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Global Sensitivity Analysis and Optimal Control of Typhoid Fever Transmission Dynamics

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Abstract. This paper presents a mathematical model aimed at studying the global behaviour and optimal control strategies for Typhoid fever. The primary objective of this study is to identify the most effective control strategy that minimizes the spread of the disease. To achieve this, we calculate the effective and basic reproduction numbers and utilize them to investigate the existence and stability of the equilibria. Furthermore, we investigate the global impact of each model parameter on the variables using Latin Hypercube Sampling and Partial Rank Correlation Coefficient. The necessary conditions of the optimal control problem are analyzed using Pontryagin's maximum principle, and the numerical values of the model parameters are estimated using the maximum likelihood estimator. The results indicate that the optimal use of vaccination for susceptible individuals, as well as the screening and treatment of asymptomatic infected individuals, have a significant impact on reducing the spread of the disease in endemic regions.

Keywords: global sensitivity analysis, optimal control, screening and treatment, typhoid fever.

AMS Subject Classification: 34D20; 34D23; 92D30.

1 Introduction

Typhoid fever (TF) is a communicable disease, found only in man and occurs due to systemic infection mainly by *salmonella typhi* organism [19]. The disease is transmitted through faecal-oral route via contaminated water and food, especially by food-handling carriers. Human beings are the only known reservoiur and host for TF [14]. Despite recent progress in water sanitation coverage, the disease remains as a substantial public health problem in many developing countries. It is endemic to areas characterized by rapid population growth, increased urbanization, and limited safe water, infrastructure and health systems like Africa, India, South and Central America [28].

Globally, it is estimated that Typhoid fever causes over 16 million cases of illness each year, resulting in over 600,000 deaths [17]. While improvements in water and sanitation led to the elimination of Typhoid from most developed countries during the twentieth century, the global burden of Typhoid fever has recently been estimated to be between 13.5 and 26.9 million episodes and 190,000 to 216,000 deaths annually [1]. Being an important communicable disease in the United Republic of Tanzania national list, TF has received considerable control efforts at national, regional and district levels. Mathematical modeling of the spread of infectious diseases continues to provide important insights into diseases behavior and control. Over the years, it has also become an important tool in understanding the dynamics of diseases and in decision making processes regarding intervention programs for controlling these diseases in many countries. Malisa and Nyaki [14] analyzed the prevalence and constraints of Typhoid fever and its control in an endemic area of Singida region in Tanzania and found that, despite all the efforts the disease continues to persist in Tanzania leading to significant morbidity and mortality. Tilahun *et al.* [27] proposed and analyzed a compartmental nonlinear deterministic mathematical model for the Typhoid fever outbreak and optimal control strategies in a community with varying population. There have also been studies of epidemiological models where optimal control methods were applied, these includes, [27] proposed and analyzed a compartmental nonlinear deterministic mathematical model for the Typhoid fever outbreak and optimal control strategies in a community with varying population. Mushayabasa, [18] analysed the impact of optimal screening on Typhoid dynamics and [29] studied a general SIR epidemic model and applied stability analysis theory to find the equilibrium solutions and then used optimal control to determine the optimal vaccination strategies to reduce the susceptible and infective individuals. Sethi [25] formulated and analyzed an optimal control problem with a simple epidemic model to examine the effect of a quarantine program. Gupta and Rink [6] considered the application of optimal control to find the most economical use of active and passive immunization in controlling infectious diseases. However, none of these

studies have considered the aspect of optimal control to reduce spread of Typhoid disease through the combination of vaccination of susceptible population, screening and treatment of unaware infectives, and treatment of symptomatic infectious individuals. In addition, global sensitivity analysis is considered to be another new approach to the study of the dynamics and control of Typhoid Fever. It is against this background, this study intends to apply optimal control theory to minimize the spread of disease by some control strategies and minimize the cost of applying controls in order to best combat the its spread.

2 Model formulation

A mathematical model for the transmission dynamics of Typhoid fever incorporating the time-dependent controls to some parameters is formulated in this section. Some assumptions used in this section are similar to those in [4,7,8,22] but the time dependent parameters $u_1(t), u_2(t)$ and $u_3(t)$ makes the difference between the previous studies and the current work on TF. The most important reason for taking preventive and control measures on TF is to minimize the disease incidences and prevalence, and if possible eradicate it from the population. Susceptibility level for healthy individuals against the infection is minimized by protective measures whereas the number of infective individuals in the population is reduced by control measures [21]. In this paper, vaccination of susceptible humans, $u_1(t)$ is introduced as a time dependent control variable that aims at reducing the number of asymptomatic and symptomatic infected humans in the population. Consequently, the control reduces the disease transmission to the vaccination failure rate $(1 - u_1(t))(\beta_1 I + \beta_2 I_c)$ and $(1 - u_1(t))(1 - \rho)(\beta_1 I + \beta_2 I_c)S$ respectively. That is, if vaccination coverage is 100% effective, zero TF incidence is expected in that particular region. We introduce $u_2(t)$, a control variable that measures the efficiency of screening and treatment of carriers. Furthermore, the control variable $u_3(t)$ is introduced as the measure of effectiveness of treatment of symptomatic individuals ψ. To determine the necessary conditions for optimal impact of incorporated parameters, we use Pontryagin's Maximum Principle as the method for obtaining the optimal combination of incorporated controls. The aim is to minimize or eliminate the spread of TF while minimizing the cost of administering these controls.

2.1 Model assumptions

Formulation of the model is guided by the following assumptions:

(*i*) The mixing of individuals in the population is homogeneous;

(*ii*) Immunized individuals cannot be infected unless their resistance to infection wanes;

(*iii* There is constant natural mortality rate in each class;

(*iv*) The birth rate for each population is greater than natural mortality rate.

The compartmental diagram with the time dependent control strategies is shown in Figure 1 whereas the variables and parameters used in this model are

respectively summarized in Table 1 and Table 2.

