Mathematical modelling and optimal control of typhoid fever

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Abstract

Typhoid fever is a disease caused by a salmonella bacterium (Salmonella typhi) and transmitted by ingestion of water and/or food contaminated with faeces (stool). In this paper, we derive and analyse a model for the control of typhoid fever which takes into account an imperfect vaccine combined with some other control measures already studied in the literature. We begin by analysing the model without control. We compute the basic reproduction number $\mathcal{R}_0$ and prove the local and global stability of the disease–free equilibrium whenever $\mathcal{R}_0$ is less than one through Lyapunov's theory. When $\mathcal{R}_0$ is greater than one, we prove the local asymptotic stability of the unique endemic equilibrium through the Centre Manifold Theory and we find that the model exhibits a forward bifurcation. Then, we extend the model by reformulating it as an optimal control problem, with the use of three time dependent controls, to assess the impact of vaccination combined with protection/environment sanitation and treatment on the spread of the disease in human population. By using optimal control theory, we establish conditions under which the spread of the disease can be stopped, and we examine the impact of combined control tools on the transmission dynamic of the disease. Pontryagin's maximum principle is used to characterize the optimal control. Numerical simulations and efficiency analysis show that, if we want to reduce significantly the spread of typhoid fever, treatment must be taken into account in all control strategies.

Key words: Typhoid fever, Asymptotic stability, Centre Manifold Theory, Optimal control, Pontryagin's maximum principle (PMP), Efficiency analysis.

AMS Classification: 49J15, 92D30.

1 Introduction

Typhoid fever is a disease caused by a salmonella bacterium (Salmonella typhi) and transmitted by ingestion of water and/or food contaminated with faeces (stool). Typhoid

fever is prevalent in areas of the world where hygiene is precarious [42, 43]. The disease is mainly manifested by a fever that gradually rises to 40°C, headaches, insomnia, fatigue and anorexia. Fever may be accompanied by digestive signs (stomach ache, diarrhoea or constipation, vomiting). The symptoms can last several weeks. In some cases, the infected host is asymptomatic but participates in the transmission of the disease. In severe forms without treatment, evolution can be fatal in 10% of cases. The treatment of typhoid fever is based on antibiotic medication. There are 11 to 21 million estimated cases of typhoid fever and approximately 128,000 to 161,000 deaths annually, compared to an estimated 6 million cases of paratyphoid fever and 54,000 annual deaths [20, 42, 43].

Although some progress has been made in the fight against typhoid fever, such as antibiotic treatments, vaccination and environmental sanitation as a means of prevention, typhoid fever is still a public health problem in developing countries. There are two available vaccines to prevent typhoid fever. Although their price in the market of vaccine has become affordable, access in some developing countries remains a problem [43]. Thus, the authorities of the areas where this disease occurs must choose between treatment and/or prevention means.

To better understand the transmission dynamics of some diseases and appropriate control methods, mathematical models have been developed. So, many mathematical models reflecting the transmission dynamics of typhoid fever have emerged (see for example [6, 10, 13, 16, 21, 23, 28, 29, 30, 31, 32, 33, 34, 35, 38, 39]. But, only few of these works have been conducted to explore control strategies for typhoid fever (see [16, 23, 29, 33, 34, 38, 39]).

In this paper we formulate a mathematical model for the transmission dynamics of typhoid fever in human populations, which takes into account incubation period, imperfect vaccine combined with protection or environment sanitation and treatment as control mechanisms. We begin by the formulation of the autonomous model which take only constant vaccination as control strategy. We compute the basic reproduction number $\mathcal{R}_0$ and investigate the existence and stability of equilibria. Through Lyapunov's theory, we prove that the disease–free equilibrium is globally asymptotically stable whenever $\mathcal{R}_0$ is less than one. We use the Center Manifold Theory to prove that our model exhibits a forward bifurcation when $\mathcal{R}_0$ is equal to one, and the unique endemic equilibrium is locally asymptotically stable. So, the phenomenon of backward bifurcation not occurs, which means that the condition $\mathcal{R}_0 < 1$ is sufficient for going out of the disease in human populations.

Then, we extend our autonomous model by adding density dependent death rate of humans and three times-dependent controls (vaccination, protection/environment sanitation and treatment of symptomatic infectious). Optimal control theory is used to establish conditions under which the spread of typhoid fever can be stopped and examine the impact of a possible combination of these three controls on the disease transmission. The characterization of the optimal control is obtained by the application of Pontryagin's maximum principle. We use numerical simulations and efficiency analysis to determine the best combination of these controls, in terms of efficacy.

We organize the paper as follows. In Section 2, we present the typhoid fever transmission dynamics model and carry out some analysis by determining the basic reproduction

number $\mathcal{R}_0$, and different equilibria of the model. We then demonstrate the stability of equilibria and examine the non-existence of the backward bifurcation in the model. Optimal control problem and its mathematical analysis are presented in Section 3. We devoted Section 4 for numerical simulations and efficiency analysis.

2 Model formulation and its analysis

We subdivide the human population into six compartments: susceptible humans (S), vaccinated (V), infected humans in latent period (E), asymptomatic infectious humans or carriers (C), symptomatic infectious humans (I) and recovered humans (R). Unlike the proposed models in literature, we take into account the latent period. The loss of immunity of recovered humans is also taken into account. Following Mutua et *al.* [30], we assume in this work that direct transmission of typhoid through person to person is negligible[1]. We add a compartment, B, which represents bacteria in the environment.

We assume, like some compartment models with imperfect vaccine, that the immunity obtained by the vaccination process, is temporary. So, we denote the waning rate of vaccine by θ. The recruitment in human population is at the constant rate Λ_h, and newly recruited individuals enter the susceptible compartment S. In each human compartment, individuals go out from the dynamics at natural mortality rates μ_h. The human susceptible population is decreased following by *(1)* infection, which can be acquired via effective contact with bacteria through contaminated food or water, at a mass action incidence rate νBS, *(2)* by vaccination at a vaccination rate ξ. Latent humans E become asymptomatic infectious (carriers) C at a rate $q\gamma_1$ where q represents the probability of a latent to become carrier, or symptomatic infectious (I) at a rate $(1-q)\gamma_1$. carrier humans becomes recoveries at rate $p\gamma_2$ where p represents the probability of an asymptomatic to becomes symptomatic, or moves to symptomatic infectious class at a rate $(1-p)\gamma_2$. Symptomatic infectious humans recover at a constant rate, σ or die as consequence of infection, at a disease-induced death rate δ. After infection, recovered humans loose their immunity at a rate α. For bacteria compartment, we assume that bacteria population increases up only through excretion of symptomatic infectious at a rate p_i or carriers at a rate p_c, and decreases at a rate μ_b.

