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Typhoid fever dynamical model with cost-effective optimal control

Kazeem A. Tijani*, Chinwendu E. Madubueze, Reuben I. Gweryina

Department of Mathematics, Joseph Sarwuan Tarka University, Makurdi, Benue state, Nigeria

Abstract

Typhoid fever is a highly communicable and infectious disease that can be fatal and causes severe complications if unattended to timely. The infection, at times, can be more complex, challenging, and impossible to treat as antibiotics become less effective. Hence, the effect of limited clinical efficacy of the antibiotics with corresponding relapse response to treatment on infected humans is considered in this paper by formulating a deterministic model for direct and indirect transmission mode of Typhoid infection. The basic reproduction number is analytically derived and used to implement the global sensitivity analysis. Following the sensitivity analysis result, the optimal control analysis is carried out and simulated numerically with four controls: sanitation and hygiene practice and awareness campaign control, sterilisation and disinfection control, the potency of antibiotics control and screening control. Finally, the cost-effectiveness analysis for infected and susceptible humans with four cases that compared fifteen strategies is analysed. The results indicate that the sanitation and hygiene practice and awareness campaign is good to implement for single control implementation, while for double control implementation, Strategy 6, which is the combination of Strategy 1 and the potency of antibiotics administered to typhoid patients, is the best to consider. Combining Strategy 6 and screening control is the most cost-effective for triple controls. Furthermore, the overall computation of cost-effectiveness among all the most cost-effective with all the controls combined suggests that sanitation and hygiene practice and awareness campaign is the most cost-effective strategy to implement for eradicating typhoid infection in the population and for preventing susceptible populations from contracting the bacteria.

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1. Introduction

Typhoid fever is a highly communicable bacterial infection that can be fatal and cause severe complications without prompt treatment. It is caused by salmonella typhi [1]. The mode of transmission is through faecal-oral means [2], which can be environment to humans indirectly through contaminated food or water [3]. According to Ref. [4], typhoid transmission can also be direct, that is, person-to-person transmission; this could be very rare. In Ref. [3], the disease is peculiar in places with poor sanitation and areas lacking potable water. Yearly, it is estimated that about 11-20 million people contract typhoid fever, out of which between 128,000 and 161,000 people die from it worldwide.

The disease is much more common in Africa and South-East Asia than in other regions of the world, making the dis-

*Corresponding author: Tel.: +234-813-120-2994;
Email address: kazeemtijani1987@yahoo.com (Kazeem A. Tijani)

ease endemic in Africa and South-East Asia. For example, in Nigeria, typhoid incidence ranges from 3.9% to 18.6% in a population of about 100,000 [5]. It is noteworthy to state that some individuals who have totally recovered from a disease like salmonella typhi and still harbour and shed the bacteria in the environment for a prolonged period without knowing such individuals are called chronic or active carriers [6].

About one in every 5 cases of Typhoid infection can be fatal if untreated, while fewer than 4 in every 100 cases are fatal with treatment. Symptoms of Typhoid fever usually begin between 6 and 30 days after exposure to the bacteria [7]. The incubation period for typhoid fever is typically between 6 to 30 days, and 1 to 10 days for paratyphoid fever [8]. If Typhoid fever is diagnosed early, antibiotics may be prescribed for the treatment from 7 to 14 days. However, some typhoid fever patients experience relapse response to treatment in which the symptoms of the bacteria return, though this entails further treatment with antibiotics [1]. Meanwhile, after antibiotics treatment, about $2-5\%$ of people who recover from typhoid fever still harbour the bacteria and continue shedding the organism for over a year; these people are called Chronic Carriers [1, 7].

The mathematical modelling of infectious diseases is an essential tool for analysing the dynamic nature of the infectious disease. It helps develop control strategies to forecast appropriate control strategies [9, 10]. An optimal control problem requires regularising and solving problems by choosing the best way in a dynamic process, which depends on controls and is always subject to constraints [11].

Lauer *et al.* [12] stated that cost-effectiveness analysis (CEA) is a kind of economic evaluation and assessment geared towards efficiency to achieve the most for the available resources or, to be precise, the value of money. Several authors have studied the dynamics of typhoid disease incorporating control measures, such as [13–19]. Meanwhile, the optimal control analysis of typhoid infection has been investigated by Refs. [13], [20], where Ref. [13] considered only indirect transmission with vaccination, hygiene practices, screening and sterilisation as controls. In contrast, Ref. [20] considered both direct and indirect transmission modes of Typhoid fever with education campaigns, sanitation, screening, and early treatment as control measures. Employing the cost-effectiveness of the optimal controls, Refs. [10, 13] (with only indirect transmission) and Ref. [15] (in the presence of direct and indirect transmission). In Ref. [9], the authors examined sanitation, hygiene, and treatment as control measures.

Complementing the work of Ref. [16], we constructed a mathematical model of the type S, I_s, I_m, I_c, T, R, and B_c. We include severe and mild compartments and logistic growth in the bacteria compartment. We also introduced the incidence function of limited clinical efficacy of antibiotics with corresponding relapse response to treatment in which some treatment individuals failed to recover [13] but returned to the severe infected compartment instead of the recovery compartment because infections like pneumonia, tuberculosis, blood poisoning, gonorrhoea, and foodborne diseases like typhoid – are sometimes becoming more brutal and more challenging, and even impossible to treat as antibiotics become less effective [21]. We also carry out global sensitivity analysis, optimal control and cost-effectiveness analysis for both infected cases and susceptible individuals in this study.

The rest of the paper is arranged as Section 2 is the model formulation, while Section 3 is the mathematical analysis. Section 4 is the optimal control analysis and cost-effectiveness analysis. Finally, the paper is concluded in Section 5.

2. Formulation of Model

For the formulation of the model, the total human population, $N(t)$, at any time, t, is subdivided into six (6) subpopulations: Susceptible humans, $S(t)$, Mild infected humans, $I_m(t)$, Severe infected humans, $I_s(t)$, Infected carrier humans, $I_c(t)$, Treatment humans, $T(t)$ and Recovered humans, $R(t)$, $N(t) = S(t) + I_s(t) + I_m(t) + I_c(t) + T(t) + R(t)$. $B_c(t)$ represents the bacteria-contaminated environment. Susceptible humans, $S(t)$, are likely to be infected by typhoid fever infection when they have contact with a contaminated environment or infected humans. Severe infected humans, $I_s(t)$, are symptomatic infected individuals. Mild infected humans, $I_m(t)$, represent infected humans with mild symptoms. Infected carrier humans, $I_c(t)$, stands for asymptomatic infected individuals treated or people on the verge of total natural recovery but still carrying Salmonella Typhi [1], [8]. Treatment humans, $T(t)$, are individuals undergoing treatment assuming that they cannot infect susceptible people due to their restriction to a particular place and that they do not shed the bacteria in the environment. Recovery humans, $R(t)$, have recovered from the disease entirely by treatment.

Figure 1 and Table 1 are detailed descriptions of the model parameters and the systematic diagram. Consequently, with the systematic diagram of Figure 1, the descriptions of the model's parameters in Table 1, and the initial conditions, $S(0) > 0, I_s(0) \geq 0, I_m(0) \geq 0, I_c(0) \geq 0, T(0) \geq 0, R(0) \geq 0, B_c(0) \geq 0$, defining the force of function, $\lambda_1 = \frac{\beta_1(I_s+\alpha_1 I_m+\alpha_2 I_c)}{N} + \frac{\beta_2 B_c}{K+B_c}$, the treatment functions, $T(I_s) = \frac{\theta_1 I_s}{1+\omega_1 I_s}$ and $g(T) = \frac{\theta_2 T}{1+\omega_2 T}$ and the model parameters are assumed to be nonnegative, the autonomous system of equations for the typhoid fever model is obtained as follows:

$$\left.\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda_1 S - \mu S + \sigma_4 R,\\
\frac{dI_s}{dt} &= (1-p)\lambda_1 S + \phi I_m + g(T) - T(I_s) - (\mu + d_1) I_s,\\
\frac{dI_m}{dt} &= p\lambda_1 S - (\mu + d_2 + \sigma_1 + \phi + \eta) I_m,\\
\frac{dI_c}{dt} &= \eta I_m + \tau T - (\mu + \sigma_2) I_c,\\
\frac{dT}{dt} &= T(I_s) - (\mu + d_3 + \tau + \sigma_3) T - g(T),\\
\frac{dR}{dt} &= \sigma_1 I_m + \sigma_2 I_c + \sigma_3 T - (\mu + \sigma_4) R,\\
\frac{dB_c}{dt} &= \alpha B_c (1 - \frac{B_c}{K}) + \pi_1 I_s + \pi_2 I_m + \pi_3 I_c - \mu_B B_c.
\end{aligned}\right\} \quad (1)$$

Table 1. Description and parameter values of the model.

Parameter	Description	Parameter Value	Source
Λ	Recruitment rate	100	[10]
β_1	contact rate for Human to human	0.005	Assumed
β_2	contact rate for environment to human	0.085	Assumed
ϕ	Progress rate from I_m to I_s	0.04	Assumed
σ_4	Loss of recovery immunity rate	0.000904	[23]
α	Growth rate for B_c	0.0014	Assumed
σ_1	Progress rate from I_m to R	0.004	Assumed
σ_2	Progress rate from I_c to R	0.0004	[10]
σ_3	Progress rate from T to R	0.002485	[24]
$p \in (0, 1)$	Proportion of $S(t)$ that progresses to I_m	0.3	Assumed
η	Progress rate from I_m to I_c	0.03	Assumed
μ	Natural death rate for humans	0.016305	Calculated
d_1	Disease-induced death rate for I_s	0.21	[25]
d_2	Disease-induced death rate for I_m	0.004	Assumed
d_3	Disease-induced death rate for T	0.015	[26]
pi_1	Shedding rate for I_s	0.7	Assumed
pi_2	Shedding rate for I_m	0.8	Assumed
pi_3	Shedding rate for I_c	0.9	[16]
μ_B	Bacteria decay	0.0345	[27]
τ	Progress rate from T to I_c	0.055	Assumed
θ_1	Maximum treatment intake over a period of time	0.2827	[24]
θ_2	Limited clinical efficacy of antibiotics	0.5	Assumed
K	Carrying capacity	500000	[22]
ω_1	The degree of the effect of demand for treatment	0.62	[16]
ω_2	Relapse response to treatment	0.56	Assummed
α_1, α_2	Modification parameters for $I_m$and I_c	0.6, 1.2	[24]

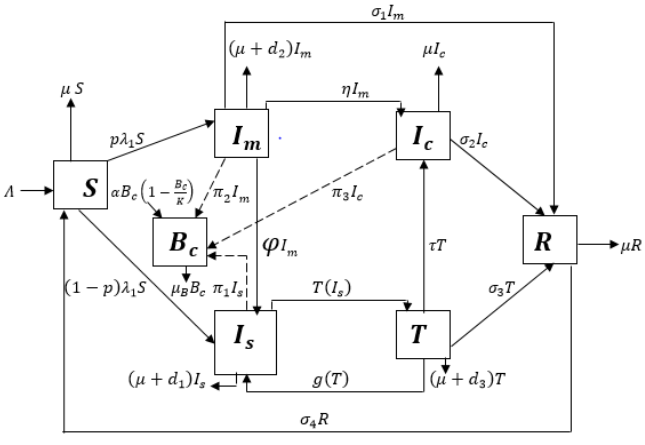

Figure 1. The systematic diagram for typhoid fever. The broken lines indicate the shedding of the bacteria into the environment.

3. Mathematical Analysis of the Model

The basic properties of the system of equations (1) and its reproduction number are established in this section.

3.1. Invariant Region

The mathematical well-posedness of the model is proven in this subsection to show that the system (1) is epidemiologically meaningful. Defining

$$\frac{dN}{dt} = \Lambda - \mu N - d_1 I_s - d_2 I_m - d_3 I_c \leq \Lambda - \mu N \tag{2}$$

and initial conditions, $N(0) = N_0$ and $B_c(0) = B_{c0}$, we state the following theorem.

