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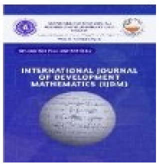

Mathematical Modeling and Analysis of MDR-TB with Vaccination and Re-infection

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Abstract

Tuberculosis (TB) is still one of the major infectious diseases in the world and a leading public health problem, particularly in developing countries where Multi-Drug-Resistant Tuberculosis (MDR-TB) seriously threatens the efforts to control it. A deterministic compartmental model is developed to study TB transmission dynamics with vaccination, reinfection, treatment failure and development of MDR-TB. The total human population is stratified into six disjoint classes: susceptible unvaccinated, susceptible vaccinated, exposed, infectious with drug-susceptible TB, infectious with MDR-TB, and recovered individuals. The positivity and boundedness of solutions were proved to ensure biological feasibility of the qualitative properties of the model. We obtained the disease-free and endemic equilibrium states and calculated the basic reproduction number $\mathcal{R}_0$ using the next-generation matrix method. The stability analysis revealed that the disease-free

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equilibrium is locally and globally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$. Furthermore, by developing a suitable Lyapunov function and using LaSalle's invariance principle, the global asymptotic stability of the endemic equilibrium is established for $\mathcal{R}_0 > 1$. Numerical simulations are performed to illustrate the effects of critical epidemiological parameters on the disease progression and to verify the analytical results. Sensitivity analysis based on Partial Rank Correlation Coefficients (PRCC) shows that the effective contact rate is the most critical parameter influencing TB transmission, while the treatment and recovery parameters play a strong role in reducing the spread of the disease. The study shows that effective vaccination, better treatment adherence and strong MDR-TB case management are necessary to cut down TB burden and attain long-term control over the disease.

1 Introduction

Tuberculosis (TB) is still a major global public health challenge, especially in low- and middle-income countries (World Health Organization, 2023). TB is preventable if proper precautions are taken and it is treatable with proper medical care (Bagcchi, 2023). The disease is an airborne disease caused by *Mycobacterium tuberculosis*, which can infect any part of the body, but most commonly affects the lungs. Tuberculosis (TB) is the leading infectious killer in the world, with 10 million new cases and 1.5 million deaths reported annually, the World Health Organization (WHO) reports. Globally, an estimated 1.6 million people died from TB in 2021, including 187,000 people living with HIV/AIDS. Tuberculosis (TB) has re-emerged as the second leading infectious cause of death globally and the thirteenth leading cause of death overall after the COVID-19 pandemic (World Health Organization, 2022). There is a wide gap between TB incidence and case detection rates. In 2021, 4.2 million people with active TB did not reach health facilities leading to a drastic reduction in reported and screened cases: 7.1 million cases were reported in 2021 versus 6.4 million in 2019 (World Health Organization, 2022). Despite these challenges, TB treatment has saved some 74 million lives between 2000 and 2021. However, drug-resistant TB (DR-TB) is expected to increase, with 450,000 new cases reported in 2021 (World Health Organization, 2022).

There are three main medical strategies for controlling TB, preventive treatment of people with latent TB infection to prevent re-activation, curative treatment of active TB patients and vaccination to reduce transmission (Gabriela et al., 2007). The most commonly used vaccine against TB is the Bacillus Calmette-Guérin (BCG). It has been shown to be effective in protecting children with rates of success above 50% against pulmonary TB and 80% against disseminated forms of the disease (Peter and Mark, 2005). However, an important epidemiological consideration is that children rarely transmit TB and transmission is primarily driven by adults (Nadolinskaia et al., 2020). However, BCG vaccination has shown variable protection against pulmonary TB in adults, thus leaving a critical gap in adult TB prevention strategies. Drug-resistant TB represents a serious challenge in many developing countries where treatment is long and expensive (World

Health Organization, 2022). In some countries, treatment for TB may be available but not always free, with patients incurring a financial burden and some choosing home-based rather than hospital-based care. Also, patients who do not improve in hospital settings may opt to leave and continue care at home (Abimbode et al., 2020). Multidrug-resistant TB (MDR-TB) may develop during the course of treatment of TB and, rarely, progress to extensively drug-resistant TB (XDR-TB). This is generally due to the improper use of drugs, poor prescription, early discontinuation of treatment, or inferior drugs. However, treatment for MDR-TB and XDR-TB is still feasible but it is more time consuming and labor intensive. Current treatment success rates for MDR-TB are 28% and 52% (World Health Organization, 2022; Yongqi et al., 2011).

Mathematical modelling has become an important tool for studying the dynamics of TB and evaluating intervention strategies. Christopher (2006) developed a model that allows the drug-resistant strains to have a similar relative fitness as the drug-sensitive strains, showing that at least 70% of drug-resistant patients must be identified and treated to end DR-TB epidemics. In recent years, simple compartmental models have been extensively used to study the effects of inadequate immunization . These models classify individuals as susceptible , vaccinated , infectious , or recovered and include frameworks such as SVI and SVIR . There were several studies that specifically discussed MDR-TB and vaccination. Bimal and Jyohka (2014) presented a mathematical model with vaccination and quarantine classes considering both the vaccinated and MDR-TB patients. Their work established system thresholds, equilibria and reproduction numbers and carried out stability analysis. Simulations indicated that isolating MDR-TB patients accelerates recovery and essentially eliminates TB transmission, while vaccination reduces the number of active TB cases. Ayinla and Wan Ainun (2019) developed a deterministic compartmental model to study the effect of isolating MDR-TB patients. Their model exhibited two equilibria leading to backward bifurcation, and numerical simulations indicated that quarantine policies could be effective in controlling the cases of MDR-TB via reducing the incidence of the disease. Abdullahi et al. (2019) extended the SEIRS epidemiology model of tuberculosis by including passive immunity and MDR-TB. Their analysis showed that the disease free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$ and globally asymptotically stable if $\mathcal{R}_0 \leq 1$. They concluded that to control tuberculosis, drug efficacy should be improved and second line treatment enforced.