The above assumptions lead to the following nonlinear system of ordinary differential

[1] http://www.vdh.Virginia.gov/epidemiology/factsheets/Typhoid_Fever.htm

equations,

$$\dot{S}(t) = \Lambda_h + \alpha R(t) + \theta V(t) - (\nu B(t) + k_1)S(t), \tag{1a}$$
$$\dot{V}(t) = \xi S(t) - [(1-\epsilon)\nu B(t) + k_2]\, V(t), \tag{1b}$$
$$\dot{E}(t) = \nu B(t)\,[S(t) + \pi V(t)] - k_3 E(t), \tag{1c}$$
$$\dot{C}(t) = q\gamma_1 E(t) - k_4 C(t), \tag{1d}$$
$$\dot{I}(t) = q_1\gamma_1 E(t) + p_1\gamma_2 C(t) - [k_5 + \sigma]\, I(t), \tag{1e}$$
$$\dot{R}(t) = p\gamma_2 C(t) + \sigma I(t) - k_6 R(t), \tag{1f}$$
$$\dot{B}(t) = p_c C(t) + p_i I(t) - \mu_b B(t) \tag{1g}$$

subject to the initial conditions $S(0) \geq 0$, $V(0) \geq 0$, $E(0) \geq 0$, $C(0) \geq 0$, $I(0) \geq 0$, $R(0) \geq 0$ and $B(0) \geq 0$. For a better readability, we set $k_1 = \xi + \mu_h$, $k_2 = \theta + \mu_h$, $k_3 = \gamma_1 + \mu_h$, $k_4 = \mu_h + \gamma_2$, $k_5 = \delta + \mu_h$, $k_6 = \mu_h + \alpha$, $\pi = 1 - \epsilon$, $q_1 = 1 - q$, $p_1 = 1 - p$ and $k_1 k_2 - \theta\xi = \mu_h(k_2 + \xi) > 0$.

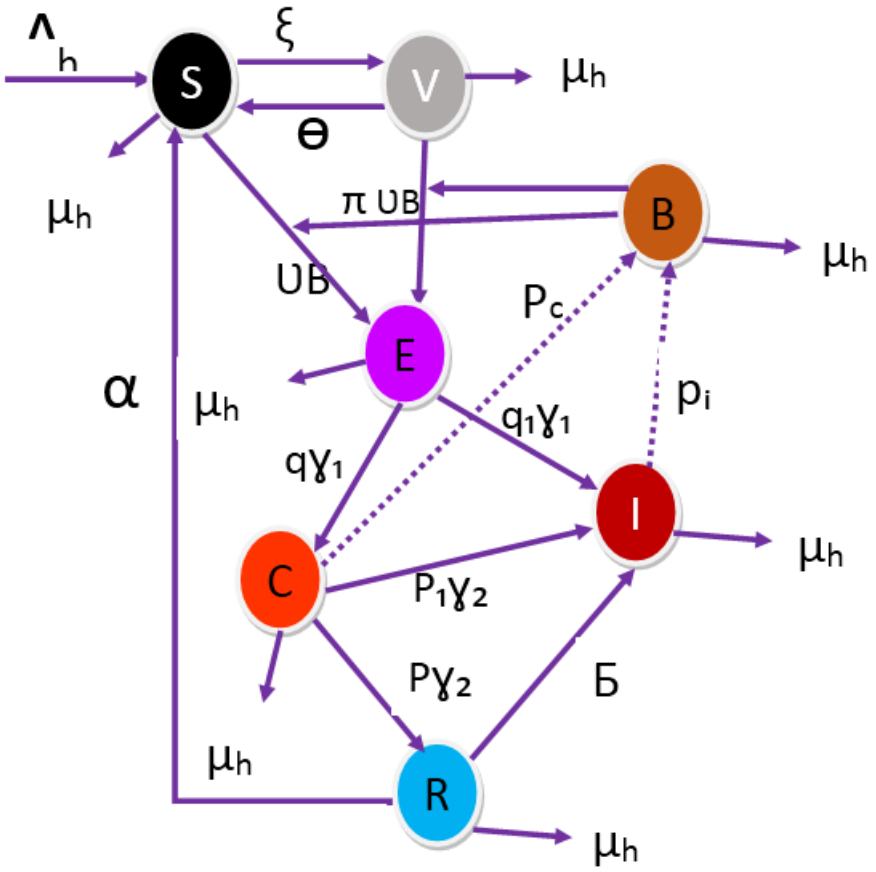

Figure 1: Schematic of the typhoid model.

A synoptic table of the state variables and the description of model parameters are given in Tables 1 and 2, respectively. Figure 1 depicts the flow exchange between compartments of the model. All variables and parameters are nonnegative.

Table 1: Description of state variables of the mosquito-borne epidemic model (1)

State variable	Description
S	Number of susceptible humans
V	Number of vaccinated humans
E	Number of exposed humans
C	Number of infectious humans without clinical signs (carriers)
I	Number of infectious humans with clinical signs
R	Number of recovered humans with partial immunity
B	Number of bacteria concentration

Table 2: Description and values of model parameters(1).

Parameter	Description	Baseline value	Source
Λ_h	Recruitment rate of humans	467 humans day^{-1}	[30]
μ_h	Natural mortality rate in humans	(1/(65×365)) day^{-1}	[2]
γ_1	Rate of progression to carriers	1/8 day^{-1}	Assumed
γ_2	Recovery rate from carriers	0.000315 day^{-1}	[30]
δ	Typhoid-induced death rate	0.002 day^{-1}	[30]
ν	Infection rate of typhoid	1.37x10E-9 day^{-1}	[30]
σ	Recovery rate from infectious	0.0657 day^{-1}	[30]
μ_b	Bacterial decay rate	0.0645 day^{-1}	[30]
ϵ	Vaccine efficacy	0.48-0.956	[18, 34]
ξ	Vaccination rate	0.5Varied [0,1]	
θ	Waning rate of vaccination effect	9.041x 10E-04day^{-1}	[27]
α	Removal rate from recovered subclass to susceptible subclass	0.000904day^{-1}	[5]
p_c	Bacteria excretion (carriers)	1	[30]
p_i	Bacteria excretion (infectious)	10	[30]
q	Probability of exposed E to become carriers C	0.3	Assumed
p	Probability of carriers C to become removed R	0.7	Assumed

2.1 Nonnegativity and boundedness of solutions

Using [37, Theorem 5.2.1], it then follow that for any $(S_0, V_0, E_0, C_0, I_0, R_0, B_0) \in \mathbb{R}^7_+$, system (1) has a unique local nonnegative solution $(S(t), V(t), E(t), C(t), I(t), R(t), B(t))$ through the initial value $(S(0), V(0), E(0), C(0), I(0), R(0), B(0)) = (S_0, V_0, E_0, C_0, I_0, R_0, B_0)$.

Let $N(t) := S(t) + V(t) + E(t) + C(t) + I(t) + R(t)$. Then $N(t)$ satisfies

$$\dot{N}(t) \leq \Lambda_h - \mu_h N - \delta I$$

which implies that

$$\dot{N}(t) \leq \Lambda_h - \mu_h N,$$

and hence

$$\limsup_{t \longrightarrow \infty} N(t) \leq \frac{\Lambda_h}{\mu_h}.$$

So $N(t)$ is bounded.

Using this last inequality, we obtain from the last equation of (1) that

$$\dot{B}(t) \leq \frac{(p_i + p_c)\Lambda_h}{\mu_h} - \mu_b B.$$

Solving the above equation gives

$$B(t) \leq \frac{(p_i + p_c)\Lambda_h}{\mu_h \mu_b} + K \exp(-\mu_b t),$$

which implies the nonnegativity of B. So, taking the limit of above equation, we obtain

$$\limsup_{t \longrightarrow \infty} B(t) \leq \frac{(p_i + p_c)\Lambda_h}{\mu_h \mu_b}.$$

So $B(t)$ is also bounded. Hence, the above result implies that the solutions of system (1) are nonnegative and bounded in the region

$$\Omega = \left\{ (S, V, E, C, I, R, B) \in \mathbb{R}_+^7 : S + V + E + C + I + R \leq \frac{\Lambda_h}{\mu_h}; B \leq \frac{(p_i + p_c)\Lambda_h}{\mu_h \mu_b} \right\}.$$

2.2 Basic reproduction number and local stability of the disease–free equilibrium

The disease free equilibrium point of model system (1) is given by $\mathcal{Q}_0 = (S_0, V_0, 0, 0, 0, 0, 0)$ where $S_0 = \Lambda_h k_2/(\mu_h(k_2 + \xi))$ and $V_0 = \Lambda_h \xi/(\mu_h(k_2 + \xi))$.

