FUDMA Journal of Sciences (FJS)
ISSN online: 2616-1370
ISSN print: 2645 - 2944
Vol. 4 No. 3, September, 2020, pp 437 – 445
DOI: https://doi.org/10.33003/fjs-2020-0403-258

ON OPTIMAL CONTROL AND COST-EFFECTIVENESS ANALYSIS FOR TYPHOID FEVER MODEL

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ABSTRACT
Typhoid fever is a disease of a major concern in the developing world because it adversely affects on health and finance of a large chunk of people in this part of the world. This paper is aim to develop an extend and improve the optimal control model of typhoid transmission dynamics that can select the best cost-effective strategy for some interventions. Thus, an optimal control model for typhoid, incorporating control functions representing measures of personal hygiene and sanitation, diagnosis and treatment, and vaccination, was formulated. The corresponding optimality system was characterized via the Pontryagin's maximum principle. The optimality system was numerically simulated for all possible strategies using Runge-Kutta method of order four. For cost-effectiveness analysis, the method of incremental cost-effectiveness ratio (ICER) was employed. The results show that the model is able to select the most cost-effective strategy for any given set of parameter values and initial conditions.

Keywords: Optimal control, Pontryagin's maximum principle, cost-effectiveness, Runge-Kutta (RK4), cost-effectiveness ratio (ICER).

INTRODUCTION

Typhoid fever is a systemic infection caused by Salmonella Typhi through ingestion of food or water contaminated with the faeces of infected persons. The acute illness is characterized by prolong headache, fever, nausea, loss of appetite, constipation and sometimes diarrhea. According to the most recent estimates, between 11 and 21 million cases of typhoid and 128,000 to 161,000 typhoid related-deaths occur annually worldwide (WHO, 2019; Browne et al., 2020; Espinoza et al., 2019).
Globally, 10.9, 12.5, 26, 22 and 25.9 million new cases of typhoid fever; and 116.8, 149, 190, 210 and 181 thousand typhoid-related deaths in 2017, 2015, 2010, 2000 and 1990 respectively (Mather et al., 2019; Amicizia et al., 2019; Radhakrishnan et al., 2018; Buckle et al., 2012; Mukhopadhyay et al., 2019; Deksissa et al., 2019; *Ohanu et al*., 2019). A bulk of these burdens is borne by the developing sub-Saharan African countries.

Mathematical models are veritable tools for studying the dynamics of infectious diseases. See, for example, Anderson and May (1991). Optimal control techniques have been used to determine best control strategies for infectious diseases such as malaria, Ebola, Influenza, tuberculosis, hepatitis B, tungiasis, to mention a few. See [Khamis et al. (2018); Otieno et al. (2016); Lashari et al. (2012); Nwanga et al. (2014); Ebenezer et al. (2016); Kahuru et al. (2017); Hattaf et al. (2009); Silver et al.(2014); Athithan and Gosh (2016); Tchuenche et al. (2011)]. Mathematical models for typhoid transmission dynamics are scanty (Tilahun et al., 2017). Tilahum et al. (2017) presented a deterministic mathematical model to investigate the dynamics of typhoid fever with optimal control strategies. However we noticed a flaw in the associated system of differential equations emanating from their model descriptions. Thus the current study improves and extended the Tilahun et al. (2017) by incorporating the dynamics of vaccinated individuals. Further, this paper extended and improved optimal control model for typhoid transmission dynamics that can select the best strategy for some interventions, analytically characterize and numerically explore the corresponding optimality system.

The paper is organized as follows. Brief introduction on Typhoid fever was presented in section 1, the basic Typhoid fever model is presented and an optimal control model is designed in section 2, analysis of the optimal control model is done in section 3, and numerical simulations are performed and the results are presented in section 4. Cost-effectiveness analysis is carried out in section 5. Discussion of results and the conclusive remarks are passed in section 6

Model Formulation

The model by Tilahun et al, (2017) incorporates human and pathogen populations. The human population is partitioned into susceptible, carriers, symptomatically infectious persons and recovered individuals denoted $S, I, C,$ *and* R respectively. So that,

$$N = S + C + I + R$$

The pathogen population is represented by B_c.

The variables and parameters used in the model by Tilahun et al (2017) are defined in Table 1.