However, existing models have not simultaneously considered the combined effects of vaccination, reinfection, treatment failure and progression to MDR-TB in a unified framework. The interaction of these factors is not well understood, particularly in high-burden settings where resources are limited and transmission pressures are high. Here we formulate a deterministic compartmental model to study the transmission dynamics of TB with vaccination, reinfection, treatment failure and progression of MDR-TB. The specific objectives are to: (1) develop a six-compartment model (susceptible unvaccinated, susceptible vaccinated, exposed, infectious with drug-susceptible TB, infectious with MDR-TB and recovered); (2) establish qualitative properties of the model including positivity and boundedness; (3) obtain the disease-free and endemic equilibria and compute the basic reproduction number $\mathcal{R}_0$; (4) carry out stability analysis using Lyapunov functions and LaSalle's invariance principle; and (5) perform numerical simulations and sensitivity analysis to identify key drivers of TB transmission. The rest of this paper is organized as follows. Section 2 deals with the formulation of the model. Basic properties of the model is and the model theoretical analysis are presented in Section 3 Section 4. Sensitivity analysis is described in Section 5. Implications of findings are discussed in Section 6. Section 7 concludes with recommendations for policy and future research areas.

2 Mathematical Model Formulation

The proposed model stratifies the human population into six mutually-exclusive epidemiological compartments to describe the transmission dynamics of Tuberculosis (TB). These compartments are: susceptible unvaccinated individuals (S_u), susceptible vaccinated individuals (S_v), exposed individuals (E_H), infectious individuals (I_H), multi-drug-resistant infectious individuals (I_R), and recovered individuals (R_H).Individuals enter the population at a constant rate Λ_H. Of these new recruits, a proportion z enters the unvaccinated susceptible class S_u and the remaining proportion $(1-z)$ enters the vaccinated susceptible class S_v. Natural mortality occurs at rate μ_H in both susceptible classes. Susceptible unvaccinated individuals (S_u) get infected with TB after effective contact with infectious individuals at a force of infection λ_H adjusted by the vaccine efficacy factor ε. Thus, a fraction $\varepsilon\lambda_H$ of unvaccinated individuals are exposed and enter into the E_H compartment. Similarly, vaccinated susceptibles (S_v) are infected at a reduced rate $(1-\varepsilon)\lambda_H$, where ϵ represents the degree of partial protection conferred by vaccination. The exposed individuals (E_H) are those who were infected but are not yet infectious. They transfer to the infectious class (I_H) at rate σ, or die naturally at rate μ_H. Infectious individuals (I_H) may be treated at a per capita rate τ_H.

A proportion $(1-\eta)$ of treated individuals successfully recover at a rate $(1-\eta)\tau_H$ and enter the recovered class (R_H). A fraction η of treated individuals fail treatment, developing multi-drug resistant TB and enter the I_R compartment at a rate $\eta\tau_H$. In addition, infectious people die from natural causes or from the disease at a combined rate $\mu_H + d_i$.Those who acquire multi-drug resistance are moved to the compartment I_R. These individuals may recover at a rate ρ_H, or die from natural and disease induced causes at a combined rate $\mu_H + d_r$.Recovered individuals (R_H) lose immunity and become susceptible again at rate $(1-\gamma)\lambda_H$, thus re-entering the infection cycle. Natural mortality at rate μ_H is also experienced by recovered individuals.The vaccine-induced immunity wanes at rate ω_H, causing vaccinated individuals to move from the vaccinated susceptible class S_v to the unvaccinated susceptible class S_u. Similarly, public health interventions may vaccinate people at a rate ϕ_H or administer booster doses, moving individuals from S_u to S_v. The infection rate of humans is given as $\lambda_H = \frac{\beta_H(I_H+\kappa I_R)}{N_H}$. The equations for the TB model is given by the following deterministic system of nonlinear differential equations in (1) and the schematic diagram is depicted in Figure 1 while state variable and parameters are presented in Tables 1 and 2 respectively.

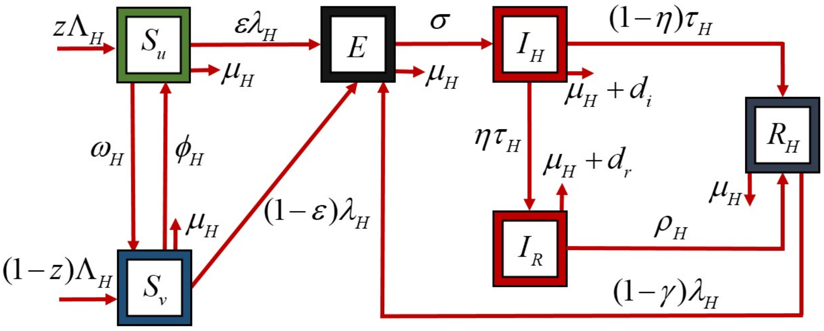

Figure 1. Schematic Diagram of the TB Model

$$
\begin{aligned}
\frac{dS_u}{dt} &= z\Lambda_H + \phi S_v - (\epsilon\lambda_H + \mu_H + \omega)S_u \\
\frac{dS_v}{dt} &= (1-z)\Lambda_H + \omega S_u - (\phi + \mu_H + (1-\epsilon)\lambda_H)S_v \\
\frac{dE_H}{dt} &= \epsilon\lambda_H S_u + (1-\epsilon)\lambda_H S_v + (1-\gamma)\lambda_H R_H - (\sigma + \mu_H)E \\
\frac{dI_H}{dt} &= \sigma E - (\mu_H + \tau_H + d_i)I_H \\
\frac{dI_R}{dt} &= \eta\tau_H I_H - (\rho_H + d_r + \mu_H)I_R \\
\frac{dR_H}{dt} &= \rho_H I_R + (1-\eta)\tau_H - (\mu_H + (1-\gamma)\lambda_H)R_H
\end{aligned} \tag{1}
$$

with initial conditions:

$$S_u \geq 0, S_v \geq 0, E_H > 0, I_H > 0, I_R > 0, R_H > 0. \tag{2}$$

Table 1. Description of Model State Variables

Variable	Description
$S_u(t)$	Number of susceptible unvaccinated individuals at time t
$S_v(t)$	Number of susceptible vaccinated individuals at time t
$E_H(t)$	Number of exposed (latently infected, not yet infectious) individuals at time t
$I_H(t)$	Number of infectious individuals with drug-sensitive tuberculosis (DS-TB) at time t
$I_R(t)$	Number of infectious individuals with multidrug-resistant tuberculosis (MDR-TB) at time t
$R_H(t)$	Number of recovered individuals at time t (may have temporary or permanent immunity)
$N_H(t)$	Total human population at time t, where $N_H = S_u + S_v + E_H + I_H + I_R + R_H$