Theorem 3.1. All feasible solutions of the model are uniformly bounded in a proper subset $D = D_H \times D_{B_c}$, where

$$D_H = \left\{(S, I_s, I_m, I_c, T, R) \in \Re_+^6 : N(t) \leq \frac{\Lambda}{\mu}\right\},$$

and $D_{B_c} = \left\{B_c \in \Re_+ : B_c \leq \frac{(\pi_1 + \pi_2 + \pi_3)\Lambda}{\mu(\mu_B - \alpha)}\right\}$, are subset for the human population and bacteria, respectively provided $\mu_B > \alpha$.

Proof. Applying the approach of integrating factors to equation (2) to get

$$N(t) \leq \frac{\Lambda}{\mu} + \left(N_0 - \frac{\Lambda}{\mu}\right)e^{-\mu t}, \tag{3}$$

$N(t) \leq \frac{\Lambda}{\mu}$ as $t \to \infty$ in equation (3), implying that the feasible solutions of the human population are in the region, $D_H = \left\{(S, E, I_s, I_m, I_c, T, R) \in \Re_+^6 : N(t) \leq \frac{\Lambda}{\mu}\right\}$. With $I_s, I_m, I_c \leq$

$N(t) \leq \frac{\Lambda}{\mu}$, it means that the last equation of the model (1) can be written as

$$\begin{aligned}\frac{dB_c}{dt} &\leq \frac{\Lambda}{\mu}(\pi_1+\pi_2+\pi_3) - (\mu_B-\alpha)B_c - \frac{B_c^2}{K},\\ &\leq (\pi_1+\pi_2+\pi_3)\frac{\Lambda}{\mu} - (\mu_B-\alpha)B_c.\end{aligned} \tag{4}$$

Employing the method of integrating factor to equation (4) yields

$$\begin{aligned}\frac{dB_c}{dt} &\leq \frac{(\pi_1+\pi_2+\pi_3)\Lambda}{\mu(\mu_B-\alpha)}\\ &+\left(B_{c_0} - \frac{(\pi_1+\pi_2+\pi_3)\Lambda}{\mu(\mu_B-\alpha)}\right)e^{-(\mu_B-\alpha)t},\end{aligned} \tag{5}$$

with $\mu_B > \alpha$. As $t \to \infty$ in equation (5), $B_c \leq \frac{(\pi_1+\pi_2+\pi_3)\Lambda}{\mu(\mu_B-\alpha)}$, this exist for $\mu_B > \alpha$. Therefore, the feasible solution for the bacteria concentration enters the region,

$$D_{B_c} = \left\{B_c \in \Re_+ : B_c \leq \frac{(\pi_1+\pi_2+pi_3)\Lambda}{\mu(\mu_B-\alpha)}\right\},$$

provided $\mu_B > \alpha$. Thus, the feasible region for the model system (1) is given by $D = D_H \times D_{B_c}$ provided $\mu_B > \alpha$ and this completes the proof.

In addition, with the non-negative parameters of system (1), it is sufficient to state that the solutions of the system of equations of the model (1) are non-negative. Therefore, it is rich enough to study the dynamics of the typhoid model (1) in this region $D = D_H \times D_{B_c}$ whenever $\mu_B > \alpha$.

3.2. Disease-Free Equilibrium (DFE) and Basic Reproduction Number, R_0

For the computation of the Basic reproduction number, R_0, we determine the disease-free equilibrium of the system (1) that is given as

$$E_0 = \left(S^0, I_s^0, I_m^0, I_c^0, T^0, R^0, B_c^0\right) = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0\right).$$

The basic reproduction number, R_0, determines the transmission tendency of a disease. R_0 is mathematically defined as the matrix's spectral radius, FV^{-1}, where $F = \frac{\partial F_i(E_0)}{\partial x_i}$ and $V = \frac{\partial V_i(E_0)}{\partial x_i}$ are the transmission and transition matrices derived at disease-free equilibrium (DFE), E_0. Here, F_i is the appearance rate of new infections in compartments i, while V_i is the transfer of infections from one compartment i to another (see [29] for detail). Given the DFE, $E_0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0\right)$, we have

$$F = \begin{pmatrix} \beta_1(1-p) & \alpha_1\beta_1(1-p) & \alpha_2\beta_1(1-p) & 0 & \frac{\beta_2(1-p)S_0}{K} \\ \beta_1 p & \alpha_1\beta_1 p & \alpha_2\beta_1 p & 0 & \frac{\beta_2 p S_0}{K} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} \theta_1+k_5 & -\phi & 0 & -\theta_2 & o \\ 0 & k_1 & 0 & 0 & 0 \\ 0 & -\eta & k_2 & -\tau & 0 \\ -\theta_1 & 0 & 0 & \theta_2+k_3 & 0 \\ -\pi_1 & -\pi_2 & -\pi_3 & 0 & \mu_B-\alpha \end{pmatrix}$$

with

$$\left.\begin{aligned}\lambda_1 = \frac{\beta_1(I_s+\alpha_1 I_m+\alpha_2 I_c)}{N} + \frac{\beta_2 B_c}{K+B_c}, a = \frac{\theta_1}{1+\omega_1 I_s},\\ T(I_s) = \frac{\theta_1 I_s}{1+\omega_1 I_s}, g(T) = \frac{\theta_2 T}{1+\omega_2 T} b = \frac{\theta_2}{1+\omega_2 T},\\ k_1 = (\mu+d_2+\sigma_1+\phi+\eta), k_2 = (\mu+\sigma_2),\\ k_3 = (\mu+d_3+\tau+\sigma_3), k_4 = (\mu+\sigma_4), k_5 = (\mu+d_1).\end{aligned}\right\} \tag{6}$$

By the definition of R_0 as the spectral radius of FV^{-1}, we have

$$\begin{aligned}R_0 = &\frac{\beta_1 A}{k_1 k_2(\mu_B-\alpha)(k_3k_5+k_3\theta_1+k_5\theta_2)} +\\ &\frac{\beta_2 \Lambda B}{\mu K k_1 k_2(\mu_B-\alpha)(k_3k_5+k_3\theta_1+k_5\theta_2)},\end{aligned} \tag{7}$$

where

$$\begin{aligned}A &= (\mu_B-\alpha)(k_2k_3+k_2\theta_2+\tau\alpha_2\theta_1)(k_1(1-p)+p\phi)\\ &+(\mu_B-\alpha)(k_3k_5+k_3\theta_1+k_5\theta_2)(p\alpha_1k_2+p\eta\alpha_2),\\ B &= (\tau\pi_3\theta_1+\pi_1k_2\theta_2+\pi_1k_2k_3)(k_1(1-p)+p\phi)\\ &+(k_5\theta_2+k_3\theta_1+k_3k_5)(p\pi_2k_2+p\eta\pi_3),\end{aligned} \tag{8}$$

with $A, B > 0$, for $\mu_B > \alpha$ and $p < 1$.

The first term of equation (7) represents the reproduction number contribution for human-to-human interaction with the transmission rate, β_1. The second term of equation (7) is the reproduction number contribution of the human to contaminated environment interaction with the transmission rate, β_2.

By the approach of Next-generation used for the computation of R_0, we state the stability of the DFE theorem as follows.

Theorem 3.2. If E_0 is the DFE of the model, then E_0 is locally asymptomatically stable if $R_0 < 1$; otherwise, it is unstable if $R_0 > 1$.

Theorem 3.2 means that the typhoid infection can be eliminated in the population with time if $R_0 < 1$. Otherwise, it will remain in the population for $R_0 > 1$.

3.3. Global Sensitivity Analysis

Global sensitivity analysis (GSA) is examined in this subsection to determine the most sensitive parameters of R_0 as multiple points entry. It determines the behaviour and degree of each parameter of R_0. Latin Hypercube Sampling (LHS) sampling-based method with Partial Rank Correlation Coefficient (PRCC) is used to analyse GSA by generating 1000 samples from a uniform distribution of each parameter range (see [30] for details of LHS and PRCC). The PRCCs for the parameters and their corresponding p-values are presented in Table 2.

Table 2. Parameter PRCC Significance (FDR Unadjusted p-Values).

Variable	PRCC	p-value	Keep
β_1	0.90238886	0.000	TRUE
β_2	0.50226243	0.000	TRUE
α	0.06505029	4.060×10^{-2}	TRUE
θ_1	−0.09983146	1.641×10^{-3}	TRUE
θ_2	0.05531768	8.176×10^{-2}	FALSE
σ_3	−0.62992590	0.000	TRUE
π_1	0.02099216	5.093×10^{-1}	FALSE
π_2	0.15505482	8.952×10^{-7}	TRUE
π_3	0.26466933	0.000	TRUE
μ_B	−0.61194800	0.000	TRUE

The signs (+ and -) of PRCC indicate the definite qualitative relationship between the parameters and output R_0. The parameters with positive PRCC imply that increasing them increases the value of R_0, increasing the disease's spread. At the same time, the parameters with PRCC negative values indicate that R_0 decreases whenever their values increase, showing a reduction in the disease transmission dynamics. The most significant parameters are those with $|PRCC| \geq 0.5$. From Table 2, the parameters β_1, β_2, μ_B and σ_3 with $|PRCC| \geq 0.5$ are the most significant; increasing β_1 and β_2 tends to make typhoid infection worst in the population while increasing the parameters μ_B and σ_3 reduces the transmission of typhoid bacteria in the community.

Furthermore, the combined effect of some important parameters is shown in Figure 2 as a 3D plot. Figure 2 shows that increasing the shedding rate (π_3) of the infected carrier individuals will increase the value of R_0. Also, the higher the recovery rate (σ_3) of treatment individuals, the lower the value of R_0. The implication is that the typhoid infection will reduce in the community if the treatment rate is increased and the shedding rate from unaware infected persons is reduced; this will happen when people undergo screening tests during a typhoid outbreak, or someone close is infected with typhoid infection. Therefore, the main strategy to curtail the spread of the bacteria disease is to reduce the number of asymptomatic infected individuals, as it has a more significant tendency to shoot up the basic reproduction number

4. Optimal Control Analysis and Cost-Effectiveness Analysis

4.1. Optimal Control Analysis

With the result of the sensitivity analysis, we formulate an optimal control model version of the system (1) given as follows:

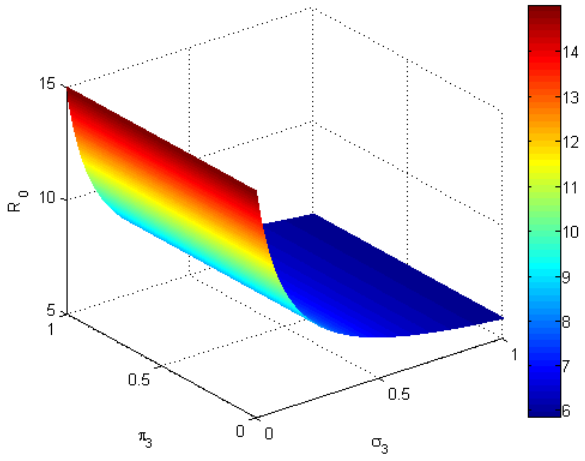

Figure 2. The Effect of the shedding rate from infected carrier individuals, π_3 and recovery rate for treatment individuals, σ_3, on the basic reproduction number, R_0.

$$
\left.
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \lambda_1(S) - \mu S + \sigma_4 R, \\
\frac{dI_s}{dt} &= (1-p)\lambda_1(S) + \phi I_m + \frac{\theta_2(1-u_3(t))T}{1+\omega_2 T} \\
&\quad - \frac{\theta_1 I_s}{1+\omega_1 I_s} - (\mu + d_1) I_s, \\
\frac{dI_m}{dt} &= p\lambda_1 S - (\mu + d_2 + \sigma_1\phi + \eta) I_m, \\
\frac{dI_c}{dt} &= \eta I_m + \tau T - (\mu + \sigma_2) I_c, \\
\frac{dT}{dt} &= \frac{\theta_1 I_s}{1+\omega_1 I_s} - (\mu + d_3 + \tau + \sigma_3 u_3(t)) T \\
&\quad - \frac{\theta_2(1-u_3(t))T}{1+\omega_2 T}, \\
\frac{dR}{dt} &= \sigma_1 I_m + \sigma_2 I_c + \sigma_3 u_3(t) T - (\mu + \sigma_4) R, \\
\frac{dB_c}{dt} &= \alpha B_c\left(1 - \frac{B_c}{K}\right) + \pi_1 I_s + \pi_2 I_m \\
&\quad + \pi_3(1-u_4(t)) I_c - (1+u_2(t))\mu_B B_c,
\end{aligned}
\right\} \tag{9}
$$

with initial conditions of the system (1).
Here, $u_1(t)$ is the sanitation and hygiene practice and awareness campaign control, $u_2(t)$, the sterilisation and disinfection control, $u_3(t)$ as the potency of antibiotics administered to typhoid patients and $u_4(t)$ is the screening control for infect carrier's humans.