Table 1: Variables and Parameters used in the model and their description

Variable/Parameter	Description
S	The number of susceptible humans at time t
C	The number of carrier at time t
I	The number of infected humans at time t
R	The number of recovered human at time t
B_C	The of bacteria at time t
Λ	Recruitment rate
δ	Waning of partial immunity to typhoid fever rate
K	Concentration of salmonella bacteria in foods and waters
v	Ingestion of salmonella bacteria
ρ	The probability that an infected person becomes a carrier after infection
θ	Rate at which carrier become symptomatic
β	Treatment rate
ϕ	Natural immunity rate from the carrier class
μ	Natural death rate of humans
α	Disease-induced death rate
σ_1	The rate of shedding salmonella in foods and waters by carriers
σ_2	The rate of shedding salmonella in foods and waters by infectives
μ_b	The death rate of salmonella bacteria

The flow of all epidemiological and demographic processes involved is described as follows. Recruitment into the susceptible class which is either by birth or immigration occurs at the rate of Λ. The recovered individuals lose partial immunity to typhoid fever to become susceptible at the rate of δ. The force of infection in the model is $\lambda = \frac{B_c v}{[k+B_c]}$, where v is ingestion rate, k is the concentration of Salmonella bacteria in foods or waters, and $\frac{B_c}{[k+B_c]}$ is the probability of individuals in consuming foods or drinks contaminated with typhoid causing bacteria. Death occurs naturally at the rate of μ. ρ is the probability that an infected person becomes a carrier after infection. Carriers become symptomatic at the rate of θ and acquire natural immunity at the rate of ϕ. The symptomatically infected persons acquire natural immunity at the rate of β. Typhoid-related mortality occurs at the rate of α. Carriers and symptomatically infected individuals discharge Salmonella at the rates of σ_1 and σ_2 respectively. The net death rate of the pathogen is given by μ_b.

From the above description of variables and parameters, the interactions and flow in the different compartments (Tilahun et al, 2017) are as depicted in the schematic flow diagram (Figure 1) below.

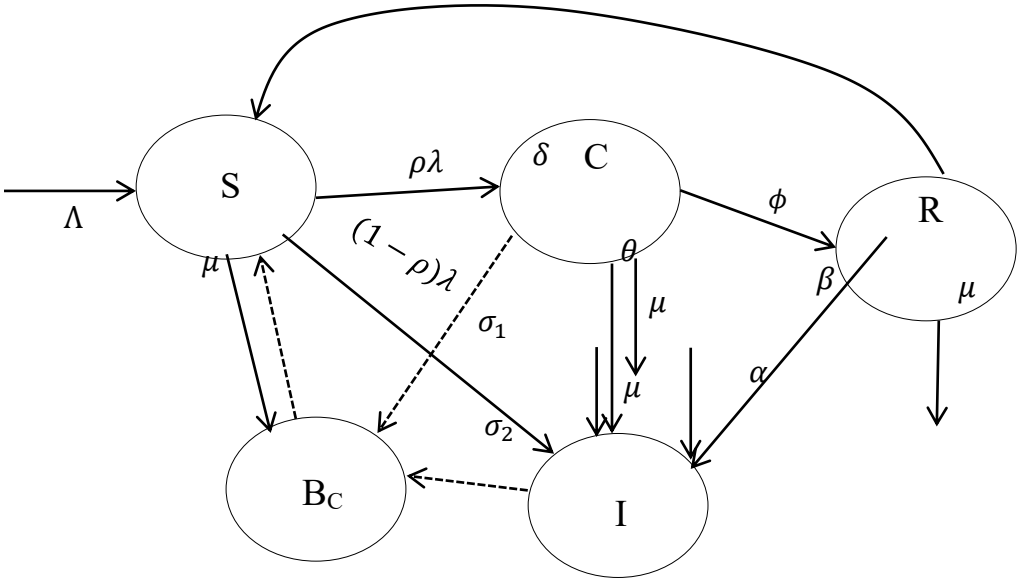

Figure 1: Flow diagram of Tilahun etal (2017) model

From the above descriptions and flow diagram, Tilahun et al (2017) presented to the following system of ordinary differential equations:

$$\frac{dS}{dt} = \Lambda + \delta R - (\mu + \lambda)S \quad (1)$$
$$\frac{dC}{dt} = \rho\lambda S - (\sigma_1 + \theta + \phi + \mu)C \quad (2)$$
$$\frac{dI}{dt} = (1-\rho)\lambda S + \theta C - (\sigma_2 + \beta + \mu + \alpha)I \quad (3)$$
$$\frac{dR}{dt} = \beta I + \phi C - (\mu + \delta)R \quad (4)$$
$$\frac{dB_c}{dt} = \sigma_1 C + \sigma_2 I - \mu_b B_c \quad (5)$$

where $\lambda = \frac{B_c v}{[k+B_c]}$

Modified Model Equation

The parameters σ_1 and σ_2 as defined in Tilahun et al (2017) model and captured in the model equations are flaws as the carriers and asymptotically infected individuals cannot themselves become bacteria as captured in their model (see Table1 and Equation (2) and Equation (3) above). Increasing the bacteria population in foods and waters does not decreased the population of carriers or infected individuals.