Table 2. Description of Model Parameters

Parameter	Description
Λ_H	Recruitment rate of new individuals into the human population
z	Proportion of new recruits entering the unvaccinated susceptible class S_u
$(1-z)$	Proportion of new recruits entering the vaccinated susceptible class S_v
μ_H	Natural death rate of humans (all compartments)
ε	Vaccine efficacy in reducing susceptibility to TB infection $(0 \leq \varepsilon \leq 1)$
ω_H	Rate of waning vaccine-induced immunity (progression from S_v to S_u)
ϕ_H	Rate of vaccination or booster administration (progression from S_u to S_v)
β_H	Effective contact rate for transmission of drug-sensitive TB
m	Relative infectiousness factor of MDR-TB individuals compared to drug-sensitive infectious individuals, so that $\beta_R = m\beta_H$
σ	Rate at which exposed individuals (E_H) progress to active drug-sensitive TB (I_H)
τ_H	Treatment rate of drug-sensitive infectious individuals (I_H)
η	Proportion of treated I_H individuals who develop drug resistance and move to I_R
τ_R	Treatment rate of MDR-TB infectious individuals (I_R)
d_i	Disease-induced death rate of drug-sensitive infectious individuals (I_H)
d_r	Disease-induced death rate of MDR-TB infectious individuals (I_R)
ρ_H	Recovery rate of MDR-TB individuals (I_R) to the recovered class (R_H)
γ	Fraction of recovered individuals who acquire permanent immunity
$(1-\gamma)$	Fraction of recovered individuals who remain susceptible to reinfection

2.1 Model Fitting and Parameter Estimation

The proposed TB model was calibrated using the reported tuberculosis case data from Bulgaria, obtained from the European Centre for Disease Prevention and Control (ECDC) tuberculosis surveillance database (European Centre for Disease Prevention and Control, 2024). Model fitting was performed by minimizing the sum of squared errors between model output and observed incidence data. The key parameters estimated through the fitting procedure are the effective contact rate ($\beta_H = 0.18838$), vaccination rate

($\phi_H = 0.68234$), vaccine efficacy ($\varepsilon = 0.46832$), rate of progression from exposed to active TB ($\sigma = 0.11693$), proportion of treated individuals who develop drug resistance ($\eta = 0.67401$), and the proportion of recovered individuals who acquire permanent immunity ($\gamma = 0.10648$), as shown in Table 3. The other parameters were taken from the literature or assumed on the basis of epidemiological plausibility. As seen in Figure 2, the fitted model shows good agreement with the reported TB incidence and prevalence data for Bulgaria, capturing the overall trend and magnitude of the observed cases. This validation demonstrates the model's capacity to replicate the TB dynamics observed in the real world, and supports its application for scenario analysis and intervention evaluation.

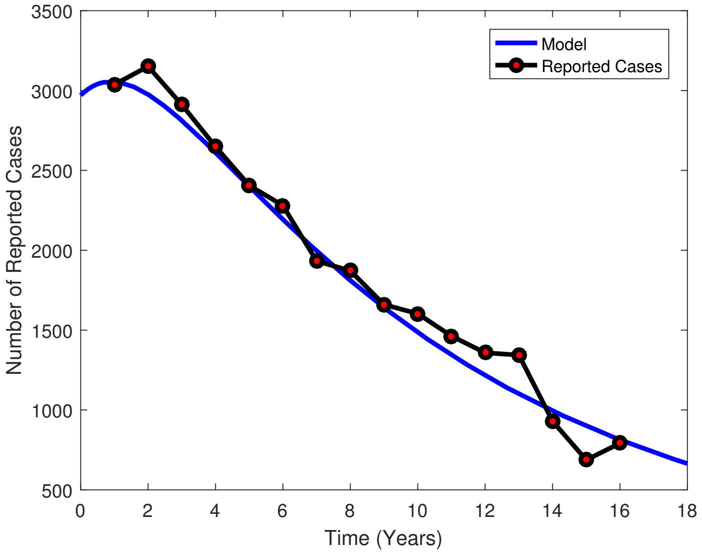

Figure 2. Fitted comparison of the Tuberculosis real data and model. The TB incidence and prevalence data used for model calibration were obtained from the European Centre for Disease Prevention and Control (ECDC) tuberculosis surveillance database for Bulgaria European Centre for Disease Prevention and Control (2024)

Table 3. Ranges and baseline values of parameters of the TB model.

Parameter	Value	Source
β_H	0.18838	Fitted
Λ_H	50000	Assumed
z	0.4	Assumed
ϕ_H	0.68234	Fitted
ε	0.46832	Fitted
ω_H	0.25	Assumed
μ_H	0.01	Assumed
γ	0.10648	Fitted
σ	0.11693	Fitted
τ_H	0.5	Assumed
d_i	0.01	Assumed
η	0.67401	Fitted
ρ_H	0.1106456	Assumed
d_r	0.0575	Assumed
τ_R	0.35	(World Health Organization, 2022)

3 Basic Properties of the TB Model

All associated parameters and state variables of the model system (1) are non-negative for all $t \geq 0$. We assert that the model has the following non-negativity result:

Theorem 3.1. *For every time $t > 0$, all solutions of the model system with non-negative initial data remain non-negative..*

Proof. Let

$$t_1 = \sup\{t > 0 : S_u > 0,\ S_v > 0,\ E_H \geq 0,\ I_H \geq 0,\ I_R \geq 0,\ R_H \geq 0 \text{ for all } t \in [0, t_1]\}.$$

Thus, $t_1 > 0$. From the first equation of the model system,

$$\frac{dS_u}{dt} = z\Lambda_H + \phi S_v - (\epsilon\lambda_H + \mu_H + \omega)S_u \geq -(\epsilon\lambda_H + \mu_H + \omega)S_u$$

which can be written as

$$\frac{d}{dt}\left[S_u(t)\exp\left\{\int_0^t \epsilon\lambda_H(u)\,du + (\mu_H + \omega)t\right\}\right] \geq 0$$

Hence,

$$S_u(t_1) \geq S_u(0)\exp\left\{-\int_0^{t_1} \epsilon\lambda_H(u)\,du - (\mu_H + \omega)t_1\right\} > 0.$$