The objective function to be minimised is given as

$$
\begin{aligned}
J(u_1(t), u_2(t), u_3(t), u_4(t)) = \int_0^{t_f} & (AI_s + BI_m + CI_c + DB_c \\
& + \frac{1}{2}\sum_{i=1}^{4} m_i u_i^2(t))
\end{aligned} \tag{10}
$$

where the coefficient associated with the infected state variables, A, B, C and D, and the control weight coefficients, m_1,

m_2, m_3, m_4, are assumed positive. The quadratic form of the control variables, $\sum_{i=1}^{4} m_i u_i^2(t)$ in equation (10), is due to the nonlinearity of the cost of controls as used in the literature on optimal control of infectious diseases [10, 31].

The objective functional goal is to minimise the number of infected humans, bacteria concentration in the environment and the cost of implementing them. Thus, the optimal controls, $U^*(t) = u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t)$ is to find a way such that

$$J(U^*(t)(t)) = \min_{\Phi_1} J\left(u_1(t), u_2(t), u_3(t), u_4(t)\right) \tag{11}$$

where

$$\begin{aligned}\Phi_1 = \{&u_i(t), i = 1, 2, 3, 4 \text{ are measurable with}\\ &u_i(t) \in [0, 1] \text{for } 0 \le t \le t_f\}.\end{aligned} \tag{12}$$

The state and the control variables of equations (9) and (10) are non-negative, as established in Subsection (3.1) and the condition in equation (12); this implies that the set Φ_1 is closed, convex and exists. The optimal control exists by applying Corollary 4.1 of Pages 68-69 in [32] as implemented in [33].

We derived the Hamiltonian and optimality system by applying the Pontryagin maximum principle (PMP) [30] to the optimal control problem. PMP transforms Equations (9) and (10) into a problem of minimizing pointwise Hamiltonian, H, that is presented as;

$$\begin{aligned}H\left(S, I_s, I_m, I_c, T, R, B_c\right) = L(I_s, I_m, I_c, B_c, U(t)) &+ \lambda_1 \frac{dS}{dt}\\ + \lambda_2 \frac{dI_s}{dt} + \lambda_3 \frac{dI_m}{dt} &+ \lambda_4 \frac{dI_c}{dt}\\ + \lambda_5 \frac{dT}{dt} + \lambda_6 \frac{dR}{dt} &+ \lambda_7 \frac{dB_c}{dt},\end{aligned} \tag{13}$$

where $U(t) = u_1(t), u_2(t), u_3(t), u_4(t)$, $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7$ are the adjoint variables for the respective state variables. Using a similar approach in Refs. [10], [33], we derive the following optimality system;

Theorem 4.1. With the optimal control $u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t)$ and solutions $S, I_s, I_m, I_c, T, R, B_c$ that minimizes $J(U)$ over Φ_1, there exist non-trivial adjoint functions $\lambda_1, \cdots, \lambda_7$ that satisfies;

$$\begin{aligned}\frac{d\lambda_1}{dt} &= \left(\frac{\beta_1(N - S)(1 - u_1(t))(I_s + \alpha_1 I_m + \alpha_2 I_c)}{N^2}\right.\\ &\left. + \frac{\beta_2(1 - u_2(t))B_c}{(K + B_c)}\right)((\lambda_1 - \lambda_2) + (\lambda_2 - \lambda_3)p)\\ &+ \lambda_1\mu,\\ \frac{d\lambda_2}{dt} &= \left(\frac{\beta_1(N - (I_s + \alpha_1 I_m + \alpha_2 I_c))(1 - u_1(t))S}{N^2}\right)\\ &\times ((\lambda_1 - \lambda_2) + (\lambda_2 - \lambda_3)p) - A + (\lambda_2 - \lambda_5)\\ &\times \left(\frac{\theta_1}{(1 + \omega_1 I_s)^2}\right) + \lambda_2(\mu + d_1) - \lambda_7\pi_1,\\ \frac{d\lambda_3}{dt} &= \left(\frac{\beta_1(\alpha_1 N - (I_s + \alpha_1 I_m + \alpha_2 I_c))(1 - u_1(t))S}{N^2}\right)\\ &\times ((\lambda_1 - \lambda_2) + (\lambda_2 - \lambda_3)p) + (\lambda_3 - \lambda_2)\phi - \lambda_7\pi_2\\ &+ (\lambda_3 - \lambda_6)\sigma_1 + \lambda_3(\mu + d_2) + (\lambda_3 - \lambda_4)\eta - B,\\ \frac{d\lambda_4}{dt} &= \left(\frac{\beta_1(\alpha_2 N - (I_s + \alpha_1 I_m + \alpha_2 I_c))(1 - u_1(t))S}{N^2}\right)\\ &\times ((\lambda_1 - \lambda_2) + (\lambda_2 - \lambda_3)p) + (\lambda_4 - \lambda_6)\sigma_2 + \lambda_4\mu\\ &- \lambda_7\pi_3(1 - u_4(t)) - C,\\ \frac{d\lambda_5}{dt} &= \left(\frac{\beta_1(I_s + \alpha_1 I_m + \alpha_2 I_c)(1 - u_1(t))S}{N^2}\right)((\lambda_1 - \lambda_2)\\ &+ (\lambda_2 - \lambda_3)p) + (\lambda_5 - \lambda_2)\left(\frac{(1 - u_3(t))\theta_2}{(1 + \omega_2 T)^2}\right)\\ &+ (\lambda_5 - \lambda_6)\sigma_3 u_3(t) + (\lambda_5 - \lambda_4)\tau + \lambda_5(\mu + d_3),\\ \frac{d\lambda_6}{dt} &= \left(\frac{\beta_1(I_s + \alpha_1 I_m + \alpha_2 I_c)(1 - u_1(t))S}{N^2}\right)\\ &\times ((\lambda_1 - \lambda_2) + (\lambda_2 - \lambda_3)p) + (\lambda_6 - \lambda_1)\sigma_4 + \lambda_6\mu,\\ \frac{d\lambda_7}{dt} &= ((\lambda_1 - \lambda_2) + (\lambda_2 - \lambda_3)p)\left(\frac{\beta_2(1 - u_2(t))B_c KS}{(K + B_c)^2}\right)\\ &- \lambda_7\alpha\left(1 - \frac{2B_c}{K}\right) + \lambda_7(1 - u_2(t))\mu_B - D.\end{aligned} \tag{14}$$

with the transversality condition $\lambda_i(t_f) = 0, i = 1, 2, 3, 4, 5, 6, 7$ and the controls $u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t)$ that satisfies the optimality condition;

$$\begin{aligned}u_1^* &= max\{0, min\left(1, \Theta_1\right)\},\\ u_2^* &= max\left\{0, min(1, \Theta_2))\right\},\\ u_3^* &= max\left\{0, min(1, \Theta_3))\right\},\\ u_4^* &= max\left\{0, min\left(1, \frac{\lambda_7\pi_3 I_c}{m_4}\right)\right\}.\end{aligned} \tag{15}$$

where,

$$\begin{aligned}\Theta_1 &= \frac{\beta_1(p\lambda_3 + (1 - p)\lambda_2 - \lambda_1)(I_s + \alpha_1 I_m + \alpha_2 I_c)S}{m_1 N},\\ \Theta_2 &= \frac{\lambda_7\mu_B B_c}{m_2} + \frac{\beta_2(p\lambda_3 + (1 - p)\lambda_2 - \lambda_1)B_c S}{m_2(K + B_c)},\\ \Theta_3 &= \frac{(\lambda_5 - \lambda_6)\sigma_3 T}{m_3} + \frac{(\lambda_2 - \lambda_5)\theta_2 T}{m_3(1 + \omega_2 T)}.\end{aligned}$$

Proof. Using PMP, the adjoint system of equation (14) is obtained by differentiating equation (13) with respect to their corresponding state variables, $S, I_s, I_m, I_c, T, R, B_c$, that is obtained by evaluating the optimal control functions $u_1(t), u_2(t), u_3(t), u_4(t)$ and after then apply negative to the differentials. The optimality condition equation (15) is obtained by solving for the controls, $u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t)$ at the respective steady states

$$\frac{\partial H}{\partial u_1(t)} = \frac{\partial H}{\partial u_2(t)} = \frac{\partial H}{\partial u_3(t)} = \frac{\partial H}{\partial u_4(t)} = 0$$

on the interior of the control set. Thus, the optimality system is equations (14) and (15) substituted into equation (9). The proof is complete.

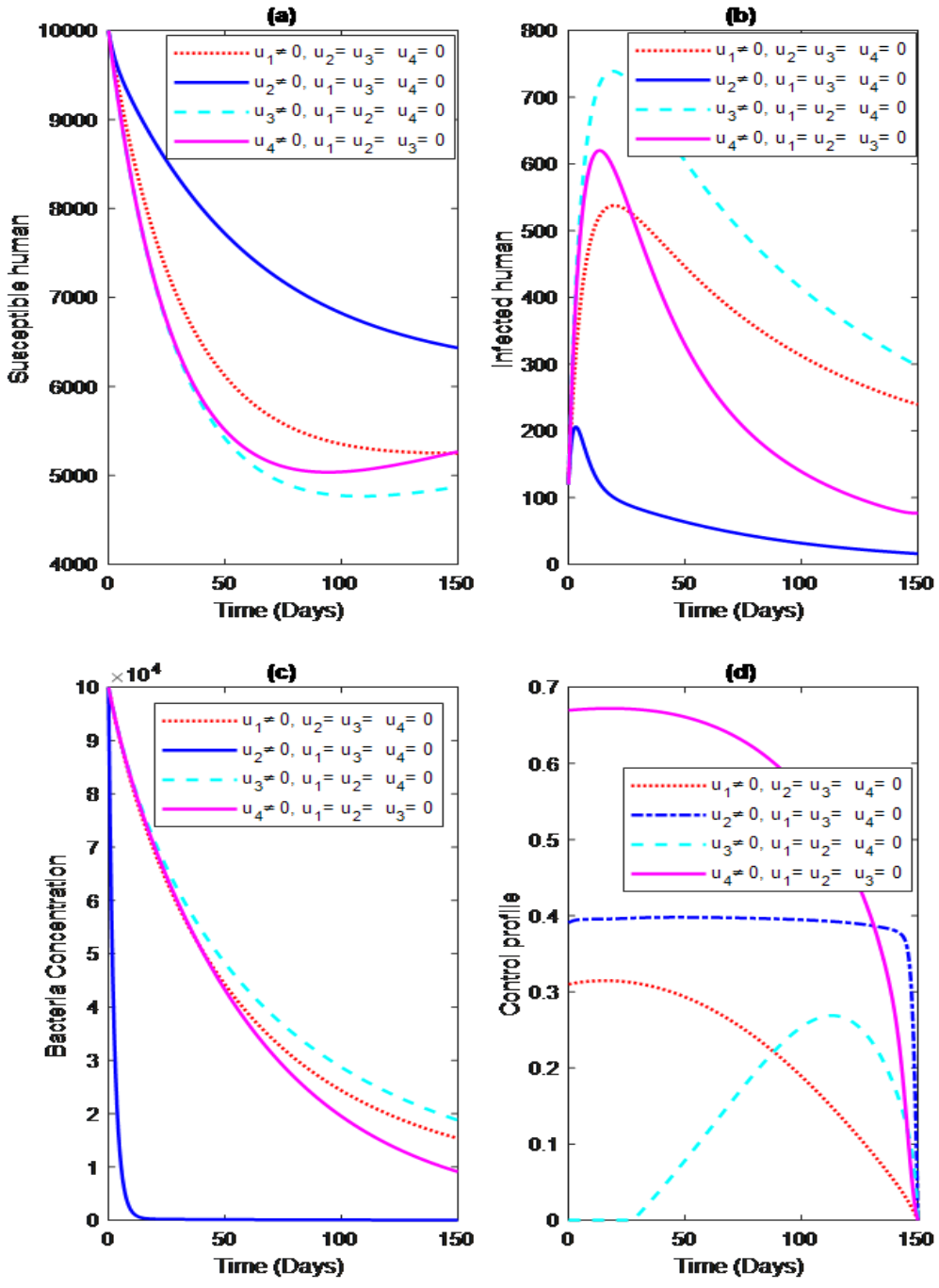

Figure 3. Simulation results for one Control Implementation: (a) Susceptible Humans, (b) Infected Humans, (c) Bacteria Concentration, $B_c(t)$, and (d) Control Profile.

