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A dynamic model of typhoid fever with optimal control analysis

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Abstract

In this study, a deterministic mathematical model of Typhoid fever dynamics with control strategies; vaccination, hygiene practice, sterilization and screening is studied. The model is first analyzed for stability in terms of the control reproduction number, R_c with constant controls. The disease-free equilibrium and endemic equilibrium of the model exist and is shown to be stable whenever $R_c < 1$ and $R_c > 1$, respectively. The model by investigation shows a forward bifurcation and the sensitivity analysis conducted revealed the most biological parameters to be targeted by policy health makers for curtailing the spread of the disease. The optimal control problem is obtained through application of Pontryagin maximum principle with respect to the above-mentioned control strategies. Simulations of the optimal control system and sensitivity of the constant control system confirms that hygiene practice with sterilization could be the best strategy in controlling the disease.

Keywords: Typhoid fever; global stability; sensitivity analysis; optimal control; bifurcation.

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1. Introduction

Typhoid fever is a life-threatening infection that is usually caused by Salmonella enteric serovar Typhi (S. Typhi) and Salmonella enteric serovar Paratyphi (S. Paratyphi, that is Paratyphi A, B, and, uncommonly is S. Paratyphi C) [1]. Typhoid fever has been a public health challenge globally. However, the disease is endemic in most developing countries in Africa and South-East Asia where potable clean water, sanitation and hygiene are either grossly inadequate or non-existent.

The transmission of S. Typhi and S. Paratyphi occur through the consumption of contaminated food or water resulting from inadequate environmental sanitation and hygiene practices [2]. People that are clinically ill from typhoid fever and those who have recovered from it pass out the bacteria in their stools (carriers) and urine [3]. A chronic carrier sheds Salmonella Typhoid more than 12 months after onset of illness. Human beings are the only known reservoir of Typhoid and the mode of transmission happens through food and water contaminated by acutely ill or chronic carriers of the bacteria [4].

Vaccine can be taken to prevent Typhoid fever but does not provide long-term immunity [5]. On the other hand, educating travelers moving to typhoid endemic regions on the importance of sanitation and hygiene precautions as well as vaccination will help immensely to preventing the rapid spread of Typhoid disease [4].

Mathematical models of infectious diseases are used to test and compare various intervention strategies especially when there are limited resources [6]. In controlling Typhoid fever, several mathematical models have been formulated. For instance, Mushayabas [7] considered the impact of education campaigns and treatment on the dynamics of Typhoid fever and Abboubakar and Racke [8] carried out a human and bacteria model without considering hygiene practice and individuals protected through vaccination in the population, while Karunditu *et al*. [9], Peter *et al*. [10], Nyerere *et al*. [11], Peter *et al*. [12], Edward and Nyerere [13], Kgosimore and Kelatlehegile [14] and Aji *et al*. [15] considered only human population without factoring in the bacteria concentration in the contaminated food and or water. Tilalum *et al.* [16], Okolo and Abu [17], Peter *et al*. [18], Abboubakar and Racke [19] and Awoke [20] studied the optimal control of typhoid transmission with control measures. None of the aforementioned works studied the combined control measures such as vaccination, hygiene practice, screening of carriers and sterilization of the bacteria in the environment as autonomous or non-autonomous system of equations. This study will bridge these gaps and form a novel contribution to the existing body of knowledge on the subject matter.

Peter *et al*. [10] forms the motivation of this work. They considered Protected, Susceptible, Infected, Treated and Recovery model without the bacteria concentration and the effect of screening of infected carriers and

hygiene practice on transmission dynamics of Typhoid fever. They assumed that the protected class belongs to only individuals that have been vaccinated before entrance into Typhoid endemic population and also optimal control and numerical simulation were not considered in their work. Modifying the work of Peter *et al*. [10], we consider Protected, Susceptible, Infected individuals, Carriers, Recovery and Bacteria concentration model in which some susceptible individuals are protected through vaccination and population practices hygiene which reduces the transmission rate. Hygiene practices which include safe water, sanitation and personal hygiene are crucial in preventing and controlling the spread of Typhoid. In addition, the screening and treating of carriers who are silent spreaders of the disease due to their asymptomatic nature and the sterilization of bacteria concentration in the immediate environment are also important in elimination of typhoid fever in the population. This work will be the first to consider sterilization of the bacteria concentration as a control measure for typhoid fever. Also, the sensitivity analysis for the prediction of appropriate intervention strategies for the control of typhoid fever spread and the optimal control analysis are carried out in this work.

Therefore, a modified version of the work of Peter *et al*. [10] is formulated in Section 2 and a comprehensive mathematical analysis of the model in Section 3. The sensitivity analysis and optimal control strategies of the Typhoid fever dynamics are considered in Section 4 while the numerical simulations and discussion are given in Section 5. Section 6 is the conclusion of the work.

2. Model description and formulation

In this section, the work of Peter *et* al. [10] is modified by considering human population (infected carriers) as well as bacteria concentration. The human population at any time, t is subdivided into five subpopulations namely; protected population, $P(t)$, susceptible population, $S(t)$, infected population, $I(t)$, carrier population, $I_c(t)$ and recovered individuals, $R(t)$. The bacteria concentration is represented by $B_c(t)$. In this study, the protected population, $P(t)$, are susceptible individuals that are vaccinated and individuals coming in from the population that is not at risk of Typhoid fever into typhoid fever endemic population. Infected population, $I(t)$, are infected individuals that are showing symptoms of the disease and are capable of spreading the bacteria in the environment while carrier population, $I_c(t)$, represents asymptomatic infected individuals that are treated but still carrying the Salmonella Typhi. Recovered individuals, $R(t)$, are individuals who have recovered from the disease by treatment or natural immunity.

The protected population, $P(t)$, of the proportion, $\alpha \in (0,1)$ is increased by birth or immigration at a rate, Λ, and also from susceptible individuals that are protected through vaccination at a rate, η. The protected population loses

immunity when the vaccine wanes at a rate, γ. The susceptible population is increased at a rate, $(1-\alpha)\Lambda$, of the unprotected population through birth or immigration and also from recovered population, $R(t)$, after losing their temporary immunity at a rate, ϕ. Susceptible population contract typhoid disease through food, water or environment contaminated by Salmonella bacteria as a result of inadequate hygiene practice measure at a rate, $(1-p)\lambda$ and progress to infected population. Here, $\lambda = \frac{\beta B_c}{K+B_c}$ is the force of infection, β is the ingestion or consumption rate of the contaminated food, water or environment, K is the carrying capacity of the bacteria in food, water or environment and $p \in (0,1)$ is the hygiene practice control measure. Infected individuals progress to carrier class at a rate, σ while some infected individuals recovered fully by treatment at rate τ_1 or they die of the disease (bacteria) at a rate, d. Carrier class, $I_c(t)$, recovered by natural immunity at a rate, τ_2 or by early treatment when they are screened at a rate, Ψ with θ as the treatment rate. The natural death rate, μ is assumed for all the human population.

For the bacteria concentration, $B_c(t)$, in the environment, they increased through the shedding from Carriers and symptomatic population, $I_c(t)$ and $I(t)$ at the rates, π_1 and π_2 respectively. The shedding rates, π_1 and π_2 are reduced by p, the level of hygiene practice the infected populations, $I_c(t)$ and $I(t)$, observed. The bacteria decays in the environment at a rate, μ_{Bc}. We assume that there is no human to human transmission but rather human aids in shedding the bacteria in the environment or contaminating the environment; neither there is immigration of infectious humans. Also, disease induced death does not occur in carrier class since they are asymptomatic, that is before the bacteria can cause death, it must have progressed to symptomatic stage. The systematic diagram of model is given in Figure 1.

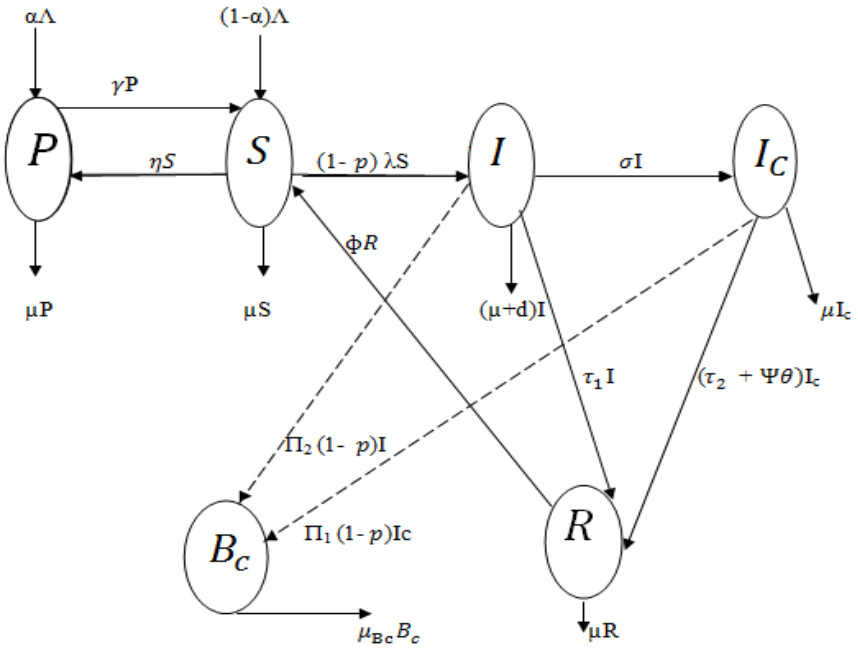

Figure 1. The systematic diagram for Typhoid fever model.