Also, from the second equation,

$$\begin{aligned}\frac{dS_v}{dt} &= (1-z)\Pi_H + \omega S_u - (\phi + \mu_H + (1-\epsilon)\lambda_H)S_v \\ &\geq -(\phi + \mu_H + (1-\epsilon)\lambda_H)S_v\end{aligned}$$

which gives

$$\frac{d}{dt}\left[S_v(t)\exp\left\{\int_0^t (1-\epsilon)\lambda_H(u)\,du + (\phi+\mu_H)t\right\}\right] \geq 0$$

Hence,

$$S_v(t_1) \geq S_v(0)\exp\left\{-\int_0^{t_1}(1-\epsilon)\lambda_H(u)\,du - (\phi+\mu_H)t_1\right\} > 0.$$

In a similar manner, it can be shown that all remaining state variables of the model system remain non-negative for all $t > 0$. Hence, all solutions of the model system with non-negative initial conditions remain non-negative. □

Theorem 3.2. *Consider the region*

$$\mathcal{Z}_H = \left\{(S_u, S_v, E_H, I_H, I_R, R_H) \in \mathbb{R}_+^6 : N_H(t) \leq \frac{\Lambda_H}{\mu_H}\right\},$$

where $N_H = S_u + S_v + E_H + I_H + I_R + R_H$. *Then,* $\mathcal{Z}_H$ *is positively invariant and attracting.*

Proof. Summing all equations of the model system gives

$$\begin{aligned}\frac{dN_H}{dt} &= \Lambda_H - \mu_H(S_u + S_v + E_H + I_H + R_H) - d_i I_H - d_r I_R \\ &\leq \Lambda_H - \mu_H N_H.\end{aligned}$$

Thus,

$$\frac{dN_H}{dt} \leq \Lambda_H - \mu_H N_H.$$

Using the comparison theorem, we obtain

$$N_H(t) \leq N_H(0)e^{-\mu_H t} + \frac{\Lambda_H}{\mu_H}\left(1 - e^{-\mu_H t}\right).$$

Hence,

$$N_H(t) \leq \frac{\Lambda_H}{\mu_H} \quad \text{as } t \to \infty.$$

Therefore, the region $\mathcal{Z}_H$ is positively invariant and attracting (Alhassan et al., 2024). □

4 Theoretical Analysis

4.1 *TB Model Disease Free Equilibrium*

The TB model has a disease-free equilibrium given as:

$$E_0 = \left[S_u^0, S_v^0, E_H^0, I_H^0, I_R^0, R_H^0\right] = \left[\frac{\Lambda_H}{\mu_H}, \frac{(1-z)(\mu_H+\omega)+\omega z}{\phi\mu_H}\Lambda_H, 0, 0, 0, 0\right] \tag{3}$$

To study the local stability of the disease free equilibrium (3) for the TB Model, we used the next generation matrix approach (Van den Driessche and Watmough, 2002) as adapted in (Abdullahi et al., 2024). From the model system (1) Matrix F of new infection terms Matrix V of linear transmission terms are given as:

$$F = \begin{bmatrix} 0 & F_0 & \kappa F_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} k_1 & 0 & 0 \\ -\sigma & k_2 & 0 \\ 0 & -\eta\tau_H & k_3 \end{bmatrix}, \tag{4}$$

where:

$$F_0 = \frac{\beta_H \left[\epsilon S_u^0 + (1-\epsilon) S_v^0\right]}{N_H^0}$$

The TB Model effective reproduction number, $\mathcal{R}_c = \rho(FV^{-1})$ (where ρ is the spectral radius of FV^{-1}), can be easily defined as follows (5):

$$\mathcal{R}_c = \frac{\beta_H \sigma \Lambda_H}{\mu_H(\sigma+\mu_H)(\mu_H+\tau_H+d_i)} \left[\epsilon + \frac{(1-\epsilon)\big((1-z)\mu_H+\omega\big)}{\phi}\right]\left(1+\frac{\kappa\eta\tau_H}{\rho_H+d_r}\right) \tag{5}$$

By setting the control parameters of the model to zero, we obtain the basic reproduction number $\mathcal{R}_0$ of the TB model as follows (6):

$$\mathcal{R}_0 = \frac{\beta_H \sigma \Lambda_H}{(\sigma+\mu_H)(\mu_H+d_i)} \left[\frac{\epsilon}{\mu_H} + \frac{(1-\epsilon)(1-z)}{\phi}\right] \tag{6}$$

$\mathcal{R}_0$ is the basic reproduction number of the TB model. It is the average number of new TB cases that an infectious individual introduced into a fully susceptible community.

Theorem 4.1. *The disease-free equilibrium* (E_0) (3) *is locally asymptotically stable when* $\mathcal{R}_0 < 1$*, and unstable when* $\mathcal{R}_0 > 1$.

Theorem 4.1 implies that if we are able to reduce $\mathcal{R}_0$ to less than one, and keep it there, then a small influx of TB-infected individuals will not cause a major outbreak in the population.

4.2 *Global Stability Analysis of DFE*

Theorem 4.2. *For the TB model system* (1)*, the disease-free equilibrium* E_0 *is unstable if* $\mathcal{R}_0 > 1$ *and globally asymptotically stable (GAS) if* $\mathcal{R}_0 < 1$.

Proof. The proof is based on the Castillo-Chavez and Song (2004) Theorem. Let $\mathcal{G}_1$ and $\mathcal{G}_2$ describe the uninfected and infected compartments of the model system respectively. Thus,

$$\mathcal{G}_1 = [S_u, S_v, R_H]^T, \qquad \mathcal{G}_2 = [E_H, I_H, I_R]^T$$

Thus, the model system can be expressed as follows:

$$\frac{d\mathcal{G}_1}{dt} = F(\mathcal{G}_1, \mathcal{G}_2), \qquad \frac{d\mathcal{G}_2}{dt} = X(\mathcal{G}_1, \mathcal{G}_2); \quad X(\mathcal{G}_1, \mathbf{0}) = \mathbf{0} \tag{7}$$