4.2. *The Optimal Control Problem Simulations*

The optimality system is simulated numerically to illustrate the dynamics of the optimal control system with time. The fourth-order Runge-Kutta method, coded in MATLAB R2007b, is used for the numerical simulations (see [28] for the fourth-order Runge-Kutta method and its stability details). Table 1 is the parameter values used for the simulations while the initial conditions and weight coefficient values are as follows; $S(0) = 10000$, $I_s(0) = 100$, $I_m(0) = 10$, $I_c(0) = 10$, $T(0) = 100$, $R(0) = 0$, $B_c(0) = 100000$, $A, B, C, D = 10$, $m_1 = 5,000$, $m_2 = 1,000,000$, $m_3 = 7,000$ and $m_4 = 20,000$. The initial conditions are obtained from Ref. [16], except $I_s(0), I_m(0)$ and $T(0)$, which are assumed. Meanwhile, the weight coefficient values are chosen so the control variables are within the region feasible, $u(t) \in [0, 1]$.

The simulations are partitioned into four (4) possible cases

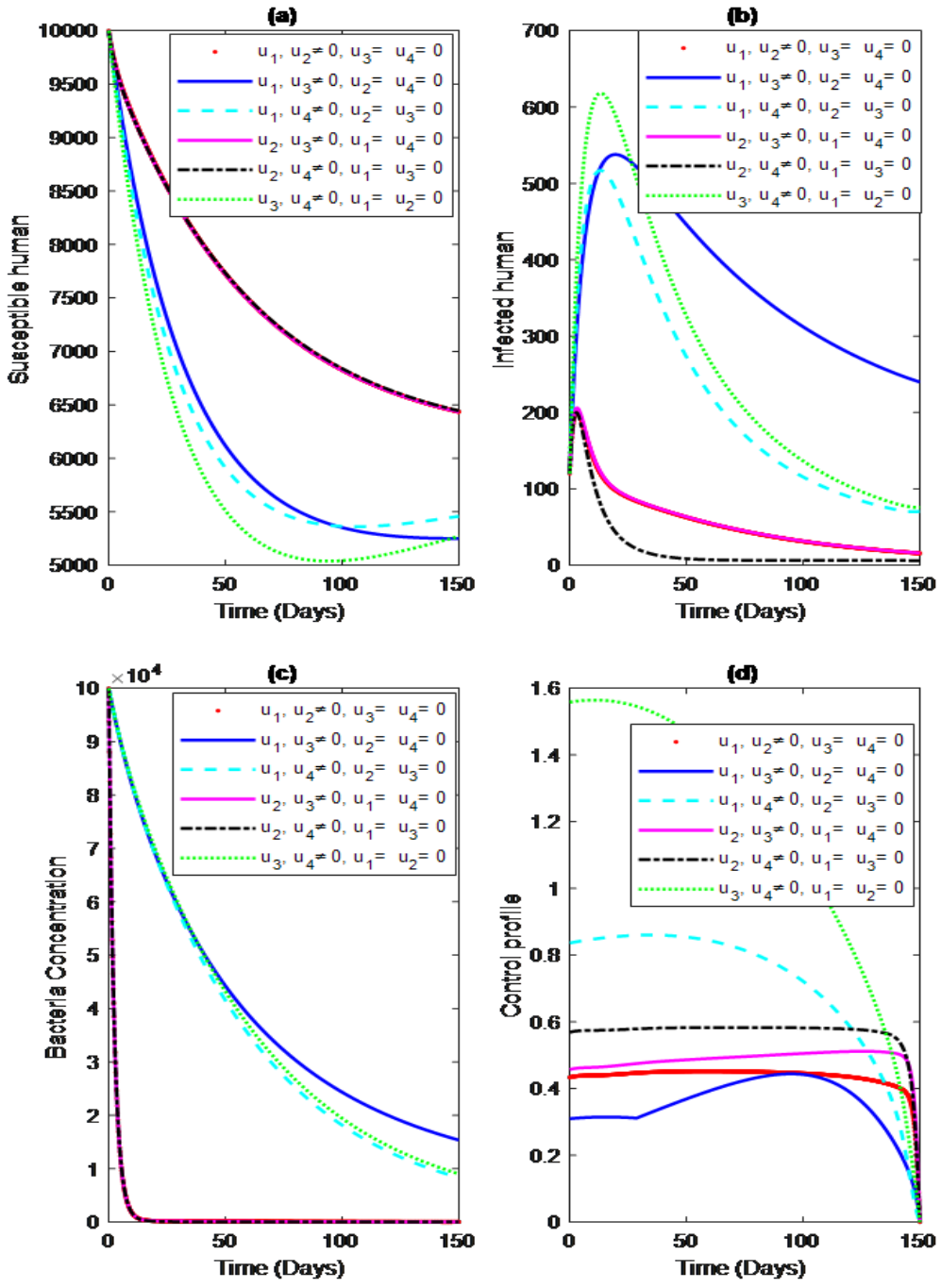

Figure 4. Simulation results for two combined Controls Implementation: (a) Susceptible Humans, (b) Infected Humans, (c) Bacteria Concentration, $B_c(t)$, and (d) Control Profile.

according to control combinations;

Case A (one control implementation)

- Strategy 1 (u_1): sanitation and hygiene practice and awareness campaign ($u_1 \neq 0, u_2, u_3, u_4 = 0$),
- Strategy 2 (u_2): sterilisation and disinfection of the contaminated environment ($u_2 \neq 0, u_1, u_3, u_4 = 0$),
- Strategy 3 (u_3): the potency of antibiotics administered to typhoid patients ($u_3 \neq 0, u_1, u_2, u_4 = 0$),
- Strategy 4 (u_4): screening control ($u_4 \neq 0, u_1, u_2, u_3 = 0$).

Case B (Two controls combine implementation)

- Strategy 5 (u_{12}): sanitation and hygiene practice and awareness campaign + sterilization and disinfection of the contaminated environment ($u_1, u_2 \neq 0, u_3, u_4 = 0$),

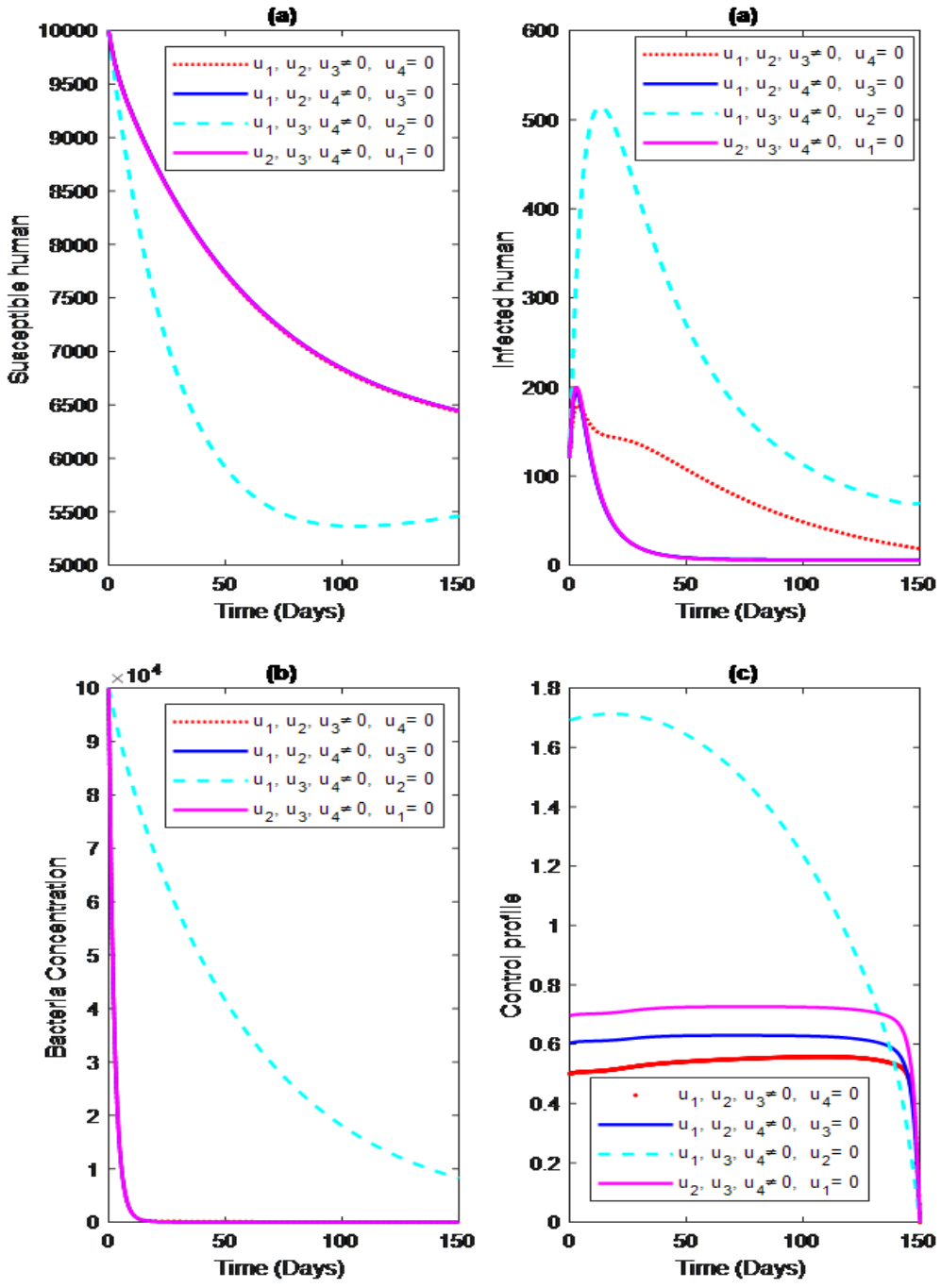

Figure 5. Simulation results for three combined Controls Implementation: (a) Susceptible Humans, (b) Infected Humans, (c) Bacteria Concentration, $B_c(t)$, and (d) Control Profile.

