New Theory Journal of
ISSN: 2149-1402

33 (2020) 01-14
Journal of New Theory
http://www.newtheory.org
Open Access

A Generalised Mathematical Model of Hard-to-treat Infections with Culturing and Antibiotic Susceptibility Testing

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Article History
Received: 04.05.2020
Accepted: 08.12.2020
Published: 31.12.2020
Original Article

Abstract – A mathematical model for hard-to-treat infections with culturing and antibiotic susceptibility testing (CAST) as an intervention strategy in a population is formulated and analysed. The analysis of the model has been done qualitatively to investigate the existence and stability of equilibria. Using the Lyapunov function, the disease-free equilibrium of the model proved to be globally asymptotically stable with respect to the threshold quantity $R_c < 1$. Of course, this entails local stability. A similar approach is employed in proving the global stability of the endemic equilibrium state in the case $R_c > 1$. However, the local stability of the endemic equilibrium is investigated using the method of row elimination. The model was validated using the Tuberculosis case in South Africa, and the result reveals that patients without adopting CAST strategy are prone to drug resistance and delay in quick response to the treatment regimen. On the contrary, individuals who have adopted the strategy have shown greater recovery potential from the infection. Based on that, self - medication, blind prescription should be avoided to curtail the consequences of drug resistance.

Keywords *– Hard- to- treat infections, Culturing, Antibiotic susceptibility testing, Global stability, Lyapunov function*

1. Introduction

In the world of medicine, the consequences of an improper diagnosis of most hard-to-treat infections such as Mycobacterium Tuberculosis, Typhoid fever, Gonorrhoea, staphylococcus etc. are responsible for high human mortality and morbidity [1]. To this paper, hard-to-treat infections refer to diseases/infections that prove incurable without culturing and antibiotic susceptibility testing. It is primarily culturing to ascertain the main cause of an infection and determine drug resistance strains under laboratory-controlled conditions to give a correct diagnosis and treatment [2]. It is observed that those who carry out culture testing tends not to have antibiotic-resistant strains and do heal quickly [3]. To achieve this, it is necessary to carry out antibiotic susceptibility testing, which involves culturing the disease in the presence of antibiotics. If the bacteria grow, they are resistant to the drugs, but if it fails to multiply, it implies that the drugs are effective and the bacteria are not resistant [4, 5].

[6] explains the need for rapid diagnostic testing to determine the causative organism of infection and maintained that diagnosis through culture before treatment plays a valuable and critical role in the cure of patients and those at risk of developing the infection. [7] identify disk diffusion and broth dilution techniques

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for bacterial culture and antibiotic susceptibility testing used in veterinary medicine and [8] made a case for integrating culture-based and molecular methods in agro-ecosystems to understand better ways of bacterial inhibition. [9] gave an overview of the current methods available to identify antimicrobial susceptibility testing of anaerobes (aerobic bacterial).

The number of mortality and morbidity cases recorded against drug resistance to diseases due to non-culturing and antibiotic susceptibility testing is alarming, and mathematical models under this area are few and not widely explored. People have made attempts to model this kind of infections on specific diseases as far back, as seen in [10, 11]. [12] projected that rapid expansion of Tuberculosis (TB) culture and drug sensitivity testing (DST) among South African adults could save >47,000 lives and prevent >7,000 multidrug-resistant (MDR)-TB cases during the 10 years from 2008 to 2017. This corresponds to a reduction of 17% in total TB mortality, 14% in MDR-TB incidence, and 47% in MDR-TB mortality. Their model projected that culture and DST impact depends most strongly on the speed and sensitivity of culture, treatment rates in diagnosed TB patients, and TB case detection rates in the absence of culture. In the paper, Detection of antibiotic resistance is essential for gonorrhoea point-of-care (POC) testing: a mathematical modelling study, [13] addressed clinically relevant situations to evaluate the potential impact of gonorrhoea POC tests on antibiotic-resistant Gonorrhoea and can guide the introduction of POC tests. [14] used mathematical modelling to provide a framework that integrates information regarding the transmission and control of foodborne pathogens and antimicrobial resistance. [15] provided a highlight on critical questions in the management of Gonorrhoea that can be addressed by mathematical models and identify key data needs. Their overarching aim is to articulate a shared agenda across gonococcus-related fields from microbiology to epidemiology that will catalyse a comprehensive evidence-based clinical and public health strategy to manage gonococcal infections antimicrobial resistance.

Because of the above, the present study uses this opportunity to consider the general dynamics of hard – to - treat infections with antibiotic susceptibility testing as a robust way of enhancing proper medical treatment. This paper's organisation begins with an introduction in Section 1 and follows model formulation in Section 2. The analysis of the model is presented in Section 3 with numerical simulations and discussion in Section 4. Finally, the conclusion is given in Section 5.

2. Model formulation and the Feasible Region

The model classifies the total population at time t, denoted by N, into susceptible individuals S, infected individuals without CAST strategy I_w, infected individuals with CAST strategy I_c and individuals who recovered from the infection R. It is assumed that individuals are recruited at a constant rate ϕ to the susceptible population S and recovered individual also become susceptible at γ rate. Susceptible individuals can be infected with disease following the contact with infected individuals at an average rate $\lambda = \beta\left(\frac{I_w+\theta I_c}{N}\right)$, where β is effective contact rate and θ is the modification parameter which takes the values $0 \leq \theta \leq 1$. When $\theta = 1$ implies that CAST strategy is ineffective in disease control while when $\theta = 0$ signifies that the strategy can effectively control the spread of the infection. Individuals with culture and antibiotic susceptibility testing can acquire the infection at a reduced rate of $(1-\pi)\lambda$ and a higher recovery rate of ρ_c compared to those without. It is also assumed that some of the infectives I_w move to join I_c class with a rate α depending on CAST strategy. It is also assumed that the natural death rate occurs in all populations at a per-capita rate of μ. It is noted that the recovery rate of infective due to CAST strategy is greater than those without the strategy ($\rho_c > \rho_w$). The mortality rate due to I_c is lower than that of I_w ($\delta_c < \delta_w$). The variables and parameters of the model (1) are hereby presented in Table 1.