Thus with descriptions and flow diagram (Table1 and Figure 1), we modify the model equations by Tilahun et al (2017) and present the following system of ordinary differential equations:

$$\frac{dS}{dt} = \Lambda + \delta R - (\mu + \lambda)S \quad (6)$$
$$\frac{dC}{dt} = \rho\lambda S - (\theta + \phi + \mu)C \quad (7)$$
$$\frac{dI}{dt} = (1-\rho)\lambda S + \theta C - (\beta + \mu + \alpha)I \quad (8)$$
$$\frac{dR}{dt} = \beta I + \phi C - (\mu + \delta)R \quad (9)$$
$$\frac{dB_c}{dt} = \sigma_1 C + \sigma_2 I - \mu_b B_c \quad (10)$$
$$\lambda = \frac{B_c v}{[k + B_c]}$$

Basic Properties

We obtain the invariant region in which the model solution is bounded. All the associated parameters and state variables are non-negatives for $t \geq 0$. Consider the biological feasible region

$$Z = \left\{(S, C, I, R) \in \mathbb{R}^4 : N \leq \frac{\Lambda}{\mu}\right\}$$

Lemma 1: The closed set Z is positively and attracting with respect to the system of equations (6) – (9).

Proof:

Adding equations (6) – (9) gives the rate of change of the total population:

$$\frac{dN}{dt} = \Lambda - \mu N - \alpha I \quad (11)$$

It is clear from equation (11) that

$$\frac{dN}{dt} \leq \Lambda - \mu N$$

it follows that

$$\frac{dN}{dt} \leq 0 \text{ if } N(t) \geq \frac{\Lambda}{\mu}$$

Thus, by a standard comparison theorem (Lakshmikantham *et al*, 1989) can be used to show that

$$N(t) \leq N(0)e^{-\mu t} + \frac{\Lambda}{\mu}(1 - e^{-\mu t})$$

In particular

$N(t) \leq \frac{\Lambda}{\mu}$ if $N(0) \leq \frac{\Lambda}{\mu}$. Thus the region Ω ispositively-invariant. However if $N(t) \leq \frac{\Lambda}{\mu}$, then either the solution enters Ω in finite time, or $N(t)$ approaches $\frac{\Lambda}{\mu}$ asymptotically. Hence the region Z attracts all solutions in $\mathbb{R}^4$.

Therefore, it is sufficient to consider the dynamics of the flow generated by equations (6) – (9) in Z, where the usual existence, uniqueness, continuation results hold for the system (6) – (9), that is the system is mathematically and epidemiological well-posed in Z.

Optimal Control Model

In this section, we modify and extend the existing optimal control model of Tilahun et al (2017) by incorporating the compartment of vaccinated individuals S_v, so that

$$N = S + C + I + S_v + R$$

The efficacy of sanitation measure at killing the pathogen is r and we define the parameter β as the rate at which the symptomatically infected persons acquire immunity. b_1, b_2 *and* w_1 are weight constants; and u_i are control variables. All other parameters retain their

descriptions as in the existing model which are depicted in Table 1 above.
Therefore, from our modified model (6) – (10), the extended optimal control equations for typhoid dynamics are presented as follows:

$$\frac{dS}{dt} = \Lambda + \delta R - (1-u_1)\lambda S - (\mu + u_3)S \quad (12)$$

$$\frac{dc}{dt} = (1-u_1)\rho\lambda S - (\theta + \phi + \mu)C \quad (13)$$

$$\frac{dI}{dt} = (1-u_1)(1-\rho)\lambda S + \theta C - (u_2 + \beta)I - (\mu + \alpha)I \quad (14)$$

$$\frac{dS_v}{dt} = u_3 S - \mu S_v \quad (15)$$

$$\frac{dR}{dt} = (u_2 + \beta)I + \phi C - (\mu + \delta)R \quad (16)$$

$$\frac{dB_c}{dt} = \sigma_1 C + \sigma_2 I - (\mu_b + r u_1)B_c \quad (17)$$

where $\lambda = \frac{B_c v}{[k+B_c]}$

The objective function is given by

$$J(u_1, u_2, u_3) = \int_0^t [A_1 u_1 S(t) + A_2 u_2 I(t) + A_3 u_3 S(t) + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2) + \alpha C_1 I(t) + C_2 I(t)]dt \quad (18)$$

where A_1, A_2 *and* A_3 represent the costs of hygiene and sanitation, vaccine and drugs per person respectively. $B_1, B_2,$ *and* B_3 represent the costs of implementation of control and C_1 *and* C_2 represent average losses of wages due to a typhoid related death and illness respectively. $U = (u_1, u_2, u_3)$ is a st of Lebesgue measurable functions.