- Strategy 6 (u_{13}): sanitation and hygiene practice and awareness campaign + potency of antibiotics administers to typhoid patients ($u_1, u_3 \neq 0, u_2, u_4 = 0$),
- Strategy 7 (u_{14}): sanitation and hygiene practice and awareness campaign + screening control ($u_1, u_4 \neq 0, u_2, u_3 = 0$),
- Strategy 8 (u_{23}): sterilization and disinfection of the contaminated environment + potency of antibiotics administers to typhoid patients ($u_2, u_3 \neq 0, u_1, u_4 = 0$),
- Strategy 9 (u_{24}): sterilization and disinfection of the contaminated environment + screening control ($u_2, u_4 \neq 0, u_1, u_3 = 0$),
- Strategy 10 (u_{34}): potency of antibiotics administers to typhoid patients + screening control ($u_3, u_4 \neq 0, u_1, u_2 =$

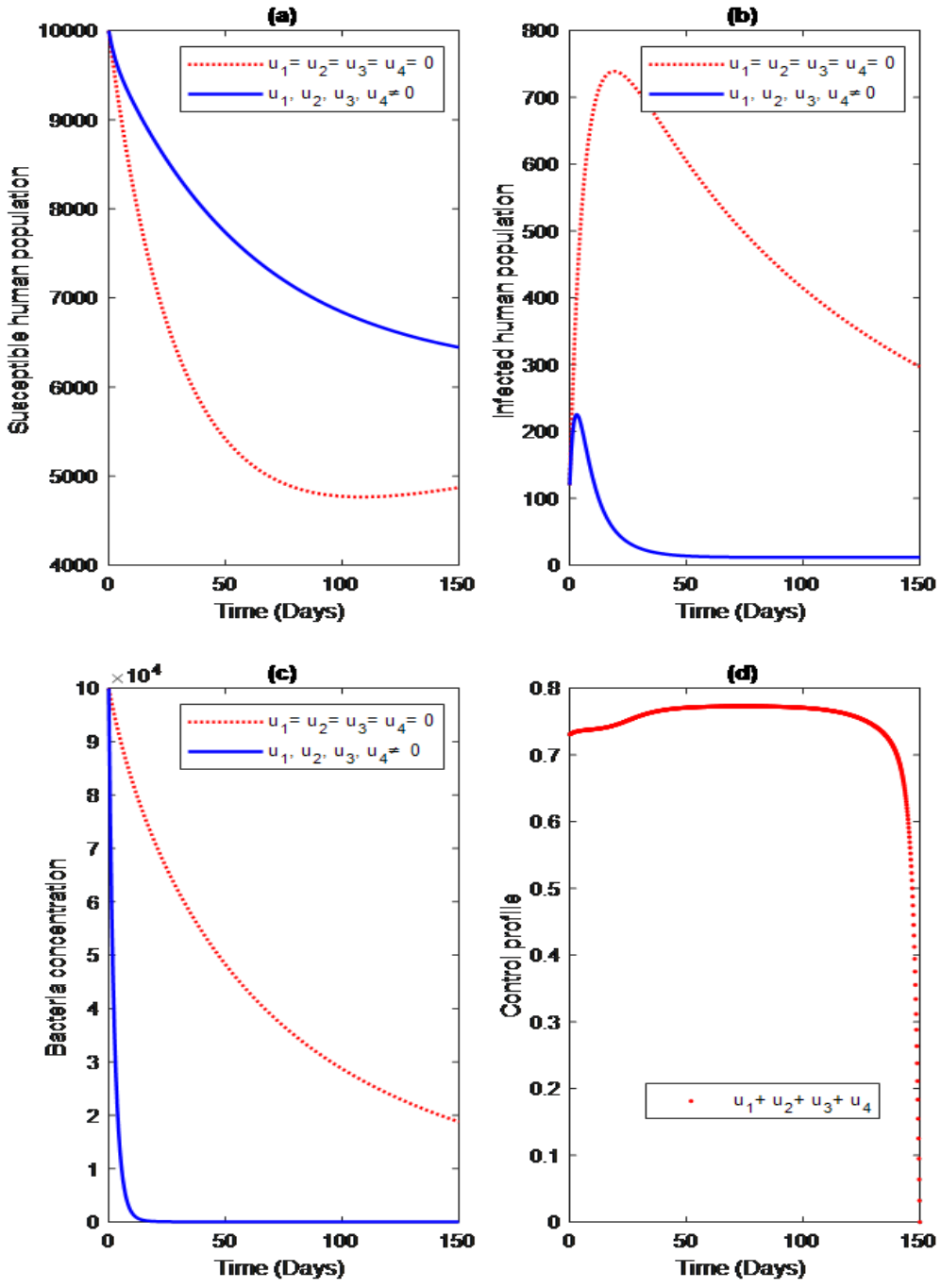

Figure 6. Simulation results for all combined Controls Implementation: (a) Susceptible Humans, (b) Infected Humans, (c) Bacteria Concentration, $B_c(t)$, and (d) Control Profile.

0).

Case C (three controls combine implementation)

- Strategy 11 (u_{123}): sanitation and hygiene practice and awareness campaign + sterilization and disinfection of the contaminated environment + potency of antibiotics administers to typhoid patients ($u_1, u_2, u_3 \neq 0, u_4 = 0$),
- Strategy 12 (u_{124}): sanitation and hygiene practice and awareness campaign + sterilization and disinfection of the contaminated environment + screening control ($u_1, u_2, u_4 \neq 0, u_3 = 0$),
- Strategy 13 (u_{134}): sanitation and hygiene practice and awareness campaign + potency of antibiotics administers to typhoid patients + screening control ($u_1, u_3, u_4 \neq 0, u_2 = 0$),

- Strategy 14 (u_{234}): sterilization and disinfection of the contaminated environment + potency of antibiotics administers to typhoid patients + screening control ($u_2, u_3, u_4 \neq 0, u_1 = 0$).

Case D (all controls combine implementation)

- Strategy 15: (u_{1234})sanitation and hygiene practice and awareness campaign + sterilisation and disinfection of the contaminated environment + potency of antibiotics administered to typhoid patients + screening control ($u_1, u_2, u_3, u_4 \neq 0$).

4.3. The Discussion of Optimal Control Problem Simulations

Figure 3 shows the simulation results when applying a single control. It shows that implementing Strategy 2 will prevent more susceptible humans from contracting the infection compared to other single strategies, followed by Strategy 1 (u_1), likewise in the infected humans and bacteria in the environment. To implement Strategy 2, u_2 must be maintained at 39% for about 145 days before declining to its lower bound at day 150 (see Figure 3d).

For the double control combinations in Figure 4, it is observed that the combined double strategies with sterilisation and disinfection of contaminated environment control (that is, u_{12}, u_{23}, u_{24}) prevented the susceptible humans from contracting the infection and also reduced the infected human population and bacteria concentration in the environment more than other double control implementations, which shows the importance of sterilisation and disinfection of contaminated environment on typhoid infection control. The best control combinations are Strategy 9 (u_{24}), sanitation and hygiene practice and awareness campaigns, and screening control. Figure 4d shows that Strategy 9 maintains a control profile at 58% for 147 days before declining to the lower bound.

According to the simulation in Figure 5, three controls combined strategies with sterilisation and disinfection of contaminated environment control (that is, u_{124}, u_{234}) have more impact than the others (that is, u_{134}, u_{123}). All the control combinations, u_{124}, u_{234}, should be maintained at their various percentages for almost 147 days before declining to achieve these results (See Figure 5d).

Figure 6(a-c) indicates that the combined implementation of all the controls (Strategy 15) significantly impacts the susceptible human population, infected human population and the bacteria in the environment than without control. Figure 6(d) shows the control profile for applying all four controls together and should be maintained at 75% for about 145 days before declining. We further determine which of these strategies is the most cost-effective to implement by conducting a cost-effective analysis of the strategies.

4.4. Cost-effectiveness analysis

Cost-effectiveness analysis is an analysis for finding the cost and economic health results of one or more control measures. It determines the most cost-effective control strategy to eliminate the disease at a reduced cost. We consider two approaches for cost-effectiveness analysis, namely, average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER) [31, 34]. Also, we consider two situations, which are to determine the strategies that avert infected cases and prevent susceptible humans from contracting the infection.

Table 3. Case A (Single Control implementation).

Strategies	Total infection averted	Total cost	ACER
Strategy 2	0.0133	3.452110^7	26042
Strategy 3	9.7645	568.2	58.19423
Strategy 4	4.1378×10^5	1.4075×10^6	3.4014
Strategy 1	2.3912×10^7	4.3414×10^7	1.8156

Table 4. Case B (Double Control implementation).

Strategies	Total infection averted	Total cost	ACER
Strategy 8	4.8620	3.4521×10^7	7.1002×10^6
Strategy 9	3.9414×10^5	3.5261×10^7	89.4626
Strategy 10	4.1392×10^5	0.1412×10^7	4.1392×10^5
Strategy 5	1.8178×10^6	3.8495×10^7	21.1769
Strategy 6	2.3912×10^7	4.3417×10^7	1.8157
Strategy 7	2.3935×10^7	4.4880×10^7	1.8751

Table 5. Case C (Triple Control implementation).

Strategies	Total infection averted	Total cost	ACER
Strategy 14	3.9422×10^5	3.5263×10^7	89.4491
Strategy 11	1.8179×10^6	3.8496×10^7	21.1758
Strategy 12	2.1442×10^6	3.8292×10^7	1.8753
Strategy 13	2.3935×10^7	4.4886×10^7	1.8753

4.4.1. Average cost-effectiveness ratio (ACER)

The average cost-effectiveness ratio (ACER) is defined as

$$ACER = \frac{\text{Total cost generated by the control}}{\text{Total number of infections averted with the control}}.$$

Here, the total cost generated by the control strategy is evaluated using the objective function in Equation (9). The strategy with the least ACER is the most cost-effective, while the strategy with the highest ACER is the least cost-effective, meaning it is costlier to implement.

For the single control implementation (CASE A), Strategy 1 is the most cost-effective, followed by Strategy 4, Strategy 3 and then Strategy 2 for infected cases averted (see Table 3) and susceptible cases prevented (see Table 6). For Case B, the double control implementation, Strategy 6 is the most cost-effective strategy compared to other double combined control strategies for infected cases averted (see Table 4) and susceptible cases prevented (see Table 7). At the same time, for Case C, Strategy 13 is the most cost-effective strategy for infected cases averted (see Table 5) and susceptible cases prevented (see Table 8).

4.4.2. Incremental cost-effectiveness ratio (ICER)

Incremental cost-effectiveness ratio (ICER) is the changes between the costs and health benefits of any two intervention strategies competing for the same limited resources. In the ICER approach, two competing control intervention strategies are compared incrementally; one is compared with the following less effective alternative strategy [23]. It is calculated using

Table 6. The most Cost-Effective Strategy of each case in ascending order of Total Infections Averted.

Strategies	Total infection averted	Total cost	ACER
Strategy 15	2.1452×10^6	3.9035×10^7	18.1965
Strategy 1	2.3912×10^7	4.3414×10^7	1.8156
Strategy 6	2.3912×10^7	4.3417×10^7	1.8157
Strategy 13	2.3935×10^7	4.4886×10^7	1.8753

Table 7. Case A (Single Control Implementation) for susceptible cases prevented.

Strategies	Total susceptible prevented	Total cost	ACER
Strategy 3	70.6242	5.7228×10^5	8.1032×10^3
Strategy 4	1.8324×10^5	1.6921×10^6	9.2343
Strategy 1	5.5059×10^5	2.7246×10^5	0.4949
Strategy 2	1.8734×10^6	5.3383×10^8	284.9462

Table 8. Case B (Double Control implementation) for Susceptible cases prevented.

Strategies	Total susceptible prevented	Total cost	ACER
Strategy 10	1.8509×10^5	1.0635×10^7	57.4601
Strategy 7	4.9146×10^5	1.7971×10^6	3.6566
Strategy 6	5.5067×10^5	8.4080×10^5	1.5269
Strategy 8	1.8779×10^6	5.3415×10^8	285.1201
Strategy 5	1.8779×10^6	5.3082×10^8	282.6669
Strategy 9	1.8848×10^6	5.2583×10^8	278.9841

Table 9. Case C (Triple Control implementation) for Susceptible cases prevented.

Strategies	Total susceptible prevented	Total cost	ACER
Strategy 13	4.9345×10^5	1.0279×10^7	20.8316
Strategy 11	1.8779×10^6	5.3114×10^8	282.8378
Strategy 14	1.8849×10^6	5.2631×10^8	279.2279
Strategy 12	1.8879×10^6	5.2323×10^8	277.1452

the following formula:
Considering two strategies, p and q, as two control intervention strategies, then ICER is computed as

$$ICER = \frac{\text{Change in total costs in strategies } p \text{ and } q}{\text{Change in control benefits in strategies } p \text{ and } q}.$$

The difference in disease-averted costs, as well as the costs of screening, disinfection, and prevention, can be represented by the ICER numerator. The difference in health outcome, or the difference between the total number of infections avoided or the total number of susceptible cases avoided, is the denominator of the ICER. Put another way, it can be calculated as the difference between the susceptible population or the entire infectious population with and without control. The strategy with the highest ICER value is excluded from the computation of ICERs since it is the most expensive and ineffective to implement. The total infection averted is arranged in ascending order.