Table 1: Parameters of the Model.

Parameter	Interpretation
S	Number of susceptible persons
I_w	Number of infected persons without CAST strategy
I_c	Number of infected persons with CAST strategy
R	Number of recovered persons due to treatment
Φ	Recruitment number of susceptible persons
π	The fraction of susceptible persons who become infected and do not adopt CAST strategy
α	The rate of adopting CAST strategy
β	Effective contact rate
λ	The force of infection
μ	Natural death rate
θ	Modification parameter
δ_w	Disease induced death rate for infectives without CAST strategy
δ_c	Disease induced death rate for infectives with CAST strategy
ρ_c	Recovery rate based on CAST intervention strategy
ρ_w	Recovery rate based on ordinary medical test prescription (without CAST strategy)
γ	The rate at which recovered persons regain susceptibility

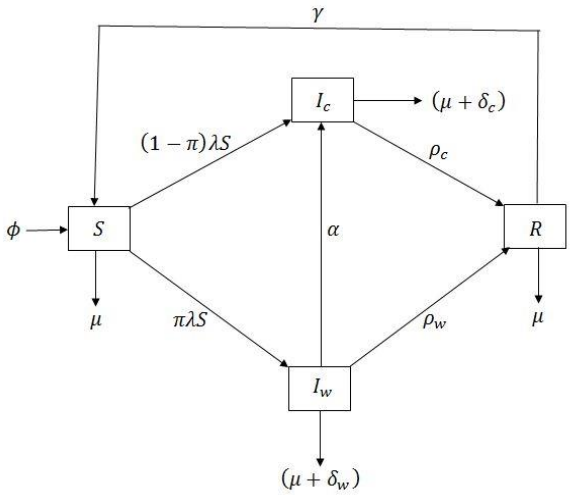

Fig. 1. Flow diagram of the generalised model of hard-to-treat infections

2.1. Model Equations

Using the description of model and Fig. 1, we derive the differential equations below.

$$\left.\begin{aligned} \frac{dS}{dt} &= \phi - \lambda S + \gamma R - \mu S \\ \frac{dI_w}{dt} &= \pi\lambda S - (\mu + \alpha + \rho_w + \delta_w) I_w \\ \frac{dI_c}{dt} &= (1-\pi)\lambda S + \alpha I_w - (\mu + \rho_c + \delta_c) I_c \\ \frac{dR}{dt} &= \rho_w I_w + \rho_c I_c - (\mu + \gamma) R \end{aligned}\right\}, \tag{1}$$

where

$$\lambda = \beta\left(\frac{I_w + \theta I_c}{N}\right). \tag{2}$$

Adding the whole equations of (1) yields

$$\frac{dN}{dt} = \phi - \mu N - \delta_w I_w - \delta_c I_c. \tag{3}$$

2.2. The feasible region

This sub-section examines the model's invariant region (1) whereby the system is mathematically and epidemiologically well-posed.

Theorem 2. 1. The model (1) is a dynamical system on the biologically feasible region:

$$D = \{(S, I_w, I_c, R) \in \mathbb{R}_+^4 : N_+ \leq N(t) \leq S^0\},$$

where $S^0 = \frac{\phi}{\mu}$ and $N_+ = \frac{\phi}{\mu+\delta_w+\delta_c}$.

Proof. The proof follows a two-step approach [16]

Step 1. We prove that the solution $S(t),\ I_w(t),\ I_c(t)$ and $R(t)$ of the model (1) based on the initial conditions such that $S(0),\ I_w(0),\ I_c(0)$ and $R(0)$ are non-negative. Let $\tilde{t} = sup\{t > 0 : S > 0, I_w \geq 0, I_c \geq 0, R \geq 0\}$. Then, $\tilde{t} > 0$ and it shows from the first equation of the model (1) that

$$\frac{dS}{dt} = \phi - \big(\mu + \lambda(t)\big)S + \gamma R \geq \phi - \big(\mu + \lambda(t)\big)S,$$

The above inequality equation has the form

$$\frac{d}{dt}\left[S(t)exp\left\{\mu t + \int_0^t \lambda(s)ds\right\}\right] \geq \phi\exp\left\{\mu t + \int_0^t \lambda(s)ds\right\}.$$

Thus,

$$S(\tilde{t})exp\left\{\mu\tilde{t} + \int_0^{\tilde{t}} \lambda(s)ds\right\} - S(0) \geq \int_0^{\tilde{t}} \phi\exp\left\{\mu p + \int_0^p \lambda(v)dv\right\}dp,$$

So that

$$S(\tilde{t}) \geq S(0)exp\left\{-\left(\mu\tilde{t} + \int_0^{\tilde{t}} \lambda(s)ds\right)\right\} + (0)exp\left\{-\left(\mu\tilde{t} + \int_0^{\tilde{t}} \lambda(s)ds\right)\right\} \times \int_0^{\tilde{t}} \phi\exp\left\{\mu p + \int_0^p \lambda(v)dv\right\}dp > 0.$$

Similarly, it can be proven that $I_w \geq 0, I_c \geq 0, and\ R \geq 0$ for all $t > 0$.

