AMERICAN JOURNAL OF

# BIOSCIENCE AND BIOINFORMATICS (AJBB)

ISSN: 2995-0481 (Online)

VOLUME 3 ISSUE 1 (2024)

PUBLISHED BY

E-PALLI PUBLISHERS, DELAWARE, USA

American Journal of Bioscience and Bioinformatics (AJBB)

Volume 3 Issue 1, Year 2024
ISSN: 2995-0481 (Online)
DOI: https://doi.org/10.54536/ajbb.v3i1.3503
https://journals.e-palli.com/home/index.php/ajbb

# Transmission Dynamics of Typhoid Fever Outbreak: A Mathematical Modelling and Optimal Control Approach

Adrian Asamoah[1*], Henry Otoo[1], Peter K. Nyarko[1]

**Article Information**

**Received:** August 14, 2024
**Accepted:** September 19, 2024
**Published:** November 02, 2024

**Keywords**

*Booster Vaccination, Epidemiology, Optimal Control, Sensitivity Analysis, Typhoid Fever*

## ABSTRACT

In this paper, we propose and analyze a deterministic mathematical model for the control of typhoid fever. This model incorporates five effective control strategies, including vaccination, booster vaccination, personal hygiene, treatment, and bacteria sterilization, in order to effectively stop the spread of the disease in the population. The model consists of seven compartments, each representing a different stage in the disease's progression: vaccinated, susceptible, carrier, infected, recovered, booster vaccinated, and bacterial. Using the next-generation matrix approach, we calculated the reproduction number $\mathcal{R}_0$, which measures the disease's potential for spreading. Our stability analysis, using the Routh-Hurwitz criteria, revealed that the disease-free equilibrium point is locally asymptotically stable when $\mathcal{R}_0$ is less than 1, among other conditions. This means that typhoid can be completely eradicated if the rate of secondary infection is kept below a certain threshold. Further sensitivity analyses were conducted to determine the key parameters that impact $\mathcal{R}_0$. Based on our findings, we formulated an optimal control problem and utilized Pontryagin's Maximum Principle to determine the most effective strategy for controlling and eliminating the disease. Our results show that a combination of vaccination, booster vaccination, personal hygiene, treatment, and bacteria sterilization is the most optimal approach. With our comprehensive model and effective control strategies, we are one step closer to wiping out typhoid fever for good.

## INTRODUCTION

Typhoid fever, caused by *Salmonella enterica* serotype Typhi (S Typhi) is a growing public health concern in Oceania, Asia and Sub-Saharan Africa due to its serious infection load and difficulty in measuring the burden of the bacteria due to the lack of monitoring platforms and diagnostic tools (Patel *et al.*, 2024; Garret *et al.*, 2022; Marks *et al.*, 2017).

The disease spread from the small intestines through the bloodstream by macrophages in the reticuloendothelial system, causing symptoms like psychosis, rose spots, feeling of fever, hepatomegaly, abdominal pain, dry cough, and diarrhoea or constipation. When treatment is delayed, complications such as intestinal perforation gastrointestinal bleeding and typhoid encephalopathy arise (Kailan Suhuyini & Seidu, 2023; Milligan *et al.*, 2018; Antillón *et al.*, 2017).

In the year 2021, the global estimate for the disease was 7.15 million cases leading to 93300 deaths and 7.08 million DALYS (IHME, 2021). An estimated 1% of cases in Asia will result in death, while 5.4% will occur in Africa (Marchello *et al.*, 2020).

The bacterium S. Typhi, can be transmitted directly or indirectly through sexual intercourse (oral or anal) or contaminated food or water (Awoke, 2019; Mayer & Neilson, 2010).

The disease is predominant in urban settings where overpopulation and access to water, sanitation, and hygiene (WASH) infrastructure is limited (Kim *et al.*, 2019; Im *et al.*, 2020; Nkuh *et al.*, 2023).

Typhoid can be treated with ampicillin, chloramphenicol or cotrimoxazole as a first-line of antibiotic. However, the global emergence of antimicrobial resistance has reduced the effectiveness of existing treatments, leading to the spread of the disease across continents (Browne, 2020; Klemm *et al.*, 2018; da Silva *et al.*, 2022).

The need for typhoid vaccination in endemic areas is even more pressing given the growth of highly drug-resistant typhoid strains in Asia (Briger *et al.*, 2022; Yousafzai *et al.*, 2021).

There are two forms of typhoid fever vaccine, that is the oral vaccine (Ty21a) and an injectable vaccine (typhoid conjugate vaccine, Tya, and Vi capsular polysaccharide). The oral vaccine is administered to people from 6 years whiles the injectable is from 2 years. Over time, typhoid vaccine lose their efficacy hence the need for booster shot is required every two years for injectable vaccines and every five years for oral vaccines (WHO, 2019).

Mathematical models has been an experimental station used to simulate the course of an epidemic or disease outbreak and transmission dynamics. (Eubank *et al.*, 2020). By including a controller in the system, epidemiology models can be managed.

The application of optimal control method is one approach that has gained much attention recently. This has been implemented by researchers to COVID-19 (Abioye *et al.*, 2021), criminal gang population (Ibrahim *et al.*, 2023), tackling unemployment in countries like Bangladesh (Mallick & Biswas, 2020) and impact of water on solar performance (Emmanuel *et al.*, 2023).



[1] Department of Mathematics, University of Mines and Technology, Ghana
[*] Corresponding author's e-mail: pg-aasamoah0622@st.umat.edu.gh

The use of optimal control method to study typhoid fever has been introduced by other researchers using different control intervention. See studies like
Mushayabasa (2016), Tilahun *et al.*, (2017), Awoke (2019), Wameko *et al.*, (2020), Abboubakar and Racke (2021), Peter *et al.*, (2021), Siduppa *et al.*, (2023) and Atte Momoh *et al.*, (2023).
In the present contribution, the researchers develop a deterministic mathematical model for typhoid fever transmission dynamics that incorporates vaccination, booster vaccination, personal hygiene, sterilization of the bacteria, and treatment as control measures. Motivated by the non-optimal control model presented by (Kailan Suhuyini & Seidu, 2023), the study modify their model to capture the asymptomatic class then apply the optimal control theory to investigate the best combinations of controls to stop the spread of the disease and eliminate the bacteria from the environment.

## MATERIALS AND METHODS

The proposed model consists of human population subdivided into six compartments and a bacteria compartment.
Susceptible class (S), singly vaccination class (V), carrier or asymptomatic (C), infected class (I), recovered class (R), booster vaccination ($V_B$) and bacteria (B). The total number of people in each compartment, or N(t), represents the size of human population at any given moment, t : $N(t) = S(t) + V(t) + C(t) + I(t) + R(t) + V_B(t)$.

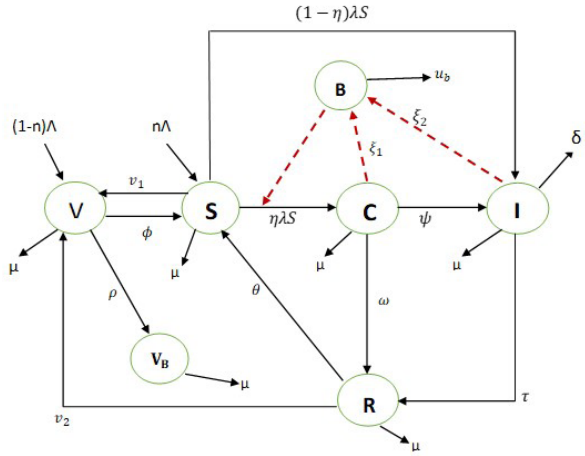


**Figure 1:** Schematic representation of the typhoid model

The model considered both the human population and bacteria population as interest of study.
Recruitment into human population is constant at rates nΛ and (1-n)Λ in which newly recruited humans enter S(t) and V(t) classes respectively. Where n and (1-n) are the proportions of the recruits who are susceptible and vaccinated respectively. Immunity to single vaccinated person is temporal, and loss to immunity is represented by ϕ. Persons who are susceptible and have received the typhoid jab moved to vaccinated class at a rate of $v_1$. When susceptible individuals come into contact with the bacteria (from human or environment), they move to the carrier compartment (C(t)), where they remain there for a period of time (latent period). Since the model captured both the direct and indirect transmissions, the infection rate for persons who are susceptible is $\lambda=\lambda_h+\lambda_b$, where human-to-human transmission is $\lambda_h=\beta\gamma_1 C(t)+\beta\gamma_2 I(t)$; whiles environment-to-human transmission is $\lambda_b$ which is defined as $\beta\gamma_3 B(t)$. Persons in the carrier compartment (C(t)) develop asymptomatic infection and move to the Infectious class (I(t)) at a rate ψ after the incubation period. A Susceptible person can equally transition to the infectious symptomatic class (I(t)) at rate the of $(1-\eta)\lambda S$. ω explains the level at which natural immunity is been developed by the carrier class. Likewise individuals in the symptomatic compartment recover through treatment at a dependable level of τ or may experience disease-induced mortality at a frequency of δ. Following the infection, recovered persons experience gradual loss of immunity at a rate of θ or vaccination rate at $v_2$. The booster vaccinated class grows as a result of receiving the booster vaccine by the vaccinated compartment at a frequency of ρ. μ represent natural death rate for the human compartments while $\mu_b$ represent the bacteria decay. $\xi_1$ and $\xi_2$ explains the bacteria excretion (carrier and infectious). $B_b$ (t) represent the environment to human infection rate. $\gamma_1$ and $\gamma_2$ also represent human-to-human transmission rate. The following differential equations are developed from the schematic diagram

$$dV/dt=(1-n)\Lambda+v_1 S+v_2 R-(\rho+\phi+\mu) V ;$$
$$dS/dt=n\Lambda+\phi V+\theta R-(v_1+\lambda+\mu) S;$$
$$dC/dt=\eta\lambda S-(\psi+\omega+\mu)C ;$$
$$dI/dt=(1-\eta)\lambda S+\psi C-(\tau+\delta+\mu) I;$$
$$dR/dt=\tau I+\omega C-(v_2+\theta+\mu) R;$$
$$dV_B/dt=\rho V-\mu V_B;$$
$$dB/dt=\xi_1 C+\xi_2 I-\mu_b B. \quad (1)$$

Subject to the initial conditions;
$V(0)= V_0$, $S(0)= S_0$, $C(0)= C_0$, $I(0)= I_0$, $R(0)= R_0$, $V_B(0)= V_{(B0)}$, and $B(0)=B_0$
And $N(t)= V(t)+S(t)+C(t)+I(t)+R(t)+V_B(t)$ is the entire population at time $t$.
For better readability, the work set
$k_1=(\rho+\phi+\mu)$, $k_2=(v_1+\mu)$, $k_3=(\psi+\omega+\mu)$, $k_4=(\tau+\delta+\mu)$, $k_5=(v_2+\theta+\mu)$

**Table 1:** Typhoid fever model parameters notation and values

| Parameter | Description | Values | Reference |
|---|---|---|---|
| Λ | Human Birth rate | 100 | Abboubakar and Racke (2021) |
| μ | Natural mortality rate | $3.42081\times10^{(-5)}$ | Alharbi *et al.*, (2023) |
| $v_1$ | Vaccination rate | 0.054 | Abboubakar and Racke (2021) |

| | | | |
|---|---|---|---|
| $\phi$ | Vaccination waning rate | 0.0292 | Mushayabasa *et al.*,(2014) |
| $\rho$ | Booster vaccination | 0.75 | Kailan Suhuyini and Seidu (2023) |
| $\xi_1$ | Bacteria excretion (Carrier) | 0.81 | Pitzer *et al.*, (2014) |
| $\xi_2$ | Bacteria excretion (Infectious) | 0.75 | Pitzer *et al.*, (2015) |
| $\theta$ | Rate of transition from recovered to susceptible classes | 0.7204 | Adetunde, I. (2008) |
| $\omega$ | Recovery rate from Carrier | 0.676 | Bailey, N.T. (1982) |
| $v_2$ | Rate of vaccination | 0.220 | Kailan Suhuyini and Seidu (2023) |
| n | Fraction of recruited susceptible | 0.670 | Kailan Suhuyini and Seidu (2023) |
| $\tau$ | Treatment rate | 0.851 | Abboubakar and Racke (2021) |
| $\psi$ | Rate of progression into Infection | 0.142 | Kailan Suhuyini and Seidu (2023) |
| $\beta$ | Transmission rate | 0.714 | Kailan Suhuyini and Seidu (2023) |
| $\eta$ | proportion of susceptible | 0.650 | Kailan Suhuyini and Seidu (2023) |
| $\delta$ | Disease-induced mortality | 0.0022 | Abboubakar and Racke (2021) |
| $\gamma_1$ | Infectiousness from carrier | 0.02 | Peter *et al.*, (2018) |
| $\gamma_2$ | Infectiousness from infected | 0.01 | Peter *et al.*, (2018) |
| $\gamma_3$ | Infectiousness from bacteria | 0.01 | Peter *et al.*, (2018) |
| $\mu_b$ | Rate of bacteria decay | 0.217 | Pitzer *et al.*, (2015) |

**Basic Properties**

**Non-Negativity of Solution**

Theorem 1. Let $\Omega=\{(V,S,C,I,R,V_B,B)\in\mathbb{R}^+_7\}$. If non-negative conditions and initial conditions are assumed for system (1), then all its solutions remain non-negative t>0. Thus, V(t)≥0, S(t)≥0, C(t)≥0, I(t)≥0, R(t)≥0, $V_B$ (t)≥0, B(t)≥0 of the system is non-negative for all t>0.

**Proof**

Considering the first equation from the model (1)

$dV/dt=(1-n)\Lambda+ v_1 S+v_2 R-(\rho+\phi+\mu)V$

Accordingly,

$dV/dt \geq -(\rho+\phi+\mu) V$

$\int 1/v\, dV \geq -\int(\rho+\phi+\mu)\, dt$

Integrating both sides results

$In|V|\geq-(\rho+\phi+\mu)t+c$

This implies that

$V \geq e^{-(\rho+\phi+\mu)t+C}$

Consequently $V(t) \geq V_0\, e^{-(\rho+\phi+\mu)t} \geq 0 \forall t > 0$

Following the same approach, the study can proof for {S(0)≥0, C(0)≥0, I(0)≥0, R(0)≥0, B(0)≥0, $V_B(0)\geq0$)}. Hence the solution for the model is non-negative.