4.5. Calculation of ICERs for infected cases averted

4.5.1. ICER for single control implementation for infected cases averted

For Case A, the ICERs are calculated using Table 3 as follows:

$$\text{ICER}(2)=\frac{3.4521 \times 10^7 - 0}{0.01326 - 0} = 2.603318 \times 10^6,$$

$$\text{ICER}(3)=\frac{568.2 - 3.4521 \times 10^7}{9.764 - 0.01326} = -3.549186 \times 10^6,$$

$$\text{ICER}(4)=\frac{1.4075 \times 10^6 - 568.2}{4.1378 \times 10^5 - 9.76} = 3.3989,$$

$$\text{ICER}(1)=\frac{4.3414 \times 10^7 - 1.4075 \times 10^6}{2.391 \times 10^7 - 4.1378 \times 10^5} = 1.7878.$$

The computed results show that the ICER value of Strategy 2, ICER (2), strongly dominates other strategies. The implication is that application of u_2 is more costly and less effective than when u_1, u_3, and u_4 are implemented. Thus, Strategy 2 is eliminated from the list of alternative control strategies. Hence, we compute the ICERs for u_3, u_4, and u_1 as follows, in the ascending order of the total number of infections averted;

$$\text{ICER}(3)=\frac{568.2 - 0}{9.764 - 0} = 58.1934,$$

$$\text{ICER}(4)=\frac{1.4075 \times 10^6 - 568.2}{4.1378 \times 10^5 - 9.764} = 3.3989,$$

$$\text{ICER}(1)=\frac{4.3414 \times 10^7 - 1.4075 \times 10^6}{2.391 \times 10^7 - 4.1378 \times 10^5} = 1.7878.$$

Following the computed outcomes, the ICER value of Strategy 3 is higher than Strategies 4 and 1. Therefore, Strategy 3 is eliminated from the list of alternative control strategies. Hence, we compute the ICERs for u_4 and u_1 as follows, in the ascending order of the total number of infections averted to get;

$$\text{ICER}(4)=\frac{1.4075 \times 10^6 - 0}{4.1378 \times 10^5 - 0} = 3.4002,$$

$$\text{ICER}(1)=\frac{4.3414 \times 10^7 - 1.4075 \times 10^6}{2.391 \times 10^7 - 4.1378 \times 10^5} = 1.7878.$$

Since the ICER of Strategy 4 is higher than that of Strategy 1, it implies that Strategy 4 is costlier and less effective; Strategy 4 is thereby eliminated from the list of alternative control interventions. Hence, the remaining Strategy 1 (the sanitation and hygiene practice and awareness campaign) is the most cost-effective optimal control strategy in combating the bacteria disease for single control implementation. It is illustrated in Figure 7, that is, expenditure on Strategy 1 produced effective results by averting the highest number of infections.=

4.5.2. ICER for double control implementation for infected cases averted

The ICER for Case B is calculated as follows using Table 4;

$$\text{ICER}(8)=\frac{3.4521 \times 10^7 - 0}{4.8620 - 0} = 7.100165 \times 10^7,$$

$$\text{ICER}(9)=\frac{3.5261 \times 10^7 - 3.4521 \times 10^7}{3.9414 \times 10^5 - 4.8620} = 1.8775,$$

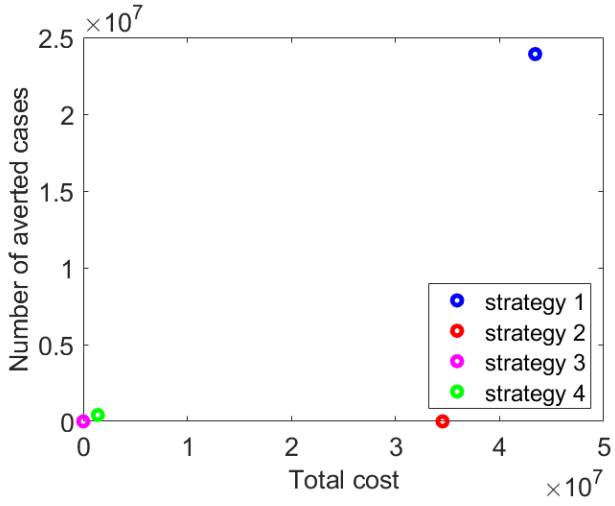

Figure 7. Plots displaying the comparison of infection averted cases for single control implementation (Case A).

$$\text{ICER(10)}=\frac{0.1412\times10^7-3.5261\times10^7}{4.1378\times10^5-3.9414\times10^5}=-1711.3,$$
$$\text{ICER(d5)}=\frac{3.8495\times10^7-0.1412\times10^7}{1.8178\times10^6-4.1392\times10^6}=26.4147,$$
$$\text{ICER(6)}=\frac{4.3417\times10^7-3.8495\times10^7}{2.3912\times10^7-1.8178\times10^6}=0.2228,$$
$$\text{ICER(7)}=\frac{4.4880\times10^7-4.3417\times10^7}{2.3935\times10^7-2.3912\times10^7}=63.6087.$$

The results show that ICER (8) is greater than the ICERs of other strategies for Case B; thus, Strategy 8 is eliminated from the list of alternative strategies. Hence, we compute the ICERs for the remaining Strategies 9, 10, 5, 6 and 7 as follows, in the ascending order of the total number of infections averted to get

$$\text{ICER(9)}=\frac{3.5261\times10^7-0}{3.9414\times10^5-0}=89.4631,$$
$$\text{ICER(10)}=\frac{0.1412\times10^7-3.5261\times10^7}{4.1378\times10^5-3.9414\times10^5}=-1711.3,$$
$$\text{ICER(5)}=\frac{3.8495\times10^7-0.1412\times10^7}{1.8178\times10^6-4.1392\times10^6}=26.4147,$$
$$\text{ICER(6)}=\frac{4.3417\times10^7-3.8495\times10^7}{2.3912\times10^7-1.8178\times10^6}=0.2228,$$
$$\text{ICER(7)}=\frac{4.4880\times10^7-4.3417\times10^7}{2.3935\times10^7-2.3912\times10^7}=63.6087.$$

The ICER(9) is greater than other strategies, implying that Strategy 9 is costlier than other competing strategies. We eliminate Strategy 9 from the competing alternative interventions for Case B. Hence, we calculate the ICERs of the other remaining strategies as follows in their ascending order of infection averted:

$$\text{ICER(10)}=\frac{0.1412\times10^7-0}{4.1378\times10^5-0}==3.4113,$$
$$\text{ICER(5)}=\frac{3.8495\times10^7-0.1412\times10^7}{1.8178\times10^6-4.1392\times10^6}=26.4147,$$
$$\text{ICER(6)}=\frac{4.3417\times10^7-3.8495\times10^7}{2.3912\times10^7-1.8178\times10^6}=0.2228,$$
$$\text{ICER(7)}=\frac{4.4880\times10^7-4.3417\times10^7}{2.3935\times10^7-2.3912\times10^7}=63.6087.$$

From the results, Strategy 7 could be more efficient and more effective. Therefore, Strategy 7 is eliminated from the list of alternative control interventions. So, we compute the ICERs for the remaining three strategies by following their ascending order of infection averted as follows:

$$\text{ICER(10)}=\frac{0.1412\times10^7-0}{4.1378\times10^5-0}3.4113,$$
$$\text{ICER(5)}=\frac{3.8495\times10^7-0.1412\times10^7}{1.8178\times10^6-4.1392\times10^6}=26.4147,$$
$$\text{ICER(6)}=\frac{4.3417\times10^7-3.8495\times10^7}{2.3912\times10^7-1.8178\times10^6}=0.2228.$$

It shows that Strategy 5 has a higher ICER value than other strategies, meaning it is strongly dominated, costlier and less effective. Therefore, Strategy 5 is eliminated from competing alternative control strategies. So, we evaluate the ICERs of the remaining two strategies in increasing order of their infected averted, and this is shown as follows:

$$\text{ICER(10)}=\frac{0.1412\times10^7-0}{4.1378\times10^5-0}=3.4113,$$
$$\text{ICER(6)}=\frac{4.3417\times10^7-0.1412\times10^7}{2.3912\times10^7-4.1392\times10^5}=1.7876.$$

The results show that the ICER of Strategy 10 is higher than other strategies; hence, it is more expensive and less effective. Therefore, Strategy 10 is eliminated, and the only strategy left is Strategy 6. The implication is that Strategy 6 (combination of sanitation and hygiene practice and awareness campaign and potency of antibiotics administered to typhoid patients) is the most cost-effective strategy to contain the bacteria disease for double control implementation, as shown graphically in Figure 8, that is, cost expended on Strategy 6 produced high result by averting highest number of infection.

4.5.3. ICER for triple control implementation for infected cases averted

The ICER for Case C is calculated as follows using the details in Table 5;

$$\text{ICER(14)}=\frac{3.5263\times10^7-0}{3.9422\times10^5-0}=89.4501,$$
$$\text{ICER(11)}=\frac{3.8496\times10^7-3.5263\times10^7}{1.8179\times10^6-3.9422\times10^5}=2.2709,$$
$$\text{ICER(12)}=\frac{3.8292\times10^7-3.8496\times10^7}{2.1442\times10^6-1.8179\times10^6}=-0.6252,$$

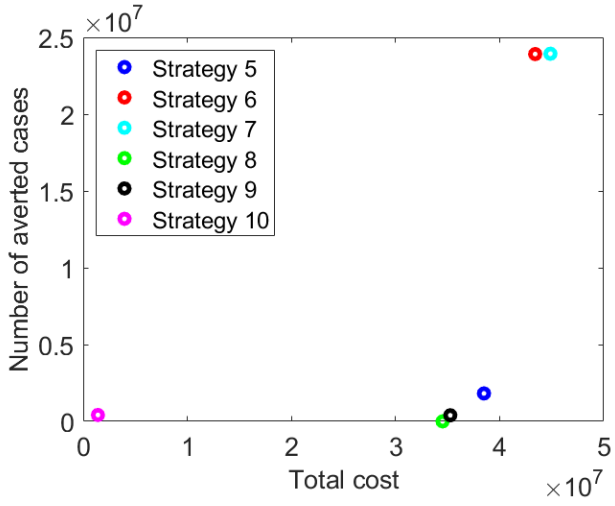

Figure 8. Plots displaying the comparison of infection-averted cases for double control implementation (Case B).