Table 1. Model variables.

Variable	Description
$S(t)$	Number of susceptible humans at time t
$I(t)$	Number of symptomatic infected humans at time t
$I_c(t)$	Number of asymptomatic infected humans at time t
$R(t)$	Number of recovered humans at time t

2.2 Compartmental flow diagram for the disease dynamics

The interactions between susceptible, symptomatic, asymptomatic, and recoverd individuals are illustrated in Figure 1. The resulting model is shown as

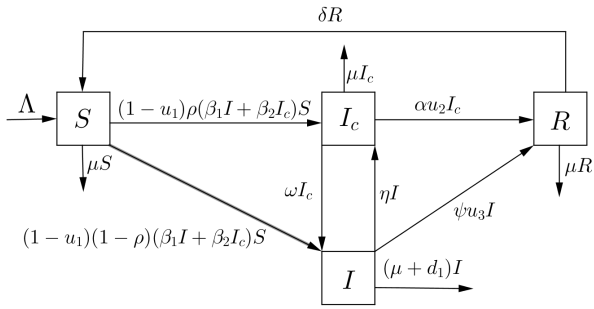


Figure 1. A schematic diagram for transmission dynamics of Typhoid fever.

a system of differential equations (2.1)

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda + \delta R - ((1-u_1(t))(\beta_1 I + \beta_2 I_c) + \mu)S,\\
\frac{dI}{dt} &= (1-u_1(t))(1-\rho)(\beta_1 I + \beta_2 I_c)S + \omega I_c - (\eta + \psi u_3(t) + \mu + d_1)I,\\
\frac{dI_c}{dt} &= (1-u_1(t))\rho(\beta_1 I + \beta_2 I_c)S + \eta I - (\omega + \alpha u_2(t) + \mu + d)I_c, \qquad (2.1)\\
\frac{dR}{dt} &= \alpha u_2 I_c + \psi u_3 I - (\delta + \mu)R,
\end{aligned}$$

subject to the following non-negative initial conditions: $S(0) > 0$, $I_c(0) \geq 0$, $I(0) \geq 0$, and $R(0) \geq 0$.

3 Model properties and analysis

3.1 Invariant region

In this subsection, we investigate whether model variables have biological interpretation and a unique bounded solution that exists for all the time. From

the model system (2.1), we have

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dI_c}{dt} + \frac{dR}{dt} \leq \Lambda - \mu N - dI_c - d_1 I.$$

Solving this, we obtain

$$0 \leq N(t) \leq \Lambda/\mu + N(0)e^{-\mu t}.$$

As $t \to \infty$, we have $0 < N(t) \leq \frac{\Lambda}{\mu}$. Hence, the model solution is feasible and positively invariant in the region

$$\Omega = \left\{(S,\, I,\, I_c,\, R) \geq 0 \in \mathbb{R}_+^4 : S + I + I_c + R \leq \Lambda/\mu\right\}.$$

The existence of the feasibility solution of the model, which is positively invariant in $\mathbb{R}_+^4$, implies that the model system is well-posed epidemiologically and mathematically. Well-posedness of the model allows us to continue with other mathematical analysis.

3.2 Equilibrium points

Setting the LHS of model system (2.1) equals to zero and solve at $I = I_c = 0$, we have the disease-free equilibrium E_0 given by

$$E_0 = (\Lambda/\mu,\, 0,\, 0,\, 0)\,.$$

The endemic equilibrium is $E^* = (S^*,\, I^*,\, I_c^*,\, R^*)$, where

$$\begin{aligned}
S^* &= \frac{\Lambda(\delta+\mu) + \alpha u_2 I_c^* + \psi u_3 I^*}{(\delta+\mu)((1-u_1)\rho(\beta_1 I^* + \beta_2 I_c^*) + \mu)},\\
I^* &= \frac{(1-u_1)(1-\rho)(\beta_1 I^* + \beta_2 I_c^*)S^* + \omega I^*}{\eta + \psi u_3 + \mu + d_1},\\
I_c^* &= \frac{(1-u_1(t))\rho(\beta_1 I^* + \beta_2 I_c^*)S + \eta I}{\omega + \alpha u_2 + \mu + d)I_c},\\
R^* &= \left(\alpha u_2 I_c^* + \psi u_3 I^*\right)/(\delta+\mu).
\end{aligned}$$

3.3 The effective reproduction number

Computation of the effective reproduction number, R_e for model system (2.1) using the standard method of the next generation matrix developed by Diekmann *at al.* [2, 3] is done in this subsection. R_e is defined as the measure of the average number of infections caused by a single infectious individual introduced in a community in which intervention strategies are administered [23]. When there are no interventions or controls, the number of secondary infections caused by typical infected individual during the entire infectiousness period is called basic reproduction number, R_0. Upon computation, the effective reproduction number was found to be

$$R_e = \frac{1}{2}\Big(R_{11} + R_{22} + \sqrt{(R_{22} - R_{11})^2 + 4R_{12}R_{21}}\,\Big),$$

where

$$R_{11} = \frac{(\beta_1(\omega + \alpha u_2 + \mu + d) + \beta_2\eta)(1-u_1)(1-\rho)\Lambda}{\mu(\eta(\alpha u_2 + \mu + d) + (\psi u_3 + \mu + d_1)(\omega + \alpha u_2 + \mu + d))},$$
$$R_{12} = \frac{(\beta_1\omega + \beta_2(\eta + \psi u_3 + \mu + d_1))(1-u_1)(1-\rho)\Lambda}{\mu(\eta(\alpha u_2 + \mu + d) + (\psi u_3 + \mu + d_1)(\omega + \alpha u_2 + \mu + d))},$$
$$R_{22} = \frac{(\beta_1\omega + \beta_2(\eta + \psi u_3 + \mu + d_1))(1-u_1)\rho\Lambda}{\mu(\eta(\alpha u_2 + \mu + d) + (\psi u_3 + \mu + d_1)(\omega + \alpha u_2 + \mu + d))},$$
$$R_{21} = \frac{(\beta_1(\omega + \alpha u_2 + \mu + d) + \eta\beta_2)(1-u_1)\rho\Lambda}{\mu(\eta(\alpha u_2 + \mu + d) + (\psi u_3 + \mu + d_1)(\omega + \alpha u_2 + \mu + d))}.$$