The basic reproduction number $\mathcal{R}_0$, defined as a number of secondary infections produced by a single infected individual when introduced to a completely susceptible population, is a threshold quantity and enables us to calibrate the disease dynamics. Because it is very important when we want to implement some strategies to control the disease dynamics, efforts have been made to calculate $\mathcal{R}_0$. So, the basic reproduction number is also defined as the largest eigenvalue of the next generation matrix [40]. The approach developed by van den Driessche & Watmough (2002)[40] is used here to calculate the basic reproduction number for the typhoid model (1).

Let us denoted by $x = (S, V, E, C, I, R, B)^t$. Then, the model system (1) can be written as

$$\dot{x} = \mathcal{F}(x) - \mathcal{V}(x)$$

where

$$\mathcal{F}(x) = \begin{pmatrix} \nu B(S + \pi V) \\ 0 \\ 0 \\ p_c C + p_i I \end{pmatrix}$$

and

$$\mathcal{V}(x) = \begin{pmatrix} -k_3 E \\ q\gamma_1 E - k_4 C \\ q_1\gamma_1 E + p_1\gamma_2 C - (k_5 + \sigma) I \\ -\mu_b \end{pmatrix}$$

Next, we obtain

$$F = \begin{pmatrix} 0 & 0 & 0 & \nu(S_0 + \pi V_0) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & p_c & p_i & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} k_3 & 0 & 0 & 0 \\ -q\gamma_1 & k_4 & 0 & 0 \\ -q_1\gamma_1 & -p_1\gamma_2 & (k_5 + \sigma) & 0 \\ 0 & 0 & 0 & \mu_b \end{pmatrix}$$

We obtain FV^{-1} as

$$FV^{-1} = \begin{pmatrix} 0 & 0 & 0 & \dfrac{\nu(S_0 + \pi V_0)}{\mu_b} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \dfrac{p_i\left(\gamma_1 k_4 \mu_b q_1 + \gamma_1\gamma_2\mu_b p_1 q\right)}{k_3 k_4 \mu_b\left(\sigma + k_5\right)} + \dfrac{\gamma_1 p_c q}{k_3 k_4} & \dfrac{\gamma_2 p_1 p_i}{k_4\left(\sigma + k_5\right)} + \dfrac{p_c}{k_4} & \dfrac{p_i}{\sigma + k_5} & 0 \end{pmatrix}$$

Now, the basic reproduction number is defined as the largest eigenvalue (spectral radius) of the next generation matrix FV^{-1} and can be obtained as

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\frac{\nu\Lambda_h(k_2 + \pi\xi)\gamma_1\left[p_c q(\sigma + k_5) + p_i(k_4(1-q) + \gamma_2 q(1-p))\right]}{\mu_b\mu_h k_3 k_4(k_2 + \xi)(\sigma + k_5)}} \tag{2}$$

We note that,

$$\mathcal{R}_0 = \sqrt{\mathcal{R}_{0,I} + \mathcal{R}_{0,c}},$$

where

$$\mathcal{R}_{0,I} = \nu\frac{\Lambda_h(k_2 + \pi\xi)}{\mu_h(k_2 + \xi)}\frac{\gamma_1}{\mu_h + \gamma_1}p_i\left(q_1 + q\frac{\gamma_2 p_1}{\mu_h + \gamma_4}\right)\frac{1}{\mu_h + \delta + \sigma}\frac{1}{\mu_b},$$

is the number of expected new cases caused by a symptomatic infectious human. It equals the product of the rate of infection for single infected individual in a population of susceptible individual $\nu(S_0 + \pi V_0) = \nu\Lambda_h(k_2 + \pi\xi)/(\mu_h(k_2 + \xi))$, the probability that an

infected human survives the latent stage and becomes symptomatic infectious $p_i(\gamma_1/(\mu_h+\gamma_1))\,(q_1+q\gamma_2 p_1/(\mu_h+\gamma_4))$, the duration of the symptomatic state $1/(\mu_h+\delta+\sigma)$, and the lifespan of bacteria $1/\mu_b$.

$$\mathcal{R}_{0,C}=\nu\frac{\Lambda_h(k_2+\pi\xi)}{\mu_h(k_2+\xi)}\frac{\gamma_1}{\mu_h+\gamma_1}p_c q\frac{1}{\mu_h+\gamma_2}\frac{1}{\mu_b},$$

is the number of expected new cases caused by a carrier human. It is equal to the product of the rate of infection for single infected individual in a population of susceptible individual $\nu(S_0+\pi V_0)=\nu\Lambda_h(k_2+\pi\xi)/(\mu_h(k_2+\xi))$, the probability that an infected human survives the latent stage and becomes carrier $p_c q\gamma_1/(\mu_h+\gamma_1)$, the duration if the carrier stage $1/k_4=1/(\mu_h+\gamma_2)$, and the lifespan of bacteria $1/\mu_b$.

The basic reproduction number is equal to the arithmetic mean of $\mathcal{R}_{0,I}$ and $\mathcal{R}_{0,C}$ because infection from human to human goes through ingestion of water or food contaminated with the faeces of symptomatic or asymptomatic human.

Now, using [40, Theorem 2], we state the following result pertaining to the local stability of the disease–free equilibrium $\mathcal{Q}_0$. See appendix B for the proof.

Proposition 2.1. *The disease–free equilibrium $\mathcal{Q}_0$ of the model (1) is locally asymptotically stable if $\mathcal{R}_0<1$ and unstable if $\mathcal{R}_0>1$.*

2.3 Global stability of the disease–free equilibrium

Theorem 2.1. *The disease–free equilibrium (DFE) $\mathcal{Q}_0$ is globally asymptotically stable in Ω if $\mathcal{R}_0<1$.*

Proof. The proof is based on using the following Lyapunov function:

$$\mathcal{L}:=a_1E+a_2C+a_3I+a_4B$$

where $a_1=1$, $a_2=k_3(k_8p_c+p_ip_1\gamma_2)/[k_4p_iq_1\gamma_1+q\gamma_1(k_8p_c+p_ip_1\gamma_2)]$, $a_3=k_3k_4p_i/[k_4p_iq_1\gamma_1+q\gamma_1(k_8p_c+p_ip_1\gamma_2)]$ and $a_4=k_3k_4k_8/[k_4p_iq_1\gamma_1+q\gamma_1(k_8p_c+p_ip_1\gamma_2)]$.