The system of differential equation is derived using the Figure 1 as follows.

$$\left.\begin{aligned}
\frac{dP}{dt} &= \alpha\Lambda + \eta S - (\gamma + \mu)P \\
\frac{dS}{dt} &= (1-\alpha)\Lambda + \gamma P + \phi R - (\eta + \mu + (1-p)\lambda)S \\
\frac{dI}{dt} &= (1-p)\lambda S - (\sigma + \tau_1 + \mu + d)I \\
\frac{dI_c}{dt} &= \sigma I - (\tau_2 + \Psi\theta + \mu)I_C \\
\frac{dR}{dt} &= \tau_1 I + (\tau_2 + \Psi\theta)I_C - (\mu + \phi)R \\
\frac{dB_c}{dt} &= \pi_2(1-p)I + \pi_1(1-p)I_C - \mu_B B_c
\end{aligned}\right\} \quad (1)$$

with initial conditions, $P(0) > 0$, $S(0) > 0$, $I_C(0) \geq 0, I(0) \geq 0$, $R(0) \geq 0$, $B_C(0) \geq 0$, where $\lambda = \frac{\beta B_c}{(K+B_c)}$ and the model parameters are assumed to be nonnegative.

3. Mathematical Analysis of the Model

3.1 Invariant Region

Invariant region is a region where the model solutions are uniformly bounded.

Theorem 1. All feasible solutions of the model are uniformly bounded in a proper subset $D = D_H \; X \; D_{B_c}$, where $\mathrm{D_H} = \left\{(\mathrm{P, S, I}, I_{C,}\mathrm{R}) \in \mathrm{R}_+^5 : \mathrm{N(t)} \leq \frac{\Lambda}{\mu}\right\}$ is a subset for human population and $D_{B_c} = \left\{B_c \in \mathbb{R}_+ : B_c \leq \frac{[(\pi_2 + \pi_1)(1-p)]\Lambda}{\mu\mu_B}\right\}$ is a subset for bacteria concentration in environment.

Proof. The total human population, $N(t)$ is given by $N = P + S + I + I_c + R$ with initial conditions $N(0) = N_0$ and $B_c(0) = B_{c0}$ for the bacteria in the environment. This implies that from equation (1) that $\frac{dN}{dt} = \Lambda - \mu N - dI$. In the absence of disease-induced death rate, that is, $d = 0$, we have $\frac{dN_H}{dt} \leq \Lambda - \mu N$ which by method of integrating factor and the initial condition, $N(0) = N_0$ gives

$$N(t) \leq \frac{\Lambda}{\mu} + \left(N_0 - \frac{\Lambda}{\mu}\right) e^{-\mu t}. \tag{2}$$

As $t \to \infty$ in equation (2), we have $N(t) \leq \frac{\Lambda}{\mu}$. This means that the feasible solutions of the model for the human population are in the region, $\mathrm{D_H} = \left\{(\mathrm{P, S, I}, I_{C,}\mathrm{R}) \in \mathrm{R}_+^5 : \mathrm{N(t)} \leq \frac{\Lambda}{\mu}\right\}$.

For bacteria concentration since $N(t) \leq \frac{\Lambda}{\mu}$, it means that $I \leq \frac{\Lambda}{\mu}$ and $I_C \leq \frac{\Lambda}{\mu}$, we have from the last equation of (1) that

$$\frac{dB_c}{dt} = \pi_2(1-p)N + \pi_1(1-p)N - \mu_B B_c \leq \pi_2(1-p)\frac{\Lambda}{\mu} + \pi_1(1-p)\frac{\Lambda}{\mu} - \mu_B B_c \; . \tag{3}$$

Solving equation (3) with $B_c(0) = B_{c0}$ as the initial condition yields

$$B_c \leq \frac{(\pi_2 + \pi_1)(1-p)\Lambda}{\mu\mu_B} + \left(B_{c_0} - \frac{(\pi_2 + \pi_1)(1-p)\Lambda}{\mu\mu_B}\right) e^{-\mu_B t}. \tag{4}$$

As t → ∞ in equation (4), we have $B_c \leq \frac{(\pi_2 + \pi_1)(1-p)\Lambda}{\mu\mu_B}$. Therefore, the feasible solution of the bacterial population enters the region $D_{B_c} = \left\{B_c \in \mathbb{R}_+ : B_c \leq \frac{[(\pi_2 + \pi_1)(1-p)]\Lambda}{\mu\mu_B}\right\}$. This completes the proof.

Theorem 1 implies that the model is well posed mathematically and epidemiologically. Therefore, it is sufficient enough to study the dynamics of the model (1) in the region $D = D_H \times D_{B_c}$.

3.2 Positivity of the Solutions

Theorem 2. Let $\mathrm{D} = \{P, S, I, I_C, R, B_c\} \in \mathbb{R}_+^{\,6}$ be solution set such that $P(0) = P_0,\ S(0) = S_0,\ I_C(0) = I_{C0}, \mathrm{I}(0) = I_0,\ R(0) = R_0$ and $B_C(0) = B_{C0}$ are positive, then the elements of the solution set D are all positive for $t \geq 0$.

Proof. From the first equation of the model equations (1), we have

$$\frac{dP}{dt} = \alpha\Lambda + \eta S - (\gamma + \mu)\mathrm{P} \geq -(\gamma + \mu)\mathrm{P}. \qquad (5)$$

Integrating equation (5) with initial conditions $P(0) = P_0$ yields

$$P(t) \geq P_0 e^{-(\gamma+\mu)\mathrm{t}} \geq 0\ .$$

In a similar way, the rest of the equations of the model equation (1) with initial conditions, $S(0) = S_0, I(0) = I_0 I_C\,(0) = I_{c0}, R(0) = R_0$ and $B_c(0) = B_{c_0}$ give

$$S(t) \geq S_0 \exp\left(\int_0^t -(\eta + \mu + (1-p)\lambda)\right) du \geq 0,$$
$$I(t) \geq I_0 \exp\{-(\sigma + \tau_1 + \mu + d)\mathrm{t}\} \geq 0,$$
$$I_C\,(t) \geq I_{c0} \exp\{-(\tau_2 + \Psi\theta + \mu)t\} \geq 0,$$
$$R(t) \geq R_0 \exp\{-(\mu + \phi)\mathrm{t}\} \geq 0,$$
$$B_c(t) \geq B_{c0} \exp(-\mu_B t) \geq 0.$$

Therefore, the solution set $\{P(t),\ S(t),\ I(t), I_c(t),\ R(t),\ B_c(t)\}$, of the system (1) is positive for all $t \geq 0$ since exponential functions and their initial conditions are positive.

3.3 Disease-free equilibrium point and Control Reproduction Number

We compute the control reproduction number, R_c, which is define as the average number of secondary cases reproduced when an infected person is introduced into a population where control measures like vaccination, screening, sanitation and hygiene are in place.

In obtaining this, we apply the next-generation matrix approach [21] at the disease-free disease (DFE). The disease-free equilibrium (DFE) is obtained by equating the right hand side of the equation (1) to zero and solve simultaneously for the disease-free equilibrium, $E_0 = (P^0, S^0, I^0, I_C^0, R^0, B_C^0)$. We have DFE,

$$E_0 = \left(\frac{\Lambda(\alpha\mu+\eta)}{\mu(\gamma+\eta+\mu)}, \frac{\Lambda(\gamma+\mu(1-\alpha))}{\mu(\gamma+\eta+\mu)}, 0, 0, 0, 0\right).$$

By the principle of next-generation matrix approach, we have

$$F = \begin{pmatrix} 0 & 0 & \frac{a\beta S_0}{K} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} k_3 & 0 & 0 \\ -\sigma & k_4 & 0 \\ -\pi_2(1-p) & -\pi_1(1-p) & \mu_B \end{pmatrix}, \quad (6)$$

where

$a = (1-p),\ \ k_1 = (\gamma + \mu), k_2 = (\eta + \mu),\ \ k_3 = (\sigma + \tau_1 + \mu + d),\ \ k_4 = (\tau_2 + \Psi\theta + \mu),\ k_5 = (\mu + \phi).$ (7)

Solving for the maximum eigenvalue of the matrix, FV^{-1}, we have

$$R_c = \frac{a\beta S_0[(\sigma\pi_1+\pi_2 K_4)(1-p)]}{K\mu_B K_3 K_4}. \quad (8)$$

With the definition of equation (7), we have

$$R_c = \frac{\beta\Lambda(1-p)(\gamma+(1-\alpha)\mu)[(\sigma\pi_1+\pi_2(\tau_2+\Psi\theta+\mu))(1-p)]}{\mu K\mu_B(\gamma+\eta+\mu)(\sigma+\tau_1+\mu+d)(\tau_2+\Psi\theta+\mu)}. \quad (9)$$

The control reproduction number, R_c, can be written as

$$R_c = R_I + R_{IC}, \quad (10)$$

where

$$R_I = \frac{\beta(1-p)^2\pi_2 S_0}{K\mu_B(\sigma+\tau_1+\mu+d)}, \ R_{Ic} = \frac{\beta(1-p)^2\sigma\pi_1 S_0}{K\mu_B(\tau_2+\Psi\theta+\mu)(\sigma+\tau_1+\mu+d)} \quad (11)$$

denote the reproduction numbers which the infected population and carrier population contributed respectively through their shedding in the environment.