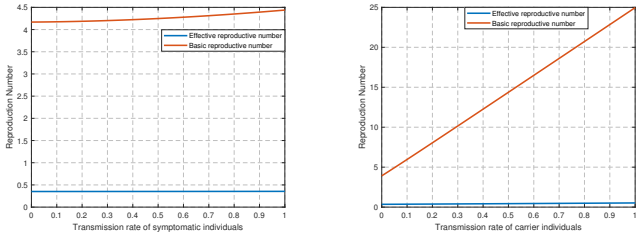
When there are no controls ($u_1 = u_2 = u_3 = 0$) for the disease, the effective reproduction is reduced to the basic reproduction number given by

$$R_0 = 0.5\Big(R_{11}^0 + R_{22}^0 + \sqrt{(R_{22}^0 - R_{11}^0)^2 + 4R_{12}^0 R_{21}^0}\Big),$$

where

$$R_{11}^0 = \frac{(\beta_1(\omega + \mu + d) + \eta\beta_2)(1-\rho)\Lambda}{\mu(\eta(\mu + d) + (\mu + d_1)(\omega + \mu + d))},$$
$$R_{12}^0 = \frac{(\beta_1\omega + \beta_2(\eta + \mu + d_1))(1-\rho)\Lambda}{\mu(\eta(\mu + d) + (\mu + d_1)(\omega + \mu + d))},$$
$$R_{22}^0 = \frac{(\beta_1\omega + \beta_2(\eta + \mu + d_1))\rho\Lambda}{\mu(\eta(\mu + d) + (\mu + d_1)(+\mu + d))},$$
$$R_{21}^0 = \frac{(\beta_1(\omega + \mu + d) + \beta_2\eta)\rho\Lambda}{\mu(\eta(\mu + d) + (\mu + d_1)(\omega + \mu + d))}.$$

The numerical simulations for the comparison between effective or control reproductive number and basic reproductive number with respect to variations in some parameters are illustrated in Figure 2. Parameter values used for the simulations are presented in Table 2.



(a) (b)

Figure 2. Variations in reproduction number with respect to changes in effective contact rate.

Figure 2 shows that R_0 increases with the increase in disease transmission coefficient or effective contact rate. Whereas, the effective contact rate has no

significant impact on the control or effective reproduction number. In particular, when effective contact rate for symptomatic infectious individuals is 0.2, R_0 and R_e are respectively 4.2 and 0.4. In addition, when the effective contact rate is for asymptomatic individuals is 0.1 , R_0 and R_e are 5.6 and 0.7 respectively. More importantly, Figure 2 reveals that R_e is always less than 1. This

Table 2. Model parameter values.

Par.	Description	Value	Source
Λ	Recruitment rate	0.0005	[22]
β_1	Transmission rate for symptomatic infectious individuals	0.0025	[17]
β_2	Transmission rate for carrier individuals	0.0125	[17]
ρ	Proportion of newly infected and asymptomatic individuals	0.5	[10]
α	Screening and treatment rate of asymptomatic individuals	0.5	[18]
ω	Rate at which carriers develop symptoms	0.010	[22]
η	Rate at which infectives become carriers	0.04	[22]
μ	Natural mortality rate of individuals	1/60/3	[16]
ψ	Recovery rate of symptomatic infected individuals	0.10	[22]
δ	Rate at which recovered individuals become susceptible	0.025	[22]
d_1	Disease-induced mortality rate of symptomatic individuals	0.066	[18]
d	Disease-induced mortality rate of carriers	0.004	[18]

implies that, with proper implementation of vaccination, treatment of symptomatic infectious individuals, and screening and treatments of asymptomatic infectious individuals, the Typhoid-free environment can be attained. Generally, the controls u_1, u_2 and u_3 have high impact on R_e by keeping it always less than R_0.

3.4 Local stability of the typhoid-free equilibrium

In this subsection, eigenvalue method is employed to investigate the local stability of the Typhoid-free equilibrium point for the model system (2.1).

Theorem 1. *The disease free equilibrium for the model system(2.1) is locally asymptotically stable if $R_e < 1$ and unstable if $R_e > 1$.*

Proof. We show that the variational matrix $J(E_0)$ of the Typhoid-free model system have only negative eigenvalues. The Jacobian matrix for system (2.1) is given by

$$J(E_0) = \begin{bmatrix} -\mu & -(1-u_1)\beta_1\rho S^0 & -(1-u_1)\beta_2\rho S^0 & \sigma \\ 0 & (1-u_1)(1-\rho)\beta_1 S^0 - A & (1-u_1)(1-\rho)\beta_2 S^0 + \omega & 0 \\ 0 & (1-u_1)\rho\beta_1 S^0 + \eta & (1-u_1)\rho\beta_2 S^0 - B & 0 \\ 0 & \psi u_3 & \alpha u_2 & -(\delta+\mu) \end{bmatrix},$$

where $A = (\eta + \psi u_3 + \mu + d_1)$, $B = (\omega + \alpha u_2 + \mu + d)$.