**Boundedness of Solutions**

Given a non-negative initial condition $(V(0),S(0),C(0),I(0),R(0),B(0),V_B(0))\in\mathbb{R}^+_7$, the human subsystem of system (1) yields N(t) as a solution to the differential equation.

$d N(t)/dt=\Lambda-\mu N(t)-\delta I(t)$

which implies that

$d N(t)/dt \leq \Lambda-\mu N(t)$

and therefore

$$\lim_{t\to\infty} N(t) \leq \frac{\Lambda}{\mu}$$

Hence, N(t) is bounded

Following the above inequality, the study obtain from the bacteria equation in (1)

$dB/dt \leq (\Lambda(\xi_1+\xi_2))/\mu-\mu_b B$

Solving the above inequality gives

$$B(t) \leq \frac{\Lambda(\xi_1+\xi_2)[1-e^{-\mu_b t}]}{\mu_b\mu} + B(t)e^{-\mu_b t}$$

Taking the limit

$$\lim_{t\to\infty} B(t) \leq \frac{\Lambda(\xi_1+\xi_2)}{\mu_b\mu}$$

Hence B(t) is equally bounded

Therefore the above result suggest that the system solution (1) are non-negative and bounded in the region $\Omega=\{(V_0, S_0, C_0, I_0, R_0, B_0, V_{B_0})\ R^+_7: V + S + C + I + R+ V_B+ B \leq \Lambda/\mu; B(t) \leq (\Lambda(\xi_1+\xi_2))/(\mu_b\mu)\}$

**Existence of Equilibria**

For the developed model, the disease free and endemic equilibrium is obtained. A Disease Free Equilibrium (DFE) is a state solution to the model in which the epidemic is eradicated from the studied population. An Endemic Equilibrium (EE) point is defined as a positive steady state solution when the disease persists in the studied population.

**Disease Free Equilibrium (DFE)**

The DFE which is the point at which typhoid fever is eradicated from the population and is given by $\varepsilon^0=(V^0, S^0, 0, 0, 0, V^0_B, 0)$ , where

$$V^0=\frac{\Lambda((1-n)k_2+nv_1)}{k_1k_2-\phi v_1}, S^0=\frac{\Lambda((1-n)\phi+nk_1)}{k_1k_2-\phi v_1}, V_B^0=\frac{\rho\Lambda((1-n)k_2+nv_1)}{\mu(k_1k_2-\phi v_1)}$$

**The Basic Reproduction Number ($\mathcal{R}_0$)**

Diekmann *et al.*, (1990) define the basic reproduction number ($\mathcal{R}_0$) which is an epidemiological quantity as the average number of secondary infection cases an infectious person would produce in a population or community where all persons are susceptible to the disease.

**The Next Generation Matrix**

The size of the $\mathcal{R}_0$ can be computed by using the popular technique known as the next generation matrix approach. This approach, which was formulated by Diekmann *et al.*, (1990) but modified by Driessche and Watmough (2002) by constructing n×n matrix from the model equations and considering only the infective classes

Following the technique in Driessche and Watmough (2002), the infected sub-system of model system (1) is given by the following set of equations

$dC/dt = \eta\lambda S - k_3 C$ ;

$dI/dt = (1-\eta)\lambda S + \psi C - k_4 I$;

$dB/dt = \xi_1 C + \xi_2 I - \mu_b B$ (2)

Driessche and Watmough (2002) define the matrix $F$ as the component comprising the infection terms (transmission) and $V$ comprises all the other terms (transitions). The matrix F and matrix $V$ are then given by

$$\mathcal{F} = \begin{bmatrix} \beta S^0\eta\gamma_1 & \beta S^0\eta\gamma_2 & \beta S^0\eta\gamma_3 \\ \beta S^0(1-\eta)\gamma_1 & \beta S^0(1-\eta)\gamma_2 & \beta S^0(1-\eta)\gamma_3 \\ 0 & 0 & 0 \end{bmatrix}$$

$$\mathcal{V} = \begin{bmatrix} k_3 & 0 & 0 \\ -\psi & k_4 & 0 \\ -\xi_1 & -\xi_2 & \mu_b \end{bmatrix}$$

$$\mathcal{V}^{-1} = \begin{bmatrix} \frac{1}{k_3} & 0 & 0 \\ \frac{\psi}{k_3k_4} & \frac{1}{k_4} & 0 \\ \frac{\xi_1k_4+\xi_2\psi}{k_3k_4\mu_b} & \frac{\xi_2}{k_4\mu_b} & \frac{1}{\mu_b} \end{bmatrix}$$

The $\mathcal{R}_0$ shall be set to the spectral radius ($\rho FV^{-1}$), that is $\mathcal{R}_0 = \rho(FV^{-1})$. However, the largest eigenvalue denotes the next generation matrix Therefore,

$$\mathcal{F}\mathcal{V}^{-1} = \begin{bmatrix} \beta S^0\eta\gamma_1 & \beta S^0\eta\gamma_2 & \beta S^0\eta\gamma_3 \\ \beta S^0(1-\eta)\gamma_1 & \beta S^0(1-\eta)\gamma_2 & \beta S^0(1-\eta)\gamma_3 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{k_3} & 0 & 0 \\ \frac{\psi}{k_3k_4} & \frac{1}{k_4} & 0 \\ \frac{\xi_1k_4+\xi_2\psi}{k_3k_4\mu_b} & \frac{\xi_2}{k_4\mu_b} & \frac{1}{\mu_b} \end{bmatrix}$$

The basic reproduction number which is the highest eigenvalue for system (1) is given as (3)

$$\mathcal{R}_0 = \frac{\beta S^0[\gamma_1\eta k_4\mu_b + \gamma_2[\mu_b\psi\eta + (1-\eta)k_3\mu_b\eta] + \gamma_3[(1-\eta)\xi_2k_3\eta + \eta(\xi_1k_4+\psi\xi_2)]]}{k_3k_4\mu_b}$$

**Stability Analyses**

A system's equilibrium points can be categorised as stable, unstable, or asymptotically stable based on the characteristics of the eigenvalues of the ODE system's coefficient matrix or the Jacobian matrix of the nonlinear systems around those points.

**Local Stability**

A system of ordinary differential equations (ODE) is locally asymptotically stable at a given point if all of its Jacobian matrix's eigenvalues are strictly negative or complex with negative real parts at that point. This is known as the Routh-Hurwitz stability criterion, and it is used to determine the local asymptotic stability of differential equations.

**Theorem 1**

The disease free equilibrium point is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

**Proof**

To proof the local stability of typhoid-free equilibrium, the work obtain the Jacobian matrix model system of (1) at the disease free equilibrium $\varepsilon^0$:

$$J(\varepsilon^0) = \begin{bmatrix} -k_1 & v_1 & 0 & 0 & v_2 & 0 & 0 \\ \emptyset & -k_2 & -\gamma_1\beta S^0 & -\gamma_2\beta S^0 & \theta & 0 & -\gamma_3\beta S^0 \\ 0 & 0 & \eta\gamma_1\beta S^0 - k_3 & \eta\gamma_2\beta S^0 & 0 & 0 & \eta\gamma_3\beta S^0 \\ 0 & 0 & (1-\eta)\gamma_1\beta S^0 + \psi & (1-\eta)\gamma_2\beta S^0 - k_4 & 0 & (1-\eta)\gamma_3\beta S^0 & 0 \\ 0 & 0 & \omega & 0 & -k_5 & 0 & 0 \\ \rho & 0 & 0 & 0 & 0 & -\mu & 0 \\ 0 & 0 & \xi_1 & \xi_2 & 0 & 0 & -\mu_b \end{bmatrix}$$

$$J(\varepsilon^0) = \begin{bmatrix} J_1 & J_2 \\ J_3 & J_4 \end{bmatrix}$$

*Where*

$$J_1 = \begin{bmatrix} -k_1 & v_1 \\ \phi & -k_2 \end{bmatrix}$$

$$J_2 = \begin{bmatrix} 0 & 0 & v_2 & 0 & 0 \\ -\gamma_1\beta S^0 & -\gamma_2\beta S^0 & \theta & 0 & -\gamma_3\beta S^0 \end{bmatrix}$$

$$J_3 = \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ \rho & 0 \\ 0 & 0 \end{bmatrix}$$

$$J_4 = \begin{bmatrix} \eta\gamma_1\beta S^0 - k_3 & \eta\gamma_2\beta S^0 & 0 & 0 & \eta\gamma_3\beta S^0 \\ (1-\eta)\gamma_1\beta S^0 + \psi & (1-\eta)\gamma_2\beta S^0 - k_4 & 0 & (1-\eta)\gamma_3\beta S^0 & 0 \\ \omega & 0 & -k_5 & 0 & 0 \\ 0 & 0 & 0 & -\mu & 0 \\ \xi_1 & \xi_2 & 0 & 0 & -\mu_b \end{bmatrix}$$

The eigenvalues of $J(\varepsilon^0)$ are determined from the sub-matrices $J_1$ and $J_4$. The characteristic polynomial of $J_1$ is

$Pj_1(Y)=\det(J_1-YI_1)=Y^2+Y(k_1+k_2)+k_6$ (4)

where $k_6=k_1k_2-v_1\phi=(\mu(k_2+\phi)+\rho k_2)>0$. Since all the coefficients of $Pj_1(Y)$ are positive, $J_1$ has eigenvalues with negative real parts.

The work now have to establish that $J_4$ has eigenvalues with negative real parts. The characteristic polynomial of $J_4$ is

$Pj_4(Y)=\det(J_4-YI_4)=(Y+k_5)(Y+\mu)\Psi(Y)=0$ (5)

where

$\Psi(Y):Y^3+a_1Y^2+a_2Y+a_3$

$a_1=\beta S^0[(1-\eta)\gamma_2+\eta\gamma_1]-[k_3+k_4+\mu_b]$

$a_2=\beta S^0[\eta\psi\gamma_2+k_4\gamma_1\eta+(\gamma_2(1-\eta)(k_3+\mu_b))+\mu_b\gamma_1\eta+\eta\gamma_3\xi_1)]-[k_3k_4+(k_3+k_4)\mu_b]$

$a_3=k_3k_4\mu_b(1-\mathcal{R}_0)$

Is evident that two of the eigenvalues of $J_4$ are $-k_5$ and $-\mu$ Now, to conclude on the stability of typhoid-free equilibrium depends on the zeros of $\Psi(Y)$.

These roots have negative real parts if $a_1>0$, $a_2>0$, $a_3>0$, and $a_1a_2>a_3$. Given $a_3>0$, whenever $\mathcal{R}_0<1$. Therefore, the local stability of $\varepsilon^0$ is characterized in the following results.

**Lemma 1**

The typhoid-free equilibrium point $\varepsilon^0$ is locally asymptotically stable at any time $\mathcal{R}_0<1$ and the conditions $a_1>0$, $a_2>0$, $a_3>0$, and $a_1a_2>a_3$ also hold. Otherwise, the equilibrium point is unstable.

**Global Stability of Typhoid-Free Equilibrium Points**

**Theorem 2**

$\varepsilon^0$ is globally asymptotically stable in the feasible region $\Omega$ if $\mathcal{R}\leq 1$.

**Proof**

To prove the global asymptotic stability of typhoid fever free equilibrium, the research use the method of Lyapunov functions. Defined as: $\mathcal{L}=m_1V+m_2S+m_3C+m_4I+m_5R+m_6V_B$, where $m_i$ for i=1,2,3,4,5,6 are constants to be chosen in the process of the proof are defined.

The derivative of $\mathcal{L}$ along the solution of (1) is given by

$d\mathcal{L}/dt=m_1\,dV/dt+m_2dS/dt+m_3dC/dt+m_4\,dI/dt+m_5\,dR/dt+m_6\,dV_B/dt$ (6)

Substituting the respective derivatives into (6)

$d\mathcal{L}/dt=m_1((1-n)\Lambda+v_1S+v_2R-(\rho+\phi+\mu)V)+m_2(n\Lambda+\phi V+\theta R-(v_1+\lambda+\mu)S)+m_3(\eta\lambda S-(\psi+\omega+\mu)C)+m_4((1-\eta)\lambda S+\psi C-(\tau+\delta+\mu)I)+m_5(\tau I+\omega C-(v_2+\theta+\mu)R)+m_6(\rho V-\mu V_B)$

Simplifying and rearranging

$d\mathcal{L}/dt=m_1(\Lambda-\mu V)+(m_1-m_2)v_1S+(m_1-m_5)v_2R+(m_2-m_1)\emptyset V+(m_6-m_1)\rho V+(m_2-m_6)\theta R+(m_3-m_4)\eta\lambda S+(m_4-m_2)\lambda S+(m_6-m_4)\tau I+(m_4-m_3)\psi C+(m_5-m_3)\omega C-m_2\mu S-m_3\mu C-m_4\delta I-m_4\mu I-m_5\mu R-m_6\mu V_B$

Choosing $m_1$, $m_2$, $m_3$, $m_4$, $m_5$, $m_6$ such that $m_1=m_2=m_3=m_4=m_5=m_6$ and $\Lambda-\mu V=0$

Gives,

$d\mathcal{L}/dt=-m_2\mu S-m_3\mu C-m_4\delta I-m_4\mu I-m_5\mu R-m_6\mu V_B$ (7)

It follows that $\mathcal{L}$ is positive definite and $d\mathcal{L}/dt$ is negative definite. Therefore, the function $\mathcal{L}$ is a Lyapunov function for the model (1) and by Lyapunov asymptomatic stability theorem (Nana-Kyere *et al.*, 2022), the disease-free equilibrium $\varepsilon^0$ is globally asymptotically stable.