3.4 Local stability of the disease-free equilibrium, E_0

Theorem 3. If E_0 is the DFE of the model, then E_0 is locally asymptomatically stable if $R_c < 1$, otherwise it is unstable if $R_c > 1$.

Proof. In proving this theorem, the Jacobian matrix of equation (1) at the disease-free equilibrium, E_0 is given as

$$J(E_0) = \begin{pmatrix} -\mathrm{k}_1 & \eta & 0 & 0 & 0 & 0 \\ \gamma & -\mathrm{k}_2 & 0 & 0 & \phi & \frac{-\mathrm{a}\beta S_0}{K} \\ 0 & 0 & -\mathrm{k}_3 & 0 & 0 & \frac{\mathrm{a}\beta S_0}{K} \\ 0 & 0 & \sigma & -\mathrm{k}_4 & 0 & 0 \\ 0 & 0 & \tau_1 & (\tau_2 + \Psi\theta) & -\mathrm{k}_5 & 0 \\ 0 & 0 & \pi_2(1-p) & \pi_1(1-p) & 0 & -\mu_B \end{pmatrix}. \quad (12)$$

The eigenvalues of the Jacobian matrix (12) are $-\mathrm{k}_5$ and the solutions of the polynomial

$$\lambda^5 + A\lambda^4 + B\lambda^3 + C\lambda^2 + D\lambda + E = 0 \quad (13)$$

where

$$\begin{gathered} \mathrm{A} = \mathrm{k}_1 + \mathrm{k}_2 + \mathrm{k}_3 + \mathrm{k}_4 + \mu_\mathrm{B}, \\ B = (\mathrm{k}_1 + \mathrm{k}_2)(\mathrm{k}_3 + \mathrm{k}_4 + \mu_\mathrm{B}) + \mathrm{k}_4(\mathrm{k}_3 + \mu_\mathrm{B}) + \mu(\mathrm{k}_2 + \gamma) + \mathrm{k}_3\mu_\mathrm{B}(1 - R_I), \\ C = \mu(\mathrm{k}_4 + \mu_\mathrm{B})(\mathrm{k}_2 + \gamma) + \mathrm{k}_1\mathrm{k}_2\mathrm{k}_3 + \mathrm{k}_3\mu_\mathrm{B}(\mathrm{k}_1 + \mathrm{k}_2)(1 - R_I) \\ + \mathrm{k}_3\mathrm{k}_4\mu_\mathrm{B}(1 - R_C) + \mathrm{k}_4(\mathrm{k}_1 + \mathrm{k}_2)(\mathrm{k}_3 + \mu_\mathrm{B}), \\ D = \mu\mathrm{k}_3\mu_\mathrm{B}(\mathrm{k}_2 + \gamma)(1 - R_I) + \mu\mathrm{k}_4(\mathrm{k}_3 + \mu_\mathrm{B})(\mathrm{k}_2 + \gamma) + \mathrm{k}_3\mathrm{k}_4\mu_\mathrm{B}(\mathrm{k}_1 + \\ \mathrm{k}_2)(1 - R_C), \\ E = \mu(\mathrm{k}_2 + \gamma)\mathrm{k}_3\mathrm{k}_4\mu_\mathrm{B}(1 - R_C). \end{gathered}$$

Using the theorem in Heffernan *et al.* [22], the roots of the polynomial (13) have negative real part if $A, B, C, D, E > 0$. With the definition of R_c in equation (10), we have $A, B, C, D, E > 0$ if $R_c < 1$. Therefore, the Jacobian Matrix (12) has negative real eigenvalues if $R_C < 1$. Hence, the disease-free equilibrium, E_0, is locally asymptotically stable if $R_C < 1$. This ends the proof.

3.5 Global stability of disease-free equilibrium

Theorem 4. The disease-free equilibrium, E_0, is globally asymptotically stable if $R_c < 1$.

Proof. We construct a Lyapunov function using the infected classes only and this is given by

$$L = \frac{[\sigma\pi_1(1-p)+\pi_2(1-p)\mathrm{k}_4]}{\mu_B \mathrm{k}_4 \mathrm{k}_3} I + \frac{\pi_1(1-p)}{\mu_B \mathrm{k}_4} I_C + \frac{1}{\mu_B} B_c \, . \tag{14}$$

Differentiating (14) with respect to time, t, along the solutions of the model (1) gives

$$\frac{dL}{dt} = \left(\frac{\sigma\pi_1(1-p)+\pi_2(1-p)\mathrm{k}_4}{\mu_B \mathrm{k}_4 \mathrm{k}_3}\right)\left(\frac{a\beta B_c}{(K+B_c)}\mathrm{S} - \mathrm{k}_3\mathrm{I}\right) + \frac{\pi_1(1-p)}{\mu_B \mathrm{k}_4}(\sigma I - \mathrm{k}_4 I_C) + \frac{1}{\mu_B}(\pi_2(1-p)\mathrm{I} + \pi_1(1-p)I_C - \mu_B B_c). \tag{15}$$

Expanding and simplifying (15) yields

$$\frac{dL}{dt} = \left(\frac{a\beta B_c}{(K+B_c)}\left(\frac{\sigma\pi_1(1-p)+\pi_2(1-p)\mathrm{k}_4}{\mu_B \mathrm{k}_4 \mathrm{k}_3}\right) S - 1\right) B_c = \left(\frac{R_c K S}{(K+B_c)\, S_0} - 1\right) B_c \, .$$

Since $S \leq S_0$ and $\frac{K}{(K+B_c)} \leq 1$, we have

$$\frac{dL}{dt} \leq B_c(R_c - 1).$$

Clearly, $\frac{dL}{dt} \leq 0$ if $R_c \leq 1$. If $B_c = 0$, $\frac{dL}{dt} = 0$. By virtue of LaSalle's Invariance Principle, the disease-free equilibrium, E_0, is globally asymptotically stable (GAS) whenever $R_c < 1$.

3.6 Endemic Equilibrium State

The Endemic equilibrium state E^* is a state where the disease is present in the population. At $\frac{dP}{dt} = \frac{dS}{dt} = \frac{dI}{dt} = \frac{dI_c}{dt} = \frac{dR}{dt} = \frac{dB_c}{dt} = 0$, we obtain after solving simultaneously that

$$I^* = \frac{\mathrm{k}_4 k_5(\mathrm{R_c}-1)}{B}, \quad I_c{}^* = \frac{\sigma k_5(\mathrm{R_c}-1)}{\mathrm{B}}, \quad R^* = \frac{\left(\tau_1 \mathrm{k}_4 + \sigma(\tau_2 + \Psi\theta)\right)(\mathrm{R_c}-1)}{\mathrm{B}},$$

$$B_c{}^* = \frac{[\pi_2(1-p)\mathrm{k}_4 + \sigma\pi_1(1-p)]k_5(\mathrm{R_c}-1)}{\mathrm{B}\mu_B},$$

$$S^* = \frac{\Lambda(\mathrm{k}_1 - \alpha\mu)B + \mathrm{k}_1[\sigma(\tau_2 + \Psi\theta)\phi + \phi\mathrm{k}_4\tau_1 - \mathrm{k}_3\mathrm{k}_4\mathrm{k}_5](\mathrm{R_c}-1)}{B(\mathrm{k}_1\mathrm{k}_2 - \eta\boldsymbol{\gamma})},$$

$$P^* = \frac{\alpha\Lambda\left(\mathrm{B}(\mathrm{k}_1\mathrm{k}_2 - \eta\boldsymbol{\gamma})\right) + \eta[\Lambda(\mathrm{k}_1 - \alpha\mu)B + \mathrm{k}_1[\sigma(\tau_2 + \Psi\theta)\phi + \phi\mathrm{k}_4\tau_1 - \mathrm{k}_3\mathrm{k}_4\mathrm{k}_5](\mathrm{R_c}-1)]}{\mathrm{k}_1\mathrm{B}(\mathrm{k}_1\mathrm{k}_2 - \eta\boldsymbol{\gamma})}.$$

Then, $P^*, S^*, I^*, I_c{}^*, R^*, B_c{}^*$ are all positive if and only if $\mathrm{R_c} > 1$, which established that the endemic equilibrium state, $E^* = (P^*, S^*, I^*, I_c{}^*, R^*, B_c{}^*)$ exists for $\mathrm{R_c} > 1$.

3.7 Global Stability of Endemic Equilibrium

The global stability of endemic equilibrium, E^*, is established in the absence of disease induced death.

Theorem 4. The endemic equilibrium, E^*, is globally asymptotically stable if $\mathrm{R_c} > 1$ and $d = 0$.