Optimal Control Analysis

In this section, we define the Langagian and the Hamiltonian of our control system. The Langragian is given by $L = [A_1 u_1 S(t) + A_2 u_2 I(t) + A_3 u_3 S(t) + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2) + \alpha C_1 I(t) + C_2 I(t)]$

The Hamiltonian H is the sum of L and the inner product of the adjoint variables

$\lambda_i = 1, \dots, 6$ and the right hand sides of equations (12) - (17)

That is $H = L + \sum_{i=1}^{6} \lambda_i f_i$ are the right-hand side of (12) - (17)

$$= \left[A_1 u_1 S(t) + A_2 u_2 I(t) + A_3 u_3 S(t) + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2) + \alpha C_1 I(t) + C_2 I(t)\right]$$
$$+\lambda_1[\Lambda + \delta R - (1-u_1)\lambda S - (\mu + u_3)S] + \lambda_2[(1-u_1)\rho\lambda S - (\theta + \phi + \mu)C]$$
$$+\lambda_3[(1-u_1)(1-\rho)\lambda S + \theta C - (u_2 + \beta)I - (\mu + \alpha)I] + \lambda_4[u_3 S - \mu S_v]$$
$$+\lambda_5[(u_2 + \beta)I + \phi C - (\mu + \delta)R] + \lambda_6[\sigma_1 C + \sigma_2 I - (\mu_b + r u_1)B_c]$$

The Optimality System

Suppose $U = (u_1, u_2, u_3)$ is a control vector, $x = (S, C, I, S_v, R, B_c)$ the state variables of the system $(12) - (17)$ and H the Hamiltonian, the optimality system is given by

$\frac{dx_i}{dt} = \frac{\partial H}{\partial \lambda_i}$, $-\frac{d\lambda_i}{dt} = \frac{\partial H}{\partial x_i}$, $i = 1, \dots, 6$ with transversality conditions $\lambda_i(tf) = 0$; $\frac{\partial H}{\partial u_j} = 0, j = 1, 2, 3.$

Theorem 1. Let $U = (u_1, u_2)$ be a control vector, $x = (S, C, I, S_v, R, B_c)$ be the state variables of the system $(12) - (17)$ and H the Hamiltonian. There exist an optimal control vector $U^*(t)$ and the corresponding state vector $x^*(t)$ that minimize $J(U)$ over Ω. Furthermore, there exist adjoint functions λ_i satisfying the equations

$-\frac{d\lambda_i}{dt} = \frac{\partial H}{\partial x_i}$, $i = 1, \dots, 6$ with transversality conditions $\lambda_i(tf) = 0$.

In addition, the optimal controls are given by $u_j^* = \max\{0, \min(1, R_j)\}, j = 1, 2, 3.$

Proof: We use the recipe by Fleming and Rishel (1975). The existence of an optimal control vector follows from the convexity of the integrand J with respect to U, a priori boundedness of the state solutions and the Lipscitz property of the state solutions with respect to the state variables. See [Fleming and Rishel (1975)] (corollary 4.1). The adjoint equations and transversality conditions can be obtained by using the Pontryagin's Maximum Principle such that

$$-\frac{d\lambda_1}{dt} = \frac{\partial H}{\partial S} = -\lambda_1[(1-u_1)\lambda + (\mu + u_3)] + \lambda_2(1-u_1)\rho\lambda + \lambda_3(1-u_1)(1-\rho)\lambda + \lambda_4 u_3 + A_1 u_1 + A_3 u_3$$

$$-\frac{d\lambda_2}{dt} = \frac{\partial H}{\partial C} = -\lambda_2[(\theta + \phi + \mu)] + \lambda_3\theta + \lambda_5\phi + \lambda_6\sigma_1$$

$$-\frac{d\lambda_3}{dt} = \frac{\partial H}{\partial I} = A_2 u_2 + \alpha C_1 + C_2 - \lambda_3[(u_2 + \beta + \mu + \alpha)] + \lambda_5(u_2 + \beta) + \lambda_6\sigma_2$$

$$-\frac{d\lambda_4}{dt} = \frac{\partial H}{\partial S_v} = -\lambda_4 \mu$$

$$-\frac{d\lambda_5}{dt} = \frac{\partial H}{\partial R} = \lambda_1\delta - \lambda_5(\mu + \delta)$$