To guarantee the global asymptotic stability of the disease-free equilibrium, E_0, the following conditions must be satisfied:

$$
\begin{aligned}
&(\mathcal{H}_1) : \left(\mathcal{G}_1^0, \mathbf{0}\right) \text{ is globally asymptotically stable for } \frac{d\mathcal{G}_1}{dt} = F\left(\mathcal{G}_1, \mathbf{0}\right)\\
&(\mathcal{H}_2) : \hat{X} \geq 0 \quad \text{where} \quad \hat{X}\left(\mathcal{G}_1, \mathcal{G}_2\right) = A\mathcal{G}_2 - X\left(\mathcal{G}_1, \mathcal{G}_2\right)
\end{aligned}
$$

such that $A = D_{\mathcal{G}_2} X\left(\mathcal{G}_1^0, \mathbf{0}\right)$ is an M-matrix. To verify $\mathcal{H}_1$, we have from the model system:

$$
\frac{d\mathcal{G}_1}{dt} = F\left(\mathcal{G}_1, \mathbf{0}\right) = \begin{bmatrix} z\Lambda_H + \phi S_v - (\mu_H + \omega) S_u \\ (1-z)\Lambda_H + \omega S_u - (\phi + \mu_H) S_v \\ -\mu_H R_H \end{bmatrix} \tag{8}
$$

The system above can be solved to give:

$$
\begin{bmatrix} S_u \\ S_v \\ R_H \end{bmatrix} = \begin{bmatrix} S_u^0 + (S_u(0) - S_u^0)\exp\left[-(\mu_H + \omega)t\right] \\ S_v^0 + (S_v(0) - S_v^0)\exp\left[-(\phi + \mu_H)t\right] \\ R_H(0)\exp\left(-\mu_H t\right) \end{bmatrix} \tag{9}
$$

where $(S_u^0, S_v^0, 0)$ is obtained from:

$$
\begin{aligned}
0 &= z\Lambda_H + \phi S_v^0 - (\mu_H + \omega) S_u^0 \\
0 &= (1-z)\Lambda_H + \omega S_u^0 - (\phi + \mu_H) S_v^0
\end{aligned}
$$

Clearly, $\lim_{t\to\infty} \mathcal{G}_1 = \mathcal{G}_1^0$. Hence, condition $\mathcal{H}_1$ is satisfied. To verify condition $\mathcal{H}_2$, we compute:

$$
A = D_{\mathcal{G}_2} X(\mathcal{G}_1^0, \mathbf{0}) = \begin{bmatrix} -(\sigma + \mu_H) & 0 & 0 \\ \sigma & -(\mu_H + \tau_H + d_i) & 0 \\ 0 & \eta\tau_H & -(\rho_H + d_r) \end{bmatrix} \tag{10}
$$

Clearly, A has negative diagonal entries and non-negative off-diagonal entries; hence, A is an M-matrix.

$$
X(\mathcal{G}_1, \mathcal{G}_2) = \begin{bmatrix} \epsilon\lambda_H S_u + (1-\epsilon)\lambda_H S_v + (1-\gamma)\lambda_H R_H - (\sigma + \mu_H) E_H \\ \sigma E_H - (\mu_H + \tau_H + d_i) I_H \\ \eta\tau_H I_H - (\rho_H + d_r) I_R \end{bmatrix} \tag{11}
$$

Therefore:

$$
\hat{X}\left(\mathcal{G}_1, \mathcal{G}_2\right) = A\mathcal{G}_2 - X\left(\mathcal{G}_1, \mathcal{G}_2\right) = \left[\hat{X}_1, 0, 0\right]^T \tag{12}
$$

where:

$$
\hat{X}_1 = \lambda_H \left[\epsilon\left(S_u^0 - S_u\right) + (1-\epsilon)\left(S_v^0 - S_v\right)\right]
$$

Since $S_u \leq S_u^0$, $S_v \leq S_v^0$, it follows that $\hat{X}\left(\mathcal{G}_1, \mathcal{G}_2\right) \geq 0$. Thus, conditions $\mathcal{H}_1$ and $\mathcal{H}_2$ are satisfied. Therefore, by the Castillo-Chavez and Song (2004) Theorem, the disease-free equilibrium E_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

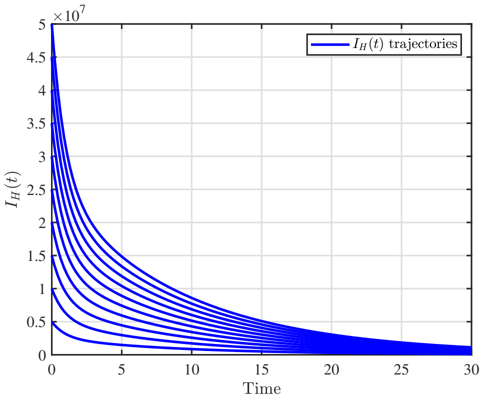

Figure 3. Global stability of infected human population I_H with different initial condition and $\mathcal{R}_0 = 0.423 < 1$.

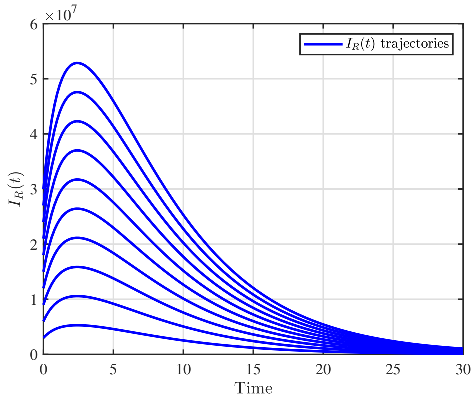

Figure 4. Global stability of infected resistant human population I_R with different initial condition and $\mathcal{R}_0 = 0.423 < 1$.