Proof. We construct the Lyapunov function given by

$$L = \frac{1}{2}[(P - P^*) + (S - S^*) + (I - I^*) + (I_c - {I_c}^*) + (R - R^*)]^2 + \left(B_c - {B_c}^* - {B_c}^* \ln \frac{B_c}{{B_c}^*}\right).$$

Taking the derivative of L along the solutions of equation (1) yields

$$L' = [(P - P^*) + (S - S^*) + (I - I^*) + (\dot{I_c} - {I_c}^*) + (R - R^*)]\frac{d}{dt}(P + S + I + I_c + R) + \left(1 - \frac{{B_c}^*}{B_c}\right)\frac{dB_c}{dt}$$

which upon substitution gives

$$\begin{aligned} L' = [(P - P^*) + (S - S^*) + (\dot{I} - I^*) + (I_c - {I_c}^*) + (R - R^*)](\Lambda \\ -\mu(P + S + I + I_c + R) - dI) \\ + \left(1 - \frac{{B_c}^*}{B_c}\right)(\pi_2(1 - p)\mathrm{I} + \pi_1(1 - p)I_C - \mu_B B_c). \end{aligned} \tag{16}$$

Substituting at endemic equilibrium,

$\Lambda = \mu(P^* + S^* + I^* + {I_c}^* + R^*) + dI^*, \mu_B = \frac{\pi_2(1-p)I^*}{{B_c}^*} + \frac{\pi_1(1-p){I_c}^*}{{B_c}^*}$

in equation (16) and simplify, we have

$L' = -\mu[(P - P^*) + (S - S^*) + (I - I^*) + (I_c - {I_c}^*) + (R - R^*)]^2 + \pi_2(1 - p)I^*\left[1 + \frac{I}{I^*} - \frac{B_c}{{B_c}^*} - \frac{{B_c}^* I}{I^* B_c}\right] + \pi_1(1 - p){I_c}^*\left[1 + \frac{I_c}{{I_c}^*} - \frac{B_c}{{B_c}^*} - \frac{{B_c}^* I}{I^* B_c}\right] - d(I - I^*)[(P - P^*) + (S - S^*) + (I - I^*) + (I_c - {I_c}^*) + (R - R^*)].$

Using the hypothesis that $d = 0$, we have

$$L' = -\mu[(P - P^*) + (S - S^*) + (I - I^*) + (I_c - {I_c}^*) + (R - R^*)]^2 + (\pi_2(1 - p)I^* + \pi_1(1 - p){I_c}^*)\left[2 - \frac{B_c}{{B_c}^*} - \frac{{B_c}^*}{B_c}\right]$$

with $\frac{I_c}{{I_c}^*} \leq 1$, $\frac{I}{I^*} \leq 1$. This implies that $L' \leq 0$ since $2 - \frac{B_c}{{B_c}^*} - \frac{{B_c}^*}{B_c} \leq 0$, by arithmetic and geometric theorem and $L = 0$ if $P = P^*$, $S = S^*$, $I = I^*$, $I_c =$

$I_c{}^*$, $R = R^*$ and $B_c = B_c^*$. This means that the endemic equilibrium, E^*, is globally asymptotically stable (GAS) whenever $R_c > 1$ and $d = 0$ according to LaSalle's Invariance Principle.

3.8 Local Stability of Endemic Equilibrium State

Due to the mathematical complexity of the stability of endemic equilibrium, the Centre manifold theory approach is used to establish the local stability of endemic equilibrium by proving the existence of a forward bifurcation of the system. A forward bifurcation means that the endemic equilibrium is locally asymptotically stable if $R_c > 1$ but near unity.

Theorem 5. The endemic equilibrium is locally asymptotically stable whenever if $R_c > 1$ but near unity.

Proof. Using the approach of Centre manifold theory by Castillo-Chavez and Song [23], let $\beta = \beta^*$ be a bifurcation parameter at $R_c = 1$ so that $\beta = \beta^* = \frac{K\mu_B k_3 k_4}{aS_0[(\sigma\pi_1+\pi_2 k_4)(1-p)]}$. This implies that the Jacobian matrix of equation (12) has negative eigenvalues and a simple zero eigenvalue.

The left and right eigenvectors associated with the Jacobian matrix (12) are $w = (w_1,\ w_2,\ w_3,\ w_4,\ w_5,\ w_6)$ and $v = (v_1,\ v_2,\ v_3,\ v_4,\ v_5,\ v_6)$ respectively where

$$w_1 = \frac{\eta(\mathrm{k_3k_4k_5}-\phi\tau_1\mathrm{k_4}-\sigma\phi(\tau_2\ +\Psi\theta))w_3}{\mathrm{k_4k_5}(\eta\gamma-k_1\mathrm{k_2})}, w_2 = \frac{k_1(\mathrm{k_3k_4k_5}-\phi\tau_1\mathrm{k_4}-\sigma\phi(\tau_2\ +\Psi\theta))w_3}{\mathrm{k_4k_5}(\eta\gamma-k_1\mathrm{k_2})}, w_4 = \frac{\sigma w_3}{\mathrm{k_4}}, w_5 = \frac{(\tau_1\mathrm{k_4}+\sigma(\tau_2\ +\Psi\theta))w_3}{\mathrm{k_4k_5}}, w_6 = \frac{\mathrm{k_3}w_3}{c}, v_1 = v_2 = v_5 = 0, v_4 = \frac{\pi_1(1-p)cv_3}{\mathrm{k_4}\mu_B}, v_6 = \frac{cv_3}{\mu_B}, w_3, v_3 > 0, c = \frac{\mathrm{a}\beta S_0}{K}.$$

Representing the state variables $P = x_1,\ S = x_2,\ I = x_3,\ I_c = x_4,\ R = x_5,$ $B_c = x_6$ so that the system (1) becomes $\frac{dX}{dt} = F = (f_1, f_2, f_3, f_4, f_5, f_6)^T$ with $f_i = f_i(x_1, x_2, x_3, x_4, x_5, x_6)$, we have the non-zero second order partial derivatives at E_0 given as $\frac{\partial^2 f_3(E_0)}{\partial x_2 \partial x_6} = \frac{(1-p)\beta^*}{k}, \frac{\partial^2 f_3(E_0)}{\partial {x_6}^2} = -\frac{2(1-p)\beta^* S_0}{k^2}, \frac{\partial^2 f_6(E_0)}{\partial x_6 \partial \beta^*} = \frac{(1-p)S_0}{k}$.

We compute the coefficients, m and n as follows $m = v_3\left(w_2 w_6 \frac{\partial^2 f_3}{\partial x_2 \partial x_6} + w_6^2 \frac{\partial^2 f_3}{\partial {x_6}^2}\right)$ and $n = w_3 v_3 \frac{\partial^2 f_3}{\partial x_3 \partial \beta^*} > 0$. Upon substituting, we have

$$m = -\frac{\mathrm{k_3}(1-p)\beta^* v_3 {w_3}^2}{ck}\left(\frac{k_1(\mathrm{k_3k_4k_5}-\phi\tau_1\mathrm{k_4}-\sigma\phi(\tau_2\ +\Psi\theta))}{\mathrm{k_4k_5}(k_1\mathrm{k_2}-\eta\gamma)} + \frac{2\mathrm{k_3}S_0}{ck}\right) < 0,$$

$$n = \frac{w_3 k_3 v_3 (1-p) S_0}{ck} > 0 ,$$

which implies that a forward bifurcation exists. Thus, the endemic equilibrium is locally asymptotically stable if $R_c > 1$ but near unity. This is shown graphically in Figure 2.

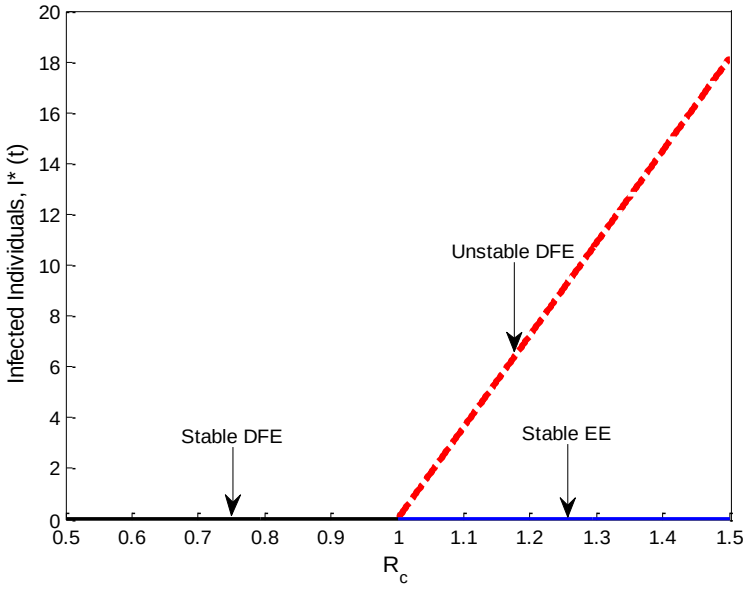

Figure 2. Forward bifurcation for typhoid model.