$$-\frac{d\lambda_6}{dt} = \frac{\partial H}{\partial B} = -\lambda_1(1-u_1)\left[\frac{(K+B_c)V - B_c V}{(K+B_c)^2}\right]S + \lambda_2(1-u_1)\left[\frac{(K+B_c)V - B_c V}{(K+B_c)^2}\right]\rho S$$
$$\lambda_3\{(1-u_1)\left[\frac{(K+B_c)V - B_c V}{(K+B_c)^2}\right](1-\rho)S\} - \lambda_6(\mu_b + r u_1)$$

with transversality conditions $\lambda_1(T) = \lambda_2(T) = \lambda_3(T) = \lambda_4(T) = \lambda_5(T) = \lambda_6(T) = 0$

The controls u_j can be solved for by using the optimality condition

$\frac{\partial H}{\partial u_1} = 0;\ \frac{\partial H}{\partial u_2} = 0;\ \frac{\partial H}{\partial u_3} = 0;$ Therefore,

$u_1^* = \max\{0, \min(1, R_1)\}, R_1 = \frac{\lambda_2 \rho \lambda S + \lambda_3(1-\rho)\lambda S - \lambda_1 \lambda S + r B_c \lambda_6 - A_1 S}{B_1}$

$u_2^* = \max\{0, \min(1, R_2)\}, R_2 = \frac{(\lambda_3 - \lambda_5) I - A_2 I}{B_2}$

$u_3^* = \max\{0, \min(1, R_3)\}, R_3 = \frac{(\lambda_1 - \lambda_4) S - A_3 S}{B_3}$

Numerical Simulation and Results

For numerical simulation, we used the parameters values in Table 1. Jn addition, the following initial values were used: $S(0) = 93803, C(0) = 25, I(0) = 50, Sv(0) = 0, R(0) = 232, Bc(0) = 14000$. We used the following values for the weight constants: $A_1 = 0.1, A_2 = 10, A_3 = 4, B_1 = 1000$.
$B_2 = 1000, B_3 = 1000, C_1 = 20000, C_2 = 10$. We simulated the optimality system to determine the effects of the following strategies.

(i) Personal hygiene and sanitation (u_1) only
(ii) Treatment (u_2) only
(iii) Vaccination (u_3) only
(iv) Personal hygiene and sanitation, and treatment (u_1, u_2) only
(v) Personal hygiene and sanitation, and vaccination (u_1, u_3) only
(vi) Treatment and vaccination (u_2, u_3) only
(vii) Personal hygiene and sanitation, treatment and vaccination (u_1, u_2, u_3) only

The results of our simulation experiments can be seen in Figures 2 – 8.

Table 2: Parameter values used for simulations

Parameter	Value	Parameter	Value
k	50,000	u_2	$0-1$
μ	0.0247	u_3	$0-1$
α	0.052	Λ	100
β	0.002	u_1	$0-1$
σ_1	0.9		
σ_2	0.8		
σ	0.000904		
θ	0.2		
ϕ	0.0003		
ρ	0.3		
$1-\rho$	0.7		
μ_b	0.001		

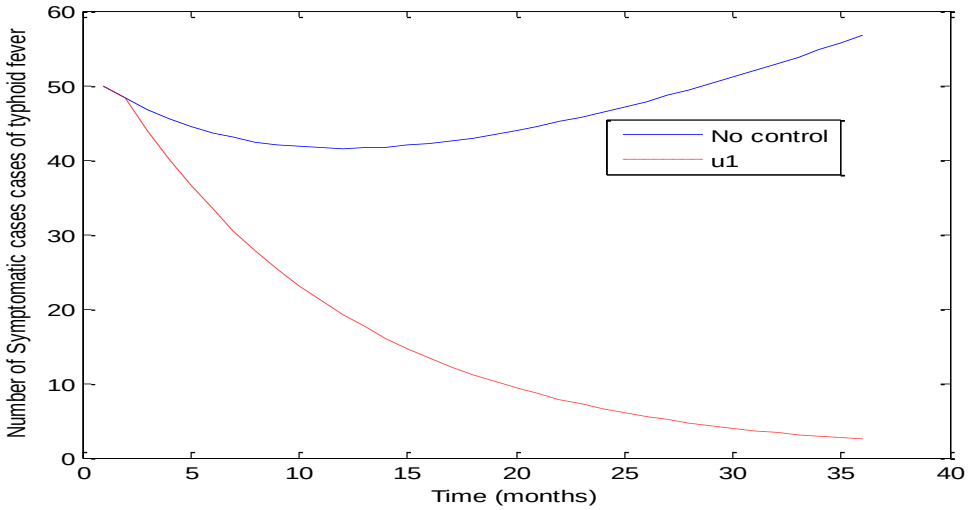

Figure 4: Graph showing the dynamics of symptomatic cases of typhoid fever with hygiene and sanitation control (u_1) only