Figures (3) and (4) describe the evolution of the time-dependent infected human population, $I_H(t)$, and the infected resistant population, $I_R(t)$, for different initial conditions when $\mathcal{R}_0 = 0.423 < 1$.From Figure (3) we can see that for any initial population size, all the trajectories of $I_H(t)$ monotonically decrease to zero, meaning that the infection cannot be sustained and will eventually die out. The evolution of $I_R(t)$ shown in figure (4) starts with a rise and a maximum, and decreases to zero. This brief increase is typical of a short accumulation of resistant diseases before their final eradication.If $\mathcal{R}_0 < 1$, then both $I_H(t)$ and $I_R(t)$ tend to zero for any initial condition, which implies that the disease-free equilibrium is globally asymptotically stable. This means the disease will die out no matter the initial level of infection. □

4.3 *Endemic Equilibrium Point* E^*

Let the endemic equilibrium of the system be denoted by:

$$E^* = (S_u^*, S_v^*, E_H^*, I_H^*, I_R^*, R_H^*) \tag{13}$$

where:

$$\begin{aligned}
S_u^* &= \frac{z\Lambda_H + \phi S_v^*}{\epsilon\lambda_H^* + \mu_H + \omega}, & S_v^* &= \frac{(1-z)\Pi_H + \omega S_u^*}{\phi + \mu_H + (1-\epsilon)\lambda_H^*}, \\
I_H^* &= \frac{\sigma E_H^*}{\mu_H + \tau_H + d_i}, & E_H^* &= \frac{\lambda_H^*\big(\epsilon S_u^* + (1-\epsilon)S_v^* + (1-\gamma)R_H^*\big)}{\sigma + \mu_H}, \\
I_R^* &= \frac{\eta\tau_H}{\rho_H + d_r} I_H^*, & R_H^* &= \frac{\rho_H}{\mu_H + (1-\gamma)\lambda_H^*} I_R^*
\end{aligned}$$

4.4 Global Asymptotic Stability (GAS) of E^*

Theorem 4.3. *The endemic equilibrium E^* of the model system is globally asymptotically stable whenever $\mathcal{R}_0 > 1$.*

Proof. Consider the Goh-Volterra type Lyapunov function defined as:

$$\begin{aligned}\mathcal{L} &= \left(S_u - S_u^* - S_u^* \ln \frac{S_u}{S_u^*}\right) + \left(S_v - S_v^* - S_v^* \ln \frac{S_v}{S_v^*}\right) \\ &+ a_1 \left(E_H - E_H^* - E_H^* \ln \frac{E_H}{E_H^*}\right) + a_2 \left(I_H - I_H^* - I_H^* \ln \frac{I_H}{I_H^*}\right) \\ &+ a_3 \left(I_R - I_R^* - I_R^* \ln \frac{I_R}{I_R^*}\right) + a_4 \left(R_H - R_H^* - R_H^* \ln \frac{R_H}{R_H^*}\right)\end{aligned} \tag{14}$$

where the constants $a_i > 0$ are chosen as:

$$a_1 = 1, \quad a_2 = 1, \quad a_3 = 1, \quad a_4 = 1 \tag{15}$$

Clearly, $\mathcal{L} \geq 0$ for all states in the feasible region and $\mathcal{L} = 0$ if and only if the system is at E^*. Differentiating $\mathcal{L}$ with respect to time, we obtain:

$$\begin{aligned}\dot{\mathcal{L}} &= \left(1 - \frac{S_u^*}{S_u}\right) \dot{S}_u + \left(1 - \frac{S_v^*}{S_v}\right) \dot{S}_v \\ &+ a_1 \left(1 - \frac{E_H^*}{E_H}\right) \dot{E}_H + a_2 \left(1 - \frac{I_H^*}{I_H}\right) \dot{I}_H \\ &+ a_3 \left(1 - \frac{I_R^*}{I_R}\right) \dot{I}_R + a_4 \left(1 - \frac{R_H^*}{R_H}\right) \dot{R}_H\end{aligned} \tag{16}$$

Substituting the model equations and $a_1 = a_2 = a_3 = a_4 = 1$ into the above expression gives:

$$\begin{aligned}\dot{\mathcal{L}} &= \left(1 - \frac{S_u^*}{S_u}\right) [z\Pi_H + \phi S_v - (\epsilon\lambda_H + \mu_H + \omega)S_u] \\ &+ \left(1 - \frac{S_v^*}{S_v}\right) [(1-z)\Pi_H + \omega S_u - (\phi + \mu_H + (1-\epsilon)\lambda_H)S_v] \\ &+ \left(1 - \frac{E_H^*}{E_H}\right) [\epsilon\lambda_H S_u + (1-\epsilon)\lambda_H S_v + (1-\gamma)\lambda_H R_H - (\sigma + \mu_H)E_H] \\ &+ \left(1 - \frac{I_H^*}{I_H}\right) [\sigma E_H - (\mu_H + \tau_H + d_i)I_H] \\ &+ \left(1 - \frac{I_R^*}{I_R}\right) [\eta\tau_H I_H - (\rho_H + d_r)I_R] \\ &+ \left(1 - \frac{R_H^*}{R_H}\right) [\rho_H I_R - (\mu_H + (1-\gamma)\lambda_H)R_H]\end{aligned} \tag{17}$$

Using the equilibrium relations:

$$
\begin{aligned}
&z\Pi_H + \phi S_v^* = (\epsilon\lambda_H^* + \mu_H + \omega)S_u^*,\\
&(1-z)\Pi_H + \omega S_u^* = (\phi + \mu_H + (1-\epsilon)\lambda_H^*)S_v^*,\\
&(\sigma + \mu_H)E_H^* = \epsilon\lambda_H^* S_u^* + (1-\epsilon)\lambda_H^* S_v^* + (1-\gamma)\lambda_H^* R_H^*,\\
&(\mu_H + \tau_H + d_i)I_H^* = \sigma E_H^*,\\
&(\rho_H + d_r)I_R^* = \eta\tau_H I_H^*,\\
&(\mu_H + (1-\gamma)\lambda_H^*)R_H^* = \rho_H I_R^*
\end{aligned}
$$

and simplifying, we obtain:

$$
\begin{aligned}
\dot{\mathcal{L}} = {} & (\mu_H + \omega)S_u^*\left(2 - \frac{S_u}{S_u^*} - \frac{S_u^*}{S_u}\right) + (\phi + \mu_H)S_v^*\left(2 - \frac{S_v}{S_v^*} - \frac{S_v^*}{S_v}\right)\\
& + (\sigma + \mu_H)E_H^*\left(2 - \frac{E_H}{E_H^*} - \frac{E_H^*}{E_H}\right) + (\mu_H + \tau_H + d_i)I_H^*\left(2 - \frac{I_H}{I_H^*} - \frac{I_H^*}{I_H}\right)\\
& + (\rho_H + d_r)I_R^*\left(2 - \frac{I_R}{I_R^*} - \frac{I_R^*}{I_R}\right) + (\mu_H + (1-\gamma)\lambda_H^*)R_H^*\left(2 - \frac{R_H}{R_H^*} - \frac{R_H^*}{R_H}\right)
\end{aligned}
\tag{18}
$$

By the inequality between arithmetic and geometric means, each term satisfies $2 - \frac{x}{x^*} - \frac{x^*}{x} \leq 0$ with equality if and only if $x = x^*$. Hence $\dot{\mathcal{L}} \leq 0$ with equality if and only if $S_u = S_u^*, \quad S_v = S_v^*, \quad E_H = E_H^*, \quad I_H = I_H^*, \quad I_R = I_R^*, \quad R_H = R_H^*$Hence the largest invariant set in $\{\dot{\mathcal{L}} = 0\}$ is the singleton $\{E^*\}$. By LaSalle's invariance principle, E^* is globally asymptotically stable if $\mathcal{R}_0 > 1$.