4. Sensitivity Analysis and Optimal Control Analysis

4.1 Sensitivity Analysis of the Model Parameters

Sensitivity analysis is used to examine the connection between uncertain parameters of a mathematical model and a property of the observable output [24]. It is used to determine the model parameters that have a great impact on reproduction number, R_c for the purpose of targeting such by intervention strategies [25]. In carrying out the sensitivity analysis, we adopted normalized forward index method as used by Rodrigues *et al*. [25] and this is given by $S_Y^{R_c} = \frac{\partial R_c}{\partial Y} \times \frac{Y}{R_c}$, where Y is the parameters reflecting in the control reproduction number, R_c. The sensitivity indices of R_c are given in Table 2 using the parameter values in Table 1.

Table 1. Parameter values of the model with their sources

Parameter	Value	Source	Parameter	Value	Source
Λ	100	[16]	μ	0.0247	[16]
γ	0.33	[26]	d	0.066	[30]
α	0.5	[27]	π_1	0.9	[30]
ϕ	0.000904	[28]	π_2	0.8	[16]
σ	0.03-0.05	[28]	μ_B	0.0345	[31]
τ_1	0.002	[16]	Ψ	0.75	[11]
τ_2	0.0003	[16]	θ	0.2	[16]
p	0.3	Assumed	β	0.9	[16]
η	0.75	[11]	K	500000	[29]

Table 2. Sensitivity index of the parameters values

Parameter	Index sign	Sensitivity index values	Parameter	Index sign	Sensitivity index values
γ	+	0.66520217	d	−	0.53789731
α	−	0.03617419	π_1	+	0.161676646
σ	−	0.08282213	π_2	+	0.838323354
τ_1	−	0.01629918	μ_B	−	0.999999999
τ_2	−	0.00027716	Ψ	−	0.138579983
p	−	1.99999999	θ	−	0.138579983
η	−	0.67891735	β	+	1.00000000

From Table 2, the parameters with positive indices (π_1, π_2, γ) indicate that they have impact on expanding the disease in the population if their values are increasing because the control reproduction number increases as their values increase. Also, the parameters in which their sensitivity indices are negative have influence in reducing the burden of the bacteria in the population as their values increase because the control reproduction number decreases as their values increase, which will lead to reducing the endemicity of the bacteria in the population.

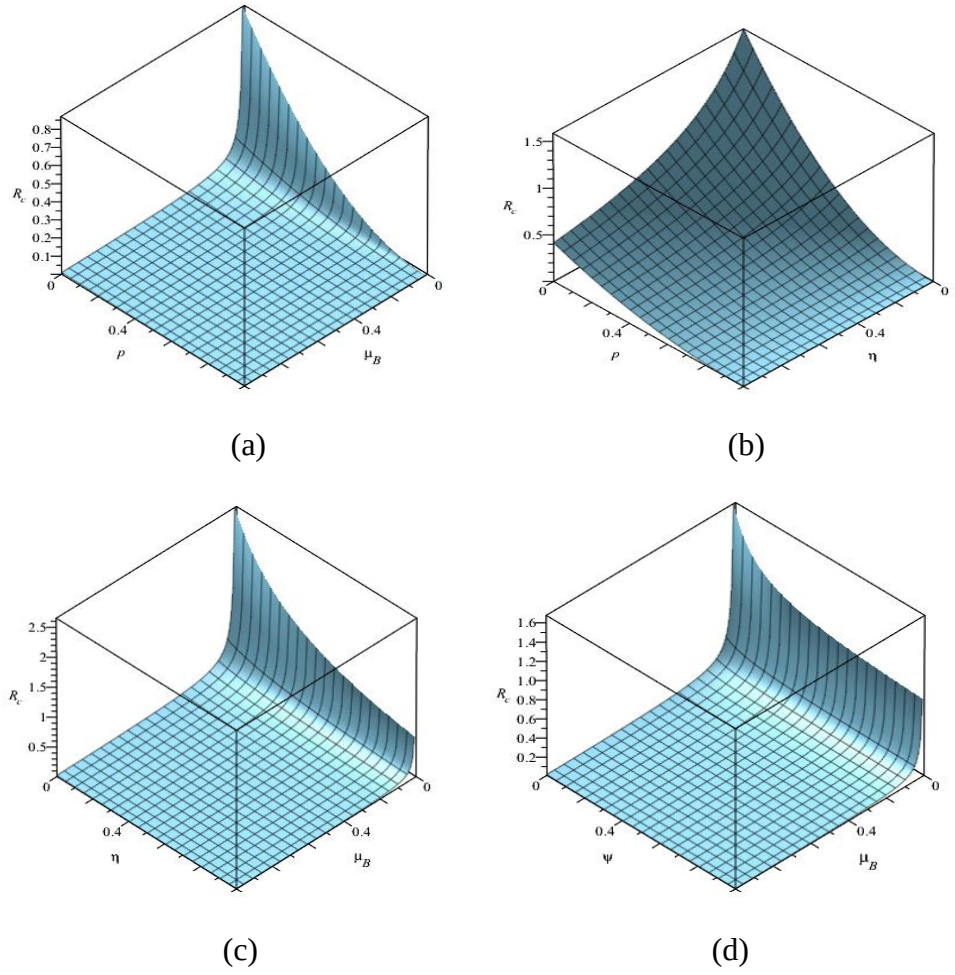

Figure 3. Simulations for the impact of model parameters on control reproduction number.

According to the phase plane (Figure 3a), the value of R_c decreases drastically as ρ and μ_B increases. Also, the value of R_c decreases sharply in Figure 3b as ρ increases, but the change of η has a significantly lower impact on R_c. The phase planes in Figures 3c and 3d illustrate similar results, which shows that R_c is much sensitive to μ_B than to η and ψ, respectively. Therefore, from all cases, μ_B has shown to be a superior force in reducing the burden of Typhoid fever. However, the combination of ρ and μ_B has proven to be the best control strategy as compared to the rest.

4.2 Optimal Control Analysis

The optimal control model is formulated from system (1) when the constant parameters, η, p, Ψ, μ_B are time dependent that is $\eta(t)$, $p(t)$, $\Psi(t)$ and $\mu_B(t)$

where $\eta(t)$ is vaccination control, $p(t)$ is hygiene practice control, $\Psi(t)$ is the screening control and $\mu_B(t)$ is the sterilization control.

The objective function to be minimized is given as

$$J(\eta(t),\ p(t),\ \Psi(t),\ \mu_B(t)) = \int_0^{tf} \left(I + I_C + Bc + \frac{m_1\eta^2(t)}{2} + \frac{m_2p^2(t)}{2} + \frac{m_3\Psi^2(t)}{2} + \frac{m_4\mu_B^2(t)}{2}\right) \quad (18)$$

subject to equation (1) with

$$\eta = \eta(t), p = p(t), \Psi = \Psi(t), \mu_B = \mu_B(t). \quad (19)$$

The coefficients, a, b, c,are the weight constants for the infected, carriers and the bacteria concentration respectively whereas $m_i,\ i = 1, 2, 3, 4$ are cost of implementing these control measures. We assume a quadratic expression for the costs based on literature. The control measures, $\eta(t),\ p(t),\ \Psi(t),\ \mu_B(t)$ are Lebesgue measurable with $0 \le \eta(t) < 0.9, 0 \le p(t) < 1, 0 \le \Psi(t) < 1,\ 0 \le \mu_B(t) < 1$ for $0 \le t \le t_f$.

We aimed to minimize the number of infectives, carriers, bacteria concentration and their costs of implementations, that is, $J(\eta(t)^*, p(t)^*, \Psi(t)^*, \mu_B(t)^*) = min\, J(\eta(t),\ p(t),\ \Psi(t),\ \mu_B(t))$. The optimal control pair is obtained using Pontryagin maximum principle [32]. This principle converts equations (18) and (1) with (19) into a problem of minimizing pointwise a Hamiltonian H with respect to $\eta(t),\ p(t),\ \Psi(t),\ \mu_B(t)$ such that;

$$H(P, S, I, I_C, R, B_C) = \frac{dJ}{dt} + \lambda_1\frac{dP}{dt} + \lambda_2\frac{dS}{dt} + \lambda_3\frac{dI}{dt} + \lambda_4\frac{dI_c}{dt} + \lambda_5\frac{dR}{dt} + \lambda_6\frac{dB_C}{dt}.$$

Thus,

$$H(P, S, I, I_C, R, B_C) = \left(aI + bI_C + \frac{m_1\eta(t)^2}{2} + \frac{m_2p(t)^2}{2} + \frac{m_3\Psi(t)^2}{2} + \frac{m_4\mu_B(t)^2}{2}\right) + \lambda_1\frac{dP}{dt} + \lambda_2\frac{ds}{dt} + \lambda_3\frac{dI}{dt} + \lambda_4\frac{dI_C}{dt} + \lambda_5\frac{dR}{dt} + \lambda_6\frac{dB_C}{dt}$$