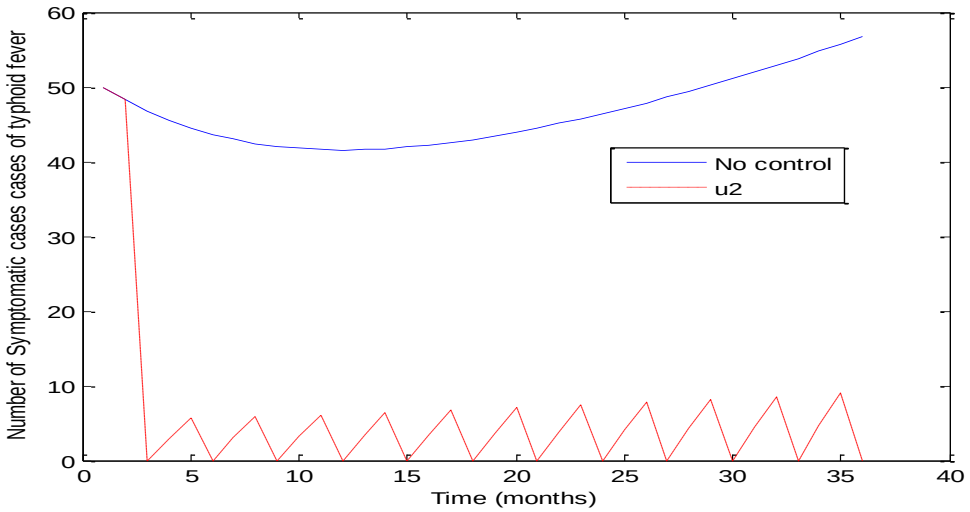

Figure 3: Graph showing the dynamics of symptomatic cases of typhoid fever with treatment control (u_2) only

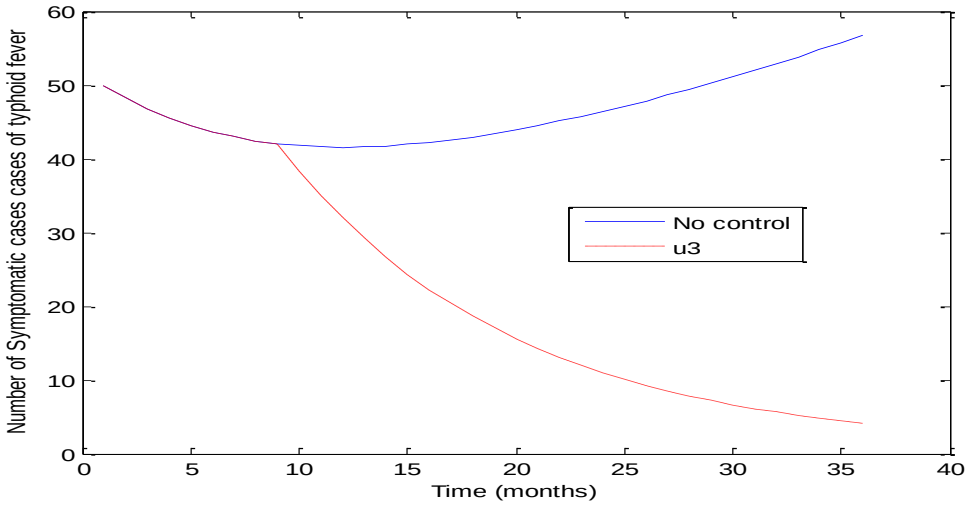

Figure 4: Graph showing the dynamics of symptomatic cases of typhoid fever with vaccination control (u_3) only