Denoting the differentiation with respect to t by a dot, the Lyapunov derivative of $\mathcal{L}$ is given by

$$\begin{aligned}
\dot{\mathcal{L}}&:=a_1\dot{E}+a_2\dot{C}+a_3\dot{I}+a_4\dot{B}\\
&=a_1\left(\nu B\left[S+\pi V\right]-k_3E\right)+a_2\left(q\gamma_1E-k_4C\right)+a_3\left(q_1\gamma_1E+p_1\gamma_2C-k_8I\right)\\
&+a_4\left(p_cC+p_iI-\mu_bB\right)\\
&\leq a_1\left(\nu B\left[S^0+\pi V^0\right]-k_3E\right)+a_2\left(q\gamma_1E-k_4C\right)+a_3\left(q_1\gamma_1E+p_1\gamma_2C-k_8I\right)\\
&+a_4\left(p_cC+p_iI-\mu_bB\right)\\
&=a_1\nu B\left(S^0+\pi V^0\right)-a_1k_3E+a_2q\gamma_1E-a_2k_4C+a_3q_1\gamma_1E+a_3p_1\gamma_2C-a_3k_8I\\
&+a_4p_cC+a_4p_iI-a_4\mu_bB\\
&=a_1\nu B\left(S^0+\pi V^0\right)-a_4\mu_bB+\left(a_3q_1\gamma_1+a_2q\gamma_1-a_1k_3\right)E+\left(a_4p_c+a_3p_1\gamma_2-a_2k_4\right)C\\
&+\left(a_4p_i-a_3k_8\right)I\\
&=\frac{\mu_bk_3k_4(k_5+\sigma)}{p_iq_1\gamma_1k_4+q\gamma_1(p_1p_i\gamma_2+p_c(k_5+\sigma))}\left(\mathcal{R}_0^2-1\right)B.
\end{aligned}$$

Thus $\dot{\mathcal{L}} < 0$ if and only if $\mathcal{R}_0 < 1$ with $\dot{\mathcal{L}} = 0$ if and only if $B = 0$ (which implies $E = I = C = 0$) or $\mathcal{R}_0 = 1$. Further, the largest compact invariant set in $\{(S, V, E, C, I, R, B) \in \Omega : \dot{\mathcal{L}} = 0\}$ is the singleton $\{\mathcal{Q}_0\}$. It follows from the LaSalle Invariance Principle [22, Chapter 2, Theorem 6.4] that every solution to the equations in (1) with initial conditions in Ω converge to DFE $\mathcal{Q}_0$ as $t \longrightarrow +\infty$. That is $(E(t), C(t), I(t), R(t), B(t)) \longrightarrow (0, 0, 0, 0)$ when $t \longrightarrow +\infty$. Substituting $E = C = I = R = B = 0$ in to the first and the second equations of the basic model (1) gives $S(t) \longrightarrow S_0$ and $V(t) \longrightarrow V_0$ as $t \longrightarrow +\infty$. Thus $(S(t), V(t), E(t), C(t), I(t), R(t), B(t)) \longrightarrow (S_0, V_0, 0, 0, 0, 0, 0)$ when $t \longrightarrow +\infty$ for $\mathcal{R}_0 \leq 1$. So, From the LaSalle principle we deduce the attractiveness of Q_0, but since Q_0 is locally asymptotically stable when $\mathcal{R}_0 < 1$, we deduce that it is not only attractive, but it is also globally asymptotically stable. □

2.4 Endemic equilibrium and its stability analysis

2.4.1 Existence of endemic equilibrium

First we introduce the following thresholds

$$\begin{aligned}
\mathcal{R}_1 &= \frac{\gamma_1\alpha((\mu_h q_1 + \gamma_2)\sigma + \gamma_2 k_5 pq)(\pi\xi + k_2)^2}{k_3 k_4 k_6 k_8 \mu_h \pi(\xi + k_2)}, \\
\mathcal{R}_2 &= \frac{(k_2 + \xi\pi)(k_1\pi + k_2)}{\mu_h\pi(\xi + k_2)}, \\
\mathcal{R}_b &= \sqrt{\mathcal{R}_2 - \mathcal{R}_1},
\end{aligned} \tag{3}$$

and the following coefficients

$$\begin{aligned}
a_2 &= \mathcal{R}_0^4 k_3^2 k_4^2 k_8^2 \mu_h^2 (\xi + k_2)^2 \pi \times \\
&\quad \times (\mu_h\gamma_1\alpha(k_5 + \sigma q) + \gamma_2\mu_h k_8(\alpha + \gamma_1) + \gamma_1\gamma_2\alpha(1 - pq)k_5 + [\mu_h^2 + (\alpha + \gamma_2 + \gamma_1)\mu_h]\mu_h k_8), \\
a_1 &= -\mathcal{R}_0^2 k_3^2 k_4^2 k_8^2 \mu_h^2 (\xi + k_2)^2 \gamma_1 \Lambda_h k_6 \pi(k_4 q_1 + \gamma_2 p_1 q)(\mathcal{R}_0^2 - \mathcal{R}_b^2), \\
a_0 &= -\gamma_1^2 \mu_h \Lambda_h^2 k_3 k_4 k_6 k_8 (k_4 q_1 + \gamma_2 p_1 q)^2 (\pi\xi + k_2)^2 (\xi + k_2)(\mathcal{R}_0^2 - 1).
\end{aligned} \tag{4}$$

Then we have the following result concerning the existence of endemic equilibria for the basic model (1).

Proposition 2.2. *The basic model (1) has:*

(i) A unique endemic equilibrium if $a_0 < 0 \Longleftrightarrow \mathcal{R}_0 > 1$.

(ii) A unique endemic equilibrium if $a_1 < 0$ and $a_0 = 0$ or $a_1^2 - 4a_2a_0 = 0$.

(iii) Two endemic equilibria if $a_0 > 0$ $(\mathcal{R}_0 < 1)$, $a_1 < 0$ $(\mathcal{R}_0 > \mathcal{R}_b)$ and $a_1^2 - 4a_2a_0 > 0$.

(iv) No endemic equilibrium otherwise.

Proof. To find equilibrium points of model system (1), we just set its right-hand side equal to zero.

$$\Lambda_h + \alpha R + \theta V - (\nu B + k_1)S = 0, \tag{5a}$$
$$\xi S - [(1-\epsilon)\nu B + k_2]\, V = 0, \tag{5b}$$
$$\nu B\,[S + \pi V] - k_3 E = 0, \tag{5c}$$
$$q\gamma_1 E - k_4 C = 0, \tag{5d}$$
$$q_1\gamma_1 E + p_1\gamma_2 C - [k_5 + \sigma]\, I = 0, \tag{5e}$$
$$p\gamma_2 C + \sigma I - k_6 R = 0, \tag{5f}$$
$$p_c C + p_i I - \mu_b B = 0. \tag{5g}$$

Solving the four last equations of (5) gives

$$E = \frac{k_4}{q\gamma_1} C, \tag{6a}$$
$$C = \frac{q}{(q_1 k_4 + q p_1 \gamma_2)}\,[k_5 + \sigma]\, I, \tag{6b}$$
$$R = \frac{p\gamma_2 C + \sigma I}{k_6}, \tag{6c}$$
$$B = \frac{p_c C + p_i I}{\mu_b}. \tag{6d}$$

Solving the two first equations of (5) gives

$$V = \frac{\xi S}{[\pi\nu B + k_2]}, \tag{7a}$$
$$S = \frac{(\Lambda_h + \alpha R)(\pi\nu B + k_2)}{[(\nu B + k_1)(\pi\nu B + k_2) - \theta\xi]}. \tag{7b}$$

Using (6) and (7) in the third equation of system (5) gives that I is a nonnegative solution of the following equation

$$I\left(a_2 I^2 + a_1 I + a_0\right) = 0 \tag{8}$$

where a_2, a_1 and a_0 are given by (4).