Step 2. We now show that the total population at time $t, N(t)$ satisfies the boundedness property

$N_+ \leq N(t) \leq S^0$ whenever $N_+ \leq N(t_0) \leq S^0$.

From equation (3), one has that

$$\phi - (\mu + \delta_w + \delta_c)N(t) \leq \frac{dN}{dt} \leq \phi - \mu N(t). \tag{4}$$

Applying the Gronwall inequality to the equation (4) yields

$$\frac{\phi}{\mu + \delta_w + \delta_c}\left[1 - e^{-(\mu+\delta_w+\delta_c)t}\right] + S(0)e^{-(\mu+\delta_w+\delta_c)t} \leq S(0)e^{-\mu t} + \frac{\phi}{\mu}(1 - e^{-\mu t})$$

which implies that

$$N_+ \leq N(t) \leq S^0.$$

Bringing step 1 and step 2 together, Theorem 2.1 follows from the classical theory of dynamical systems.

3. Existence of model equilibria and stability

3.1. Local stability of disease-free equilibrium (DFE)

The disease-free equilibrium point occurs at the state in which there is no infection. Hence, the DFE point of the model (1) is given by $\mathrm{E}_0 = (S^0, 0,0,0)$, where the infected compartment tends to zero and S^0 is the same as in Theorem 2.1.

The local stability of the DFE (E_0) depends on the control reproduction number, R_c, which is computed by a next-generation operator [17]. Using their notations F and V which denote the matrix of the new infections and transition matrix respectively, we have

$$F = \beta \begin{pmatrix} \pi & \pi\theta \\ 1-\pi & (1-\pi)\theta \end{pmatrix} \text{ and } V = \begin{pmatrix} \mu+\alpha+\rho_w+\delta_w & 0 \\ -\alpha & \mu+\rho_c+\delta_c \end{pmatrix},$$

with

$$V^{-1} = \begin{pmatrix} \dfrac{1}{\mu+\alpha+\rho_w+\delta_w} & 0 \\ \dfrac{\alpha}{(\mu+\alpha+\rho_w+\delta_w)(\mu+\rho_c+\delta_c)} & \dfrac{1}{\mu+\rho_c+\delta_c} \end{pmatrix}.$$

Therefore, the control reproduction number is

$$R_c = \rho(FV^{-1}) = \beta\left(\frac{\pi(d_2+\alpha\theta)+(1-\pi)d_1\theta}{d_1 d_2}\right), \tag{5}$$

where

$$d_1 = \mu+\alpha+\rho_w+\delta_w \text{ and } d_2 = \mu+\rho_c+\delta_c.$$

Therefore, by Theorem 2 in [17], we can claim the following result.

Lemma 3.1. The DFE of the model (1) is locally asymptotically stable if $R_c < 1$ and unstable otherwise.

Biologically, lemma 3.1 implies that an adequate pool of few infected individuals into the susceptible population will not generate an outbreak of infection except $R_c > 1$. Therefore, to ensure better control of infection, the global asymptotic stability of DFE is needed as addressed in the next subsection.

3.2. Global Stability of the DFE

The global investigation of stability at the disease-free state using Lyapunov function's construction depends on the infected compartments only.

Lemma 3.2. The DFE of the model (1) is globally asymptotically stable in D provided that $R_c < 1$ and unstable if $R_c > 1$.

Proof. Following the work of [18], we consider the Lyapunov function

$$L = AI_w + BI_c, \tag{6}$$

where $A > 0$ and $B > 0$, with the derivatives of L defined by

$$\frac{dL}{dt} = A\frac{dI_w}{dt} + B\frac{dI_c}{dt}. \tag{7}$$

Thus, substituting the corresponding right-hand side of (1) into (7) gives

$$\frac{dL}{dt} = (\pi A + (1-\pi)B)\lambda S - (d_1 A - \alpha B)I_w - d_2 B I_c\,. \tag{8}$$

Therefore, setting the coefficients of λS to the numerator of R_c (excluding β) and that of I_w to the denominator of R_c, we have

$$\pi A + (1-\pi)B = \pi(d_2 + \alpha\theta) + (1-\pi)d_1\theta,$$
$$d_1 A - \alpha B = d_1 d_2,$$

from which we obtain

$$A = d_2 + \alpha\theta > 0 \text{ and } B = d_1\theta > 0.$$

Now replacing the expressions for A and B in (8) above yields

$$\frac{dL}{dt} = \beta\left(\frac{I_w + \theta I_c}{N}\right)S(\pi(d_2 + \alpha\theta) + (1-\pi)d_1\theta) - d_1 d_2(I_w + \theta I_c),$$
$$= d_1 d_2(I_w + \theta I_c)\left(\beta\left(\frac{\pi(d_2 + \alpha\theta) + (1-\pi)d_1\theta}{d_1 d_2}\right)\frac{S}{N} - 1\right).$$

Since $S \leq N$ is in the region of the invariant set, it then follows that

$$\frac{dL}{dt} \leq d_1 d_2(I_w + \theta I_c)\left(\beta\left(\frac{\pi(d_2 + \alpha\theta) + (1-\pi)d_1\theta}{d_1 d_2}\right) - 1\right),$$
$$= d_1 d_2(I_w + \theta I_c)(R_c - 1).$$

This shows that

$$\frac{dL}{dt} < 0 \text{ if } R_c < 1$$

Equality holds at $R_c = 1$ and $I_w = I_c = 0$. Therefore, we can conclude from the LaSalle's invariance principle stated in Theorem 3.1 below that the DFE is globally asymptotically stable since $S \to \frac{\phi}{\mu}$ as $t \to \infty$ at $I_w = I_c = 0$.