,

where $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ andλ_6 are the adjoint variable functions.
So,

$$H = \left(aI + bI_c + cB_c + \frac{m_1\eta(t)^2}{2} + \frac{m_2p(t)^2}{2} + \frac{m_3\Psi(t)^2}{2} + \frac{m_4\mu_B(t)^2}{2}\right) + \lambda_1(\alpha\Lambda + \eta(t)S - (\gamma + \mu)P) + \lambda_2\left((1-\alpha)\Lambda + \gamma P + \phi R - \left(\eta(t) + \mu + \left(1 - p(t)\right)\frac{\beta B_c}{(K+B_c)}\right)S\right) + \lambda_3\left(\left(1 - p(t)\right)\frac{\beta B_c}{(K+B_c)}S - (\sigma + \tau_1 + \mu + d)I\right) +$$

$$\lambda_4(\sigma I - (\tau_2 + \Psi(\mathrm{t})\theta + \mu)I_c) + \lambda_5(\tau_1 \mathrm{I} + (\tau_2 + \Psi(\mathrm{t})\theta)I_c - (\mu + \phi)\mathrm{R}) + \lambda_6\big(\pi_2\big(1-p(\mathrm{t})\big)\mathrm{I} + \pi_1\big(1-p(\mathrm{t})\big)I_c - \mu_B(\mathrm{t})B_c\big). \quad (20)$$

Theorem 5. Given an optimal control $\eta(\mathrm{t})^*$, $p(\mathrm{t})^*, \Psi(\mathrm{t})^*, \mu_B(\mathrm{t})^*$ and corresponding state variables $P, S, I, I_C, R, and\ B_C$ that minimize the objective function $J\big(\eta(\mathrm{t}),\ p(\mathrm{t}),\ \Psi(\mathrm{t}),\ \mu_B(\mathrm{t})\big)$ over U, there exist adjoint functions $\lambda_1, \ldots \lambda_6$ satisfying;

$$\left.\begin{aligned}
\frac{d\lambda_1}{dt} &= (\lambda_1 - \lambda_2)\gamma + \mu\lambda_2, \\
\frac{d\lambda_2}{dt} &= (\lambda_2 - \lambda_1)\eta(\mathrm{t}) + \mu\lambda_2 + (\lambda_2 - \lambda_3)\big(1 - \mathrm{p}(t)\big)\tfrac{\beta B_c}{(K+B_c)}, \\
\frac{d\lambda_3}{dt} &= -a + (\lambda_3 - \lambda_4)\sigma + (\lambda_3 - \lambda_5)\tau_1 + \lambda_3(\mu + d) - \pi_2\big(1-p(\mathrm{t})\big)\lambda_6, \\
\frac{d\lambda_4}{dt} &= -b + (\lambda_4 - \lambda_5)(\tau_2 + \Psi(\mathrm{t})\theta) + \lambda_4\mu - \pi_1\big(1-p(\mathrm{t})\big)\lambda_6, \\
\frac{d\lambda_5}{dt} &= (\lambda_5 - \lambda_4)\phi + \lambda_5\mu, \\
\frac{d\lambda_6}{dt} &= -c + (\lambda_2 - \lambda_3)\big(1 - \mathrm{p}(\mathrm{t})\big)\tfrac{\beta}{(K+B_c)}\Big(1 - \tfrac{B_c}{(K+B_c)}\Big) + \lambda_6\mu_B(\mathrm{t}).
\end{aligned}\right\} \quad (21)$$

with the transversality condition, $\lambda_i(t_f) = 0, \text{for } i = 1(1)6$ and the controls $\eta^*(\mathrm{t}), p^*(\mathrm{t}), \Psi^*(\mathrm{t}) \text{and } \mu_B^*(\mathrm{t})$ satisfying the optimality condition;

$$\left.\begin{aligned}
\eta^* &= max\Big\{0, min\ \Big(1,\ \tfrac{(\lambda_2-\lambda_1)S}{m_1}\Big)\Big\}, \\
\mathrm{p}^* &= \Big\{0, min\ \Big(1, \tfrac{(\lambda_3-\lambda_2)\beta B_c S + \lambda_6\pi_2 I(K+B_c) + \lambda_6\pi_1 I_c(K+B_c)}{m_2(K+B_c)}\Big)\Big\}, \\
\Psi^* &= max\Big\{0, min\ \Big(1, \tfrac{(\lambda_4-\lambda_5)\theta I_c}{m_3}\Big)\Big\}, \\
{\mu_B}^* &= max\Big\{0, min\ \Big(1,\ \tfrac{\lambda_6 B_c}{m_4}\Big)\Big\}.
\end{aligned}\right\} \quad (22)$$

Proof. Using Pontryagin maximum principle, we obtained the adjoint equation and tranversality conditions by differentiating the Hamiltonian function with respect to state variables P, S, I, I_C, R and B_C respectively which is evaluated at the optimal control functions $\eta(\mathrm{t}),\ p(\mathrm{t}),\ \Psi(\mathrm{t}),\ \mu_B(\mathrm{t})$. So, the adjoint system (21) is obtained using the following derivatives

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial P}, \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial S}, \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I}, \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial I_C}, \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial R}, \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial B_c}$$

while the interior of the control set of equation (22) is obtained by solving for $\eta(\mathrm{t}),\ p(\mathrm{t}),\ \Psi(\mathrm{t}),\ \mu_B(\mathrm{t})$ in the respective equations

$$\frac{\partial H}{\partial \eta(t)} = 0,\ \frac{\partial H}{\partial p(t)} = 0, \frac{\partial H}{\partial \Psi(t)} = 0\ , \frac{\partial H}{\partial \mu_B(t)} = 0.$$

This completes the proof.

The optimality system involves equation (1) with (19), equations (21) and (22).

5. Numerical Simulations and Discussion

The numerical simulations of the optimality system involving equations (1) with (19), (21) and (22) are implemented using Runge-Kutta method with the aid of MATLAB R2007b. The simulations are carried out to examine the impact of the control measures on Typhoid fever. The parameter values used for the simulations are in Table 2 while the initial c onditions are from Mushanyu *et al*. (2018) as follows; $S(0) = 10000, I(0) = 10, I_c(0) = 10, R(0) = 0, B_c(0) = 100000.$ $P(0) = 100$ is assumed. The weight constants for simulation are given as $m_1 = 9 \times 10^{-1}, m_2 = 5 \times 10^5, m_3 = 7 \times 10^2$ and $m_4 = 4 \times 10^6$.

(a) **Optimal and constant control.** The importance of time-dependent control measures is considered in Figure 3. With optimal control, a typhoid-free population is attained within 200 days compared with constant control which shows the endemicity of the typhoid in the population. This is achieved when u_1 is at the upper bound for 150 days and u_2, u_3 and u_4 are below a bound of 0.3 for 175 days before they decline to their final time. This implies that control measures should be implemented in time to achieve a typhoid free population.

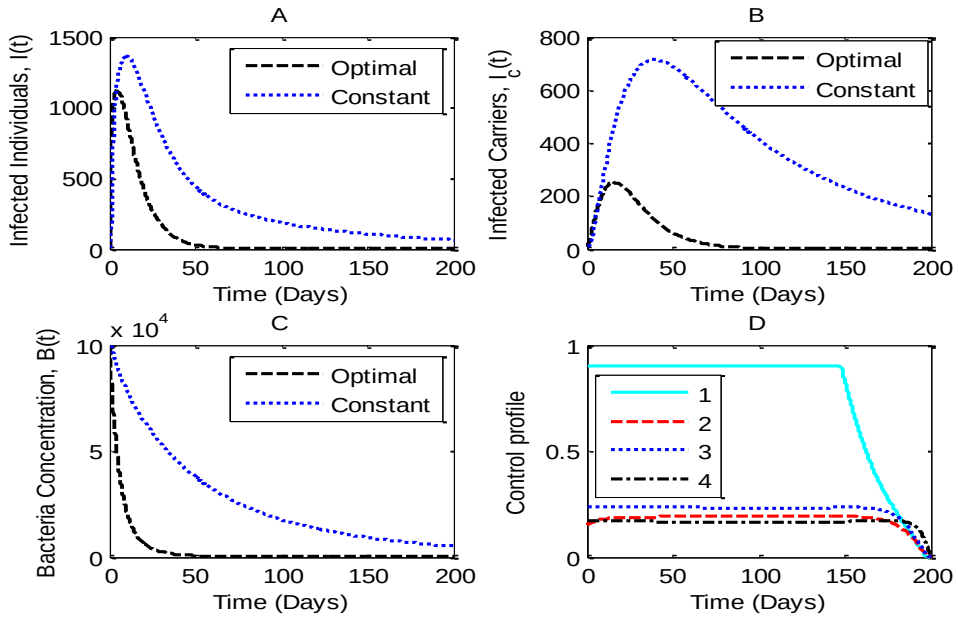

Figure 4. Solutions of Typhoid model for the infected state variables with and without control measures with control profile.

(b) **Vaccination and hygiene practices.** We minimize the objective function for vaccination and hygiene practices ($u_1, u_2 \neq 0, u_3 = u_4 = 0$) to assess their effect on the disease. The number of infected individuals and bacteria concentration are reduced when compared to without control (See Figure 5). This is obtained when u_1 is at its upper bound for all the time 200 days and u_2 attains a bound of 0.9 and decline after 5 days (Figure 5D). However, typhoid disease still remains in the population.