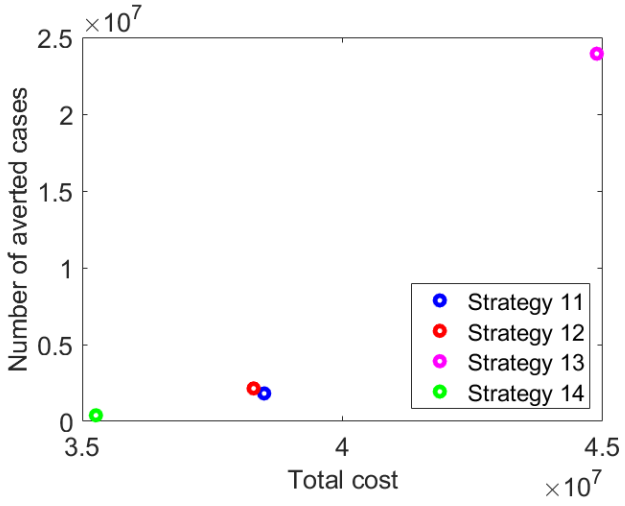

Figure 9. Plots displaying the comparison of infection-averted cases for triple control implementation (Case C).

$$\text{ICER}(13)=\frac{4.4886\times10^{7}-3.8292\times10^{7}}{2.3935\times10^{7}-2.1442\times10^{6}}=0.3026.$$

The computations show that the ICER of Strategy 14 is more expensive and less effective. Therefore, it is eliminated from the list of alternating control strategies for Case C. Hence, we compute the ICERs of the remaining three strategies in ascending order of the infection they averted as follows:

$$\text{ICER}(11)=\frac{3.8496\times10^{7}-0}{1.8179\times10^{6}-0}=97.6511,$$

$$\text{ICER}(12)=\frac{3.8292\times10^{7}-3.8496\times10^{7}}{2.1442\times10^{6}-1.8179\times10^{6}}=-0.6252,$$

$$\text{ICER}(13)=\frac{4.4886\times10^{7}-3.8292\times10^{7}}{2.3935\times10^{7}-2.1442\times10^{6}}=0.3026.$$

The results reveal that Strategy 11 has a higher ICER value than the other two strategies, which means that Strategy 11 is more expensive and less effective. Therefore, Strategy 11 is eliminated from competing alternative intervention strategies. Hence, we calculate the ICERs for the remaining two strategies in ascending order of infection averted;

$$\text{ICER}(12)=\frac{3.8292\times10^{7}-0}{2.1442\times10^{6}-0}=17.8584,$$

$$\text{ICER}(13)=\frac{4.4886\times10^{7}-3.8292\times10^{7}}{2.3935\times10^{7}-2.1442\times10^{6}}=0.3026.$$

The results indicate that the ICER(12) >ICER(13) implies that Strategy 12 is more costly and less expensive. Therefore, Strategy 13, the combination of hygiene practice and awareness campaign, the potency of antibiotics administered to typhoid patients, and screening control, is the most cost-effective triple combined control strategy to fight the typhoid disease for Case C, and it is shown graphically in Figure 9, which shows that expenditure on Strategy 13 produced effective result by averting highest number of infection compare to others that have no significant infection averted.

4.5.4. *Overall ICER for infection cases averted*

Furthermore, the details in Table 6 are used to compute the overall ICERs for the most cost-effective strategy in each of Cases A, B, and C, including Case D, and the result shows that Strategy 1 is the most cost-effective strategy that can be used in the eradication of the typhoid fever disease in the population follow by Strategy 15.

$$\text{ICER}(15)=\frac{3.9035\times10^{7}-0}{2.1452\times10^{6}-0}=18.1964,$$

$$\text{ICER}(1)=\frac{4.3414\times10^{7}-3.9035\times10^{7}}{2.3912\times10^{7}-2.1452\times10^{6}}=0.2012,$$

$$\text{ICER}(13)=\frac{4.4886\times10^{7}-4.3414\times10^{7}}{2.3935\times10^{7}-2.3912\times10^{7}}=64.$$

From these results, Strategy 13 has higher ICER than the two other strategies, which implies that Strategy 13 is strongly dominated, costlier and less effective. Hence, Strategy 13 is eliminated from the alternative control intervention strategies list. Therefore, the ICERs of the remaining two strategies are computed in increasing order of their total infections averted, and this is shown as follows:

$$\text{ICER}(15)=\frac{3.9035\times10^{7}-0}{2.1452\times10^{6}-0}=18.1964,$$

$$\text{ICER}(1)=\frac{4.3414\times10^{7}-3.9035\times10^{7}}{2.3912\times10^{7}-2.1452\times10^{6}}=0.2012.$$

Strategy 15, a combination of all four controls, has greater ICER than Strategy 1, meaning that Strategy 15 is costlier and less effective. Hence, it is eliminated from the list of alternative control strategies. Therefore, Strategy 1, a hygiene practice and awareness campaign, is the most cost-effective strategy to contain typhoid bacteria. Furthermore, it is noteworthy that Strategy 6 is omitted, which is the combination of sanitation and hygiene practice and awareness campaign, and potency of antibiotics administered to typhoid patients since both

Strategies 1 and 6 have the same total infections averted. However, with the cost-minimisation technique, Strategy 1 is the most cost-effective strategy.

4.6. Calculation of ICERs for susceptible humans prevented

4.6.1. ICER for single control implementation susceptible human prevented

For Case A, the ICERs are calculated using Table 7 as follows:

$$\text{ICER}(3)=\frac{5.7228\times10^{5}-0}{70.6242-0}=8103.1714,$$

$$\text{ICER}(4)=\frac{1.6921\times10^{6}-5.7228\times10^{5}}{1.8324\times10^{5}-70.6242}=6.1136,$$

$$\text{ICER}(1)=\frac{2.7246\times10^{5}-1.6921\times10^{6}}{5.5059\times10^{5}-1.8324\times10^{5}}=-3.8645,$$

$$\text{ICER}(2)=\frac{5.3383\times10^{8}-2.7246\times10^{5}}{1.8734\times10^{6}-5.5059\times10^{5}}=403.3516.$$

The computed results show that the ICER value of Strategy 3, ICER (2), strongly dominates other strategies. The implication is that the application of u_3, the potency of antibiotics administered to typhoid patients, is more costly and less effective than when each of u_1, u_2, and u_4 is applied. Thus, Strategy 3 is eliminated from the list of alternative control strategies. Hence, we compute the ICERs for u_4, u_1, and u_2 as follows, in the ascending order of the total susceptible prevented;

$$\text{ICER}(4)=\frac{1.6921\times10^{6}-0}{1.8324\times10^{5}-0}=9.2343,$$

$$\text{ICER}(1)=\frac{2.7246\times10^{5}-1.6921\times10^{6}}{5.5059\times10^{5}-1.8324\times10^{5}}=-3.8645,$$

$$\text{ICER}(2)=\frac{5.3383\times10^{8}-2.7246\times10^{5}}{1.8734\times10^{6}-5.5059\times10^{5}}=403.3516.$$

Following the computed outcomes, the ICER value of Strategy 2 is higher than Strategies 4 and 1, which means it is costlier and less effective. Therefore, Strategy 2 is eliminated from the list of alternative control strategies. Hence, we compute the ICERs for $u_4$andu_1 as follows, in the ascending order of the total susceptible prevented to get;

$$\text{ICER}(4)=\frac{1.6921\times10^{6}-0}{1.8324\times10^{5}-0}=9.2343,$$

$$\text{ICER}(1)=\frac{2.7246\times10^{5}-1.6921\times10^{6}}{5.5059\times10^{5}-1.8324\times10^{5}}=-3.8645.$$

Since the ICER of Strategy 4 is higher than that of Strategy 1, it implies that Strategy 4 is costlier and less effective; Strategy 4 is thereby eliminated from the list of alternative control interventions. Hence, the remaining Strategy 1 (the sanitation and hygiene practice and awareness campaign) is the most cost-effective optimal control strategy in preventing the susceptible populations from contracting typhoid infection for single control implementation, Case A, and this is displayed in Figure 10, that is, implementing Strategy 1 will have more susceptible people prevented from contracting the typhoid disease with a less cost than when compared to other strategies such as Strategy 2 that will prevent more susceptible people at a high cost.

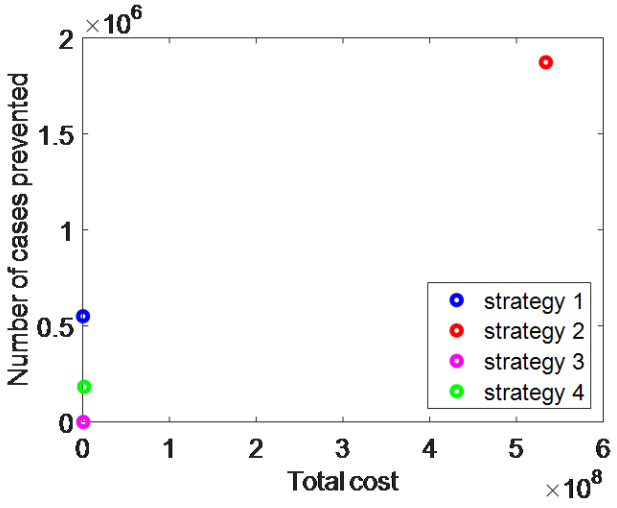

Figure 10. Plots displaying the comparison of susceptible cases prevented for single control implementation (Case A).

4.6.2. ICER for Double control implementation for susceptible cases prevented

The ICER for Case B is calculated as follows using Table 8;

$$\text{ICER}(10)=\frac{1.0635\times10^{7}-0}{1.8509\times10^{5}-0}=57.4583,$$

$$\text{ICER}(7)=\frac{1.7971\times10^{6}-1.0635\times10^{7}}{4.9146\times10^{5}-1.8509\times10^{5}}=-28.8471,$$

$$\text{ICER}(6)=\frac{8.4080\times10^{6}-1.7971\times10^{6}}{5.5067\times10^{5}-4.9146\times10^{5}}=-16.1510,$$

$$\text{ICER}(8)=\frac{5.3415\times10^{8}-8.4080\times10^{6}}{1.8734\times10^{6}-5.5067\times10^{5}}=403.1883,$$

$$\text{ICER}(5)=\frac{5.3082\times10^{8}-5.3415\times10^{8}}{1.8779\times10^{6}-1.8734\times10^{6}}=-740,$$

$$\text{ICER}(9)=\frac{5.2583\times10^{8}-5.3082\times10^{8}}{1.8848\times10^{6}-1.8779\times10^{6}}=-723.1884.$$

The results show that the ICER value for Strategy 8 is greater than the ICERs of other strategies for Case B; this implies that Strategy 8 is strongly dominated over others. The implication is that Strategy 8 is costlier and less effective than other Strategies. Therefore, Strategy 8 is eliminated from the list of alternative Strategies. Hence, we compute the ICERs for the remaining Strategies 10, 7, 6, 5 and 9 as follows, in the ascending order of the total susceptible prevented to get;

$$\text{ICER}(10)=\frac{1.0635\times10^{7}-0}{1.8509\times10^{5}-0}=57.4583,$$

$$\text{ICER}(7)=\frac{1.7971\times10^{6}-1.0635\times10^{7}}{4.9146\times10^{5}-1.8509\times10^{5}}=\text{-}28.8471,$$

$$\text{ICER}(6)=\frac{8.4080\times10^{6}-1.7971\times10^{6}}{5.5067\times10^{5}-4.9146\times10^{5}}=\text{-}16.1510,$$

$$\text{ICER}(5)=\frac{5.3082\times10^{8}-8.4080\times10^{6}}{1.8779\times10^{6}-5.5067\times10^{5}}=399.3123,$$

$$\text{ICER}(9)=\frac{5.2583\times10^{8}-5.3082\times10^{8}}{1.8848\times10^{6}-1.8779\times10^{6}}=\text{-}723.1884.$$

The ICER of Strategy 5 is more than other strategies, indicating that Strategy 5 is strongly dominated and is more expensive and less efficient. Therefore, Strategy 5 is eliminated from the list of competing alternative interventions. Hence, we calculate the ICERs of the other remaining strategies, and this is computed as follows by following their increasing order of susceptible prevented;

$$\text{ICER}(10)=\frac{1.0635\times10^{7}-0}{1.8509\times10^{5}-0}=57.4583,$$

$$\text{ICER}(7)=\frac{1.7971\times10^{6}-1.0635\times10^{7}}{4.9146\times10^{5}-1.8509\times10^{5}}=\text{-}28.8471,$$

$$\text{ICER}(6)=\frac{8.4080\times10^{6}-1.7971\times10^{6}}{5.5067\times10^{5}-4.9146\times10^{5}}=\text{-}16.1510,$$

$$\text{ICER}(9)=\frac{5.2583\times10^{8}-8.4080\times10^{6}}{1.8848\times10^{6}-5.5067\times10^{5}}=393.5068.$$

From the results, the ICER of Strategy 9 is more significant than others, implying that Strategy 7 is costlier and less effective. Therefore, Strategy 9 is eliminated from the list of alternative control interventions. So, we compute the ICERs for the remaining three strategies by following their ascending order of susceptible prevented as follows:

$$\text{ICER}(10)=\frac{1.0635\times10^{7}-0}{1.8509\times10^{5}-0}=57.4583,$$

$$\text{ICER}(7)=\frac{1.7971\times10^{6}-1.0635\times10^{7}}{4.9146\times10^{5}-1.8509\times10^{5}}=\text{-}28.8471,$$

$$\text{ICER}(6)=\frac{8.4080\times10^{6}-1.7971\times10^{6}}{5.5067\times10^{5}-4.9146\times10^{5}}=\text{-}16.1510.$$

This shows that Strategy 10 has a higher ICER value than other strategies, meaning it is strongly dominated, costlier and less effective. Therefore, Strategy 10 is eliminated from competing alternative control strategies. So, we evaluate the ICERs of the remaining two strategies in increasing order of their susceptible prevented, and this is shown as follows:

$$\text{ICER}(7)=\frac{1.7971\times10^{6}-0}{4.9146\times10^{5}-0}=3.6567,$$

$$\text{ICER}(6)=\frac{8.4080\times10^{6}-1.7971\times10^{6}}{5.5067\times10^{5}-4.9146\times10^{5}}=\text{-}16.1510.$$

The results show that the ICER of Strategy 7 is higher than other strategies; hence, it is more expensive and less effective. Therefore, Strategy 7 is eliminated, and the only strategy left is Strategy 6. The implication is that Strategy 6 (a combination of sanitation and hygiene practices, an awareness campaign, and the potency of antibiotics administered to typhoid patients) is the most cost-effective in preventing susceptible populations from the bacteria disease. It is shown graphically in Figure 11, that is, implementing Strategy 6 will cost less in preventing more susceptible people from contracting the typhoid disease compared to other Strategies 5, 8 and 9 that have a high cost of implementation.