Note that for $I = 0$, we have the disease-free equilibrium $\mathcal{Q}_0$ of which the stability analysis has been studied in the previous paragraph. Now we consider $I \neq 0$. Clearly, $a_2 > 0$, and $a_0 < 0$ (resp.$a_0 > 0$) if and only if $\mathcal{R}_0 > 1$ (resp. $\mathcal{R}_0 < 1$). Thus Proposition 2.2 is established using Descartes' rule of signs [41]. □

Item *(iii)* of proposition 2.2 indicates the possibility of the occurrence of the backward bifurcation phenomenon in model (1). This phenomenon occurs when the disease–free equilibrium coexists with at least two endemic equilibria when the basic reproduction number is less than unity [1, 4, 7, 9, 11, 40]. In the following paragraph, we will explore the direction of the bifurcation and prove the local stability of the unique endemic equilibrium whenever $\mathcal{R}_0 > 1$.

2.4.2 Direction of the bifurcation and local stability of the endemic equilibrium

In order to determine the direction of the bifurcation and to prove the stability of the endemic equilibrium point, we make use of the bifurcation theory approach which is based on the Center Manifold Theory [8] as described by Theorem 4.1 of Castillo-Chavez and Song [9] (see Appendix (A)).

Note that the Jacobian matrix of system (1) evaluated at the disease-free equilibrium at $\mathcal{R}_0 = 1$ and bifurcation parameter $\nu = \nu^*$ where

$$\nu^* = \frac{\mu_b \mu_h k_3 k_4 (k_2 + \xi)(\sigma + k_5)}{\Lambda_h (k_2 + \pi\xi)\gamma_1 \left[p_c q(\sigma + k_5) + p_i(k_4(1-q) + \gamma_2 q(1-p))\right]}, \tag{9}$$

has a simple zero eigenvalue and the other eigenvalues are negative, which implies that the disease-free equilibrium is a non-hyperbolic equilibrium when $\mathcal{R}_0 = 1$.

To conduct this analysis, we assume that $S = x_1$, $V = x_2$, $E = x_3$, $C = x_4$, $I = x_5$, $R = x_6$ and $B = x_7$.

The system (1) can be written as

$$\frac{dx_1}{dt} = \Lambda_h + \alpha x_6 + \theta x_2 - (\nu x_7 + k_1)x_1 \equiv f_1, \tag{10a}$$

$$\frac{dx_2}{dt} = \xi x_1 - [\pi\nu x_7 + k_2]\, x_2 \equiv f_2, \tag{10b}$$

$$\frac{dx_3}{dt} = \nu x_7 \left[x_1 + \pi x_2\right] - k_3 x_3 \equiv f_3, \tag{10c}$$

$$\frac{dx_4}{dt} = q\gamma_1 x_3 - k_4 x_4 \equiv f_4, \tag{10d}$$

$$\frac{dx_5}{dt} = q_1\gamma_1 x_3 + p_1\gamma_2 x_4 - k_8 x_5 \equiv f_5, \tag{10e}$$

$$\frac{dx_6}{dt} = p\gamma_2 x_4 + \sigma x_5 - k_6 x_6 \equiv f_6, \tag{10f}$$

$$\frac{dx_7}{dt} = p_c x_4 + p_i x_5 - \mu_b x_7 \equiv f_7 \tag{10g}$$

The Jacobian of the model system (1) around the disease–free equilibrium point $\mathcal{Q}_0$ evaluated at $\mathcal{R}_0 = 1$ is

$$J^*(\mathcal{Q}_0) = \begin{pmatrix} -k_1 & \theta & 0 & 0 & 0 & \alpha & -\nu^* S_0 \\ \xi & -k_2 & 0 & 0 & 0 & 0 & -\nu^* \pi V_0 \\ 0 & 0 & -k_3 & 0 & 0 & 0 & \nu^*(S_0 + \pi V_0) \\ 0 & 0 & q\gamma_1 & -k_4 & 0 & 0 & 0 \\ 0 & 0 & q_1\gamma_1 & p_1\gamma_2 & -(k_5 + \sigma) & 0 & 0 \\ 0 & 0 & 0 & p\gamma_2 & \sigma & -k_6 & 0 \\ 0 & 0 & 0 & p_c & p_i & 0 & -\mu_b \end{pmatrix}.$$

Let $u = [u_1, u_2, u_3, u_4, u_5, u_6, u_7]$ denote the left eigenvector and $w = [w_1, w_2, w_3, w_4, w_5, w_6, w_7]^T$ denote the right eigenvector of $J^*(\mathcal{Q}_0)$ corresponding to the zero eigenvalue. We obtain

that

$$u_1 = u_2 = u_6 = 0;\ u_3 = \frac{\mu_b}{\nu^*(S_0+\pi V_0)}u_7,\ u_4 = \frac{1}{q\gamma_1}\left(k_3u_3 - q_1\gamma_1u_5\right),\ u_5 = \frac{p_i}{k_8}u_7,\ u_7 > 0,$$
$$w_1 = -\frac{\nu^*(k_2S_0+\theta\pi V_0)}{k_1k_2-\theta\xi}w_7,\ w_2 = -\frac{\nu^*(\xi S_0+k_1\pi V_0)}{k_1k_2-\theta\xi}w_7,\ w_3 = \frac{\nu^*(S_0+\pi V_0)}{k_3}w_7,$$
$$w_4 = \frac{q\gamma_1}{k_4}w_3,\ w_5 = \frac{1}{k_8}\left(q_1\gamma_1w_3 + p_1\gamma_2w_4\right),\ w_6 = \frac{1}{k_6}(p\gamma_2w_4+\sigma w_5),\ w_7 > 0.$$

The non-zero partial derivatives associated with the functions f_i, $i = 1, .., 7$ of the system (10) calculated at $\mathcal{R}_0 = 1$ and $\nu = \nu^*$ are

$$\left(\frac{\partial^2 f_3}{\partial x_1\partial x_7}\right)_{Q_0} = \nu^*,\ \left(\frac{\partial^2 f_3}{\partial x_2\partial x_7}\right)_{Q_0} = \pi\nu^*,\ \left(\frac{\partial^2 f_3}{\partial x_7\partial \nu^*}\right)_{Q_0} = S_0+\pi V_0.$$

From [9, 40], we obtain the bifurcation constants a and b as given below:

$$a = \sum_{k,i,j=1}^{7} u_kw_iw_j\left(\frac{\partial^2 f_k}{\partial x_i\partial x_j}\right)_{Q_0} = -2\nu^*\frac{\mu_b}{\mu_h}u_7w_7^2 < 0,$$

and

$$b = \sum_{k,i=1}^{7} u_kw_i\left(\frac{\partial^2 f_k}{\partial x_i\partial \nu^*}\right)_{Q_0} = \frac{\mu_b}{\nu^*}u_7w_7 > 0.$$

Since $a < 0$ and $b > 0$, we claim the following result:

Theorem 2.2. *The typhoid fever model (1) exhibits a forward bifurcation at $\mathcal{R}_0 = 1$, and the unique endemic equilibrium is locally asymptotically stable whenever $\mathcal{R}_0 > 1$.*

Using Theorems 2.1 and 2.2, we conclude that the typhoid fever model (1) does not exhibits the backward bifurcation phenomenon. This coincides with some earlier results concerning the non-occurrence of the backward bifurcation phenomenon in some epidemiological models with mass action incidence rates [3, 4, 19, 26]. Figure 2 illustrates the forward bifurcation phenomenon.