**Endemic Equilibrium Point (EE)**

At the EE point ($E^{**}$) typhoid fever exists. The state variables all nonzero, evaluating the state variables ($V^{**}$, $S^{**}$, $C^{**}$, $I^{**}$, $R^{**}$, $V_B{}^{**}$, $B^{**}$) of equations of the system (1) by setting the right-hand side to zero,

$0=(1-n)\Lambda+v_1S+v_2R-(\rho+\phi+\mu)V$;

$0=n\Lambda+\phi V+\theta R-(v_1+\lambda+\mu)S$;

$0=\eta\lambda S-(\psi+\omega+\mu)C$;

$0=(1-\eta)\lambda S+\psi C-(\tau+\delta+\mu)I$;

$0=\tau I+\omega C-(v_2+\theta+\mu)R$;

$0=\rho V-\mu V_B$;

$0=\xi_1C+\xi_2I-\mu_bB$. (8)

The EE points of the dynamical system is as follows, where

$$V^{**}=\frac{(1-n)\Lambda}{k_1}+\left[\frac{v_1}{k_1}+v_2\left(\frac{\omega\eta}{k_5k_3k_1}+\left(\frac{\eta\psi}{k_5k_4k_3k_1}+\frac{1-\eta}{k_5k_4k_1}\right)\tau\right)\lambda^{**}\right]S^{**}$$

$$S^{**}=\frac{\Lambda(nk_1+\phi(1-n))}{\Gamma\lambda^{**}k_1+k_2k_1-v_1\phi},\ \text{where}\ \Gamma=1-\frac{(v_2\phi+k_1\theta)}{k_5k_4k_3k_1}[(\psi\tau+k_4\omega)\eta+\tau k_3(1-\eta)]$$

$$C^{**}=\frac{\lambda^{**}S^{**}[\eta\Lambda(nk_1+(1-n)\phi)]}{(k_1k_2+\Gamma\lambda^{**}k_1-v_1\phi)k_3}$$

$$I^{**}=\lambda^{**}S^{**}\left(\frac{\eta\psi}{k_4k_3}+\frac{1-\eta}{k_4}\right)$$

$$R^{**}=\lambda^{**}S^{**}\left[\frac{\omega\eta}{k_5k_3}+\tau\left(\frac{1-\eta}{k_5k_4}+\frac{\eta\psi}{k_5k_4k_3}\right)\right]$$

$$V_B{}^{**}=\frac{\rho}{\mu}S^{**}\left[\frac{v_1}{k_1}+v_2\left(\frac{\omega\eta}{k_5k_3k_1}+\left(\frac{\eta\psi}{k_5k_4k_3k_1}+\frac{1-\eta}{k_5k_4k_1}\right)\tau\right)\lambda^{**}\right]+\frac{\rho\Lambda(1-n)}{k_1\mu}$$

$$B^{**}=\lambda^{**}S^{**}\left[\xi_2\left(\frac{1-\eta}{\mu_bk_4}+\frac{\eta\psi}{k_4k_3\mu_b}\right)+\frac{\eta\xi_1}{k_3\mu_b}\right] \quad (9)$$

$$\text{Where}\ \lambda^{**}=\beta(\gamma_1C^{**}+\gamma_2I^{**}+\gamma_3B^{**}) \quad (10)$$

Substituting $C^{**}, I^{**}$ and $B^{**}$ into (10)

$$\lambda^{**}=\beta\left(\begin{array}{c}\gamma_1\left[\frac{\lambda^{**}S^{**}[\eta\Lambda(nk_1+(1-n)\phi)]}{(k_1k_2+\Gamma\lambda^{**}k_1-v_1\phi)k_3}\right]+\gamma_2\left[\lambda^{**}S^{**}\left(\frac{\eta\psi}{k_4k_3}+\frac{1-\eta}{k_4}\right)\right]\\+\gamma_3\left[\lambda^{**}S^{**}\left[\xi_2\left(\frac{1-\eta}{\mu_bk_4}+\frac{\eta\psi}{k_4k_3\mu_b}\right)+\frac{\eta\xi_1}{k_3\mu_b}\right]\right]\end{array}\right) \quad (11)$$

$\lambda^{**}$ is explicitly expressed with the other model parameters
Simplifying (11) results

$$\lambda^{**}\left(\lambda^{**} - \frac{(k_2k_1 - v_1\phi)}{\Gamma}(\mathcal{R}_0 - 1)\right) = 0 \quad (12)$$

From (12), the disease free equilibrium is $\lambda^{**}= 0$ whiles the persistent of the disease equilibrium is given by

$$\lambda^{**} = \frac{(k_2k_1 - v_1\phi)}{\Gamma}(\mathcal{R}_0 - 1) \quad (13)$$

**Lemma 2**

Equation (13) exhibit a typhoid free equilibrium when $\mathcal{R}_0< 1$

**Proof**

Given $((k_2k_1 - v_1\phi)/\Gamma)>0$ , it implies that $\lambda^{**} > 0$ when $\mathcal{R}_0 >1$ and $\lambda^{**} \leq 0$ when $\mathcal{R}_0 \leq 1$.
If $\lambda^{**}>0$, it explains the existence of endemic equilibrium. Hence the proof.

**Sensitivity Analysis**

In this subsection, the impact of the system (1) parameters on the $\mathcal{R}_0$ is tested to determine how these parameters affect the transmission of typhoid illness. To obtai$\mathcal{R}_0$he sensitivity index, the study partially differentiated in relation to the parameters of the model (1). The work employed the normalized forward sensitivity index for the analytical equation for the $\mathcal{R}_0$'s sensitivity to each parameter as follows:

$\delta^{(\mathcal{R}_0)}= \partial\mathcal{R}_0/\partial\delta\times\delta/\mathcal{R}_0 = -0.00072$

The work calculate the sensitivity indices for each parameter utilized in the $\mathcal{R}_0$ in a similar manner. Table 2 depicts the $\mathcal{R}_0$ sensitivity indices in relation to the parameters.

**Table 2:** Sensitivity indices of $\mathcal{R}_0$ with respect to each parameter

| Parameter | Sensitivity Indices |
|---|---|
| $\mu$ | -0.00005 |
| $\mu_b$ | -0.97912 |
| $\delta$ | -0.00072 |
| $\omega$ | -0.80844 |
| $\tau$ | -0.27995 |
| $\psi$ | -0.04796 |
| $\gamma_1$ | +0.25095 |
| $\gamma_2$ | +0.06299 |
| $\gamma_3$ | +0.68606 |
| $\xi_1$ | +0.46836 |
| $\xi_2$ | +0.21770 |

**Interpretation of Sensitivity Indices**

Table (2), presents sensitivity indices for key parameters, showing that positive parameters $\gamma_1$, $\gamma_2$, $\gamma_3$, $\xi_1$ and $\xi_2$ significantly influence the disease spread within the community. Conversely, negative parameters like $\mu$, $\mu_b$, $\delta$, $\omega$, $\tau$ and $\psi$ reduce disease burden by decreasing the $\mathcal{R}_0$.

**Typhoid Fever Optimal Control Model**

The optimal control problem is formulated by restructuring the compartmental model (1) into an optimal control model with admissible controls that are considered to be continuous in time. The controls introduced to the new model are defined as follows: booster vaccination control rate ($\rho$), vaccination control rate ($v_1$) bacteria sterilization control rate ($u_b$), treatment control rate( $\tau$) , personal hygiene control rate ($u_1$).
The considered time is denoted by t∈[0,T], where T is defined to be the final time.
Now, the new structured model is defined below

$$\begin{aligned}
\frac{d}{dt}V &= (1-n)\wedge + v_1S + v_2R - (\rho + \phi + \mu)V;\\
\frac{d}{dt}S &= n\wedge + \phi V + \theta R - (v_1 + \lambda + \mu)S;\\
\frac{d}{dt}C &= (1-u_1)\eta\lambda S - (\psi + \omega + \mu)C;\\
\frac{d}{dt}I &= (1-\eta)(1-u_1)\lambda S + \psi C - (\tau + \delta + \mu)I;\\
\frac{d}{dt}R &= \tau I + \omega C - (v_2 + \theta + \mu)R;\\
\frac{d}{dt}V_B &= \rho V - \mu V_B;\\
\frac{d}{dt}B &= (1-u_1)\xi_1 C + (1-u_1)\xi_2 I - \mu_b B
\end{aligned} \quad (14)$$

with V≥0, S≥0, C≥0, I≥0, R≥0, $V_B$≥0, B≥0
A lot of intervention has been introduced to curtail the spread of the typhoid fever among the population and also to reduce the bacteria in the environment. In an attempt to do so, the work investigate the optimal level of effort that will be required in controlling the disease spread. The work introduces five time dependent controls as follows:

a. First control: $0 \leq v_1 \leq 1$
b. Second control: $0 \leq \rho \leq 1$
c. Third control: $0 \leq \tau \leq 1$
d. Fourth control: $0 \leq u_1 \leq 1$
e. Fifth control: $0 \leq u_b \leq 1$

The infection term $\lambda=\beta\gamma_1C(t)+\beta\gamma_2I(t)+\beta\gamma_3B(t)$ is modified as $(1-u_1)\lambda$
The excretion of the typhoid fever bacteria into the environment by the carrier population and the infected population is reduced as a result of personal hygiene. The excretion parameter for the infected population is modified as $\xi_2\rightarrow(1-u_1)\xi_2$ whiles the carrier population is modified as $\xi_1\rightarrow(1-u_1)\xi_1$
The work introduce a measure control set:

$$\mathfrak{C} := \{\Delta = (v_1^*, \rho^*, \tau^*, u_1^*, u_b^*) \mid \Delta_j(t)$$

is Lebesgue measurable, $0 \leq \Delta_j \leq 1$, $t \in [0, t_f]$ for j=1, 2, 3, 4, 5}
The aim of the considered control strategy is to:

a. Reduce the typhoid Carriers and Symptomatic infectious persons
b. Making the environment free from Salmonella bacterium

Intending to achieve our goals, the study design an objective functional following (Nana-Kyere *et al.*, 2022) as:

$$J=\int_0^{t_f}[A_1(C(t) + I(t)) + A_2B(t) + 1/2\, h_1 v_1^2 + 1/2\, h_2\rho^2 + 1/2\, h_3\tau^2 + 1/2\, h_4 u_1^2 + 1/2\, h_5 u_b^2]dt \quad (15)$$

The constants $A_1$ are weight related to symptomatic infectious and asymptomatic infectious individuals and $A_2$ denote the total number of Bacteria B. Additionally; the weights $h_1$, $h_2$, $h_3$, $h_4$ and $h_5$ are positive and are needed

to stabilize units in the objective functional. Again, the weights are included in the objective functional to highlight the importance of the controls in reducing the carriers, infected and bacteria populations in the community. The weights are in association with time-dependent control functions $v_1$, $\rho$, $\tau$, $u_1$, $u_b$, respectively. The main objective of the control mode is to identify an optimal control functions ($v^*_1$, $\rho^*$, $\tau^*$, $u^*_1$, $u^*_b$) that makes

$$\mathcal{J}(v_1^*, \rho^*, \tau^*, u_1^*, u_b^*) = \min_{\Delta} \mathcal{J}(v_1^*, \rho^*, \tau^*, u_1^*, u_b^*) \quad (16)$$

The core idea behind the optimal control problem is that the study must first confirm the existence optimal control for equation (14) before determining the optimality system.

**Existence of an Optimal Control**

**Theorem 3**

Consider the objective functional J given by equation (15) with ($v^*_1$, $\rho^*$, $\tau^*$, $u^*_1$, $u^*_b$) $\in \mathbb{C}$ subject to the constraint state system (14). There exist ($v^*_1$, $v^*_2$, $\rho^*$, $u^*_1$, $u^*_2$) $\in \mathbb{C}$ such that $J(v^*_1, \rho^*, \tau^*, u^*_1, u^*_b) = \min \{J(v_1, \rho, \tau, u_1, u_b) \mid (v_1, \rho, \tau, u_1, u_b) \in \mathbb{C}\}$

**Proof**

The integrand of the objective functional given by equation (15) is convex on the closed, convex control set $C$. Since the model is linear in the control variables and is bounded by a linear system in the state variables, then the conditions for existence of optimal control are satisfied (Fleming & Rishel, 1975), Theorem 4.1 page 68].