Theorem 3.1. [19] (La Salle Invariance Principle). Let $H(x)$ be a locally Lipschitz function defined over a domain $G \subset R^n$ and $\Omega \subset G$ be a compact set that is positively invariant concerning $\dot{x} = H(x)$. Let $V(x)$ be a continuously differentiable positive definite function on G such that $\dot{V}(x) \leq 0$ in Ω for all $x \in G$. Let $E = \{x \in \Omega | \dot{V}(x) = 0\}$, and M be the largest invariant set in E. Then every solution starting in Ω approaches M as $t \longrightarrow \infty$.

3.3. Existence of Endemic Equilibrium State (EES)

The endemic equilibrium state defines the persistence of an infection in the population. Suppose $E^{**} = (S^{**}, {I_w}^{**}, {I_c}^{**}, R^{**}) > 0$ is the endemic equilibrium of the model (1). Then,

$$0 = \phi - \lambda^{**}S^{**} + \gamma R^{**} - \mu S^{**},$$
$$0 = \pi\lambda^{**}S^{**} - d_1 {I_w}^{**},$$
$$0 = (1-\pi)\lambda^{**}S^{**} + \alpha {I_w}^{**} - d_2 {I_c}^{**},$$
$$0 = \rho_w {I_w}^{**} + \rho_c {I_c}^{**} - d_3 R^{**}.$$

Therefore,

$$\begin{cases} S^{**} = \dfrac{\phi + \gamma R^{**}}{\lambda^{**} + \mu}, \\ {I_w}^{**} = \dfrac{\pi}{d_1}\lambda^{**}S^{**}, \\ {I_c}^{**} = \left(\dfrac{\alpha\pi}{d_1 d_2} + \dfrac{1-\pi}{d_2}\right)\lambda^{**}S^{**}, \\ R^{**} = \left(\dfrac{\pi}{d_1}\left(\dfrac{\rho_w}{d_3} + \dfrac{\rho_c\alpha}{d_2 d_3}\right) + \dfrac{(1-\pi)\rho_c}{d_2 d_3}\right)\lambda^{**}S^{**}. \end{cases} \quad (9)$$

To be specific, the value of S^{**} is

$$S^{**} = \frac{\phi}{\mu + \lambda^{**}\left(1 - \frac{\gamma}{d_3}\left(\frac{\pi}{d_1}\left(\rho_w + \frac{\rho_c \alpha}{d_2}\right) + (1-\pi)\frac{\rho_c}{d_2}\right)\right)}. \tag{10}$$

Recall from (2) that the force of infection at the equilibrium state is

$$\lambda^{**} = \beta\left(\frac{I_w^{**} + \theta I_c^{**}}{N^{**}}\right) = \frac{R_c - 1}{K}, \tag{11}$$

with

$$K = \frac{\pi}{\mu}\left(1 + \frac{\rho_w}{d_3} + \frac{\alpha}{d_2}\left(1 + \frac{\rho_c}{d_3}\right)\right) + \frac{1-\pi}{d_2}\left(1 + \frac{\rho_c}{d_3}\right).$$

Note that $\lambda^{**} \neq 0$ defines the endemic equilibrium which exists at the point, $R_c > 1$. From the above, the following result can be inferred.

Lemma 3.3. If $R_c > 1$, then the model (1) admits a unique positive endemic equilibrium state.

3.4. Local Stability of EES

The linearised form of system (1) at E^{**} gives the Jacobian, J,

$$J = \begin{pmatrix} -\left(\mu + \beta\frac{({I_w}^{**} + \theta {I_c}^{**})}{N^{**}}\right) & -\beta\frac{S^{**}}{N^{**}} & -\beta\theta\frac{S^{**}}{N^{**}} & \gamma \\ \pi\beta\frac{({I_w}^{**} + \theta {I_c}^{**})}{N^{**}} & -\left(d_1 - \pi\beta\frac{S^{**}}{N^{**}}\right) & \pi\beta\theta\frac{S^{**}}{N^{**}} & 0 \\ (1-\pi)\beta\frac{({I_w}^{**} + \theta {I_c}^{**})}{N^{**}} & \alpha + (1-\pi)\beta\frac{S^{**}}{N^{**}} & -\left(d_2 - (1-\pi)\beta\theta\frac{S^{**}}{N^{**}}\right) & 0 \\ 0 & \rho_w & \rho_c & -(\mu+\gamma) \end{pmatrix}. \tag{12}$$

The transition by row reduction into an upper triangular matrix of the Jacobian is given by

$$T_U = \begin{pmatrix} -g_1 & -g_2 & -g_3 & \gamma \\ 0 & -A_1 & -A_2 & A_3 \\ 0 & 0 & -(A_1B_2 + A_2B_1) & (A_3B_1 + A_1B_3) \\ 0 & 0 & 0 & Q \end{pmatrix}, \tag{13}$$

where

$A_1 = g_1g_5 + g_2g_4, \quad A_2 = g_3g_4 - g_1g_6, A_3 = \gamma g_4,$

$B_1 = g_1g_8 - g_2g_7, \quad B_2 = g_1g_9 + g_3g_7, \quad B_3 = \gamma g_7,$

and $Q = (A_1B_2 + A_2B_1)(\rho_w A_3 - g_{10}A_1) + (\rho_c A_1 - \rho_w A_2)(A_3B_1 + A_1B_3),$

with

$$g_1 = \mu + \beta\frac{({I_w}^{**} + \theta {I_c}^{**})}{N^{**}}, g_2 = \beta\frac{S^{**}}{N^{**}}, \quad g_3 = \beta\theta\frac{S^{**}}{N^{**}}, g_4 = \pi\beta\frac{({I_w}^{**} + \theta {I_c}^{**})}{N^{**}},$$

$$g_5 = \left(d_1 - \pi\beta\frac{S^{**}}{N^{**}}\right), \quad g_6 = \pi\beta\theta\frac{S^{**}}{N^{**}}, \quad g_7 = (1-\pi)\beta\frac{({I_w}^{**} + \theta {I_c}^{**})}{N^{**}},$$

$$g_8 = \alpha + (1-\pi)\beta\frac{S^{**}}{N^{**}}, \quad g_9 = \left(d_2 - (1-\pi)\beta\theta\frac{S^{**}}{N^{**}}\right), \quad g_{10} = (\mu+\gamma).$$

For the system to be Locally Asymptotically Stable at the endemic state, we now show that all the diagonal elements of the upper triangular matrix, which are the eigenvalues of (12) are negative.