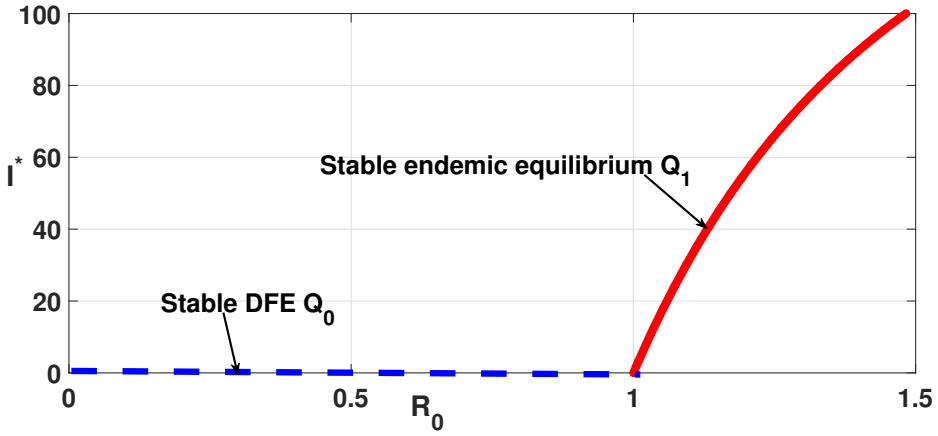

Figure 2: The forward bifurcation curve for model system 1 in the ($\mathcal{R}_0$, I^*) plane.

3 Optimal control model

We extend the model (1) to include:

1. Density dependent death rates of humans. Generally, most mathematical models of transmission dynamics of infectious diseases assume that the populations involved die at constant rates. However, others factors like density increase the death rate of the populations involved. To be realistic, we include density death rates in typhoid model (1). Following Chitnis et *al.* [11, 12], the natural mortality rate of humans become $\mu_h \to \mu_{1h} + \mu_{2h}N_h$, where $\mu_{1h} = 1.6 \times 10^{-5}\ day^{-1}$ represents the density-independent part of the death (and emigration) rate for humans, and $\mu_{2h} = 3.0 \times 10^{-7}\ humans^{-1} \times day^{-1}$ represents the density-dependent part of the death (and emigration) rate for humans.

2. Several possible interventions in order to reduce or limit the proliferation of bacteria population and the explosion of the number of infected humans. In addition of controls used in [38], we add vaccination as control variable to reduce or even eradicate the spread of typhoid fever disease. To this aim, we introduce three time dependent controls as follows:

   (a) The first control $0 \leq \xi(t) \leq 1$ denotes the rate of susceptible individuals that one decides to vaccinate at time t. We assume that only susceptible humans receive vaccine.

   (b) The second control $0 \leq u_1(t) \leq 1$ represents efforts made to keep the places clean, and thus prevent contamination of water and food by the bacteria that cause typhoid fever (sanitation and proper hygiene controls). Thus the

infection term is modified as follows:

$$\nu B(t)S(t) := (1-u_1(t))\nu B(t)S(t) \text{ and } \pi\nu B(t)V(t) := (1-u_1(t))\pi\nu B(t)V(t). \tag{11}$$

Note also that this control increases the bacterial decay rate. Thus, the bacterial decay rate becomes

$$\mu_b := \mu_b + b_1 u_1(t), \tag{12}$$

where $b_1 = 0.3$ denotes bacterial mortality rates induced by chemical intervention.

(c) The third control $0 \leq u_2(t) \leq 1$ represents efforts made for treatment, which consists of all the accompanying measures such as: the patient's care (use of ambulances to transport patients, isolating infected patients in hospitals) and the administration of proper treatment. We assume that the efficacy and duration of the treatment varies from one person to another (depending of the immune response of the patient) [2]. Thus we modify the recovery rate such that $\sigma := \sigma + b_2 u_2(t)$, where $b_2 = 0.7$ represents the proportion of effective treatment for infectious $I(t)$. Unlike models in the literature, we take into account the fact that treatment permits to decrease the disease induced death of infected humans with clinical signs of the disease. Then $\delta := (1-b_2u_2(t))\delta$. Its also permits to decrease the bacteria excretion of infectious humans with clinical signs. So $p_i := (1-b_2u_2(t))p_i$.

Note that $0 \leq \xi(t), u_1(t), u_2(t) \leq 1$ means that when the control is zero there is no effort invested (i.e. no control) and when it is one, the maximum control effort is invested.

It follows, after incorporating the above assumptions and extension, that the extended typhoid fever model, which incorporates density-dependent death rates as well as time-dependent control terms, consists of the following non-autonomous system of differential equations.

$$\dot{S}(t) = \Lambda_h + \alpha R(t) + \theta V(t) - \xi(t)S(t) - (1-u_1(t))\nu B(t)S(t) \tag{13a}$$
$$- (\mu_{1h} + \mu_{2h}N_h)S(t), \tag{13b}$$
$$\dot{V}(t) = \xi(t)S(t) - (1-u_1(t))\pi\nu B(t)V(t) - (\theta + \mu_{1h} + \mu_{2h}N_h)V(t), \tag{13c}$$
$$\dot{E}(t) = (1-u_1(t))\nu B(t)\left[S(t) + \pi V(t)\right] - (\gamma_1 + \mu_{1h} + \mu_{2h}N_h)E(t), \tag{13d}$$
$$\dot{C}(t) = q\gamma_1 E(t) - (\gamma_2 + \mu_{1h} + \mu_{2h}N_h)C(t), \tag{13e}$$
$$\dot{I}(t) = q_1\gamma_1 E(t) + p_1\gamma_2 C(t) - (\sigma + b_2u_2(t))\, I(t) - (1-b_2u_2(t))\, \delta I(t) \tag{13f}$$
$$- (\mu_{1h} + \mu_{2h}N_h)\, I(t), \tag{13g}$$
$$\dot{R}(t) = p\gamma_2 C(t) + (\sigma + b_2u_2(t))I(t) - (\alpha + \mu_{1h} + \mu_{2h}N_h)R(t), \tag{13h}$$
$$\dot{B}(t) = p_c C(t) + (1-b_2u_2(t))p_i I(t) - (\mu_b + b_1u_1(t))B(t), \tag{13i}$$

with initial conditions given at t = 0.

We mention that in the absence of anti-typhoid fever controls, the non-autonomous system (13) reduces to the autonomous system (1) when $\xi(t) := \xi$ and $u_1(t) = u_2(t) = 0$.

Remark 3.1. *In the proposed model (13), we take into account the fact that the protection on the human side can be maximal ($u_1(t) = 1$). On the other hand, the measures taken to clean up the residential areas must take into account the preservation of the environment. That is why $u_1(t)$ is multiplied by b_1 at the level of additional bacterial mortality due to the spraying of chemical products.*

The rate of change of the total population of humans and bacteria is given by

$$\begin{aligned} \dot{N}_h(t) &= \Lambda_h - (\mu_{1h} + \mu_{2h}N_h(t))N_h(t) - (1 - b_2u_2(t))\delta I(t) \\ \dot{B}(t) &= p_cC(t) + (1 - b_2u_2(t))p_iI(t) - (\mu_b + b_1u_1(t))B(t) \end{aligned} \tag{14}$$

Using the same approach as the subsection 2.1, we conclude that N_h and B are bounded. Since the Lebesgue measurable controls ξ, u_1 and u_2 are also bounded, it follows from Lukes [25] that the non-negative bounded solutions to the state system exist.

Let us consider the objective (cost) function given by

$$J(\xi, u_1, u_2) = \int_0^T \left(A_1I(t) + A_2B(t) + \frac{1}{2}D_1u_1^2 + \frac{1}{2}D_2u_2^2 + \frac{1}{2}D_3u_3^2 \right) dt \tag{15}$$

subject to the state system given by Eq.(13).