Observe that the Jacobian matrix $J(E_0)$ have $\lambda_1 = -\mu$ and $\lambda_2 = -(\delta+\mu)$ as its eigenvalues. Eliminating the rows and columns containing $-\mu$ and $-(\delta+\mu)$, the matrix $J(E_0)$ is reduced to

$$J_1(E_0) = \begin{bmatrix} (1-u_1)(1-\rho)\beta_1 S^0 - A & (1-u_1)(1-\rho)\beta_2 S^0 + \omega \\ (1-u_1)\rho\beta_1 S^0 + \eta & (1-u_1)\rho\beta_2 S^0 - B \end{bmatrix}.$$

Since $S^0 = \frac{\Lambda}{\mu}$, the matrix $J_1(E_0)$ can written as

$$J_1(E_0) = \begin{bmatrix} -A\left(1 - \frac{(1-u_1)(1-\rho)\beta_1\Lambda}{\mu A}\right) & (1-u_1)(1-\rho)\beta_2 S^0 + \omega \\ (1-u_1)\rho\beta_1 S^0 + \eta & -B\left(1 - \frac{(1-u_1)\rho\beta_2\Lambda}{\mu B}\right) \end{bmatrix}.$$

Observe that the quantity $\frac{(1-u_1)(1-\rho)\beta_1\Lambda}{\mu A}$ is the mean number of infected individuals due to one symptomatic individual, and $\frac{(1-u_1)\rho\beta_2\Lambda}{\mu B}$ is the mean number of infected individuals due one asymptomatic individual. At the disease-free equilibrium, the two quantities are less than unity making $J_1(E_0)$ a Metzler stable matrix whose eigenvalues are negative. Hence, the eigenvalues of the Jacobian matrix $J(E_0)$ are all negative. Thus, the Typhoid-free equilibrium for model system (2.1) is locally asymptotically stable at $R_e < 1$. □

3.5 Global stability of the typhoid-free equilibrium

In this subsection, we analyze the global behaviour of the Typhoid-free equilibrium point for the model system (2.1) by applying Lyapunov approach. In particular, we formulate the Lyapunov function and prove that its time derivative at the Typhoid-free equilibrium is non-positive.

Theorem 2. *The Typhoid-free equilibrium point for the model system (2.1) is globally asymptotically stable on Ω if $R_0 < 1$.*

Proof. We use the approach in [26] to define the explicit Lyapunov function candidate L for model system (2.1) as

$$L = (S - S^* lnS) + I + I_c + R. \tag{3.2}$$

The time derivative for Equation (3.2) is given by

$$\begin{aligned}
\frac{dL}{dt} &= \left(1 - \frac{S^*}{S}\right)\frac{dS}{dt} + \frac{dI}{dt} + \frac{dI_c}{dt} + \frac{dR}{dt} \\
&= \left(1 - \frac{S^*}{S}\right)(\Lambda + \delta R - ((1-u_1(t))(\beta_1 I + \beta_2 I_c) + \mu)S) \\
&\quad + (1-u_1(t))(1-\rho)(\beta_1 I + \beta_2 I_c)S + \omega I_c - (\eta + \psi u_3(t) + \mu + d_1)I \\
&\quad + (1-u_1(t))\rho(\beta_1 I + \beta_2 I_c)S + \eta I - (\omega + \alpha u_2(t) + \mu + d)I_c \\
&\quad + \alpha u_2 I_c + \psi u_3 I - (\delta + \mu)R \\
&= \left(1 - \frac{S^*}{S}\right)(\Lambda - \mu S) - \delta R\frac{S^*}{S} - (1-u_1)(\beta_1 I + \beta_2 I_c)S\left(1 + \left(1 - \frac{S^*}{S}\right)\rho\right).
\end{aligned}$$

At Typhoid-free equilibrium point $S^* = \dfrac{\Lambda}{\mu}$, and $I = I_c = R = 0$. It follows that

$$\frac{dL}{dt} = -\mu S\left(1 - S^*/S\right)^2.$$

Thus, $\frac{dL}{dt} \leq 0$. Now, by using LaSalle's extension to Lyapunov's method [11], the limit set of each solution is contained in the largest invariant set for which $S = S^*$ which is the singleton $\{E_0\}$. This means that the Typhoid-free equilibrium E_0 is globally asymptotically stable on Ω. □

4 Global sensitivity analysis

In this section, we study the influence of the model parameters using global sensitivity analysis techniques; Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC). Unlike local sensitivity, with global sensitivity analysis we are able to analyse the influence of a parameter on each model variable for the entire simulation period without holding other parameters as constants [15, 20]. The probability distribution functions for all parameters were obtained using Latin Hypercube Sampling with sample size of 1000 as indicated by Figure 3. The PRCCs for each parameter are generated from the probability distribution functions and they indicate the influence the parameter has on each state variable. PRCC value approaching 1 and -1 indicates that a parameter have strong influence on a variable while values between 0.3 and -0.3 indicate weak influence.

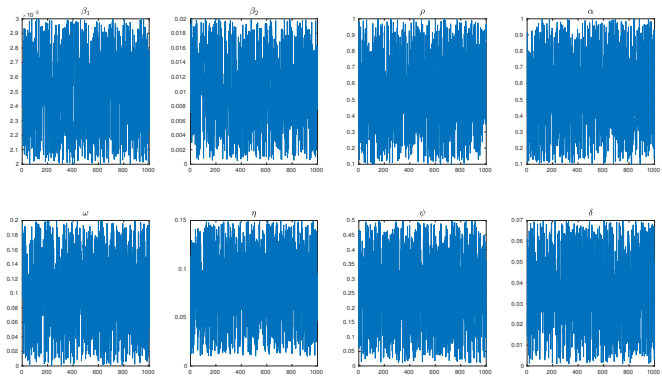


Figure 3. Probability distribution functions of parameters using a sample size of 1000.

4.1 Susceptible humans

The time variable PRCCs for susceptible humans are shown in Figure 4a. Proportion of newly infected and asymptomatic individuals (ρ), and transmission rate for carrier individuals (β_2) have the most negative values throughout. This implies that, an increase in any of the two parameters leads to a decrease in susceptible humans. Screening and treatment rate of asymptomatic individuals (α) and recovery rate of symptomatic infected individuals (ψ) have most positive values throughout, meaning that their increase leads to an increase in susceptible humans and vice versa. Furthermore, the rate at which recovered individuals become susceptible (δ) have strong positive influence on the first two years and eventually decline to weak region. This suggests that, any control measure on it will have high efficiency on the first two years. Figure 4b shows an extract of PRCCs at the 6^{th} year.