Then, from (13)

$$\lambda_1 = -g_1 = -\left(\mu + \frac{(R_c - 1)}{K}\right) < 0 \text{ iff } R_c > 1. \tag{14}$$

Similarly,

$$\lambda_2 = -A_1 = -\left(d_1\left(\mu + \frac{(R_c - 1)}{K}\right) - \mu\beta\pi\frac{S^{**}}{N^{**}}\right) < 0 \text{ iff } R_c > 1. \tag{15}$$

For $\lambda_3 = -(A_1B_2 + A_2B_1) < 0,$

it implies that $(A_1B_2 + A_2B_1) > 0$, and detail simplification gives

$$\begin{aligned}\lambda_3 = -\mu\beta\frac{S^{**}}{N^{**}}&\left(\theta\left(\beta\frac{S^{**}}{N^{**}}(\mu\pi - \alpha) - d_1(1-\pi)(1+\mu)\right) - \left(\mu + \left(\frac{R_c - 1}{K}\right)\right)(d_2\pi + \alpha\theta)\right) \\ &-d_1d_2\left(\left(\frac{R_c - 1}{K}\right)^2 + 2\mu\left(\frac{R_c - 1}{K}\right) + \mu^2\right) < 0 \text{ iff } R_c > 1.\end{aligned} \tag{16}$$

Lastly,

$$\lambda_4 = Q = (A_1B_2 + A_2B_1)(\rho_wA_3 - g_{10}A_1) + (\rho_cA_1 - \rho_wA_2)(A_3B_1 + A_1B_3).$$

Since $(A_1B_2 + A_2B_1)$ and $(A_3B_1 + A_1B_3)$ are positive, we are left to show that $(\rho_wA_3 - g_{10}A_1)$ and $(\rho_cA_1 - \rho_wA_2)$ are negative. This implies that

$\rho_wA_3 - g_{10}A_1 < 0 \Leftrightarrow \rho_wA_3 < g_{10}A_1$ yields

$$\rho_w < g_{10}\frac{A_1}{A_3}, \tag{17}$$

and

$\rho_cA_1 - \rho_wA_2 < 0 \Leftrightarrow \rho_cA_1 < \rho_wA_2.$

This gives

$$\rho_c\frac{A_1}{A_2} < \rho_w. \tag{18}$$

Combining equations (17) and (18), we get the inequality

$$\rho_c\frac{A_1}{A_2} < \rho_w < g_{10}\frac{A_1}{A_3}$$

from which we arrived at

$\lambda_4 < 0$ iff $\rho_c > \frac{-\mu(\mu+\gamma)\theta S^{**}}{\gamma\pi N^{**}({I_w}^{**} + \theta {I_c}^{**})} = -(\mu+\gamma)\mu\beta\theta\frac{S^{**}}{N^{**}}\frac{K}{\gamma\pi(R_c - 1)}$, provided $R_c > 1$.

Lemma 3.4. The endemic equilibrium is locally asymptotically stable iff $R_c > 1$.

3.5. Global Stability of the Endemic Equilibrium $\mathbf{E}^{**}$

Lemma 3.5. The endemic equilibrium point of the model (1) is globally asymptotically stable if and only if $R_c|_{\alpha=\gamma=0} > 1$.

Proof. We consider a nonlinear Lyapunov function of Volterra type as applied in [20]

$$L_1 = S - S^{**} - S^{**}\ln\left(\frac{S}{S^{**}}\right) + \frac{1}{\pi}\left[I_w - {I_W}^{**}\ln\left(\frac{I_w}{{I_W}^{**}}\right)\right] + \frac{1}{1-\pi}\left[I_c - {I_c}^{**}\ln\left(\frac{I_c}{{I_c}^{**}}\right)\right].$$

The derivative of L_1 with respect to time is given by

$$L_1' = \left(1-\frac{S^{**}}{S}\right)\frac{dS}{dt}+\frac{1}{\pi}\left(1-\frac{{I_w}^{**}}{I_w}\right)\frac{dI_w}{dt}+\frac{1}{1-\pi}\left(1-\frac{{I_c}^{**}}{I_c}\right)\frac{dI_c}{dt}. \quad (19)$$

Putting the equations of the model (1) at $\gamma = 0$ in (19), we have

$$L_1' = \left(1-\frac{S^{**}}{S}\right)\left[\phi-\beta\left(\frac{I_w+\theta I_C}{N}\right)S-\mu S\right]+\frac{1}{\pi}\left(1-\frac{{I_w}^{**}}{I_w}\right)\left[\beta\pi\left(\frac{I_w+\theta I_C}{N}\right)S-(\mu+\alpha+\rho_w+\delta_w)I_w\right]$$
$$+\frac{1}{1-\pi}\left(1-\frac{{I_c}^{**}}{I_c}\right)\left[\beta(1-\pi)\left(\frac{I_w+\theta I_C}{N}\right)S+\alpha I_w-(\mu+\rho_c+\delta_c)I_c\right].$$