**The Optimality System**

The Pontryagin's Maximum Principle (PMP) to derive the necessary conditions that the five controls along with the state variables must satisfy (Pontryagin *et al.*, 1986). The Hamiltonian function for the system, where $\lambda_i$ i= 1, 2, 3, 4, 5, 6, 7 are the adjoint variables:

$$\begin{aligned}\mathbb{H} \coloneqq\ & A_1\big(C(t)+I(t)\big)+A_2B(t)+\frac{1}{2}h_1v_1^2+\frac{1}{2}h_2\rho^2+\frac{1}{2}h_3\tau^2+\frac{1}{2}h_4u_1^2+\frac{1}{2}h_5u_b^2+\lambda_1[(1-\\ & n)\wedge+v_1S+v_2R-\phi V-\rho V-\mu V]+\lambda_2\big[n\Lambda+\phi V+\theta R-v_1S-(1-u_1)\big(\beta(\gamma_1C+\gamma_2I+\\ & \gamma_3B)\big)S-\mu S\big]+\lambda_3\big[(1-u_1)\big(\beta(\gamma_1C+\gamma_2I+\gamma_3B)\big)S\eta-\psi C-\omega C-\mu C\big]+\lambda_4\big[(1-\eta)(1-\\ & u_1)\big(\beta(\gamma_1C+\gamma_2I+\gamma_3B)\big)S+\psi C-\delta I-\tau I-\mu I\big]+\lambda_5[\tau I+\omega C-\theta R-v_2R-\mu R]+\\ & \lambda_6[\rho V-\mu V_B]+\lambda_7[(1-u_1)\xi_1C+(1-u_1)\xi_2I-\mu_bB] \end{aligned} \quad (17)$$

The above results presents the adjoint system and control characterization

**Theorem 4**

Given an optimal control ($v^*_1$, $\rho^*$, $\tau^*$, $u^*_1$, $u^*_b$) and corresponding state solutions V, S, C, I, R, $V_B$, B of the corresponding state system (14), there exist adjoint variables $\lambda_i$ i= 1, 2, 3, 4, 5, 6, 7, satisfying:
with transversality conditions

$$\begin{aligned}\frac{d\lambda_1}{dt} &= \lambda_1[\phi+\rho+\mu]-\lambda_2\phi-\lambda_6\rho\\ \frac{d\lambda_2}{dt} &= -\lambda_1v_1+\lambda_2\big[v_1+(1-u_1)\big(\beta(\gamma_1C+\gamma_2I+\gamma_3B)\big)-\mu\big]-\lambda_3\big[(1-u_1)\big(\beta(\gamma_1C+\gamma_2I+\\ &\gamma_3B)\big)\eta\big]-\lambda_4[(1-\eta)(1-u_1)\big(\beta(\gamma_1C+\gamma_2I+\gamma_3B)\big)]\\ \frac{d\lambda_3}{dt} &= -A_1+\lambda_2[(1-u_1)S\beta\gamma_1]-\lambda_3[(1-u_1)S\eta\beta\gamma_1-\psi-\omega-\mu]-\lambda_4[(1-u_1)S(1-\\ &\eta)\beta\gamma_1+\psi]-\lambda_5\omega-\lambda_7((1-u_1))\xi_1\\ \frac{d\lambda_4}{dt} &= -A_1+\lambda_2[(1-u_1)S\beta\gamma_2]-\lambda_3[(1-u_1)S\eta\beta\gamma_2]-\lambda_4[(1-u_1)S(1-\eta)\beta\gamma_2-\delta-\\ &\tau-\mu]-\lambda_5I-\lambda_7\xi_2(1-u_1)\\ \frac{d\lambda_5}{dt} &= -\lambda_1v_2-\lambda_2\theta+\lambda_5[\theta+v_2+\mu]\\ \frac{d\lambda_6}{dt} &= \lambda_6\mu\\ \frac{d\lambda_7}{dt} &= -A_2+\lambda_2[(1-u_1)S\beta\gamma_3]-\lambda_3(1-u_1)S\eta\beta\gamma_3-\lambda_4(1-u_1)S(1-\eta)\beta\gamma_3+\\ &\lambda_7\mu_b \end{aligned} \quad (18)$$

$\lambda_i(T)=0$, for i= 1, 2, 3, 4, 5, 6, 7 (19)

with control functions which satisfy the optimality condition given by

$$\begin{aligned} v_1^* &= \max\left\{0, \min\left\{1, \frac{(\lambda_2-\lambda_1)S}{h_1}\right\}\right\}\\ \rho^* &= \max\left\{0, \min\left\{1, \frac{(\lambda_1-\lambda_6)V}{h_2}\right\}\right\}\\ \tau^* &= \max\left\{0, \min\left\{1, \frac{\lambda_3\lambda S\eta+\lambda_4(1-\eta)\lambda S+\lambda_7\mathcal{E}_1C+\lambda_7\mathcal{E}_2I-\lambda_2\lambda S}{h_3}\right\}\right\},\\ &\text{where } \lambda=\beta(\gamma_1C+I\gamma_2+\gamma_3B)\\ u_1^* &= \max\left\{0, \min\left\{1, \frac{\lambda_4I-\lambda_5I}{h_4}\right\}\right\}\\ u_b^* &= \max\left\{0, \min\left\{1, \frac{\lambda_7B}{h_5}\right\}\right\} \end{aligned} \quad (20)$$

**Proof**

With reference to the Hamiltonian (17), the adjoint system (18) is determined by partially differentiating the Hamiltonian (17) with respect to the corresponding state variables V, S, C, I, R,$V_B$, B as

$$\begin{aligned} \frac{d\lambda_1}{dt} &= -\frac{\partial\mathbb{H}}{\partial V}\\ \frac{d\lambda_2}{dt} &= -\frac{\partial\mathbb{H}}{\partial S}\\ \frac{d\lambda_3}{dt} &= -\frac{\partial\mathbb{H}}{\partial C}\\ \frac{d\lambda_4}{dt} &= -\frac{\partial\mathbb{H}}{\partial I}\\ \frac{d\lambda_5}{dt} &= -\frac{\partial\mathbb{H}}{\partial R}\\ \frac{d\lambda_6}{dt} &= -\frac{\partial\mathbb{H}}{\partial V_B}\\ \frac{d\lambda_7}{dt} &= -\frac{\partial\mathbb{H}}{\partial B} \end{aligned} \quad (21)$$

The characterization of the controls of (20) are derived by solving ($v^*_1$, $\varrho^*$, $\tau^*$, $u^*_1$, $u^*_b$) from the equation:

$$\frac{\partial \mathbb{H}}{\partial v_1} = \frac{\partial \mathbb{H}}{\partial \rho} = \frac{\partial \mathbb{H}}{\partial \tau} = \frac{\partial \mathbb{H}}{\partial u_1} = \frac{\partial \mathbb{H}}{\partial u_b} = 0 \quad (22)$$

Therefore, the needed characterization is obtained using the bounds on the controls. The optimal system which comprises the state system (14) with initial conditions, the adjoint system with the terminal conditions and the characterization (20).

## RESULTS AND DISCUSSION

The study examines how the different combinations of the controls on the model equation (14) produce different outcomes with the parameters in Table 1 and with the initial conditions V(0)=300, S(0)=1200, C(0)=36, I(0)=21, R(0)=54, $V_B$ (0)=144 and B(0)=600.

The study apply the forward-backward scheme based on the Runge-Kutta's fourth order iterative method to solve the optimality system of the optimal control model numerically using OCTAVE. Following Abboubakar and Racke (2021) and Nana-Kyere *et al*, (2022) the constants $A_1$=10, $A_2$= 8, $h_1$= 30.17e, $h_2$= 25.02e, $h_3$= 36.79e, $h_4$=32e, and $h_5$= 25.39e were used to balance the terms of the objective functional's equation.

For easy simulations and readability the following controls $\nu_1$, $\rho$ , $\tau$ and $\mu_b$ where replaced with u1, u2, u3 and u5 respectively.

Where first vaccination ($u1^*(t)$), booster vaccine( $u2^*(t)$), treatment ($u3^*(t)$), personal hygiene($u4^*(t)$) and bacteria sterilization ($u5^*(t)$) represent the controls.

It should be noted that persons who took the booster vaccine must have already taken the first dosage of the vaccine, when considering various combination strategies, all the different combinations involving u2(t) without u1(t) are disregarded. However, it is possible that some individuals will receive the first dosage of the vaccine and not the booster vaccine, therefore, combination strategies that use ,u1(t) but not u2(t) are taken into consideration.

The study now classify the combinations of the control interventions into two control interventions (as Category A), three control interventions (as Category B) , four control interventions (as Category C) and five control interventions (as Category D).

### Category A

### Strategy A1

Combinations of first dosage of vaccine (u1(t)) and booster vaccine (u2(t))

(u1(t)≠0, u2(t)≠0, u3(t)=0, u4(t)=0, u5(t)=0)

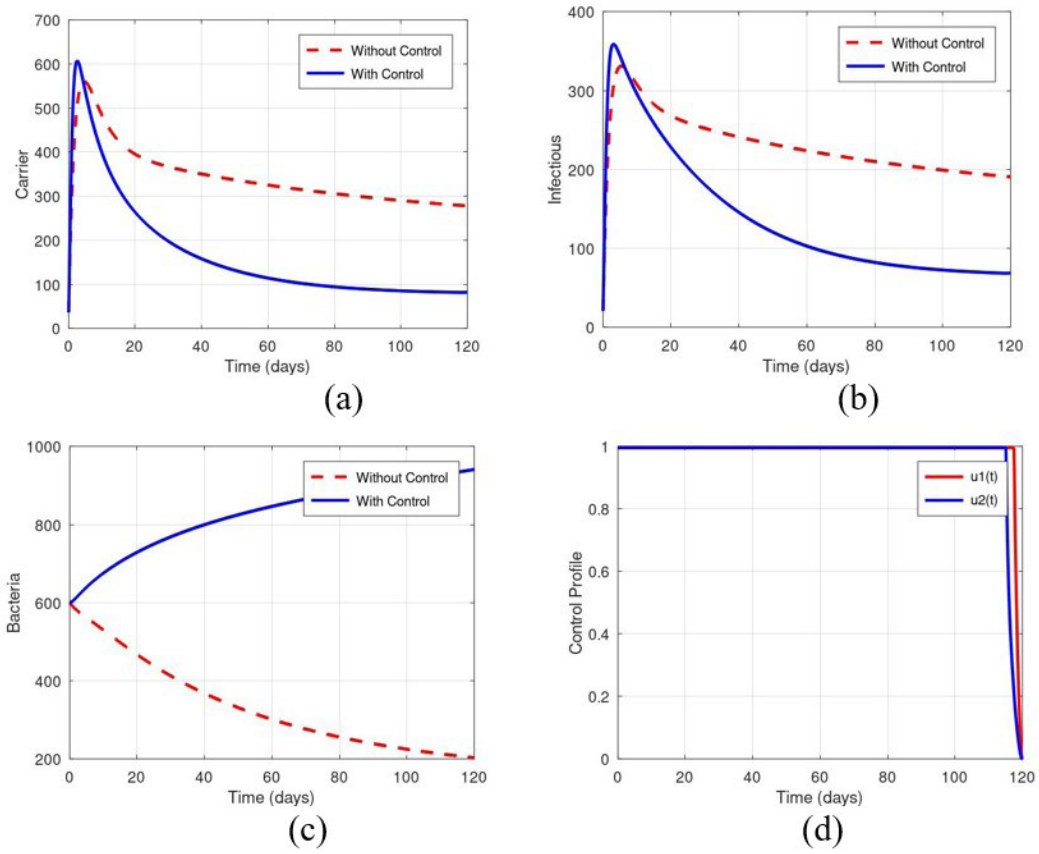


**Figure 2:** Impact of strategy A1 on the optimal control typhoid fever model (14)

From the Figure 2, it can be observed that the invention controls are targeting only the human population. Throughout the intervention period, the size of carriers and that of the infected populations in the human population rises sharply then begins to diminish rapidly at the early days of introducing the intervention controls. This decrease is attained when the two controls, u1(t) and u2(t) are maintained at the upper bound for within

the intervention period and keeping them maximally for about 119 days and 118 days respectively, following that, it ought to be progressively decreased until it reaches its minimum at the end of the control implementation period as shown in Figure 2 (d). Even though there is a decline in the carrier and infected population compared with the absence of control from Figure 2 (a) and (b), it outcome does not give the desired expectation.

**Strategy A2**

Combinations of first dosage of vaccine (u1(t)) and treatment (u3(t))

(u1(t)≠0,u3(t)≠0,u2(t)=0,u4(t)=0,u5(t)=0)

Figure 3 showcases the effect of applying an optimal

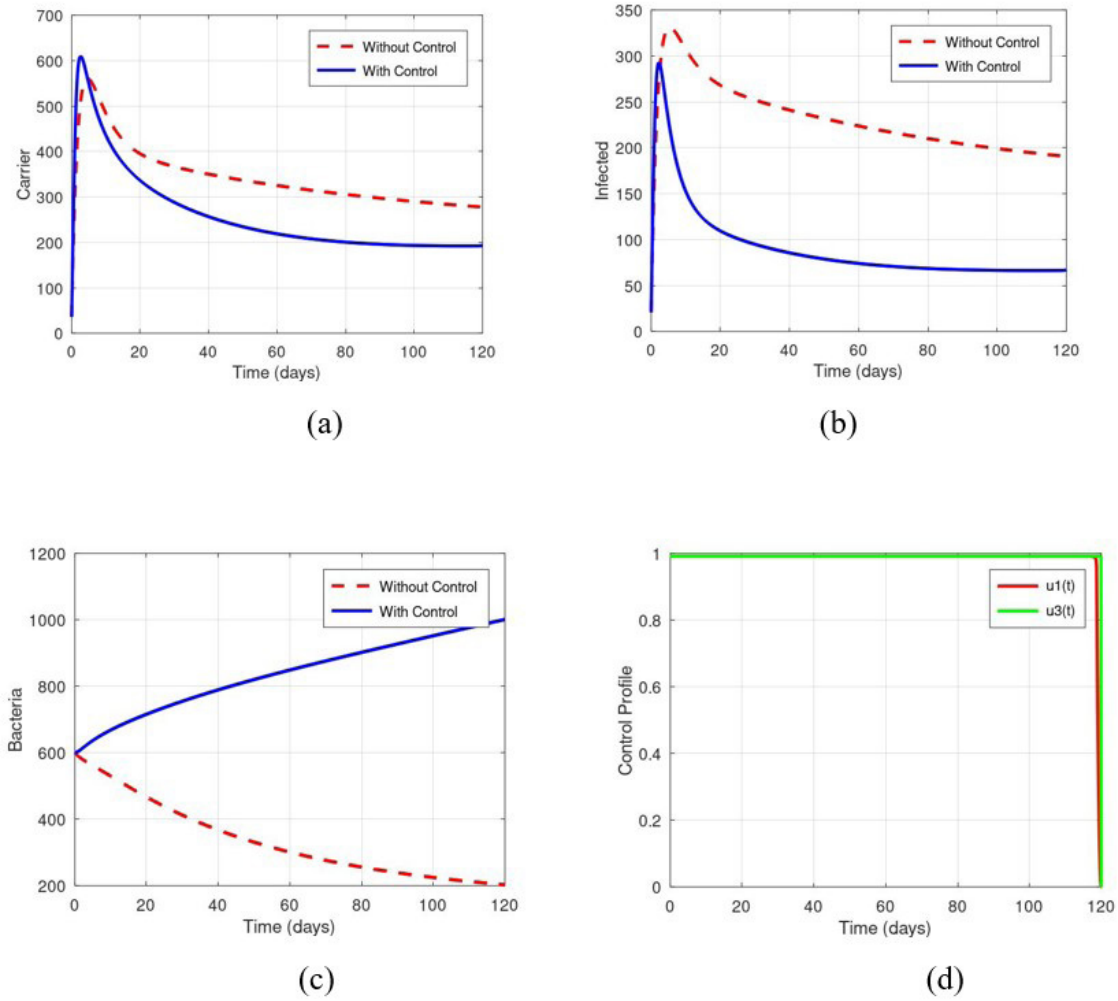


**Figure 3:** Impact of strategy A2 on the optimal control typhoid fever model (14)

combination of first jab of the typhoid fever vaccine, u1(t) together with treatment, u3(t) in reducing typhoid fever among the carriers of the bacteria and those infected with the disease in the population. Figure 3 (a) and (b) shows a fall in the carrier population and infected population respectively. On the part of the control of the control profile, Figure 3 (d), optimal controls u1(t) and u3(t) are continuously sustained at the highest level throughout the intervention period before dropping to their lowest levels at the conclusion of the intervention period, which help to explain the observed positive outcomes.