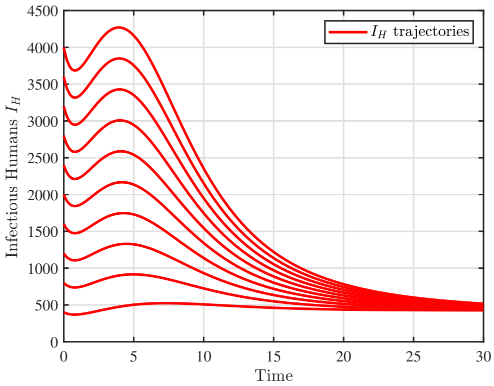

Figure 5. Global stability of infected human population I_H with different initial conditions and $\mathcal{R}_0 = 8.012 > 1$.

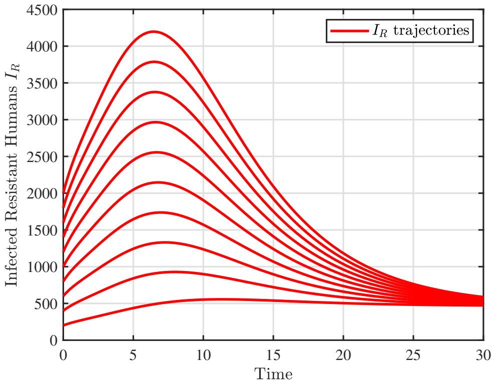

Figure 6. Global stability of infected resistant human population I_R with different initial conditions and $\mathcal{R}_0 = 8.012 > 1$.

Figures 5 and 6 show the time evolution and global stability of infected populations with different initial conditions for $\mathcal{R}_0 = 8.012 > 1$, indicating high disease transmission potential. In Figure 5 all trajectories increase and reach their maximum early on in the first few time units. The peak magnitude is a function of the initial condition . Larger initial infections lead to earlier and more pronounced peaks . After this temporary increase all curves fall and attain a common steady state level. This behavior confirms the global stability of the endemic equilibrium as the infectious population converges to the same long term value regardless of the initial position. A similar pattern can be seen in Figure 6. The infected resistant population also rises to an initial-condition-dependent peak before gradually decreasing. The fact that all trajectories converge to the same equilibrium level also implies global asymptotic stability of this compartment. ☐

5 Sensitivity Analysis

The sensitivity analysis of the Partial Rank Correlation Coefficient (PRCC) shows the relative importance of model parameters on the basic reproduction number $\mathcal{R}_0$ (Figure 9) and the control reproduction number $\mathcal{R}_c$ (Figure 7). The most influential parameter with a strong positive correlation for $\mathcal{R}_0$ is the human-to-human transmission rate β_H. That means the more intense the transmission, the more likely it is that the disease will be transmitted through the population. On the other hand, the human natural death rate μ_H and the disease-induced death rate d_i are strongly negatively correlated. The death rate removes individuals from the infectious pool, and thus decreases the overall transmission. Similarly, the parameters ε, r and d_r have moderate negative correlations, indicating that these parameters help to reduce $\mathcal{R}_0$, but to a lesser extent than μ_H and d_i. The correlations among parameters such as δ , τ_H , η , and ρ_H are weak or almost zero, which suggests that they have little effect on $\mathcal{R}_0$ in baseline. A similar, but more subtle pattern is observed for the control reproduction number $\mathcal{R}_c$. The transmission parameter β_H continues to be positively correlated and central to maintaining disease transmission, even in the presence of control measures. However, the human natural death rate μ_H is the most dominant negative contributor because it has a stronger suppressive effect on $\mathcal{R}_c$ than on $\mathcal{R}_0$. This emphasizes the importance of removal processes to reduce transmission under intervention scenarios. Interestingly, the treatment parameter η is moderately positively correlated with $\mathcal{R}_c$, which indicates that it plays a more important role when the control strategies are applied. Also, the parameters such as ρ_H, d_r have a moderate negative influence which indicates the importance of them in reducing the disease transmission under control measures. The other parameters still exhibit weak or negligible correlations, which supports their minor role in the overall dynamics.

The results of PRCC consistently indicate that β_H is the most important driver of disease transmission. This highlights the importance of interventions that reduce effective contact or transmission probability. Meanwhile, the parameters associated with the removal processes, in particular, μ_H and d_i, play a key role in suppressing the spread of infection. The differences between $\mathcal{R}_0$ and $\mathcal{R}_c$ also imply that some parameters may have more influence in the control situation, which points to the dynamic interplay between the natural evolution of the disease and the intervention attempts. These results highlight the importance of targeting interventions that reduce transmission and increase recovery or removal rates for effective disease control.

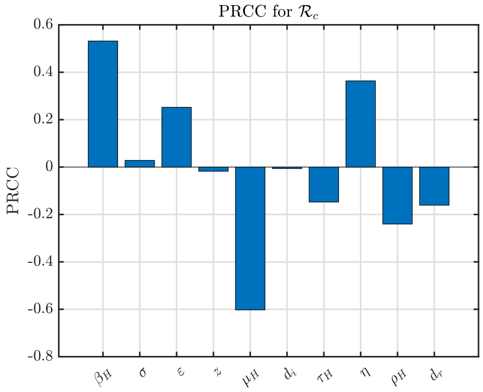

Figure 7. PRCC plot for $\mathcal{R}_c$ versus the parameters of model (1).