The main goal is to minimize the number of infected humans with clinical manifestations of the disease (I(t)), and keeping our environment on sanitation without bacteria which causes typhoid fever, while minimizing costs. In (15), A_1 and A_2 denote, respectively, the weight constants of the infected human with clinical manifestations (I_h) and the total number of Bacteria B. On the other hand, D_1, D_2 and D_3 are costs for vaccination, prevention and/or environment sanitation, and treatment, respectively. For sake of simplicity, we choose quadratic costs to make the problem convex and thus guarantee that a unique solution exists [2, 24]. Our main goal is to find optimal control functions (ξ^*, u_1^*, u_2^*) such that $J(\xi^*, u_1^*, u_2^*) = \min\{J(\xi, u_1, u_2) \,|\, (\xi, u_1, u_2) \in \Gamma\}$ where $\Gamma = \{c = (\xi, u_1, u_2) \,|c_i(t)$ is Lebesgue measurable on [0,T], $0 \leq c_i \leq 1$, $i = 1, 2, 3\}$ is the control set.

The next step is to prove the existence of an optimal control for system (13) and then derive the optimality system.

3.1 Existence of an optimal control

Theorem 3.1. *Consider the objective functional J given by Eq. (15) with $(\xi, u_1, u_2) \in \Gamma$ subject to the constraint state system (13). There exist $(\xi^*, u_1^*, u_2^*) \in \Gamma$ such that $J(\xi^*, u_1^*, u_2^*) = \min\{J(\xi, u_1, u_2) \,|\, (\xi, u_1, u_2) \in \Gamma\}$.*

Proof. We observe that the integrand of the objective function given by (15) is convex on the closed, convex control set Γ. Since the model is linear in the control variables and is bounded by a linear system in the state variables, then the conditions for the existence of optimal control are satisfied [17, Theorem 4.1.,page 68]. □

3.2 The optimality system

To derive the necessary conditions that the three optimal controls and corresponding states must satisfy, we use Pontryagin's maximum principle [36]. To this aim, we define the Hamiltonian function for the system, where λ_i, $i = 1, .., 7$ are the adjoint variables:

$$\begin{aligned}
\mathbb{H} := {} & A_1 I(t) + A_2 B(t) + \frac{1}{2} D_1 \xi^2 + \frac{1}{2} D_2 u_1^2 + \frac{1}{2} D_3 u_2^2 \\
& + \lambda_1 \left[\Lambda_h + \alpha R(t) + \theta V(t) - \xi(t) S(t) - (1 - u_1(t)) \nu B(t) S(t) - (\mu_{1h} + \mu_{2h} N_h) S(t)\right] \\
& + \lambda_2 \left[\xi(t) S(t) - (1 - u_1(t)) \pi \nu B(t) V(t) - (\theta + \mu_{1h} + \mu_{2h} N_h) V(t)\right] \\
& + \lambda_3 \left[(1 - u_1(t)) \nu B(t) \left(S(t) + \pi V(t)\right) - (\gamma_1 + \mu_{1h} + \mu_{2h} N_h) E(t)\right] \\
& + \lambda_4 \left[q \gamma_1 E(t) - (\gamma_2 + \mu_{1h} + \mu_{2h} N_h) C(t)\right] \\
& + \lambda_5 \left[q_1 \gamma_1 E(t) + p_1 \gamma_2 C(t) - (\sigma + b_2 u_2(t)) I(t) - (1 - b_2 u_2(t)) \delta I(t) - (\mu_{1h} + \mu_{2h} N_h) I(t)\right] \\
& + \lambda_6 \left[p \gamma_2 C(t) + (\sigma + b_2 u_2(t)) I(t) - (\alpha + \mu_{1h} + \mu_{2h} N_h) R(t)\right] \\
& + \lambda_7 \left[p_c C(t) + (1 - b_2 u_2(t)) p_i I(t) - (\mu_b + b_1 u_1(t)) B(t)\right].
\end{aligned} \tag{16}$$

The following result presents the adjoint system and control characterization.

Theorem 3.2. *Given an optimal control (ξ^*, u_1, u_2), and corresponding state solutions S, V, E, C, I, R, B of the corresponding state system (13), there exists adjoint variables, λ_i, $i = 1, .., 7$, satisfying*

$$\begin{aligned}
\lambda_1' &= \xi(\lambda_1 - \lambda_2) + (1 - u_1)\nu B(\lambda_1 - \lambda_3) + (\mu_{1h} + \mu_{2h} N_h)\lambda_1 \\
&\quad + \mu_{2h}(S\lambda_1 + V\lambda_2 + E\lambda_3 + C\lambda_4 + I\lambda_5 + R\lambda_6), \\
\lambda_2' &= \theta(\lambda_2 - \lambda_1) + (1 - u_1)\pi\nu B(\lambda_2 - \lambda_3) + (\mu_{1h} + \mu_{2h} N_h)\lambda_2 \\
&\quad + \mu_{2h}(S\lambda_1 + V\lambda_2 + E\lambda_3 + C\lambda_4 + I\lambda_5 + R\lambda_6), \\
\lambda_3' &= \gamma_1(\lambda_1 - q\lambda_4 - q_1\lambda_5) + (\mu_{1h} + \mu_{2h} N_h)\lambda_3 \\
&\quad + \mu_{2h}(S\lambda_1 + V\lambda_2 + E\lambda_3 + C\lambda_4 + I\lambda_5 + R\lambda_6), \\
\lambda_4' &= \gamma_2(\lambda_4 - p_1\lambda_5 - p\lambda_6) + (\mu_{1h} + \mu_{2h} N_h)\lambda_4 - p_c\lambda_7 \\
&\quad + \mu_{2h}(S\lambda_1 + V\lambda_2 + E\lambda_3 + C\lambda_4 + I\lambda_5 + R\lambda_6), \\
\lambda_5' &= -A_1 + (\mu_{1h} + \mu_{2h} N_h)\lambda_5 - (1 - b_2 u_2) p_i \lambda_7 + (\sigma + b_2 u_2)(\lambda_5 - \lambda_6) + (1 - b_2 u_2)\delta\lambda_5 \\
&\quad + \mu_{2h}(S\lambda_1 + V\lambda_2 + E\lambda_3 + C\lambda_4 + I\lambda_5 + R\lambda_6), \\
\lambda_6' &= \alpha(\lambda_6 - \lambda_1) + (\mu_{1h} + \mu_{2h} N_h)\lambda_6 + \mu_{2h}(S\lambda_1 + V\lambda_2 + E\lambda_3 + C\lambda_4 + I\lambda_5 + R\lambda_6), \\
\lambda_7' &= -A_2 + (1 - u_1)\nu\left[S(\lambda_1 - \lambda_3) + \pi V(\lambda_2 - \lambda_3)\right] + (\mu_b + b_1 u_1)\lambda_7,
\end{aligned}$$

with terminal conditions $\lambda_i(T) = 0$ for $i = 1, .., 7$.