This indicates that although the controls strategy does not yield the optimal outcome, the controls are effective in curtailing the spread of the disease.

**Strategy A3**

Combinations of first dosage of vaccine (u1(t)) and bacteria sterilization (u5(t))

(u1(t)≠0,u5(t)≠0,u2(t)=0,u3(t)=0,u4(t)=0)

The benefits of a twofold intervention-a first dose vaccine, u1(t) and bacteria sterilization, u5(t) – in the management of typhoid fever are illustrated in Figure 4. The number of carrier and infected people has significantly decreased and that of the bacteria population in the environment has also reduced significantly as a result of this strategy's application. This leads to the observed benefits in disease containment. Figure 4 (d) shows the control profile for the implementation period. It shows that both controls u1(t) and u5(t) are kept at upper bound almost throughout

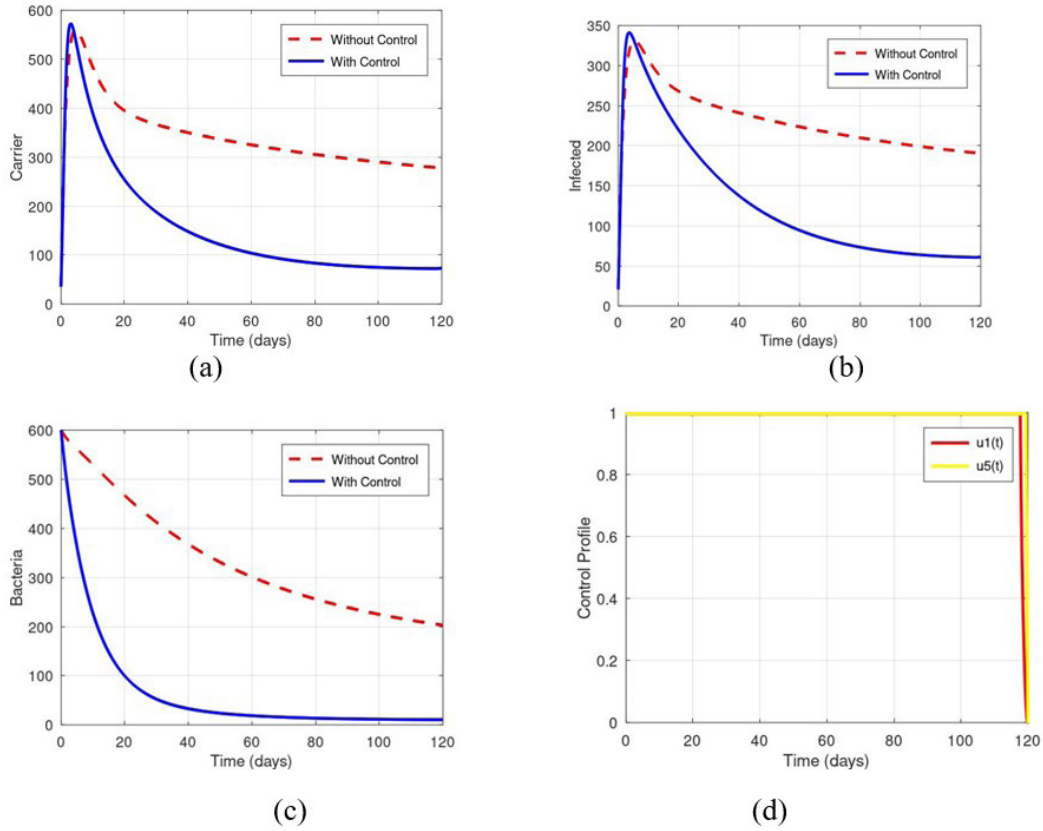


**Figure 4:** Impact of strategy A3 on the optimal control typhoid fever model (14)

before gradually descending back to the lower bound at the end of the period, leading to the observed gain in the control of the disease. This indicates that although the controls strategy does not yield the optimal outcome, the controls are effective in curtailing the spread of the disease.

**Strategy A4**

Combinations of treatment (u3(t)) and bacteria sterilization (u5(t))

(u3(t)≠0,u5(t)≠0,u1(t)=0,u2(t)=0,u4(t)=0)

In Figure 5, the study used controls u3(t) and u5(t) in

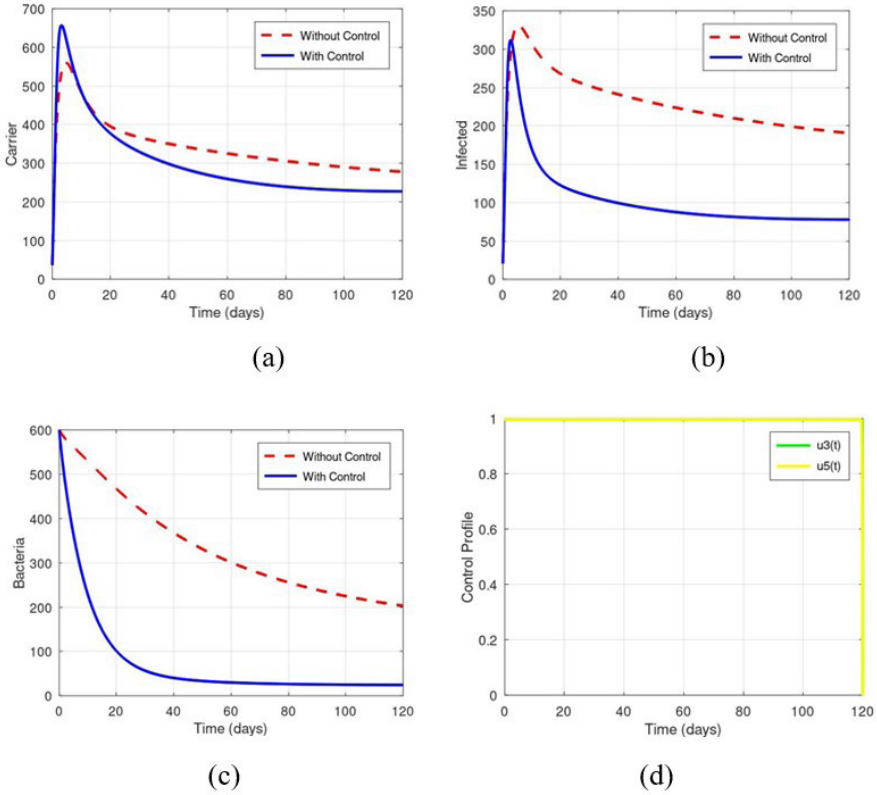


**Figure 5:** Impact of strategy A4 on the optimal control typhoid fever model (14)

an attempt to stop the typhoid fever from spreading. The control model's plot of the graphs in Figures 5(a) and (b) showed a rise in the number of the infectious people and the carrier population at the early days of the simulated period. Both graphs of the carrier population and infected population increases swiftly until it reaches a maximum height of roughly 650 and 310 respectively, at which point its dynamics abruptly alter and it starts to fall. That of Figure 5 (c) of the bacteria control graph shows a fall in the first the day of the intervention. This indicates that although the control strategies do not yield the optimal outcome, it is effective in preventing the disease from spreading further. Figure 5 (d) shows the strategy A-4 control profile. Throughout the 120-day simulated period it can be observed that both the treatment (u3(t)) and bacteria sterilization ((u5(t)) remained at the upper bound.

**Category B**

**Strategy B1**

Combinations of first dosage of vaccine (u1(t)), booster vaccine (u2(t)) and treatment (u3(t))
(u1(t)≠0,u2(t)≠0,u3(t)≠0,u4(t)=0,u5(t)=0)

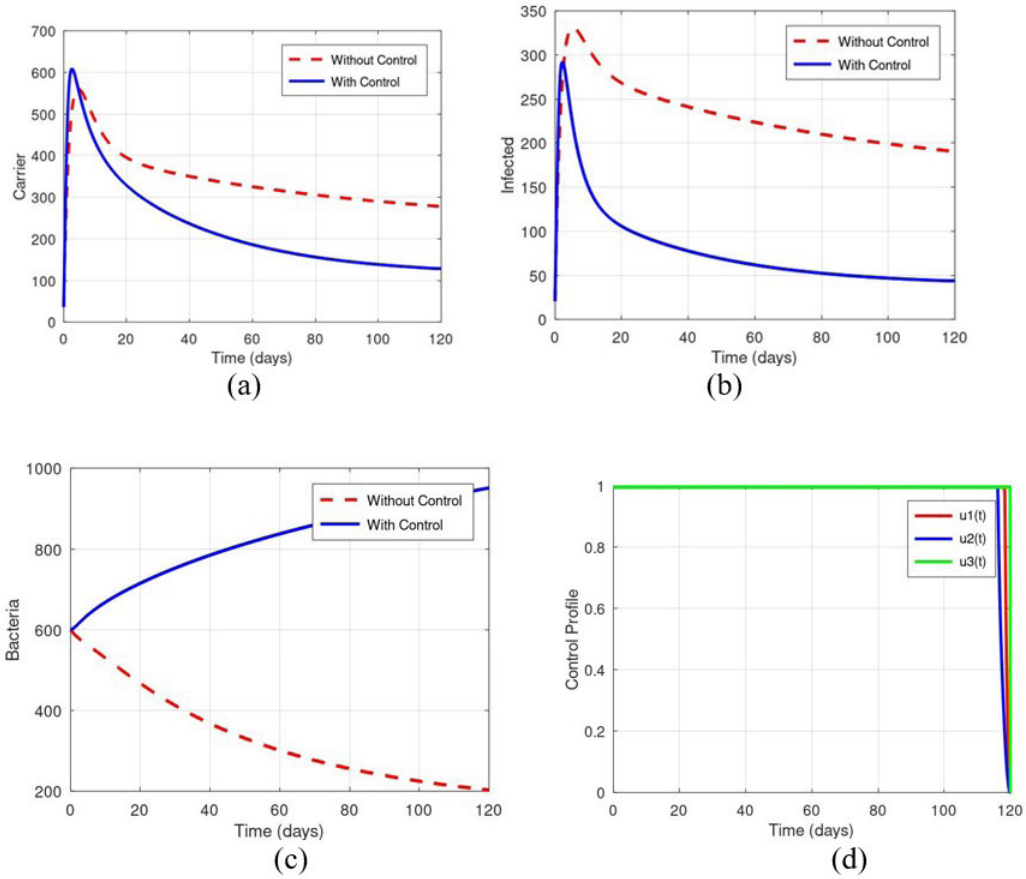


**Figure 6:** Impact of strategy B1 on the optimal control typhoid fever model (14)

From Figure 6, the controls; first dosage of vaccine (u1(t)), booster vaccine (u2(t)) and treatment (u3(t)) were used in an attempt to stop the disease from spreading among the human population. A rise in the number of infected and carrier populations were observed at the beginning of the simulated period, according to the plot of the graphs of Figure 6(a) and (b) of the non-control. However, the intended outcome of reducing the carrier and the infected populations is achieved with the optimal control approaches.

This indicates that, despite not producing the optimum outcome, the control plans u1(t),u2(t) and u3(t) is effective in stopping the disease from spreading further. As can be shown in Figure 6 (d), during the 120-day simulated period u1(t) and u3(t) stayed at upper bound throughout while u2(t) stayed at upper for about 118 days after which it declined to their lower level.