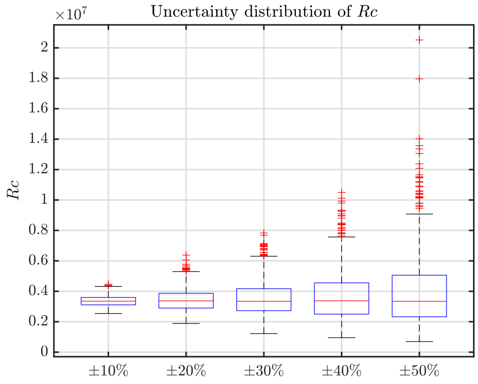

Figure 8. Box plot for the control reproduction number $\mathcal{R}_c$.

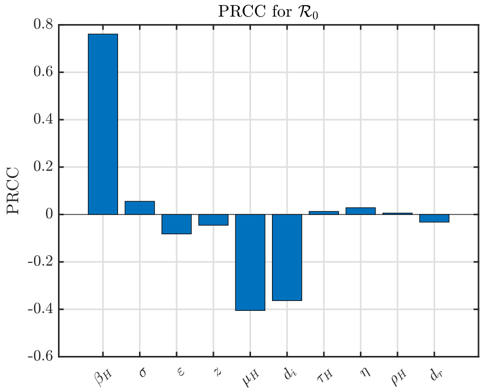

Figure 9. PRCC plot for $\mathcal{R}_0$ versus the parameters of model (1).

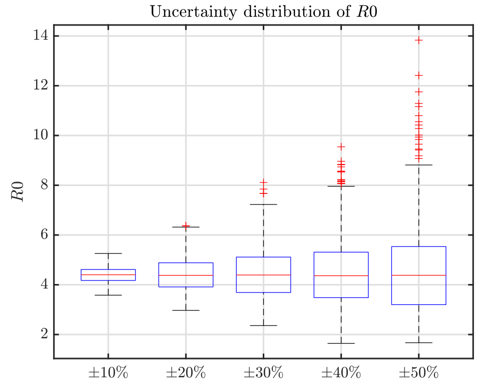

Figure 10. Box plot for the basic reproduction number $\mathcal{R}_0$.

6 Discussion

We have developed and analyzed a deterministic compartmental model for the transmission dynamics of tuberculosis (TB) with vaccination, treatment failure, reinfection and progression to multidrug resistant tuberculosis (MDR-TB). The model has six epidemiological classes, namely susceptible unvaccinated, susceptible vaccinated, exposed, infectious, MDR-TB infectious and recovered. This framework provides a realistic framework to study the joint effects of vaccination and treatment-induced resistance on TB transmission. The positivity and boundedness analysis ensured that the model is mathematically and epidemiologically well posed, i.e., all state variables remain non-negative and biologically meaningful over time. We obtained the basic reproduction number $\mathcal{R}_0$ and determined the disease-free equilibrium (DFE) and the endemic equilibrium by the next-generation matrix method. The threshold property of $\mathcal{R}_0$ indicates that the elimination of TB transmission is only possible when $\mathcal{R}_0 < 1$ while sustained persistence occurs when $\mathcal{R}_0 > 1$.

The results were also confirmed by local and global stability analysis. It was shown that the disease free equilibrium is locally asymptotically stable for $\mathcal{R}_0 < 1$ and unstable for $\mathcal{R}_0 > 1$. In addition, the DFE was shown to be globally asymptotically stable for $\mathcal{R}_0 < 1$, using the Castillo-Chavez approach . This implies that the disease would eventually die out regardless of the initial infection size. Numerical simulations support this and show that both infectious and resistant infectious populations converge to zero under different initial conditions for $\mathcal{R}_0 < 1$. For $\mathcal{R}_0 > 1$, the global asymptotic stability of the endemic equilibrium was proved using a suitable Lyapunov function and LaSalle's invariance principle. This means that if the reproduction number is above one, the disease continues to circulate in the population and tends to a stable endemic state. Simulation results showed the convergence of infectious and resistant classes to positive equilibrium values, thus confirming the persistence of the disease.

The sensitivity analysis was carried out using the Partial Rank Correlation Coefficients (PRCC) and the effective contact rate β_H was identified as the most influential parameter, which positively affects both $\mathcal{R}_0$ and $\mathcal{R}_c$. This finding suggests the importance of controlling transmission through early diagnosis, reduced contact with infective individuals and improved infection control measures for TB control. Parameters such as natural death rate μ_H, disease-induced death rates (d_i and d_r), and parameters related to recovery showed significant negative effects, highlighting the importance of early treatment and proper management of MDR-TB cases. The findings also suggest that vaccination alone may not be sufficient to eliminate TB, especially when lack of treatment results in drug resistance. Effective vaccination and better treatment adherence, early detection and proper management of MDR-TB patients together provide the potential for meaningful control of the disease and for elimination. This study has a number of limitations that should be acknowledged. The model assumes homogeneous mixing, which may oversimplify the dynamics of TB transmission in heterogeneous populations. They did not take into account age structure, spatial heterogeneity and HIV co-infection, which have major impacts on TB progression and treatment outcomes. Future work should extend the model to incorporate these factors and investigate the cost-effectiveness analysis of different combinations of interventions.

7 Conclusion

In this work, we have formulated and analyzed a mathematical model of tuberculosis transmission including vaccination and multidrug resistance. The model could capture the role of vaccination, reinfection, failure of treatment and progression to MDR-TB in disease spread. The analysis shows that the basic reproduction number $\mathcal{R}_0$ is the main threshold parameter which determines the extinction or persistence of the disease. It was shown that the disease-free equilibrium is locally and globally asymptotically stable when $\mathcal{R}_0 < 1$, and the endemic equilibrium is globally asymptotically stable when $\mathcal{R}_0 > 1$. These results indicate that reducing the reproduction number below unity is necessary for effective TB elimination. Results of sensitivity analysis showed that the transmission rate is the most important factor in disease spread, while the treatment and recovery parameters play an important role in reducing disease burden. This finding underscores the importance of the need to strengthen vaccination programs, improve treatment adherence, prevent treatment failure and reduce the emergence of MDR-TB. Therefore, public health policies for TB control should concentrate on integrated intervention strategies rather than individual control measures. Future work may extend this model by incorporating optimal control strategies, age structure, co-infection dynamics, or time-dependent interventions to further improve TB management and policy recommendations.

Conflicts of Interest

The authors declare no conflict of interest.

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