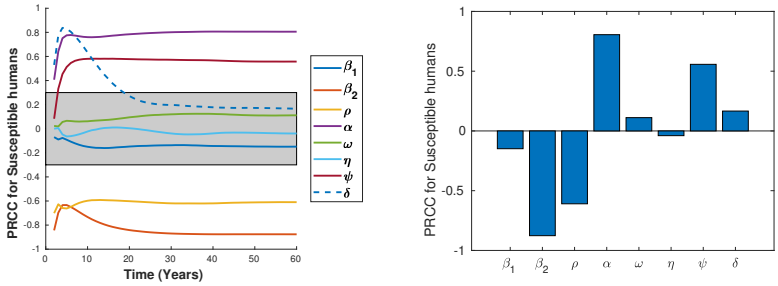


Figure 4. Sensitivity analysis PRCCs of parameters on susceptible humans. (a) PRCCs for the entire simulation time. (b) PRCCs exctracted at 6^{th} year.

4.2 Symptomatic infected humans

The time variable PRCCs for symptomatic infected humans are shown in Figure 5a. Proportion of newly infected and asymptomatic individuals (ρ) has most negative values throughout, meaning that its increase leads to a decrease in the number of symptomatic infected humans. The rate at which recovered individuals become susceptible (δ) has the most positive values throughout, meaning that its increase leads to an increase in symptomatic infected humans and vice versa. On the other hand, recovery rate of symptomatic infected individuals (ψ) have negative influence on the first five years and eventually decline to weak region. This suggests that, any control measure on it will have high efficiency on the first five years. Figure 5b shows an extract of PRCCs at the 6^{th} year. It further indicates that, the proportion of newly infected and asymptomatic individuals (ρ), and rate at which recovered individuals become susceptible (δ) are dominant.

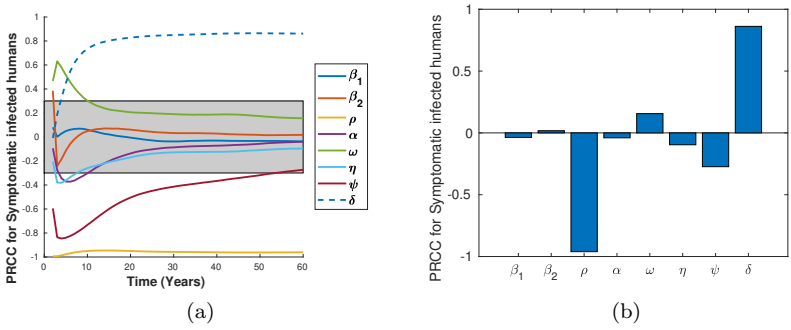
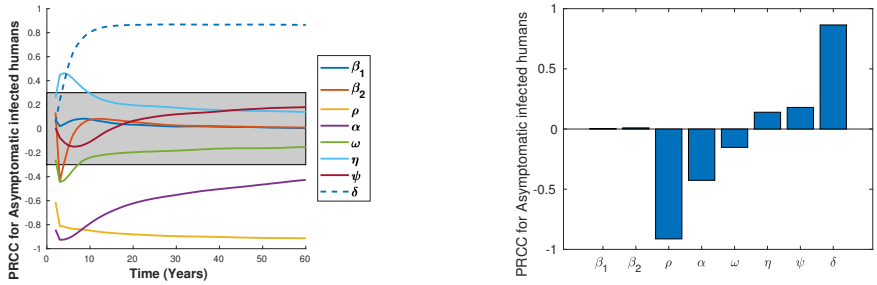


Figure 5. Sensitivity analysis PRCCs of parameters on symptomatic humans. (a) PRCCs for the entire simulation time. (b) PRCCs exctracted at 6^{th} year.



(a) (b)

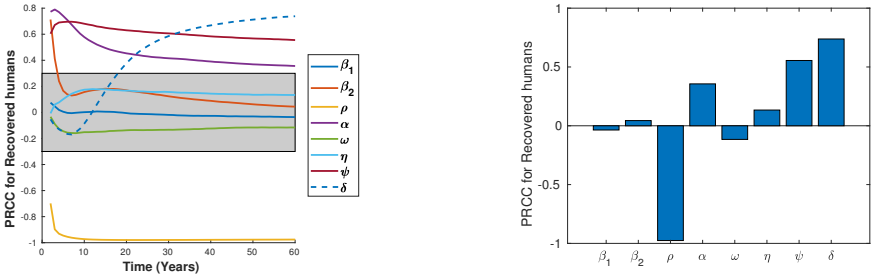
Figure 6. Sensitivity analysis PRCCs of parameters on asymptomatic humans. (a) PRCCs for the entire simulation time. (b) PRCCs exctracted at 6^{th} year.

4.3 Asymptomatic infected humans

The time variable PRCCs for asymptomatic infected humans are shown in Figure 6a. Proportion of newly infected and asymptomatic individuals (ρ) has most negative values throughout meaning that when it increases, symptomatic infected humans decreases. The rate at which recovered individuals become susceptible (δ) has most positive values throughout meaning that its increase leads to increase in asymptomatic infected humans and vice versa. On the other hand, screening and treatment rate of asymptomatic individuals (α) have strong negative influence at the beginning years and eventually decline toward weak region suggesting that any control measure on it will have high efficiency at early stages. Figure 6b shows extract of PRCCs at the 6^{th} year showing that proportion of newly infected and asymptomatic individuals (ρ) and rate at which recovered individuals become susceptible (δ) are dominant.