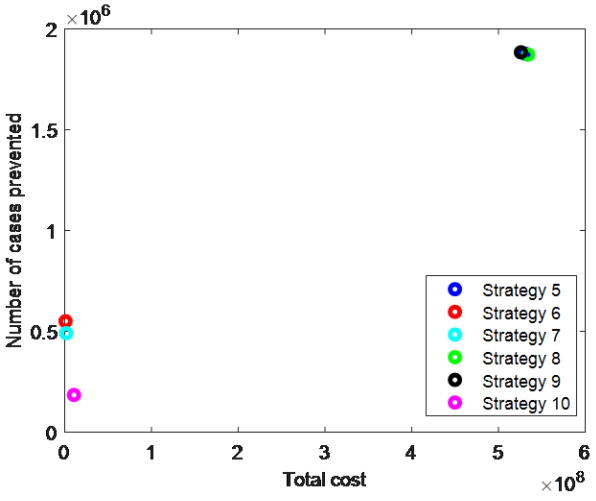

Figure 11. Plots displaying the comparison of susceptible cases prevented for double control implementation (Case B).

4.6.3. *ICER for Triple control implementation for susceptible cases prevented*

The ICER for Case C is calculated as follows using the details in Table 9;

$$\text{ICER}(13)=\frac{1.0279\times10^{7}-0}{4.9345\times10^{5}-0}=20.8309,$$

$$\text{ICER}(11)=\frac{5.3114\times10^{8}-1.0279\times10^{7}}{1.8779\times10^{6}-4.9345\times10^{5}}=376.2223,$$

$$\text{ICER}(14)=\frac{5.2631\times10^{8}-5.3114\times10^{8}}{1.8849\times10^{6}-1.8779\times10^{6}}=\text{-}690,$$

$$\text{ICER}(12)=\frac{5.2323\times10^{8}-5.2631\times10^{8}}{1.8879\times10^{6}-1.8849\times10^{6}}=\text{-}1026.6667.$$

The computations show that the ICER of Strategy 11 is more significant, which means it is more expensive and less effective and, therefore, is eliminated from the list of alternating control strategies. Hence, we compute the ICERs of the remaining three strategies by following the increasing order of the susceptible human they prevented as follows:

$$\text{ICER}(13)=\frac{1.0279\times10^{7}-0}{4.9345\times10^{5}-0}=20.8309,$$

$$\text{ICER}(14)=\frac{5.2631\times10^{8}-1.0279\times10^{7}}{1.8849\times10^{6}-4.9345\times10^{5}}=370.8585,$$

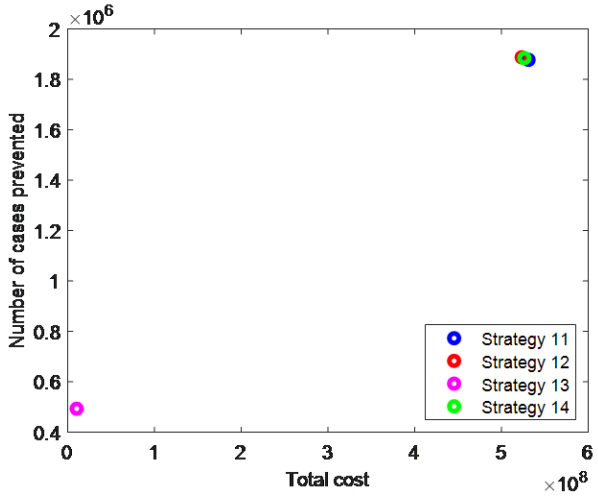

Figure 12. Plots displaying the comparison of susceptible cases prevented for triple control implementation (Case C).

Table 10. The most Cost-Effective Strategy of each Case in ascending Order of Total susceptibility prevented.

Strategies	Total susceptible prevented	Total cost	ACER
Strategy 13	4.9345×10^5	1.0279×10^7	20.8316
Strategy 1	9.7844×10^4	4.8273×10^6	49.3373
Strategy 6	$5,5067 \times 10^5$	8.4080×10^5	1.5269
Strategy 15	1.8880×10^6	5.2387×10^8	277.4758

$$\text{ICER}(12)=\frac{5.2323\times10^8-5.2631\times10^8}{1.8879\times10^6-1.8849\times10^6}=\text{-}1026.6667.$$

The results reveal that Strategy 14 has a higher ICER value than the other two strategies, which means that Strategy 11 is more expensive and less effective. Therefore, Strategy 11 is eliminated from competing alternative intervention strategies. Hence, we calculate the ICERs for the remaining two strategies by following their increasing order of susceptible prevented;

$$\text{ICER}(13)=\frac{1.0279\times10^7-0}{4.9345\times10^5-0}=20.8309,$$
$$\text{ICER}(12)=\frac{5.2323\times10^8-1.0279\times10^7}{1.8879\times10^6-4.9345\times10^5}=367.8518.$$

The results indicate that the ICER value of Strategy 12 is stronger than Strategy 13; this implies that Strategy 12 is more costly and less expensive. Therefore, Strategy 13, which is the combination of sanitation and hygiene practices and awareness campaigns, the potency of antibiotics administered to typhoid patients, and screening control, is the most cost-effective combined control strategy to prevent the susceptible populations from contracting the bacteria disease for triple control implementation. It is displayed in Figure 12, that is, Strategy 13 implementation will cost less in preventing more susceptible people from contracting the typhoid disease compared to other Strategies 11, 12 and 14 that have a high cost of implementation.

4.6.4. *Overall, ICER for susceptible cases prevented*

Furthermore, the details in Table 10 are used to compute the overall ICERs for the most cost-effective strategy in each case, including Case D for susceptible cases prevented.

$$\text{ICER}(13)=\frac{1.0279\times10^7-0}{4.9345\times10^5-0}=20.8309,$$
$$\text{ICER}(1)=\frac{2.7246\times10^5-1.0279\times10^7}{5.5059\times10^5-4.9345\times10^5}=\text{-}175.1232,$$
$$\text{ICER}(6)=\frac{8.4080\times10^6-2.7246\times10^5}{5.5067\times10^5-5.5059\times10^5}=7104.25,$$
$$\text{ICER}(15)=\frac{5.2387\times10^8-8.4080\times10^6}{1.8880\times10^6-5.5067\times10^5}=391.0991.$$

From these results, Strategy 6 is strongly dominant, costlier and less effective since it has the highest ICER value compared to others. Hence, Strategy 6 is eliminated from the alternative control intervention strategies list. Therefore, the ICERs of the remaining three strategies are computed in increasing order of their total susceptible prevented, and this is shown as follows:

$$\text{ICER}(13)=\frac{1.0279\times10^7-0}{4.9345\times10^5-0}=20.8309,$$
$$\text{ICER}(1)=\frac{2.7246\times10^5-1.0279\times10^7}{5.5059\times10^5-2.7246\times10^5}=\text{-}175.1232,$$
$$\text{ICER}(15)=\frac{5.2387\times10^8-8.4080\times10^6}{1.8880\times10^6-5.5059\times10^5}=391.5011,$$

implying that Strategy 15 is costlier and less effective. Hence, it is eliminated from the list of alternative control strategies. The ICERs of the remaining two strategies are computed in increasing order of their total susceptible prevented, and this is shown as

$$\text{ICER}(13)=\frac{1.0279\times10^7-0}{4.9345\times10^5-0}=20.8309,$$
$$\text{ICER}(1)=\frac{2.7246\times10^5-1.0279\times10^7}{5.5059\times10^5-2.7246\times10^5}=\text{-}175.1232.$$

Strategy 13 has greater ICER than Strategy 1, meaning that Strategy 13 is costlier and less effective when compared with Strategy 1. Therefore, Strategy 1, a sanitation and hygiene practice and awareness campaign, is the most cost-effective strategy and the overall best strategy that can be implemented to prevent susceptible populations from contracting bacterial disease.

5. Conclusion

A mathematical model for the dynamics of typhoid fever infection with treatment relapse of the limited clinical efficacy of antibiotics is investigated in this study. The basic reproduction number, R_0, is derived and used to investigate the sensitivity of the model parameters via Latin hypercube sampling (LHS) with a partial rank correlation coefficient (PRCC) approach. The sensitivity analysis results indicate that R_0 decreases when

the maximum treatment intake over time with high clinical efficacy of antibiotics, the recovery rate for treated individuals with a high potency of antibiotics, and the bacteria decay rate increases. Meanwhile, R_0 increases when the human-to-human contact rate, environment-to-human contact rate, relapse response to treatment, the growth rate for the bacteria, and the shedding rates for severe, mild and carrier-infected individuals increase, meaning disease invasion in the population. The sensitivity results for the parameters with PRCCs ($\geq$ 0.5), which are the bacteria decay, the treated individuals' recovery rate, the human-to-human contact rate and the environment-to-human contact rate, have more impact on R_0.

Furthermore, the optimal control model with four control measures is formulated and analysed based on the sensitivity analysis result. The controls are sanitation and hygiene practice and awareness campaign control, sterilisation and disinfection control, the potency of antibiotics administered to control and the screening control for carrier-infected humans. Also, cost-effectiveness analysis is computed to determine the most cost-effective optimal control strategy for both infected cases so that the bacteria can be eliminated and for susceptible humans so that they can be prevented from contracting the disease. In conclusion, the deduction from the study suggests that for both infected humans and susceptible humans, Strategy 1, which is the sanitation and hygiene practice and awareness campaign, is the most cost-effective strategy to contain the typhoid fever infection and prevent susceptible population from contracting the bacteria; this conforms with the work of [13]. For applying double controls (Case B), Strategy 6, combining Strategy 1 and the potency of antibiotics administered, is the most cost-effective for containing the bacteria disease and preventing susceptible humans from contracting the disease. Also, for implementing triple controls (Case C), the result dictates that Strategy 13, which combines sanitation and hygiene practice and awareness campaign, the potency of antibiotics administered, and screening control is the most cost-effective for eradicating the bacteria disease and for preventing susceptible individuals. However, the overall computation of the cost-effectiveness among the most cost-effective control strategies to be considered from each case, including Case D (all the controls), indicates that Strategy 1 is the most cost-effective control intervention to control typhoid fever bacteria and to prevent susceptible humans from contracting the disease.

However, all the combined controls (Strategy 15) may be implemented to reduce the infected cases in the community, while Strategy 13 (sanitation and hygiene practice and awareness campaign, the potency of antibiotics administered to typhoid patients and screening control) may be implemented to prevent the susceptible from contracting the infection when the cost of implementation does not matter. The study has some limitations, such as the derivation endemic equilibrium state, the model parameters uncertainty, and the control interventions' efficacy. The limitations could be considered in future research. In addition, the model in this study can be extended by considering exposed individuals.

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