**Strategy B2**

Combinations of first dosage of vaccine (u1(t)), booster vaccine (u2(t)) and bacteria sterilization (u5(t))
(u1(t)≠0,u2(t)≠0,u5(t)≠0,u2(t)=0,u3(t)=0)

Figure 7 presents the effect of implementing an optimal combination of first dosage of vaccine (u1(t)), booster vaccine (u2(t)) and bacteria sterilization (u5(t)) with the aim of reducing the carrier, infected and bacteria population within environment. When these strategies were introduced, the carrier and the infected population decreases. That of the bacteria populations drastically decreases and completely wiped out. The optimal control u5(t) gives the desired result from day 100 to the final time. These impacts are achieved when the optimal controls u1(t),u2(t) and u5(t) are consistently sustained at the highest level for the intervention period for about 118 days and 102 days for u1(t) and u2(t) whiles u5(t)

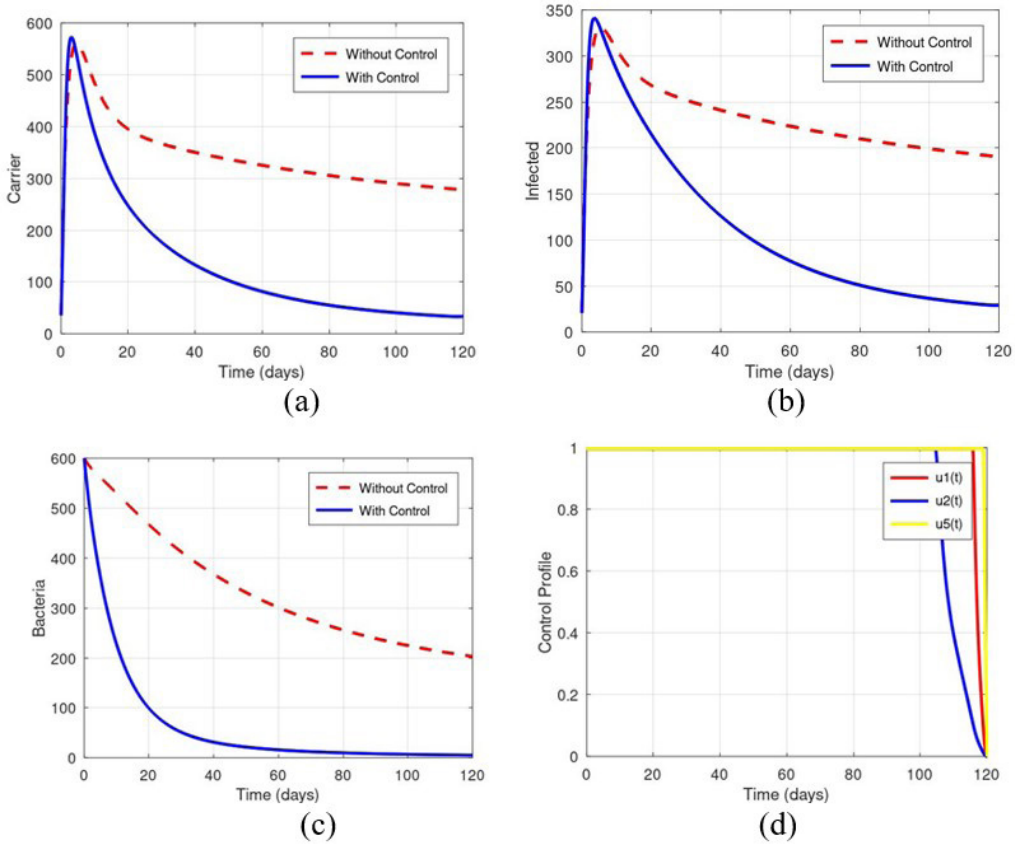


**Figure 7:** Impact of strategy B2 on the optimal control typhoid fever model (14)

120 days before they all gradually runs down to the lower level of the bounds at the end of the intervention period as depicted in Figure 7 (d).

**Strategy B3**

Combinations of first dosage of vaccine (u1(t)), treatment (u3(t)) and bacteria sterilization (u5(t))

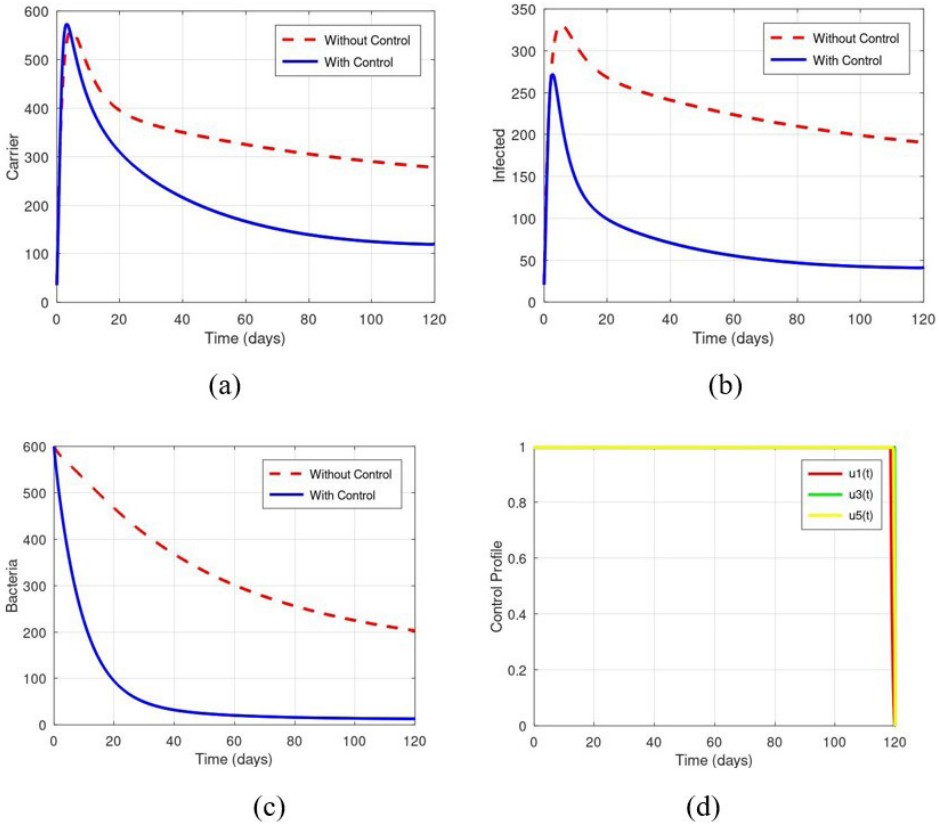


**Figure 8:** Impact of strategy B3 on the optimal control typhoid fever model (3.36)

(u1(t)≠0,u3(t)≠0,u5(t)≠0,u2(t)=0,u4(t)=0)

Figure 8, demonstrate the combined effect of implementing the optimal controls first dosage of vaccine u1(t), treatment u3(t) and bacteria sterilization u5(t) against typhoid fever. When these controls are applied concurrently, the trajectories show a notable decline in the carrier population and infected population after about 2 days and the bacteria population throughout the course of the control application time. Despite not producing the optimum outcome, the control plans u1(t),u3(t) and u5(t) is effective in stopping the disease from spreading further.

Figure 8 (d) shows the strategy B3 control profile. Throughout the 120-day simulated period the researchers observed that the optimal controls; first dose of vaccine u1(t)), treatment (u3(t)) and bacteria sterilization ((u5(t)) remained at the upper bound before declining to the lower bound at the end of the intervention period.

**Strategy B4**

Combinations of first dosage of vaccine (u1(t)), personal hygiene (u4(t)) and bacteria sterilization (u5(t))

(u1(t)≠0,u4(t)≠0,u5(t)≠0,u2(t)=0,u3(t)=0)

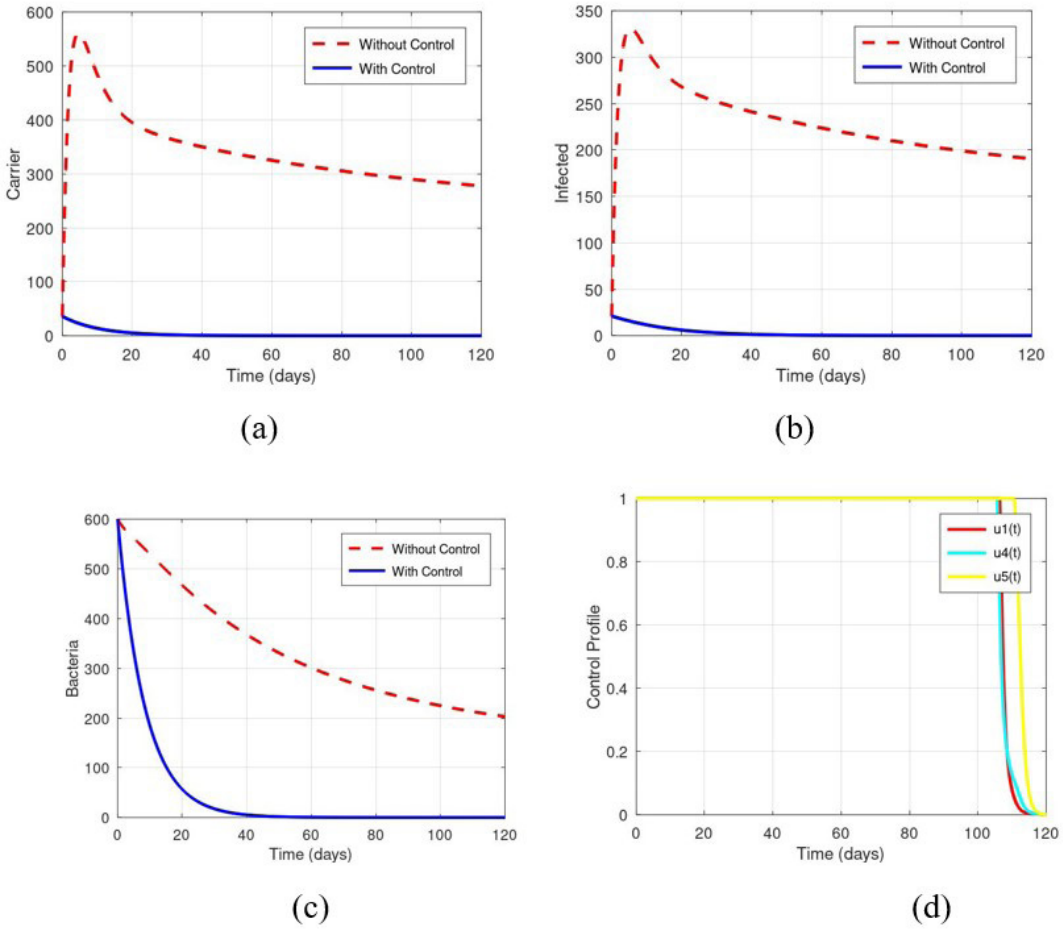


**Figure 9:** Impact of strategy B4 on the optimal control typhoid fever model (14)

In Figure 9, the effect of optimal combination of first dosage of vaccine (u1(t)), personal hygiene (u4(t)) and bacteria sterilization (u5(t)) is presented. The carrier population, infected population and bacteria population initially decreases and further wiped out from day 20, day 30 and day 40 respectively as a result of this control intervention strategy. This success is possible when the controls u1(t),u4(t) and u5(t) are sustained maximally for about 113 days, 113 days and 117 days respectively throughout the simulation period and thereafter reducing them steadily to their minimum levels at the final time of the implementation as shown in Figure 9 (d).

**Category C**

**Strategy C1**

Combinations of first dosage of vaccine (u1(t)), booster vaccine (u2(t)), treatment (u3(t)) and personal hygiene (u4(t))

(u1(t)≠0,u2(t)≠0,u3(t)≠0,u4(t)≠0,u5(t)=0)

In Figure 10, the optimal combination of first dosage of vaccine (u1(t)), booster vaccine(u2(t)), treatment (u3(t)) and personal hygiene (u4(t)) is applied in reducing the carrier, infected and bacteria population within the time of the intervention period. Throughout the time period, the carrier population and the infected population

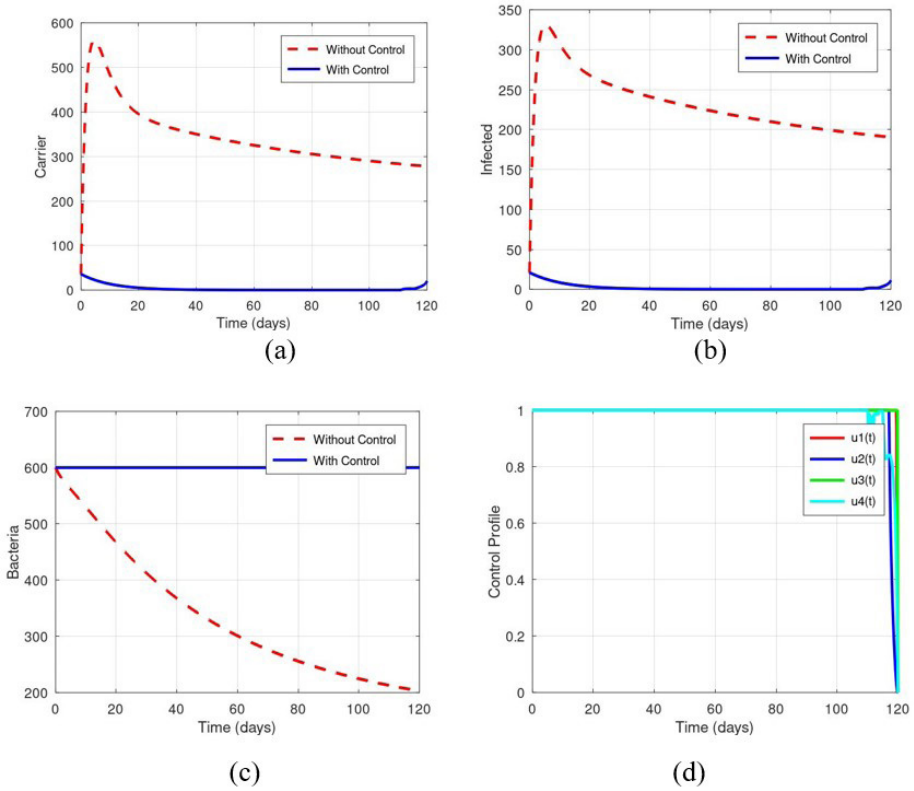


**Figure 10:** Impact of strategy C1 on the optimal control typhoid fever model (14)

decreases and then wiped out on day 20 for both the human population. Despite not producing the optimum outcome, the control plans u1(t),u2(t) ,u3(t)and u4(t) is effective in stopping the disease from spreading further. Figure 10 (d) shows the strategy C1 control profile. Throughout the 120-day simulated period the researchers observed that the optimal controls; first dose of vaccine u1(t)) and treatment (u3(t)) remained at the upper bound whiles booster vaccine(u2(t)) and personal hygiene (u4(t)) for about 118 days before declining to the lower bound at the end of the intervention period.