4.4 Recovered humans

The time variable PRCCs for asymptomatic infected humans are shown in Figure 7a. Proportion of newly infected and asymptomatic individuals (ρ) has most negative values throughout meaning that when it increases, symptomatic infected humans decreases. Recovery rate of symptomatic infected individuals (ψ) has most positive values throughout meaning that its increase leads to increase in asymptomatic infected humans and vice versa. On the other hand, rate at which recovered individuals become susceptible (δ) have weak influence on the first two years and eventually rising to positive strong influence suggesting that any control measure on it will have high efficiency from the second year. Furthermore, screening and treatment rate of asymptomatic individuals (α) have strong positive influence at the beginning years and eventually decline toward weak region suggesting that any control measure on it will have high efficiency at early stages. Figure 7b shows extract of PRCCs at the 6^{th} year showing that proportion of newly infected and asymptomatic individuals (ρ), recovery rate of symptomatic infected individuals (ψ), screening and treatment



(a) (b)

Figure 7. Sensitivity analysis PRCCs of parameters on recovered humans. (a) PRCCs for the entire simulation time. (b) PRCCs exctracted at 6^{th} year.

rate of asymptomatic individuals (α) and rate at which recovered individuals become susceptible (δ) are dominant.

5 Optimal control

To investigate the optimal level of efforts that would be required to control Typhoid fever infections, we first formulate the objective function J to be minimized, subject to the optimal control system (2.1) and the initial conditions;

$$J = \int_0^{t_f} \left(A_1 I + A_2 I_c + \frac{B_1 u_1^2}{2} + \frac{B_2 u_2^2}{2} + \frac{B_3 u_3^2}{2} \right) dt, \tag{5.1}$$

where A_1 and A_2, are positive weight constants of symptomatic and asymptomatic infected humans, respectively. The constants B_1, B_2, and B_3 are respectively the positive weights which balance the cost factors associated with control strategies u_1, u_2, and u_3. More importantly, the cost of each control strategy is assumed to be nonlinear and take quadratic form that is: $\frac{B_1 u_1^2}{2}$ is the cost of control strategy associated with vaccination of susceptible humans, $\frac{B_2 u_2^2}{2}$ is the cost associated with screening and treatment asymptomatic humans strategy, and $\frac{B_3 u_3^2}{2}$ is the cost associated with treatment of symptomatic infective individuals.

With the objective function $J(u_1, u_2, u_3)$, our goal is to minimize the number of infected humans, while minimizing the cost of controls, $u_1(t), u_2(t)$, and $u_3(t)$. We seek an optimal control $u_1^*(t), u_2^*(t)$, and $u_3^*(t)$ such that

$$J(u_1^*, u_2^*, u_3^*) = \min\{J(u_1, u_2, u_3) | u_1, u_2, u_3 \in u\},$$

where $u = \{u_1, u_2, u_3\}$ such that u_1, u_2, and u_3 are Lebesgue measurable with: $0 \leq u_1 \leq 1, \quad 0 \leq u_2 \leq 1$, and $0 \leq u_3 \leq 1$, for $t \in [0, \quad t_f]$ is the control set.

5.1 Existence of an optimal control

Theorem 3. *There exists an optimal control set $(u_1^*, u_2^*, u_3^*) \in u$ with corresponding non-negative variables (S, I, I_c, R) that minimize the objective func-*

tional $J(u_1(t), u_2(t), u_3(t))$.

Proof. The positivity and uniform boundedness of the state variables as well as the controls on $[0, t_f]$ entail the existence of a minimizing sequence $J(u_1^n(t), u_2^n(t), u_3^n(t))$, such that

$$\lim_{n\to\infty} J(u_1^n(t), u_2^n(t), u_3^n(t)) = \inf_{(u_1^n(t), u_2^n(t), u_3^n(t))\in u} J(u_1^n(t), u_2^n(t), u_3^n(t)).$$

The boundedness of all the state and control variables implies that all the derivatives of the state variables are also bounded. If the corresponding sequence of state variables be denoted by (S, I, I_c, R), then all state variables are Lipschitz continuous with the same Lipschitz constant. This implies that the sequence (S, I, I_c, R) is uniformly equicontinuous in $[0, t_f]$. Following the approach in [13], the state sequence has a subsequence that converges uniformly to (S, I, I_c, R) in [0, t_f]. In addition, we can establish that the control sequence $u^n = (S^n, I^n, I_c^n, R^n)$ has a subsequence that converges weakly in $L^2(0, t_f)$. Let $(u_1^*, u_2^*, u_3^*) \in u$ be such that $u_i^n \to u_i^*$ weakly in $L^2(0, t_f)$ for $i = 1, 2, 3$. Applying the lower semi-continuity of norms in weak L^2, we have:

$$\|u_i^*\|_{L^2}^2 \leq \lim_{n\to\infty} \inf \|u_i^n(t)\|_{L^2}^2,\ i = 1, 2, 3.$$

This means that

$$J(u_1^*, u_2^*, u_3^*) \leq \lim_{n\to\infty} \int_0^{t_f} \left(A_1 I^n + A_2 I_c^n + \frac{B_1 u_1^n}{2} + \frac{B_2 u_2^n}{2} + \frac{B_3 u_3^n}{2} \right) dt.$$

Thus, there exists a set of controls (u_1^*, u_2^*, u_3^*) that minimizes our objective functional $J(u_1, u_2, u_3)$. □

5.2 Characterization of optimal control

In this section, we derive necessary conditions for an optimal control and formulate an optimality system that characterizes the optimal control using upper and lower bound technique. The necessary condition is that an optimal control problem must satisfy Pontryagin's maximum principle [24]. The principle converts system (2.1) and Equation (5.1) into a problem of minimizing point-wise a Hamiltonian H, with respect to u_1, u_2, and u_3 defined by:

$$\begin{aligned} H =& A_1 I + A_2 I_c + \frac{B_1 u_1^2}{2} + \frac{B_2 u_2^2}{2} + \frac{B_3 u_3^2}{2} \\ &+ \lambda_S(\Lambda + \delta R - ((1 - u_1(t))(\beta_1 I + \beta_2 I_c) + \mu)S) \\ &+ \lambda_I(((1 - u_1(t))(1 - \rho)(\beta_1 I + \beta_2 I_c))S + \omega I_c - (\eta + \psi u_3(t) + \mu + d_1)I) \\ &+ \lambda_{I_c}(((1 - u_1(t))\rho(\beta_1 I + \beta_2 I_c))S + \eta I - (\omega + \alpha u_2(t) + \mu + d)I_c) \\ &+ \lambda_R(\alpha u_2 I_c + \psi u_3 I - (\delta + \mu)R), \end{aligned} \tag{5.2}$$

where λ_S, λ_I, λ_{I_c}, and λ_R,are the adjoint or co-state variables.