For convenience, let $H(I)=\frac{I_w+\theta I_C}{N}$, then simplification gives

$$L_1' = \left(1-\frac{S^{**}}{S}\right)[\,\phi-\beta H(I)S-\mu S]+\left(\frac{1}{\pi}\right)\times\left(1-\frac{{I_w}^{**}}{I_w}\right)[\beta\pi H(I)S-(\mu+\alpha+\rho_w+\delta_w)I_w]$$
$$+\left(\frac{1}{1-\pi}\right)\times\left(1-\frac{{I_c}^{**}}{I_c}\right)[\beta(1-\pi)H(I)S+\alpha I_w-(\mu+\rho_c+\delta_c)I_c]. \quad (20)$$

Using the following equilibrium relations of the model (1) obtained at $\gamma = 0$,

$$\phi = \beta H(I^{**})S^{**}+\mu S^{**},$$
$$\mu+\alpha+\rho_w+\delta_w = \frac{\beta\pi H(I^{**})S^{**}}{{I_w}^{**}},$$
$$\mu+\rho_c+\delta_c = \frac{\beta(1-\pi)H(I^{**})S^{**}+\alpha{I_w}^{**}}{{I_w}^{**}},$$

Then, equation (20) becomes

$$L_1' = \mu S^{**}\left(1-\frac{S^{**}}{S}-\frac{S}{S^{**}}\right)+\beta H(I^{**})S^{**}\left[1-\frac{H(I)S}{H(I^{**})S^{**}}-\frac{S^{**}}{S}+\frac{H(I)}{H(I^{**})}\right]$$
$$+\beta H(I^{**})S^{**}\left[\frac{H(I)S}{H(I^{**})S^{**}}-\frac{I_w}{{I_w}^{**}}+\frac{{I_w}^{**}H(I)S}{I_wH(I^{**})S^{**}}+1\right]$$
$$+\beta H(I^{**})S^{**}\left[\frac{H(I)S}{H(I^{**})S^{**}}-\frac{I_c}{{I_c}^{**}}+\frac{{I_c}^{**}H(I)S}{I_cH(I^{**})S^{**}}+1\right]$$
$$+\frac{\alpha}{1-\pi}{I_w}^{**}\left[\frac{I_w}{{I_w}^{**}}-\frac{I_c}{{I_c}^{**}}-\frac{{I_c}^{**}I_w}{I_C{I_w}^{**}}+1\right] \quad (21)$$

Adding the second, third and fourth terms of (21) and using the fact that $\frac{H(I)}{H(I^{**})}\leq 1$, since $H(I)$ is a decreasing function, we get

$$L_1' = \mu S^{**}\left(2-\frac{S^{**}}{S}-\frac{S}{S^{**}}\right)+\beta H(I^{**})S^{**}\left[4-\frac{I_w}{{I_w}^{**}}-\frac{S{I_w}^{**}}{S^{**}I_w}-\frac{I_c}{{I_c}^{**}}-\frac{{I_c}^{**}S}{I_cS^{**}}\right]$$
$$+\beta H(I^{**})S^{**}\left[-\frac{S^{**}}{S}+\frac{S}{S^{**}}\right]+\frac{\alpha}{1-\pi}{I_w}^{**}\left[\frac{I_w}{{I_w}^{**}}-\frac{I_c}{{I_c}^{**}}-\frac{{I_c}^{**}I_w}{I_C{I_w}^{**}}+1\right]. \quad (22)$$

But $\beta H(I^{**})=\lambda^{**}=\frac{R_c-1}{K}$ from (11) and setting $\alpha = 0$ in (22), we have

$$L_1' = \mu S^{**}\left(2-\frac{S^{**}}{S}-\frac{S}{S^{**}}\right)+\left(\frac{R_c-1}{K}\right)S^{**}\left[4-\frac{I_w}{{I_w}^{**}}-\frac{S{I_w}^{**}}{S^{**}I_w}-\frac{I_c}{{I_c}^{**}}-\frac{{I_c}^{**}S}{I_cS^{**}}\right]-\left(\frac{R_c-1}{K}\right)S^{**}\left[\frac{(S^{**})^2-S^2}{SS^{**}}\right],$$

from which we arrived at

$$L_1' \leq \mu S^{**}\left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}}\right) + \left(\frac{R_c - 1}{K}\right) S^{**}\left[4 - \frac{I_w}{{I_w}^{**}} - \frac{S{I_w}^{**}}{S^{**}I_w} - \frac{I_c}{{I_c}^{**}} - \frac{{I_c}^{**}S}{I_c S^{**}}\right].$$

Thus,

$L_1' \leq 0$ if and only if $R_c > 1$, $2 \leq \frac{S^{**}}{S} + \frac{S}{S^{**}}$ and $4 \leq \frac{I_w}{{I_w}^{**}} + \frac{S{I_w}^{**}}{S^{**}I_w} + \frac{I_c}{{I_c}^{**}} + \frac{{I_c}^{**}S}{I_c S^{**}}$. However, $L_1' = 0$ if $R_c = 1, S = S^{**}$, $I_w = {I_w}^{**}$ and $I_c = {I_c}^{**}$. Hence, $\{(S,\ I_w,\ I_C) = (S^{**},\ {I_w}^{**},\ {I_c}^{**})\}$ is the only singleton set in D, which is the largest compact subset where $L_1' = 0$. At this point, we can conclude by invariance principle in Theorem 3.1 that the endemic equilibrium is globally asymptotically stable.

