	Value	Source
1	α	0.0000621	A.3	**10**	ψ_2	0.06	A.11
2	ξ_1	0.826	A.4	**11**	δ_1	0.00292	A.12
3	ξ_2	0.296	A.4	**12**	δ_2	0.00032	A.13
4	ξ_3	0.050	A.4	**13**	δ_3	0.00144	A.14
5	ω	0.067	A.5	**14**	δ_4	0.0005	A.15
6	σ	0.5	A.6	**15**	η	0.4	A.9
7	γ_1	2	A.7	**16**	ρ, τ_1, τ_2	(0-1)	
8	γ_2	0.5	A.8	**17**	μ	0.0189	A.1
9	ψ_1	0.226	A.10	**18**	Λ	3,348,245	A.2

Table 2 Sensitivity Indices of R_c to Model Parameters. The parameters are ordered from the most sensitive to the least. Parameter values used are in table 1

S/No	Parameters	SA value for $\tau_1 = \tau_2 = \rho = 0.25$	SA value for $\tau_1 = \tau_2 = \rho = 0.5$
1	α	+1	+1
2	τ_1	-0.809	-0.778
3	μ	-0.155	-0.172
4	γ_1	-0.0987	-0.161
5	ξ_1	0.082	0.151
6	ρ	-0.0582	-0.124
7	ω	0.0454	0.0964
8	σ	0.0364	0.0364
9	ξ_2	0.0271	0.0261
10	τ_2	-0.0247	-0.0248
11	ψ_1	0.0179	0.00863
12	δ_1	-0.0107	-0.0115
13	γ_2	-0.00436	-0.00612

14	ψ_2	0.00256	0.00256
15	ξ_3	0.00197	0.0038
16	δ_3	-0.000171	-0.0000917
17	δ_2	-0.0000158	-0.0000257
18	δ_4	-0.00000436	-0.00000612
19	Λ	-1.84×10^{-10}	1.95×10^{-10}

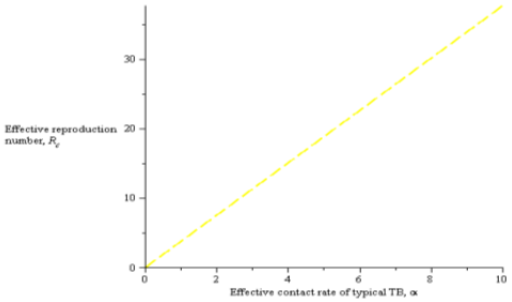

Figure 1: Effect of contact rate α on the effective reproduction number R_c . Parameter values are in table 1 with $\tau_1 = \tau_2 = \rho = 0.25$.

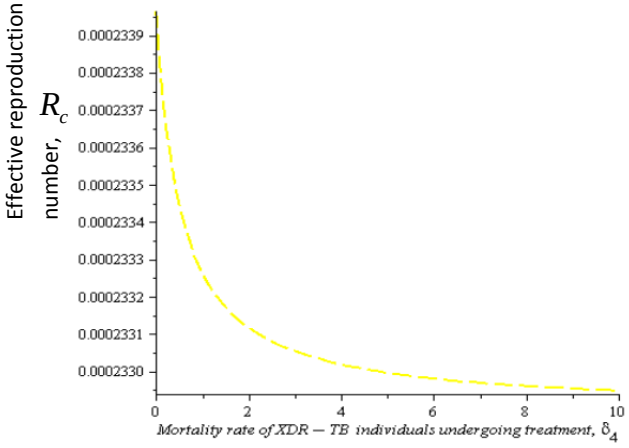

Figure 2: Effect of mortality rate of XDR-TB infected individual undergoing treatment (δ_4) on the effective reproduction number R_c . Parameter values are in table 1 with $\tau_1 = \tau_2 = \rho = 0.25$.

Conclusion

This study presents a deterministic model for the spread and control of tuberculosis incorporating extensive dug resistance effect with treatment and vaccination as control parameters. This work incorporates two treatment compartments, T_1 for TB and T_2 for extensively drug resistance TB since the drug administration and treatment duration differs considerably for both cases. The effective reproduction number is obtained and a sensitively analysis of the effective reproduction number with respect to the model parameters is performed and the most sensitive parameters of the model are identified. However, the effective contact rate of individuals with TB (α) and the treatment rate for individuals with TB which is enhanced by DOTS (τ_1) have the highest sensitivity index. The parameters with the least SA are mortality rate of XDR-TB infected individuals undergoing treatment (δ_4) and the yearly recruitment rate due to birth (Λ). Figure 1 shows the linear relationship between R_c and the effective contact rate α. It means R_c increases with increasing effective contact rate. Figure 2 shows the relationship between R_c and the mortality rate of XDR-TB individuals

undergoing treatment. This means R_c decreases with decreasing mortality rate of XDR-TB individuals undergoing treatment. Furthermore, efforts should be geared towards reducing effective contact rate between susceptible and actively infected individuals. Control programmes such as direct observation therapy strategy (DOTS) should be monitored in Nigeria to ensure compliance to treatment of infected individuals so as to decrease acquired drug resistance and transmission of drug-resistant strains.

APPENDIX A

A.1. Natural death rate (μ)

This is defined to be equal to the inverse of the life expectancy at birth [11].

The life expectancy at birth for Nigeria in 2014 is $53.02yrs$ [4].

$$\mu = \frac{1}{53.02} = 0.0189yr^{-1}$$

A.2. Yearly Recruitment Rate due to Birth (Λ)

Nigeria is composed of more than 250 ethnic groups with an estimated population of 177,155,754 [4].