Applying Pontryagin's maximum principle [24] and the existence result for the optimal control [5], we obtain:

Theorem 4. *For optimal tri controls u_1^*, u_2^*, and u_3^* that minimizes $J(u_1, u_2, u_3)$ over u, there exist adjoint variables λ_S, λ_I, λ_{I_c}, and λ_R, satisfying:*

$$\begin{aligned}
\frac{d\lambda_S}{dt} =&(1-u_1)(\beta_1 I+\beta_2 I_c)(\lambda_S-(1-\rho)\lambda_I-\rho\lambda_{I_c})+\mu\lambda_S,\\
\frac{d\lambda_I}{dt} =&-A_1+(1-u_1)\left(\lambda_S-(1-\rho)\lambda_I-\rho\lambda_{I_c}\right)\beta_1 S\\
&+\lambda_I(\eta+\psi u_3+\mu+d_1)-\psi u_3\lambda_R-\eta\lambda_{I_c},\\
\frac{d\lambda_{I_c}}{dt} =&-A_2+(1-u_1)\left(\lambda_S-(1-\rho)\lambda_I-\rho\lambda_{I_c}\right)\beta_2 S\\
&+\lambda_{I_c}(\omega+\alpha u_2+\mu+d)-\alpha u_2\lambda_R-\omega\lambda_I,\\
\frac{d\lambda_B}{dt} =&(\lambda_R-\lambda_S)\delta+\mu\lambda_S
\end{aligned} \tag{5.3}$$

with transversality conditions:

$$\lambda_S(t_f)=\lambda_I(t_f)=\lambda_{I_c}(t_f)=\lambda_R(t_f)=0. \tag{5.4}$$

The following characterization holds on the interior of the control set u

$$\begin{aligned}
u_1^* =&\max\left\{0,\min\left(1,\left(\beta_1 I+\beta_2 I_c\right)\left(\rho\lambda_{I_c}+(1-\rho)\lambda_I-\lambda_S\right)\beta S/B_1\right)\right\},\\
u_2^* =&\max\left\{0,\min\left(1,\left(\lambda_{I_c}-\lambda_R\right)\alpha I_c/B_2\right)\right\},\\
u_3^* =&\max\left\{0,\min\left(1,\left(\lambda_I-\lambda_R\right)\psi I/B_3\right)\right\},
\end{aligned} \tag{5.5}$$

where λ_S, λ_I, λ_{I_c}, and λ_R, are solutions of Equation (5.4).

Proof. The form of adjoint (or costate) system (5.3) and transversality conditions (5.4) are standard results from Pontryagin's Maximum Principle [24]. To obtain the costate system (5.3), the partial derivatives of the Hamiltonian (H) (5.2) with respect to each state variable are computed as follows:

$$\begin{aligned}
&\frac{d\lambda_S}{dt}=-\frac{\partial H}{\partial S};\quad \lambda_S(t_f)=0,\\
&\qquad\cdots\\
&\frac{d\lambda_R}{dt}=-\frac{\partial H}{\partial R};\quad \lambda_R(t_f)=0.
\end{aligned} \tag{5.6}$$

The optimality system (5.5) is obtained by finding the partial derivative of the Hamiltonian equation (5.2) with respect to each control variable and solving for the optimal values of u_i^* where the derivative vanishes; that is, $\frac{\partial H}{\partial u_i}=0$ for $i=1,2,3$. Solving for u_i^* subject to the constraints, gives the characterization equation (5.5). Next, we discuss the numerical solutions of the optimality system and the corresponding results of varying the optimal controls u_1, u_2 and u_3, the parameter choices and the interpretations from various cases. □

6 Numerical simulations

In this section, we analyze numerically the optimal control strategies for the TF transmission in model system (5.2). The controls of interest are: vaccination

of susceptible individuals, screening and treatment of asymptomatic infectious individuals, and treatment of symptomatic infectious individuals. Based on the fact that implementing a combination of controls is the most effective strategy [9], each strategy investigates the impact of the combination of at least two controls. The optimal control solution is obtained by solving the optimality system which consists of the state system (2.1) and the adjoint system (5.3). We start by solving the state equations with a guess for the controls over the simulated time using the fourth-order Runge–Kutta iterative schemes method. The adjoint equations are solved by the backward fourth-order Runge–Kutta scheme using the current iterations solutions of the state equations because of the transversality conditions (5.6).

Furthermore, the controls are updated by using a convex combination of the previous controls and the value from the characterizations (5.5). This process is repeated and the iterations are stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iteration [12]. Based on the fact that Typhoid fever is endemic in most of the Sub-Saharan Africa countries and that one control can not stop the disease transmission, we investigate the impacts of combining at least two control strategies in a period of six years. Moreover, the computation of real weights of the objective function is very involving and needs a lot of information. In view of the aforesaid, the weights of the objective function are theoretically chosen to be $A_1 = 10$, $A_2 = 15$, $B_1 = 20$, $B_2 = 10$, $B_3 = 10$ just to concede the control strategies proposed in this paper, and the parameter values used are in Table 2. The initial state variables are chosen as $S(0) = 2000, I(0) = 100, I_c(0) = 100, R(0) = 300$. The parameter values (in units per year) used in our computations are mainly from [17, 18, 22], literature similar to this work.