**Strategy C2**

Combinations of first dosage of vaccine (u1(t)), booster vaccine (u2(t)), treatment (u3(t)) and bacteria sterilization (u5(t))

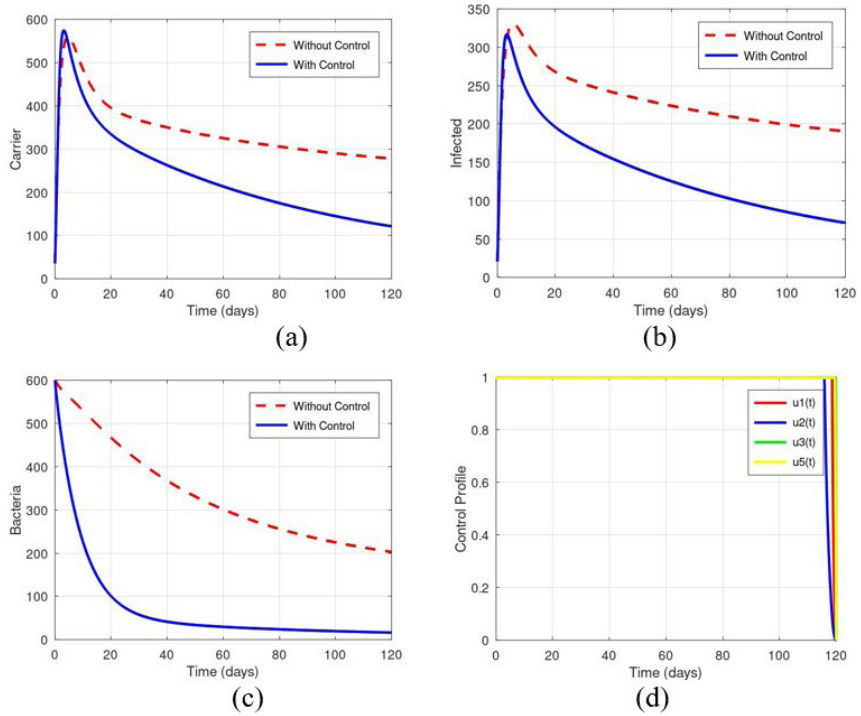


**Figure 11:** Impact of strategy C2 on the optimal control typhoid fever model (14)

(u1(t)≠0,u2(t)≠0,u3(t)≠0,u5(t)≠0,u4(t)=0)

Figure 11, demonstrate the combined effect of implementing the optimal controls first dosage of vaccine u1(t), booster vaccine u2(t), treatment u3(t) and bacteria sterilization u5(t) against typhoid fever. When these controls are applied concurrently, the trajectories show a notable decline in the carrier population and infected population after about 2 days and the bacteria population at the start of the control application time. Despite not producing the optimum outcome, the control plans u1(t),u2(t),u3(t) and u5(t) is effective in stopping the disease from spreading further.

Figure 11 (d) shows the strategy C2 control profile. Throughout the 120-day simulated period the researchers observed that the optimal controls; first dose of vaccine (u1(t)), treatment (u3(t)) and bacteria sterilization ((u5(t)) remained at the upper bound before declining to the lower bound at the end of the intervention period except booster vaccine( u2(t)), which stayed at about for about 119 days.

**Strategy C3**

Combinations of first dosage of vaccine (u1(t)), booster vaccine (u2(t)), personal hygiene (u4(t)) and bacteria sterilization (u5(t))

(u1(t)≠0,u2(t)≠0,u4(t)≠0,u5(t)≠0,u3(t)=0)

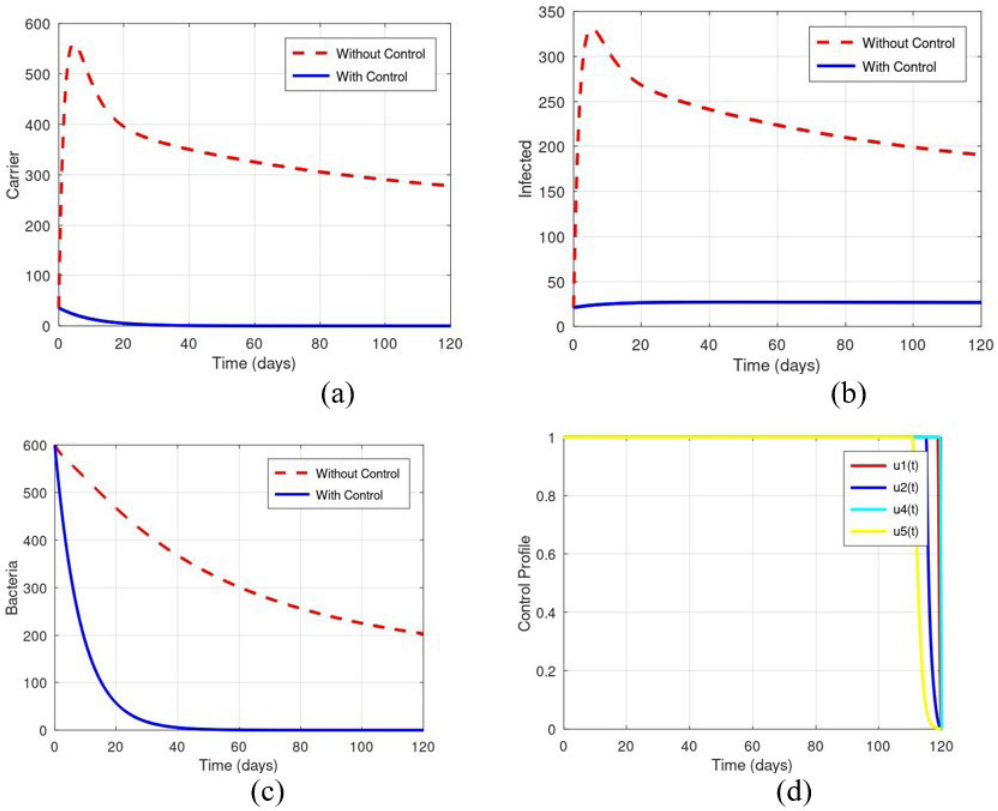


**Figure 12:** Impact of strategy C3 on the optimal control typhoid fever model (14)

Figure 12, showcases the joint applications of first dosage of vaccine (u1(t)), booster vaccine (u2(t)), personal hygiene (u4(t)) and bacteria sterilization (u5(t)) in controlling typhoid fever. By employing this intervention strategies, both the carrier population and bacteria population are completely wiped out from day 20 and 40 respectively except the infected class which stayed same throughout the control period.

As shown by Figure 12 (d) control profile, the optimal controls u1(t) and u4(t) are sustained at their upper bounds for the duration of the intervention period respectively and for about 116 days for u5(t) and 118 days for u2(t) before gradually declining to their minimum bounds during the final intervention period. These actions contribute to the disease's successful control though not the desired as expected.

**Strategy C4**

Combinations of first dosage of vaccine (u1(t)), treatment (u3(t)), personal hygiene (u4(t)) and bacteria sterilization (u5(t))

(u1(t)≠0,u3(t)≠0,u4(t)≠0,u5(t)≠0,u2(t)=0)

Figure 13, presents the outcome of optimal combination of first dosage of vaccine (u1(t)), treatment(u3(t)), personal hygiene (u4(t)) and bacteria sterilization (u5(t)) in the fight against typhoid fever. This control strategy is effective, resulting in the wiping out completing the carrier, infected and bacteria population during the

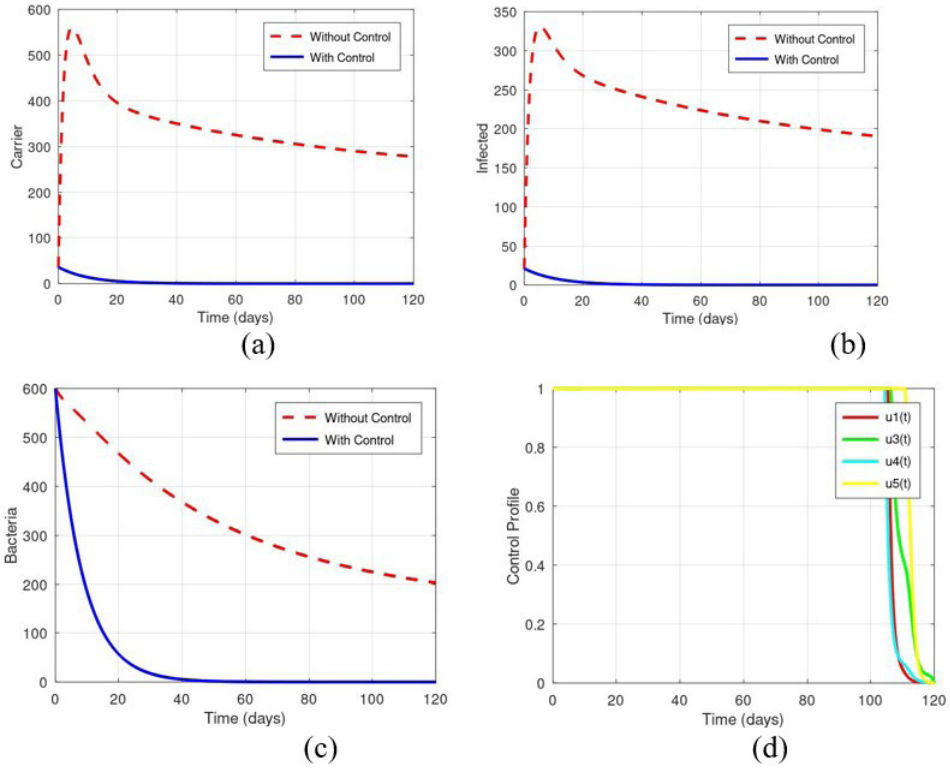


**Figure 13:** Impact of strategy C4 on the optimal control typhoid fever model (14)

control period starting on day 20 day for both the carrier and infected population and day 40 going for bacteria population. To attain this optimal outcome, it is necessary to maintain the optimal control for u1(t),u3(t)and u4(t) at the highest bound for about 112 days and u5(t) for about 117 days before progressively lowering them to their lowest levels by the end of the control period, as illustrated by Figure 13(d).

**Category D**

**Strategy D**

Combinations of first dosage of vaccine (u1(t)), booster vaccine(u2(t)), treatment (u3(t)), personal hygiene(u4(t)) and bacteria sterilization (u5(t))

(u1(t)≠0,u2(t)≠0,u3(t)≠0,u4(t)≠0,u5(t)≠0)

In Figure 14, presents the combined effect of engaging all the optimal controls: vaccine (u1(t)), booster

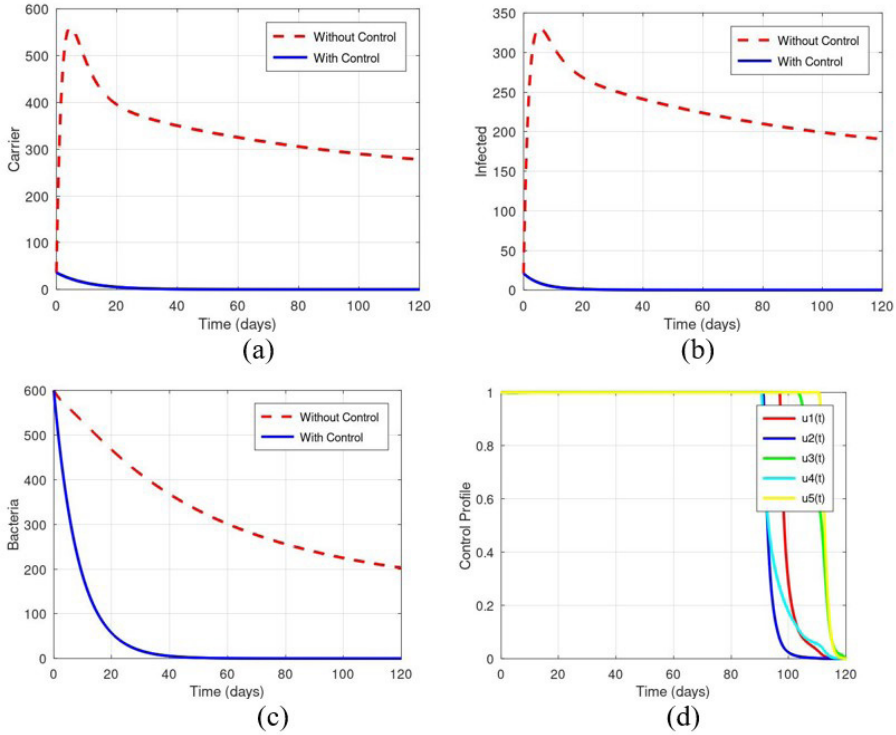


**Figure 14:** Impact of strategy D on the optimal control typhoid fever model (14)

vaccine(u2(t)), treatment (u3(t)), personal hygiene(u4(t)) and bacteria sterilization (u5(t)) with the aim of eradicating typhoid fever in the environment. When these controls are applied concurrently, the trajectories show a fall in the carrier, infected and bacteria population which ultimately results in the elimination of the disease prevalence beginning from the day 20 for the carrier class, around day 10 for the infected class and day 40 for the bacteria class throughout the course of the control application period. An outcome which is highly desired.

The control profiles, shown in Figure 14 (d) show how each measure is maintained and optimized to get the intended result. The comprehensive application of first vaccination (u1(t)) maximally for about 98 days, booster vaccine (u2(t)) and personal hygiene(u4(t)) maximally for 90 days, treatment (u3(t)) maximally for about 103 days and finally bacteria sterilization maximally for about 110 days and thereafter reduced gradually to their lowest bounds at the final time.

With vaccinations to increase immunity on both the individual and population level, treatment to ensure that infected persons receive the proper medical attention, personal hygiene to stop the spread and getting infected with the bacteria leading to being sick with typhoid fever and bacteria sterilization to eliminate the bacteria from the environment, this approach offers a comprehensive protection against the typhoid fever bacteria.

## CONCLUSION

In this paper, we formulated and analyzed a mathematical model for the transmission dynamics of typhoid fever with five(5) control interventions.

It was established that the model was positive and bounded; hence the model is well-posed mathematically and epidemiologically. Using the next-generation method, the basic reproduction ($\mathcal{R}_0$) was obtained. The disease free equilibrium was found to be both locally and globally asymptotically stable given $\mathcal{R}_0<1$ and unstable if $\mathcal{R}_0>1$. This suggests that in an unstable equilibrium, the disease will continue to spread and become endemic, but in a stable equilibrium, it will totally disappear. The Pontryagin's Maximum Principle (PMP) was applied to examine the optimal level required to eliminate and stop the spread of typhoid fever in the community. Numerical results show that the best strategy in eradicating and curtailing the spread of typhoid fever is strategy D, the optimal combination of vaccine, booster vaccine, treatment, personal hygiene and bacteria sterilization.