The average population of new birth in Nigeria is given by
$\mu \times N = 0.0189 \times 177{,}155{,}800 = 3{,}348{,}245$

A.3. Effective Contact Rate of Individuals with TB (α)

The average annual risk of infection with *Mycobacterium tuberculosis* is a calculated average from an observed prevalence of infection which approximates the incidence of infection. It gives potential information about the changes in transmission patterns of *Mycobacterium tuberculosis* in any community [18]. The annual risk of TB infection is the probability of acquiring new tuberculosis infection or re-infection over a period of one year [20]. The estimated average annual risk of TB infection is 1.9% and the prevalence rate of TB in Nigeria is 0.327% [3].

$$\alpha = 0.327\% \times 1.9/100 = 0.0000621$$

$$\alpha_1 = 0.327\% \times 2.3/100 = 0.0000752$$

Reported prevalence rate of XDR-TB is estimated to be 0.6% in [7]. Globally, 3.5% of new TB cases and 20.5% of previously treated cases are estimated to have XDR-TB [24].

$$\alpha_2 = 3.5\% \times 0.6/100 = 0.00021$$

$$\alpha_3 = 20.5\% \times 0.6/100 = 0.00123$$

Where α_1, α_2 and α_3 are contact rate for individuals with TB undergoing treatment, extensively drug resistance TB individuals and extensively drug resistance TB individuals undergoing treatment respectively.

A.4. Modification Parameter Associated with Reduced Contact Rate by Actively Infected Individuals with TB Undergoing Treatment (ξ_1), XDR-TB Individuals (ξ_2) and XDR-TB Individuals Undergoing Treatment (ξ_3)

From above, $\alpha = \alpha_1\xi_1$, $0.0000621 = 0.0000752\xi_1$, this gives $\xi_1 = 0.826$

$\alpha = \alpha_2\xi_2$, $0.0000621 = 0.00021\xi_2$, this gives $\xi_2 = 0.296$

$\alpha = \alpha_3\xi_3$, $0.0000621 = 0.00021\xi_3$, this gives $\xi_3 = 0.050$

A.5. Waning Rate of Vaccination (ω)

The BCG vaccine is 80% effective in preventing tuberculosis for a duration of $15yrs$ [5].

$$\omega = \frac{1}{15} yr^{-1} = 0.067 yr^{-1}$$

A.6. Progression Rate from L to I_1 (σ)

Approximately 5% of people with latent infection will progress to active TB within the first two years after infection and another 10% will develop the disease over their life time [12].

$$\sigma = \frac{1}{2} yr^{-1} = 0.5 yr^{-1}$$

A.7. Progression Rate from T_1 to R (γ_1)

TB can be treated using a combination of antibiotics for a minimum period of six months [24].

$$\gamma_1 = \frac{1}{6\ months} = \frac{1}{0.5} yr^{-1} = 2yr^{-1}$$

A.8. Progression Rate from T_2 to R (γ_2)

Treatment of XDR-TB requires extensive chemotherapy for up to two years as recommended by [24].

$$\gamma_2 = \frac{1}{2} yr^{-1} = 0.5 yr^{-1}$$

A.9. Waning Rate of Temporal Immunity of Recovered Individuals (η)

In a study described in [17], approximately 40% of the cases of recurrence occurred in the first 12 months.

$$\eta = 0.4 yr^{-1}$$

A.10. Progression Rate from T_1 to I_2 due to Treatment Failure (ψ_1)

Patients who are diagnosed with TB for the first time had 22.6% of treatment failure [8].

$$\psi_1 = 0.226 yr^{-1}$$

A.11. Progression Rate from T_2 to I_2 due to Non-compliance with Treatment (ψ_2)

About 6% of XDR-TB patient were reported to have defaulted from treatment [9].

$$\psi_2 = 0.06 yr^{-1}$$

A.12. Mortality Rate due to TB (δ_1)

With nearly nine million people infected and an estimated 1.6 million TB deaths each year, TB is considered a major public health issue worldwide [13]. It was realized that most of the deaths due to TB occurred within the first three weeks of treatment. The probability of death was 0.0164 [8].

$$\delta_1 = 0.0164 \times \frac{1.6}{9} yr^{-1} = 0.00292 yr^{-1}$$

A.13. Mortality Rate of TB Infected Individuals Undergoing Treatment (δ_2)

The risk of relapse and death were found to be age-related. Age between $40 - 60yrs$ is a significant risk factor for death in TB patients [16]. In another study, 6% of TB patients died within one year while on treatment [22].

$$\delta_2 = \frac{6}{100} \times \frac{1.6}{9} \times \frac{1}{50} yr^{-1} = 0.00032 yr^{-1}$$

A.14. Mortality Rate due to XDR-TB (δ_3)

[6] reported 80% death among XDR-TB patient. Since 9% of MDR-TB individuals are infected with XDR-TB, we have,

$$\delta_3 = \frac{9}{100} \times \frac{80}{100} \times \frac{1}{50} yr^{-1} = 0.00144 yr^{-1}$$

A.15. Mortality Rate of XDR-TB Infected Individuals Undergoing Treatment (δ_4)

XDR-TB is a strong predictor of long-term mortality in TB patients and an estimated 26.7% death among XDR-TB patients undergoing treatment were recorded in [10].

$$\delta_4 = \frac{9}{100} \times \frac{26.7}{100} \times \frac{1}{50} yr^{-1} = 0.0005 yr^{-1}$$

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