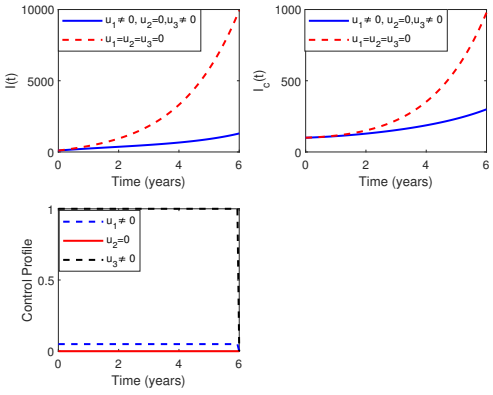


Figure 8. Dynamics of Typhoid fever with optimal vaccination, screening and treatment of asymptomatic individuals.

6.1 Optimal control strategies

6.1.1 Strategy A: optimal vaccination and treatment of asymptomatic individuals

Under this strategy, the effectiveness of vaccination u_1, screening and treatment of asymptomatic individuals, u_2 are used to minimize the objective function J whereas treatment of symptomatic individuals, u_3 is set to zero. Figure 8 illustrates the trends of the infectious classes.

Figure 8 shows that, combination of vaccination, screening and treatment of asymptomatic individuals minimizes the number of infectious individuals. In case of no controls the infective populations grows exponentially.

6.1.2 Strategy B: optimal vaccination and treatment of symptomatic individuals

In this strategy, vaccination u_1, and treatment of symptomatic infectious individuals u_3 are used to optimize the objective function J while screening and treatment of asymptomatic infectious people, u_2 is set to zero. Figure 9 illustrates the variations in the infectious classes. Figure 9 indicates that, the

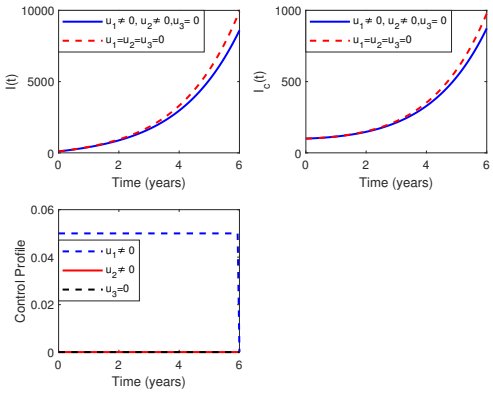


Figure 9. Dynamics of Typhoid fever with optimal vaccination and treatment of symptomatic infectious individuals.

combination of vaccination of susceptible people and treatment of symptomatic infectious have little impact on the disease control or elimination. This implies that, when planning for Typhoid fever management, elimination of the disease in carrier individuals should be given priority.

6.1.3 Strategy C: optimal treatment of symptomatic and asymptomatic individuals

In this strategy, treatment of symptomatic infectious individuals u_3, and screening and treatment of asymptomatic infectious individuals, u_2 are used to optimize the objective function J while vaccination u_1, is set to zero. Figure 10

illustrates the variations in the infectious populations. It can be seen from

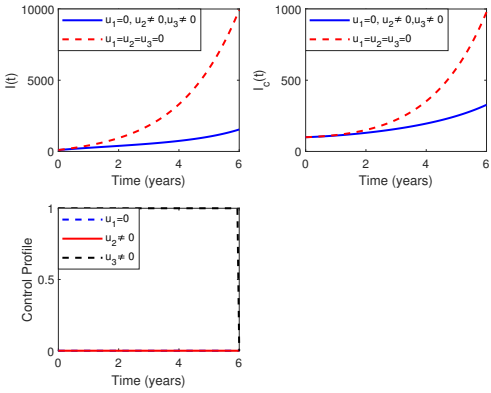


Figure 10. Dynamics of Typhoid fever with optimal treatment of symptomatic infectious, and screening and treatment of asymptomatic individuals.

Figure 10 that combination of the two strategies leads to reduction of both symptomatic and asymptomatic infectious individuals.

6.1.4 Strategy D: using all three control measures

In this strategy, vaccination of susceptible individuals u_1, treatment of symptomatic infectious idividuals u_3, and screening and treatment of asymptomatic infectious individuals, u_2 are used to minimize the objective function J. Figure 11 illustrates the variations in infectious populations. Figure 11 depicts

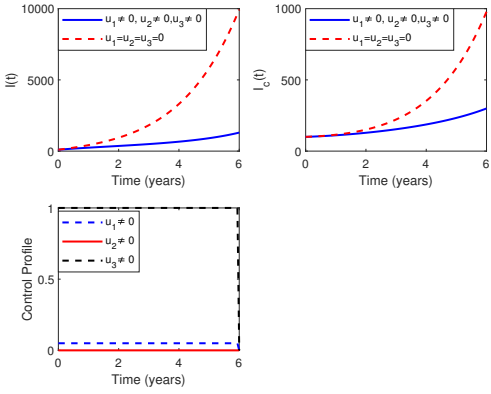


Figure 11. Dynamics of Typhoid fever with optimal vaccination, treatment of symptomatic infectious, and screening and treatment of asymptomatic infectious individuals controls.

that optimal implementation of the combination of vaccination, treatment of

symptomatic infectious, and screening and treatment of asymptomatic infectious individuals reduce the number of infected humans.

7 Conclusions

This paper aimed at formulating and analyzing a mathematical model for the impacts of different control options to the transmission dynamics of Typhoid fever. The controls evaluated were vaccination, screening and treatment of infectious individuals. Pontryagin's Maximum Principle was used to analyze the optimal control problem. Findings revealed that, demonstrate that a combination of screening and treatment of asymptomatic infectious individuals with either of the other two strategies significantly reduces the spread of the disease. The study also reveals that combining vaccination with screening and treatment of asymptomatic individuals has the same impact as using all three controls. Therefore, the research recommends implementing a cost-effective strategy by combining two controls: screening and treatment of asymptomatic infectious individuals and vaccination of susceptibles.

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