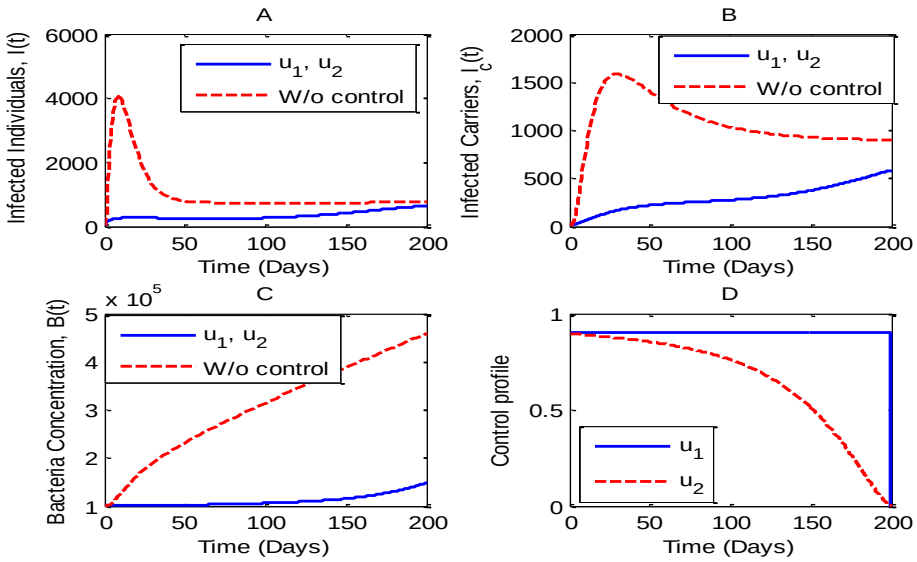

Figure 5. Solutions of Typhoid model for the infected state variables without and with vaccination (u_1) and hygiene practices (u_2) control measures only. W/o means without.

(c) **Vaccination and screening.** We minimize the objective function for vaccination and screening ($u_1, u_3 \neq 0, u_2 = u_4 = 0$). They reduced the number of infected persons and bacteria concentration but not as in case (b) (see Figures 5 and 6) as the number of carriers reduces in Figure 6B than Figure 5B. This may be as a result of screening in the combined control measures. This is achieved when the control, u_1, is maintain at the upper bound for all time (200 days) while u_3 decline after attaining upper bound for 110 days (Figure 6D).

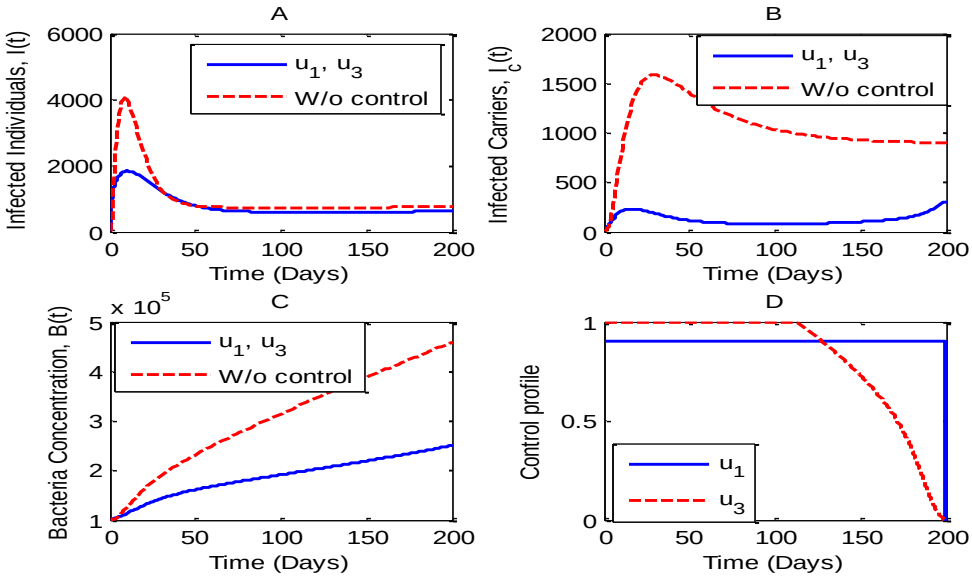

Figure 6. Solutions of Typhoid model for the infected state variables without and with vaccination (u_1) and screening (u_3) control measures only. W/o means without.

(d) **Vaccination and sterilization.** We minimize the objective function for vaccination and sterilization $(u_1, u_4 \neq 0, u_2 = u_3 = 0)$. The simultaneous implementation of u_1 and u_4 reduced the number of infected persons and bacteria concentration to zero after 70 days and 30 days respectively while the number of carriers in the population is almost zero as at 200 days. The control, u_1, maintains an upper bound for 200 days while u_4 attains a bound of 0.2 for 190 days before decline to its final time.

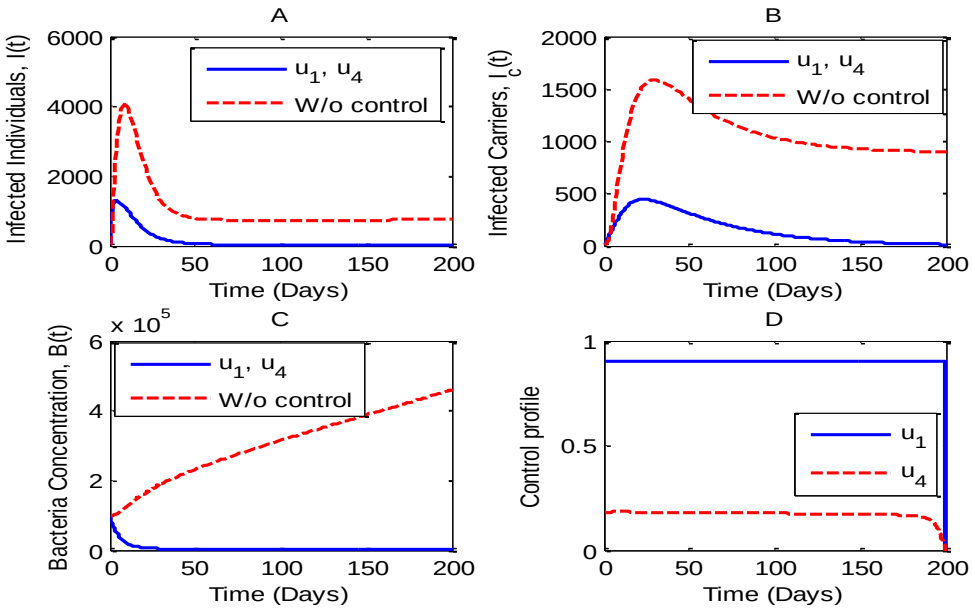

Figure 7. Solutions of Typhoid model for the infected state variables without and with vaccination (u_1) and sterilization (u_4) control measures only. Here, W/o means without.

(e) **Hygiene practices and screening.** We minimize the objective function for hygiene practices and screening $(u_2, u_3 \neq 0, u_1 = u_4 = 0)$. The observed effect is similar to case (c) except that u_3 attains an upper bound and declines after 70 days while u_2 of a bound of 0.55 and declines immediately to final time. The disease still remains endemic in the population.

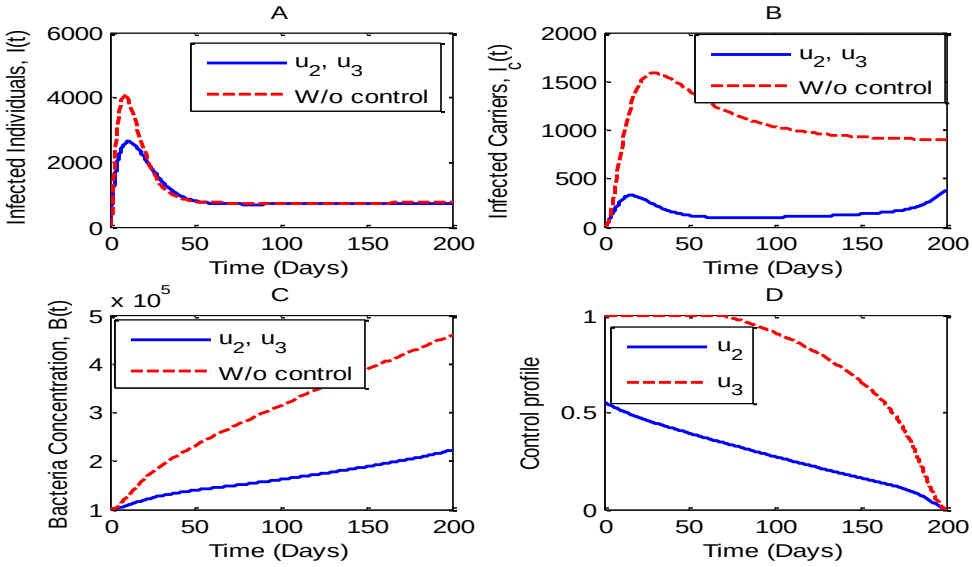

Figure 8. Solutions of Typhoid model for the infected state variables without and with hygiene practices (u_2) and screening (u_3) control measures only. Here, W/o means without.