## REFERENCE


Abboubakar, H., & Racke, R. (2021). Mathematical modeling, forecasting, and optimal control of typhoid fever transmission dynamics. *Chaos, Solitons & Fractals, 149,* 111074, 1-20. https://doi.org/10.1016/j.chaos.2021.111074

Abioye, A. I., Peter, O. J., Ogunseye, H. A., Oguntolu, F. A., Oshinubi, K., Ibrahim, A. A., & Khan, I. (2021). Mathematical model of COVID-19 in Nigeria with optimal control. *Results in Physics, 28,* 104598, 1-10. https://doi.org/10.1016/j.rinp.2021.104598

Adetunde, L. A. (2008). Mathematical methods for the dynamics of typhoid fever in Kassena-Nankana district of Upper East region of Ghana. *Journal of Modern Mathematics and Statistics, 2*(2), 45-49.

Alharbi, M. H., Alalhareth, F. K., & Ibrahim, M. A. (2023). Analyzing the Dynamics of a Periodic Typhoid Fever Transmission Model with Imperfect Vaccination. *Mathematics, 11*(15), 3298, 1-26. https://doi.org/10.3390/math11153298

Antillón, M., Warren, J. L., Crawford, F. W., Weinberger, D. M., Kürüm, E., Pak, G. D., Marks, F., & Pitzer, V. E. (2017). The burden of typhoid fever in low-and middle-income countries: a meta-regression approach. *PLoS neglected tropical diseases, 11*(2), e0005376, 1-21. https://doi.org/10.1371/journal.pntd.0005376

Awoke, T. D. (2019). Optimal control strategy for the transmission dynamics of typhoid fever. *American Journal of Applied Mathematics, 7*(2), 37-49. https://doi.org/10.11648/j.ajam.20190702.11

Bailey, N. T. (1982). The structural simplification of an epidemiological compartment model. *Journal of mathematical biology, 14,* 101-116.

Birger, R., Antillón, M., Bilcke, J., Dolecek, C., Dougan, G., Pollard, A. J., Neuzil, K. M., Frost, I., Laxminarayan, R., & Pitzer, V. E. (2022). Estimating the effect of vaccination on antimicrobial-resistant typhoid fever in 73 countries supported by Gavi: a mathematical modelling study. *The Lancet Infectious Diseases, 22*(5), 679-691. https://doi.org/10.1016/S1473-3099(21)00627-7

Browne, A. J., Kashef Hamadani, B. H., Kumaran, E. A., Rao, P., Longbottom, J., Harriss, E., Moore, C. E., Dunachie, S., Basnyat, B., Baker, S., Lopez, A. D., Day, N. P. J., Hay, S. I., & Dolecek, C. (2020). Drug-resistant enteric fever worldwide, 1990 to 2018: a systematic review and meta-analysis. *BMC medicine, 18,* 1-22. https://doi.org/10.1186/s12916-019-1443-1

da Silva, K. E., Tanmoy, A. M., Pragasam, A. K., Iqbal, J., Sajib, M. S. I., Mutreja, A., Veeraraghavan, B., Tamrakar, D., Qamar, F. N., Dougan, G., Bogoch, I., Seidman, J., Shakya, J., Vaidya, K., Carey, M.E., Rajeev, S., Irfan, S., Baker, S., Luby, S. P.,…Andrews, J. R. (2022). The international and intercontinental spread and expansion of antimicrobial-resistant Salmonella Typhi: a genomic epidemiology study. *The Lancet Microbe, 3*(8), e567-e577. https://doi.org/10.1016/S2666-5247(22)00093-3

Diekmann, O., Heesterbeek, J., & Metz, J. (1990). On the Definition and the Computation of the Basic Reproduction Ratio R0 in Models for Infection Disease in Heterogeneous Population. *Journal of Mathematical Biology, 28,* 365-382.

Van den Driessche, P., & Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences, 180*(1-2), 29-48.

Emmanuel, U., Olivier, H., Gloria, H., & Olivier, N. M. J. (2023). Experimentally Study on Optimal Control of the Inertia of Water on the Thermal Performance of All-glass Evacuated Tube Solar Collector. *American Journal of Energy and Natural Resources, 2*(1), 15–19. https://doi.org/10.54536/ajenr.v2i1.1219

Eubank, S., Eckstrand, I., Lewis, B., Venkatramanan, S., Marathe, M., & Barrett, C. L. (2020). Commentary on Ferguson, *et al.*,"Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand". *Bulletin of mathematical biology, 82,* 1-7. https://doi.org/10.1007/s11538-020-00726-x

Fleming,W.H. & Rishel,R.W.(1975). *Deterministic and stochastic optimal control.* Springer-Verlag; New York.

Garrett, D. O., Longley, A. T., Aiemjoy, K., Yousafzai, M. T., Hemlock, C., Alexander, T. Y., Vaidya, K., Tamrakar, D., Saha, S., Bogoch, I.I., Date, K., Saha, S., Islam, M.S., Sayeed, K.M.I., Bern, C., Shakoor, S., Dehraj, I., Mehmood, J.,Sajib, M.S.I. ...Luby, S. P. (2022). Incidence of typhoid and paratyphoid fever in Bangladesh, Nepal, and Pakistan: results of the Surveillance for Enteric Fever in Asia Project. *The Lancet Global Health, 10*(7), e978-e988. https://doi.org/10.1016/S2214-109X(22)00119-X

Ibrahim, O. M., Okuonghae, D., & Ikhile, M. N. (2023). Optimal control model for criminal gang population in a limited-resource setting. *International Journal of dynamics and control, 11*(2), 835-850. https://doi.org/10.1007/s40435-022-00992-8

Institute for Health Metrics and Evaluation (IHME). (2021). Typhoid fever—level 4 cause. https://www.healthdata.org/research-analysis/disease-injuries-risks/factsheets/2021-typhoid-fever-level-4-disease

Im, J., Islam, M. T., Kim, D. R., Ahmmed, F., Chon, Y., Zaman, K., Khan, A.I., Ali, M., Sur, D., Kanungo, S., Dutta, S., Bhattacharya, S.K., Dougan, G., Holt, K.E., Marks,F., Kim, J.H., Qadri, F., & Clemens, J. D. (2020). Protection conferred by typhoid fever against recurrent typhoid fever in urban Kolkata. *PLoS neglected tropical diseases, 14*(8), e0008530, 1-11. https://doi.org/10.1371/journal.pntd.0008530

Kailan Suhuyini, A., & Seidu, B. (2023). A mathematical model on the transmission dynamics of typhoid fever with treatment and booster vaccination. *Frontiers in Applied Mathematics and Statistics, 9,* Article 1151270. https://doi.org/10.3389/fams.2023.1151270

Klemm, E. J., Shakoor, S., Page, A. J., Qamar, F. N., Judge, K., Saeed, D. K., & Shaheen, G. (2018). Emergence of an extensively drug-resistant *Salmonella enterica* serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. *mBio, 9*(1), Article e00105-18. https://doi.org/10.1128/mbio.00105-18

Mallick, U. K., & Biswas, M. H. A. (2020). Mathematical approach with optimal control: Reduction of unemployment problem in Bangladesh. *Journal of Applied Nonlinear Dynamics, 9*(2), 231-246. https://doi.org/10.5890/JAND.2020.06.006

Marchello, C. S., Birkhold, M., & Crump, J. A. (2020). Complications and mortality of typhoid fever: a global systematic review and meta-analysis. *Journal of Infection, 81*(6), 902-910. https://doi.org/10.1016/j.jinf.2020.10.030

Marks, F., von Kalckreuth, V., Aaby, P., Adu-Sarkodie, Y., El Tayeb, M. A., Ali, M., Aseffa, A., Baker, S., Biggs, H.M., Bjerregaard-Andersen, M., Breiman, R., Campbell, J.I., Cosmas, L., Crump, J.A., Espinoza, L.M.C., Deerin, J.F., Dekker, D.M.,Fields, B.S., Gasmelseed,N.,…Wierzba, T. F. (2017). Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study. *The Lancet Global Health, 5*(3), e310-e323. https://doi.org/10.1016/S2214-109X(17)30022-0

Mayer, C. A., & Neilson, A. A. (2010). Typhoid and paratyphoid fever: Prevention in travellers. *Australian family physician, 39*(11), 847-851.

Milligan, R., Paul, M., Richardson, M., & Neuberger, A. (2018). Vaccines for preventing typhoid fever. *Cochrane Database of Systematic Reviews,* (5). https://doi.org/10.1002/14651858.CD001261.pub4

Momoh, A. A., Afiniki, Y., Déthié, D., & Abubakar, A. (2023). Curtailing the spread of typhoid fever: An optimal control approach. *Results in Control and Optimization, 13,* 100326, 1-19. https://doi.org./10.1016/j.rico.2023.100326

Mushayabasa, S. (2016). Modeling the impact of optimal screening on typhoid dynamics. *International Journal of Dynamics and Control, 4*(3), 330-338.

Mushayabasa, S., Bhunu, C. P., & Mhlanga, N. A. (2014). Modeling the transmission dynamics of typhoid in malaria endemic settings. *Applications and Applied Mathematics: An International Journal (AAM), 9*(1), 9.

Nana-Kyere, S., Boateng, F. A., Jonathan, P., Donkor, A., Hoggar, G. K., Titus, B. D., Kwarteng, D., & Adu, I. K. (2022). Global analysis and optimal control model of COVID-19. *Computational and Mathematical Methods in Medicine, 2022,* Article 9491847. https://doi.org/10.1155/2022/9491847

Nkuh, Y. R., Namondo, E. C., Kah, T. B., Nteimaah, L. N., & Ayuk, A. K. (2023). Community Perceptions on Health and Environmental Implications of Poor Management of Solid Waste Materials around local Dump Sites in the Buea Municipality, Cameroon. *American Journal of Education and Technology, 2*(3), 136–146. https://doi.org/10.54536/ajet.v2i3.1896

Patel, P. D., Liang, Y., Meiring, J. E., Chasweka, N., Patel, P., Misiri, T., Mwakiseghile, F., Wachepa, R., Banda, H.C., Shumba, F., Kawalazira, G., Dube, Q., Nampota-Nkomba, N., Nyirenda, O.M., Girmay, T., Datta, S., Jamka, L.P., Tracy, J.K., Laurens, M.B.,… Pair, T. (2024). Efficacy of typhoid conjugate vaccine: final analysis of a 4-year, phase 3, randomised controlled trial in Malawian children. *The Lancet, 403*(10425), 459-468. https://doi.org/10.1016/S0140-6736(23)02031-7

Peter, O. J., Afolabi, O. A., Oguntolu, F. A., Ishola, C. Y., & Victor, A. A. (2018). Solution of a deterministic mathematical model of typhoid fever by variational iteration method. *Science World Journal, 13*(2), 64-68.

Peter, O. J., Ibrahim, M. O., Edogbanya, H. O., Oguntolu, F. A., Oshinubi, K., Ibrahim, A. A., Ayoola, T.A., & Lawal, J. O. (2021). Direct and indirect transmission of typhoid fever model with optimal control. *Results in Physics, 27,* 104463, 1-9. https://doi.org/10.1016/j.rinp.2021.104463

Pitzer, V. E., Bowles, C. C., Baker, S., Kang, G., Balaji, V., Farrar, J. J., & Grenfell, B. T. (2014). Predicting the impact of vaccination on the transmission dynamics of typhoid in South Asia: a mathematical modeling study. *PLoS neglected tropical diseases, 8*(1), e2642, 1-12. https://doi.org/10.1371/journal.pntd.0002642

Pitzer, V. E., Bowles, C. C., Baker, S., Kang, G., Balaji, V., Farrar, J. J., & Grenfell, B. T. (2014). Predicting the impact of vaccination on the transmission dynamics of typhoid in South Asia: A mathematical modeling study. *PLoS Neglected Tropical Diseases, 8*(1), Article e2642. https://doi.org/10.1371/journal.pntd.0002642

Pontryagin, L. S., Boltyanskii, V. G., Gamkrelidze, R. V., & Mishchenko, E. (1986). *The mathematical theory of optimal processes* (Vol. 4).

Siduppa, M. N., Toaha, S., & Kasbawati, K. (2023). Stability analysis and optimal control of mathematical model of typhoid fever spread. *InPrime: Indonesian Journal of Pure and Applied Mathematics, 5*(1), 22-37. https://doi.org/10.15408/inprime.v5i1.27205

Tilahun, G. T., Makinde, O. D., & Malonza, D. (2017). Modelling and optimal control of typhoid fever disease with cost-effective strategies. *Computational and mathematical methods in medicine, 2017*(1), 2324518,1-16. https://doi.org/10.1155/2017/2324518

Wameko, M., Koya, P., & Wodajo, A. (2020). Mathematical model for transmission dynamics of typhoid fever with optimal control strategies. *International Journal of Industrial Mathematics, 12*(3), 283-296. http://dorl.net/dor/20.1001.1.20085621.2020.12.3.8.8

World Health Organization. (2019). Typhoid vaccines: WHO position paper—March 2019. *Weekly Epidemiological Record, 93,* 153-172.

Yousafzai, M. T., Karim, S., Qureshi, S., Kazi, M., Memon, H., Junejo, A., Khawaja, Z., Rehman, N. U., Ansari, M. S., Ali, R., Ujjan, I. U., Lohana, H. M., Memon, N. M., Hussain, M., Nigar, R., Bar-Zeev, N., & Qamar, F. N. (2021). Effectiveness of typhoid conjugate vaccine against culture-confirmed *Salmonella enterica* serotype Typhi in an extensively drug-resistant outbreak setting of Hyderabad, Pakistan: A cohort study. *The Lancet Global Health, 9*(8), e1154-e1162. https://doi.org/10.1016/S2214-109X(21)00255-2