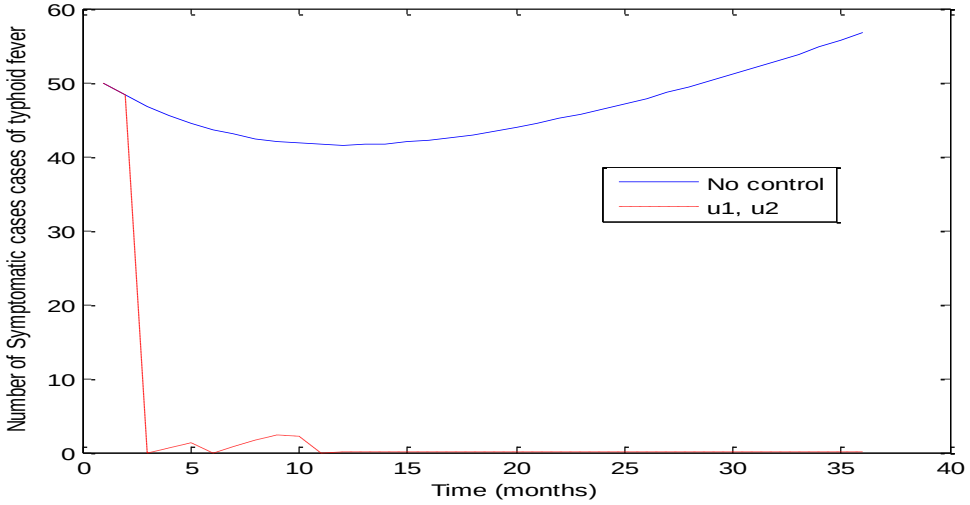

Figure 5: Graph showing the dynamics of symptomatic cases of typhoid fever with hygiene and sanitation (u_1) and treatment (u_2) controls

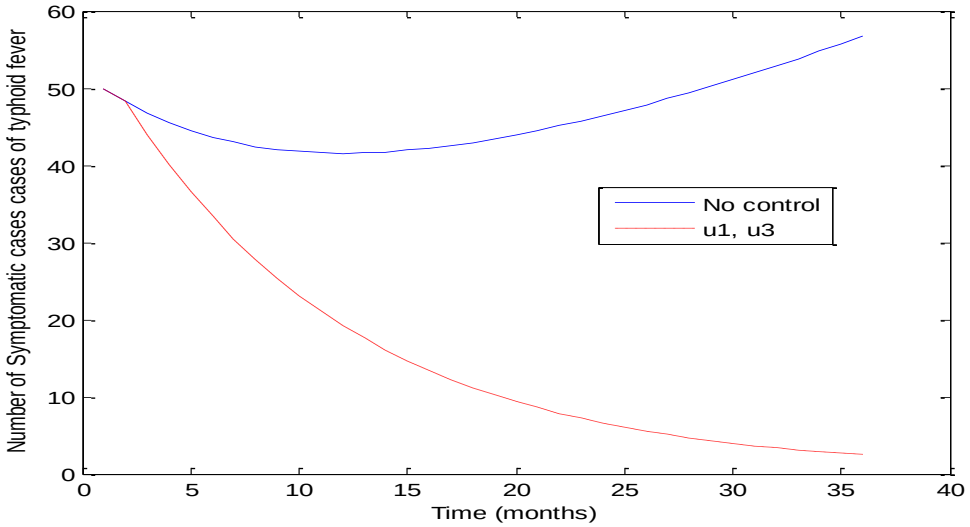

Figure 6: Graph showing the dynamics of symptomatic cases of typhoid fever with hygiene and sanitation (u_1) and vaccination (u_3) controls

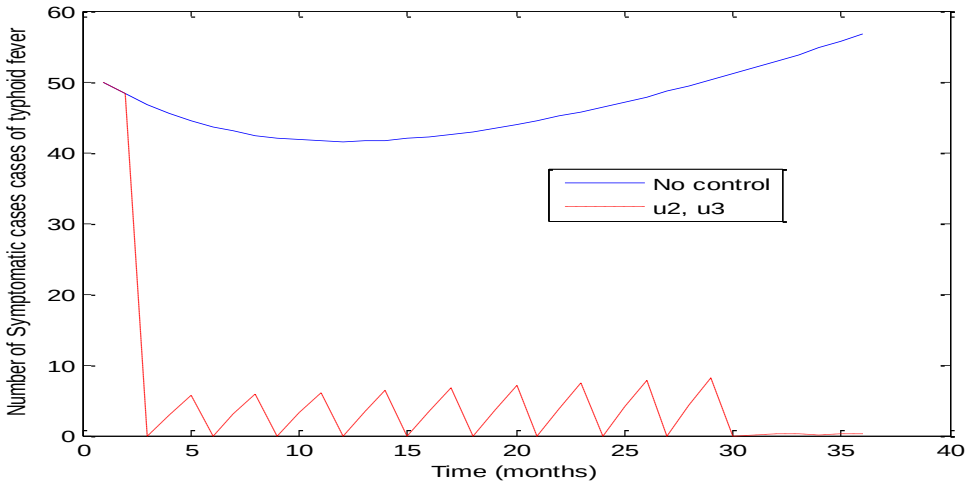

Figure 7: Graph showing the dynamics of symptomatic cases of typhoid fever with treatment (u_2) and vaccination (u_3) controls