3.6. Threshold Analysis

The control reproduction number, R_c, of a model system with CAST strategy defined by (5) is a threshold quantity that determines whether the disease will invade the host population. If R_c is less than unity, the disease will be under control, and if it is not, then there will be an outbreak of disease.

In the absence of CAST strategy, we have

$$\lim_{(\alpha,\theta,\rho_c,\delta_c)\to(0,1,0,0)} R_c = \frac{\beta\pi}{d_1} + \frac{\beta(1-\pi)}{d_2} = R_0, \tag{23}$$

where R_0 is the basic reproduction number.

Thus, the difference between equations R_c of (5) and R_0 of (23) is

$$R_0 - R_c = \frac{\beta(1-\pi)}{d_2}(1-\theta) - \frac{\beta\pi\alpha\theta}{d_1 d_2}. \tag{24}$$

Clearly from equation (24), $R_0 - R_c$ is positive if $\theta = 0$. This epidemiologically implies that CAST strategy could be essential for effective treatment of hard-to-treat infections. On the other hand, $\theta = 1$ biologically shows that $R_0 - R_c$ is negative and thus ineffective in curtailing this kind of infections.

4. Numerical results and discussion

As an application of our model developed on hard– to – treat infections, we focus on the case study of 2014 Mycobacterium Tuberculosis (TB) outbreak in South Africa.

4.1. Parameter estimation

According to the Population Reference Bureau in 2018, the total population of South Africa denoted by N was estimated as of 2014 to be 53,700,000. The Global TB Report 2015 estimated that South Africa had the second highest TB incidence rate in 593 cases per 100, 000 population. Thus, we have the total number of infected individuals with TB as in 2014 to be

$$I = \frac{593}{100{,}000} \times 53{,}700{,}000 = 318{,}441.$$

Meanwhile those individuals I_C infected with TB who adopted the CAST strategy was 101, 423 [21], and the total number of infected individuals I_w without considering the strategy becomes

$$I_w = I - I_c = 318{,}441 - 101{,}423 = 217{,}018.$$

On the other hand, the total number of people R who have recovered from TB during the year under review by [4] was 251, 344. To this effect, the number of individuals susceptible to TB in 2014 evidently satisfies the relation

$$S = N - (I_w + I_c + R) = 53{,}130{,}215.$$

The death rate is defined as the inverse of the life expectancy at birth. As in the year 2014, the life expectancy of South Africans was 60.99 years. Therefore, the natural death rate, μ, is estimated to be $\mu = \frac{1}{60.99} = 0.0163961$ per year. Also, the recruitment number ϕ can be estimated from the relation in the feasible region as

$$\phi \cong N \times \mu = 880{,}472.21$$

The rest of the parameters can be similarly estimated and appropriately assumed as presented in Table 2

Table 2: Values for population-independent parameters of the model $\left(yr^{-1}\right)$

Variable/Parameter	Value	Source
N	53,700,000	[4]
S	53,130,215	Estimated
I_w	217,018	Estimated
I_c	101,423	[21]
R	251,344	[4]
Φ	880,472.21	Estimated
π	0.5	Assumed
α	$0 \leq \alpha \leq 1$	Variable
β	0.6983	[22]
μ	0.0163961	Estimated
θ	$0 \leq \theta \leq 1$	Variable
δ_w	0.06908	Assumed
δ_c	0.03384	Assumed
ρ_c	0.06667	[4]
ρ_w	0.075	[4]
γ	0.007893	Assumed