(f) **Hygiene practices and sterilization.** We minimize the objective function for hygiene practices and sterilization as control measures $(u_2, u_4 \neq 0, u_1 = u_3 = 0)$. The combined implementation of u_2 and u_4 reduces the number of infected persons and bacteria concentration to zero after 110 days and 50 days respectively while there is still some infected carriers in the population after 200 days. The hygiene practice u_2, initially increases from 0.18 to 0.28 bound within 8 days and declines after 120 days while u_4 attains a bound of 0.2 for 195 days before declining to its final time.

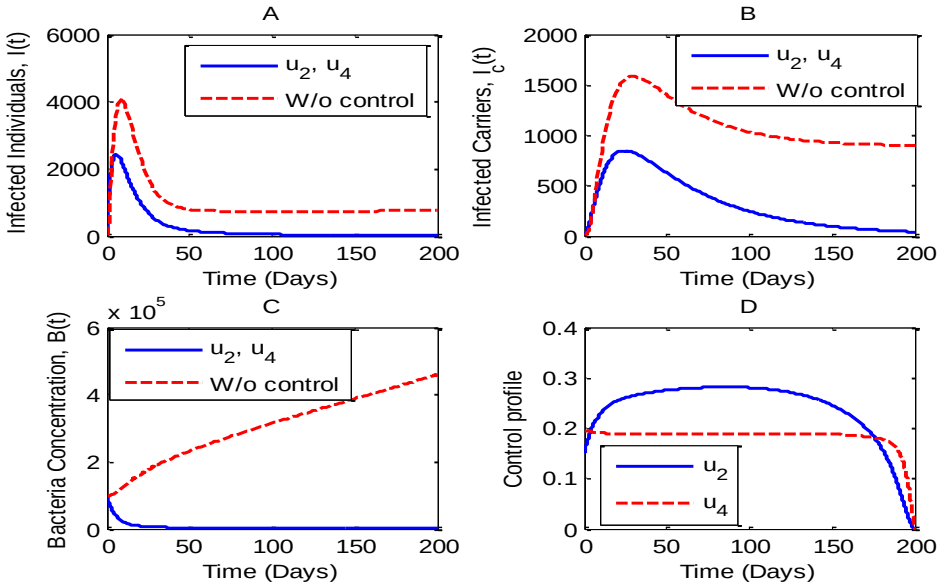

Figure 9. Solutions of Typhoid model for the infected state variables without and with hygiene practices (u_2) and sterilization (u_4) control measures only. Here, W/o means without.

(g) **Screening and sterilization.** We minimize the objective function for screening and sterilization as control measures $(u_3, u_4 \neq 0, u_1 = u_2 = 0)$. The simultaneous implementation of u_3 and u_4 behaves similar as cases (e) and (f). Here, the number of infected persons, carriers and bacteria concentration reduce to zero after 75 days, 100 days and 45 days respectively. This is achieved when u_3 and u_4 are at bound 0.28 for 170 days and 0.19 for 190 days respectively before declining to their final time.

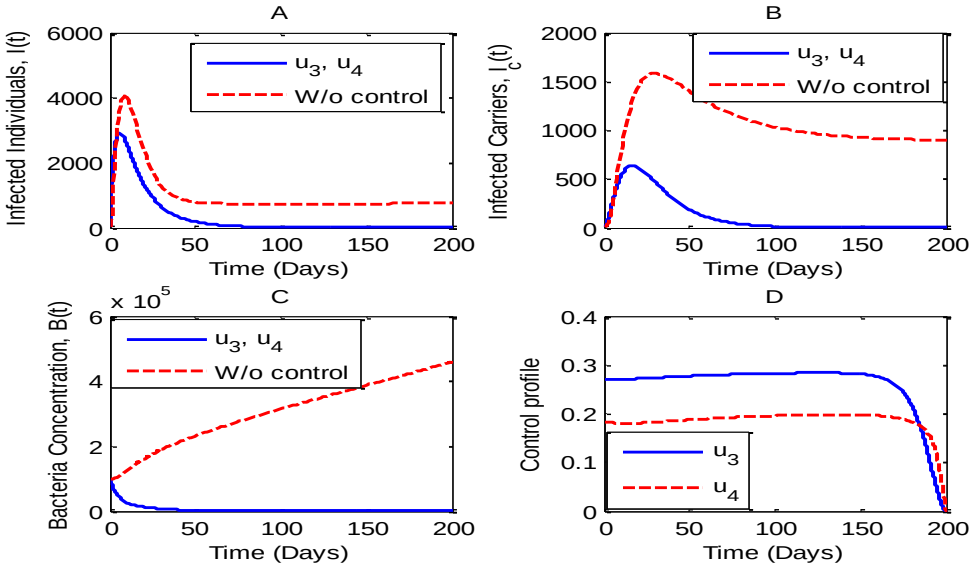

Figure 10. Solutions of Typhoid model for the infected state variables without and with screening (u_3) and sterilization (u_4) control measures only. Here, W/o means without.

(h) **Three combine control measures** We minimize the objective function for three control measures that is $u_1, u_2, u_3, \neq 0, u_4 = 0$ (123), $u_1, u_2, u_4, \neq 0, u_3 = 0$ (124), $u_1, u_3, u_4, \neq 0, u_2 = 0$ (134) and $u_2, u_3, u_4, \neq 0, u_1 = 0$ (234). We notice from Figure (10) that bacteria clearance reduces the number of infected populations $(I(t), I_c(t))$ and bacteria concentration. However, the combine implementation of vaccination, screening and sterilization gives a better result compared to $u_1, u_2, u_4,$ and $u_1, u_3, u_4,$ as it achieves a typhoid-free population in shortest period of time than others.

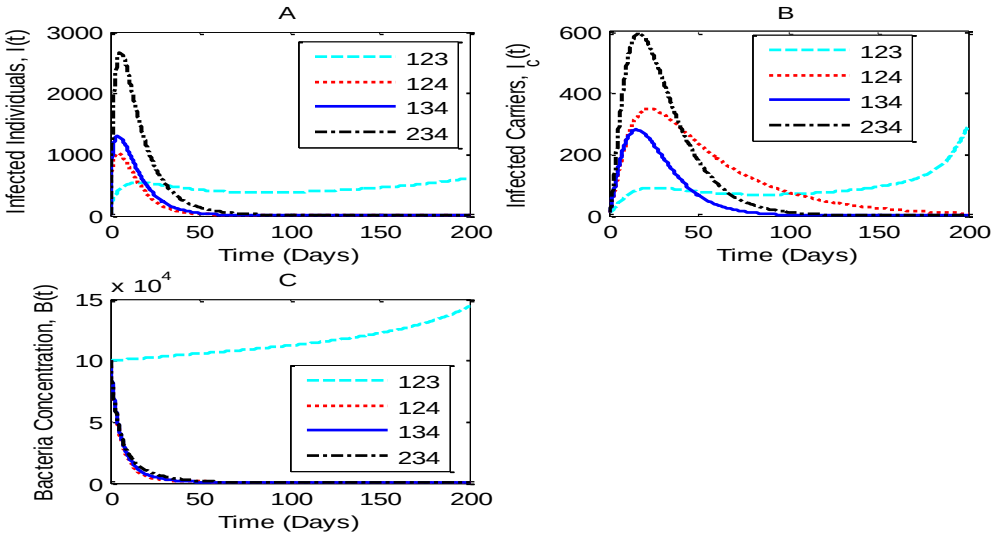

Figure 11. Solutions of Typhoid model for the infected state variables with optimal control. Here, 123 means u_1, u_2, u_3 combine, 124 means u_1, u_2, u_4 combine, 134 means u_1, u_3, u_4 combine, 234 means u_2, u_3, u_4 combine.

7. Conclusion

In this study, the mathematical model of Typhoid fever dynamics with protected human population and bacteria concentration is examined. The control measures such as vaccination, hygiene practice and screening are taken into consideration. The disease-free and endemic equilibrium states are both locally and globally stable whenever $R_c < 1$ and $R_c > 1$ respectively. The local stability of endemic equilibrium state is established using Centre manifold theorem in order to show existence of forward bifurcation while the global stability is done when disease-related death rate is neglected. The sensitivity analysis of the control reproduction number is carried out and the result indicates that the typhoid fever disease will be controlled in the population if susceptible people are vaccinated with high practice of personal hygiene as well as screening of the carriers are screened and also the bacteria in the environment is disinfect or sterilization.

The optimal control analysis is carried out for time-dependent control functions to form non-autonomous system. The Pontryagin maximum principle is used to establish the optimality conditions for the system. This is solved numerically to establish that optimal control implementation achieved infection-free population on time compare to constant control. Considering when there is limited resources to implement all the controls together, screening and bacteria sterilization should be adopted for two combined controls, while vaccination,

screening and bacteria sterilization should be implemented together for three combine controls. However, the combined implementation of all controls is more effective in eradicating the disease from the environment. It is therefore recommended that these preventive measures (vaccination, hygiene practice, screening and sterilization) should be adopted by the policy makers to eliminate the typhoid bacteria from the population.

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