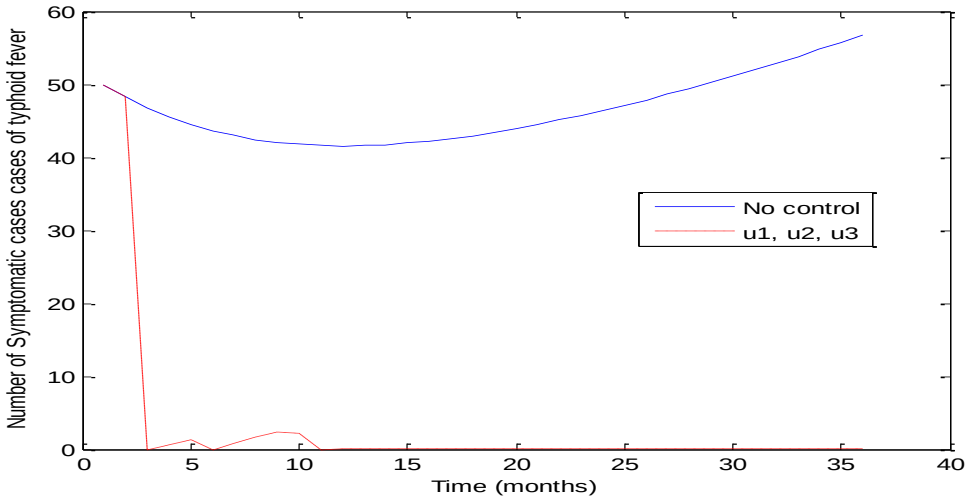

Figure 8: Graph showing the dynamics of symptomatic cases of typhoid fever with hygiene and sanitation (u_1), treatment (u_2) and vaccination (u_3) controls.

Cost-Effectiveness Analysis

In this section, the method of incremental cost-effective ratio (ICER) is used to compare cost-effectiveness of two strategies. The cost objective functional is used to evaluate the total costs associated with all possible strategies over the period. The numbers of infections averted and the total costs of the corresponding strategies are shown in Table 3.

Table 3: The number of infections averted and the total cost of the corresponding strategies

Strategy	Description	No. of infections averted	Total cost of control
A	Hygiene and sanitation	1091	715896.80
B	treatment	1456	256248.10
C	vaccination	858	1029841.57
D	Hygiene and sanitation and treatment	1565	172872.43
E	Hygiene and sanitation and vaccination	1091	715896.80
F	Treatment and vaccination	1481	325927.44
G	Hygiene and sanitation, treatment and vaccination	1565	172872.43

We compare the cost-effectiveness of strategies pair wise as follows.

$ICER(C) = \frac{1029841.57}{858} = 1200.28,\ ICER(A) = \frac{1029841.57-715896.80}{858-1091} = -1347.42$

This shows that strategy A is cheaper than strategy C.

$$ICER(A) = ICER(E) = \frac{715896.80}{1091} = 656.18, \qquad ICER(B) = \frac{715896.80 - 256248.10}{1091 - 1456} = -1259.31$$

This shows that B is better than strategies A and E.

$$ICER(B) = \frac{256248.10}{1456} = 175.99, \qquad ICER(F) = ICER(G) = \frac{256248.10 - 172872.43}{1456 - 1565} = -764.91$$

DISCUSSION AND CONCLUSION

This study has produced analytical and numerical results. The main analytical result can be found in Theorem 1. This theorem establishes the existence of the optimality system that ensues from our optimal control model. The results of our numerical experiments can be seen in Figures 2 through 8 and Table 3. As Figures 2 through 4 have depicted, single intervention of hygiene and sanitation, treatment or vaccination does not have the capability to eradicate typhoid disease from the population. Table 3 shows that vaccination as a single intervention imposes the highest cost, followed by hygiene and sanitation, and treatment. It is also observed that treatment alone produces cyclical effects on the dynamics of typhoid fever. Figure 6 shows that double intervention of hygiene and sanitation, and vaccination is not able to eradicate the disease from the population.

However, Figures 5 shows that double intervention of hygiene and sanitation, and treatment has the capability of eradicating the typhoid disease. Similarly, Figures 7 shows that double intervention of treatment and vaccination has the capability of eradicating the typhoid disease, with a higher cost compared to hygiene and sanitation, and treatment. In the same vein, triple intervention of hygiene and sanitation, treatment and vaccination produces the same impact and imposes the same cost as the double intervention of hygiene and sanitation, and treatment as shown Figure 8.

Based on the data employed, the findings show that a double intervention of hygiene and sanitation, and treatment as a strategy; and the combination of three controls as a strategy are the most cost-effective strategies.

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