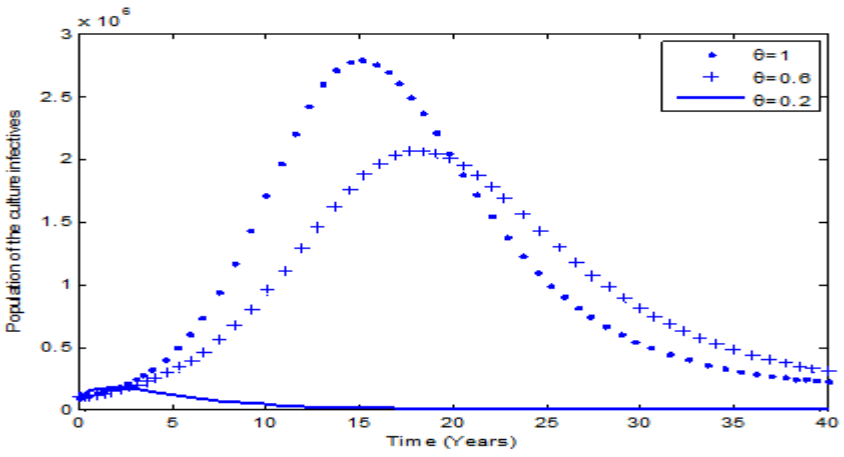

Fig. 2. Effect of θ on TB infectives, I_C with CAST strategy

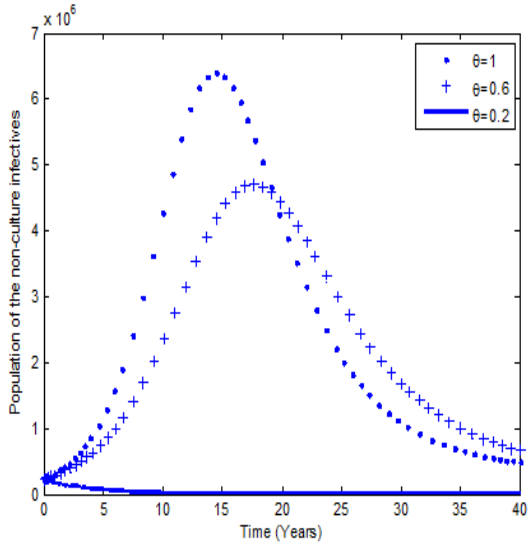

Fig. 3. Effect of θ on TB infectives, I_w without CAST strategy

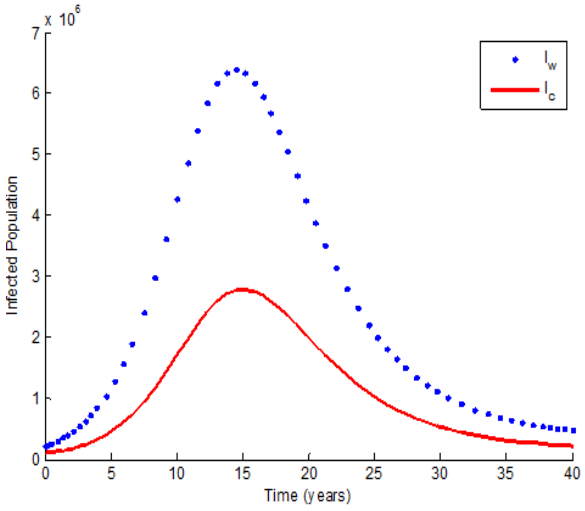

Fig. 4. The effect of the modification parameter ($\theta = 1$) on the dynamics of TB infectives

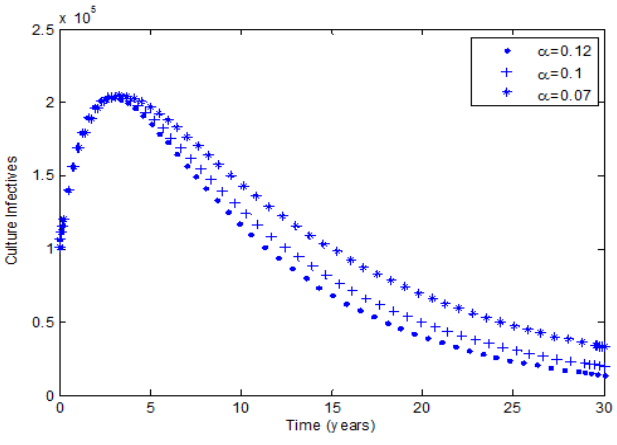

Fig. 5. Effect of α on TB infectives, I_C with CAST strategy.

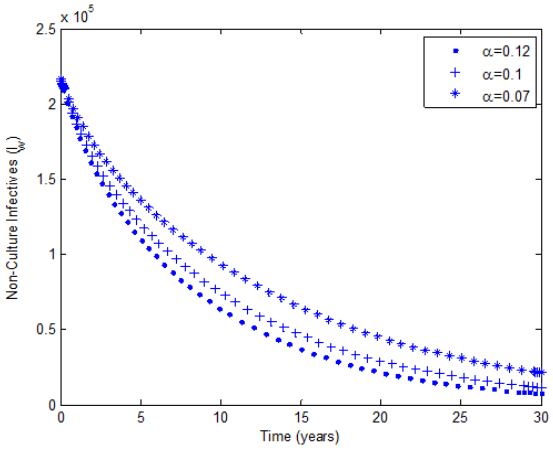

Fig. 6. Effect of α on TB infectives, I_C without CAST strategy

Fig. 2 illustrated the dynamical behaviour of infectives I_C who have gone for culture and conducted antibiotic susceptibility testing concerning the modification parameter, θ. The number of infected individuals remains high at $\theta = 1$, implying that, CAST strategy fails at that point and begins to decline as the value of θ decreases demonstrating the effectiveness of culture and antibiotic susceptibility testing. A similar consideration was carried out in Fig. 3 on those infectives I_W that have gone only for ordinary prescription treatment and indicates the same scenario only that the number of people with CAST strategy has a comparative advantage in quick response to treatment than those without the intervention strategy. A clear comparison of the above two experiments is given in Fig. 4 at $\theta = 1$ in which $I_C < I_W$. This inequality shows the significance of CAST strategy as a prerequisite to the proper treatment of infectious diseases and further discourages the ordinary diagnosis/blind prescription treatment of patients suffering from hard-to-treat infections. This result agrees with the works of [3, 6] that mandated the use of culture before medication as it prevents drug resistance and promotes timely cure from infections. The impact of α on the infectives is also given in Fig. 5 and 6. In both Figures, it is important to say that infection is easily treated in individuals who embrace CAST strategy but prove difficult for those who have gone for blind prescription or ordinary diagnosis at $\alpha = 0$. This outcome is consistent with [12] that says culture and drug sensitivity test can save more lives and prevent multi-drug resistance in patients.

5. Conclusion

This paper aims to model the role of culture and antibiotic susceptibility testing on the treatment of hard-to-treat infections. To this end, incidence function that accounts for individuals' behaviour with (out) culture has been introduced. Stability analysis concerning $\boldsymbol{R_c}$ being the key objective of any epidemiological study has been done, and the investigation reveals that the basic equilibria of the model are stable, both local and global using appropriate standard stability methods. Threshold analysis of the effective reproduction number $\boldsymbol{R_c}$ has proven that CAST strategy is very critical in mitigating and controlling the hard-to-treat diseases. Numerically, we simulate the proposed model using tuberculosis data from South Africa as a case study. The result confirms that individuals who present themselves for treatment of infection without culture and antibiotic susceptibility testing have a slow recovery pace and thus increases their mortality. Based on these findings; priority should be on culture and drug sensitivity testing by health practitioners before prescribing drugs to patients, since this will reduce fatality and boast recovery rates of individuals from hard-to-use infections. Additionally, since the study focuses on a generalised model for non-specific infection, we expect future research to target specific diseases as each disease may have its peculiar transmission dynamics.

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