Furthermore, the optimal controls ξ^* *,*u_1^**, and* u_2^* *are represented by*

$$\begin{aligned}
\xi^* &= \max\left\{0, \min\left\{1, \frac{S(\lambda_1-\lambda_2)}{D_1}\right\}\right\},\\
u_1^* &= \max\left\{0, \min\left\{1, \frac{\nu B\left[S(\lambda_3-\lambda_1)+\pi V(\lambda_3-\lambda_2)\right]+b_1 B\lambda_7}{D_2}\right\}\right\},\\
u_2^* &= \max\left\{0, \min\left\{1, \frac{b_2 I\left[p_i\lambda_7+(1-\delta)\lambda_5-\lambda_6\right]}{D_3}\right\}\right\}.
\end{aligned} \tag{17}$$

Proof. The adjoint system results from Pontryagin's principle [36]

$$\lambda_1'(t) = -\frac{\partial \mathbb{H}}{\partial S},\ \lambda_2'(t) = -\frac{\partial \mathbb{H}}{\partial V},\ \ldots, \lambda_7'(t) = -\frac{\partial \mathbb{H}}{\partial B},$$

with zero final time conditions (transversality). The characterization of the optimal control given by (17) is obtained by solving the equations on the interior of the control set

$$\frac{\partial \mathbb{H}}{\partial \xi} = 0,\ \ \frac{\partial \mathbb{H}}{\partial u_1} = 0,\ \ \frac{\partial \mathbb{H}}{\partial u_2} = 0.$$

Using the bounds on the controls, we obtain the desired characterization. □

So we get the optimality system which consists of the state system (13) with the initial conditions, the adjoint system with the terminal conditions and the control characterization (17).

4 Numerical simulations and efficiency analysis

4.1 Numerical simulations

The simulations were carried out using the values of Table 2. We use an iterative scheme to solve the optimality system. We first solve the state equations (13) with a guess for the controls over the simulated time using fourth order Runge–Kutta scheme. Then, we use the current iterations solutions of the state equation to solve the adjoint equations by a backward fourth order Runge–Kutta scheme. Finally, we update the controls by using a convex combination of the previous controls and the value from the characterizations (3.2) (see e.g. [2, 24]).

For the weights in the objective functional J (see Eq. (15))), we choose $D_1 = 30€$[2], $D_2 = 38533€$ [15], and $D_3 = 60.36€$. Figure 3 shows the optimal control profiles.

[2] https://www.chu-nantes.fr/cvi-tarif-des-vaccins-53608.kjsp

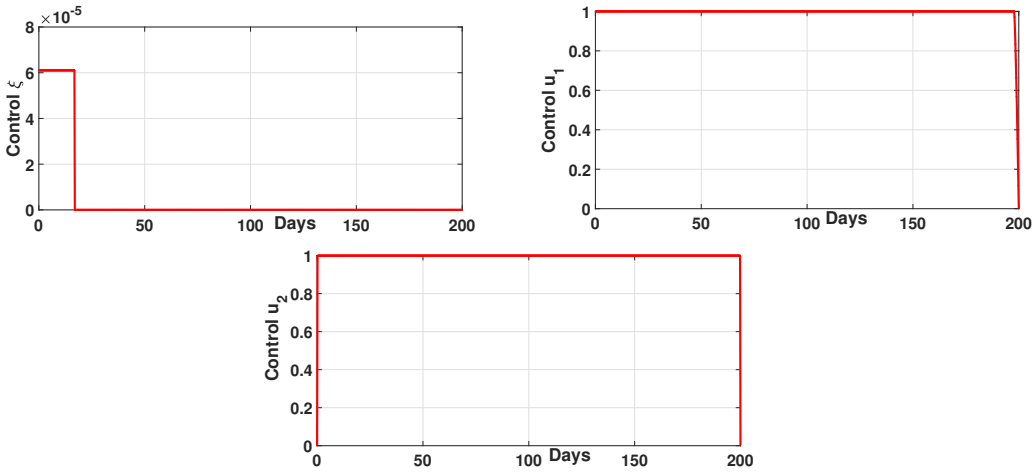

Figure 3: Control functions.

Since the purpose of this study is to determine what control strategy to adopt to considerably reduce the spread of typhoid fever epidemics, we consider different possible combinations of these controls as follows:

(i) Vaccination only We use vaccination like the only one control strategy ($\xi \neq 0, u_1 = u_2 = 0$) to minimise the objective function J, while the other control u_1 and u_2 are set to zero. On figure 4, we observe that this strategy does not have any effect on the symptomatic infectious humans (I) either on the bacteria (B).

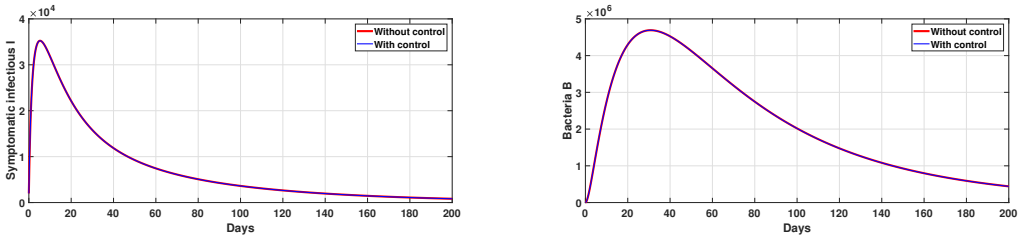

Figure 4: Simulation results of optimal control model (13) showing the effect of using optimal vaccination like the only one control strategy ($\xi \neq 0$, $u_1 = u_2 = 0$).

(ii) Protection only We use protection like the only one control strategy ($u_1 \neq 0$, $\xi = u_2 = 0$) to minimise the objective function J, while the other control ξ and u_2 are set to zero. On figure 5, we observe that this strategy does not have any effect on the symptomatic infectious humans (I) but, it permits to reduce the number of bacteria.

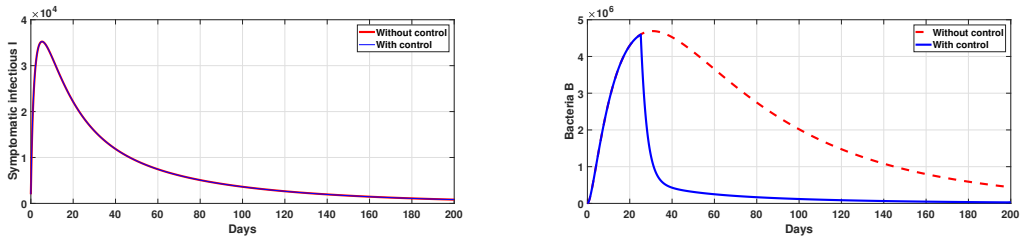

Figure 5: Simulation results of optimal control model (13) showing the effect of protection like the only one control strategy ($u_1 \neq 0$, $\xi = u_2 = 0$).

(iii) Treatment only We use treatment like the only one control strategy ($u_2 \neq 0$, $\xi = u_1 = 0$) to minimise the objective function J, while the other control ξ and u_1 are set to zero. On figure 6, we observe that this strategy has a better effect on the decrease of the total number of symptomatic infectious humans (I), and the reduction of the total number of bacteria.

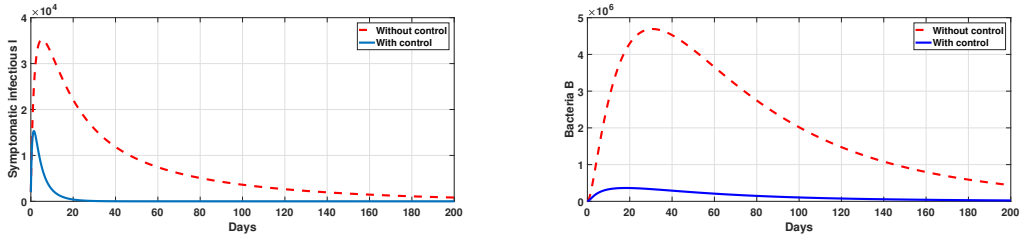

Figure 6: Simulation results of optimal control model (13) showing the effect of treatment like the only one control strategy ($u_2 \neq 0$, $\xi = u_1 = 0$).

(iv) Vaccination combined with protection We use vaccination combined with protection like the only control strategies ($\xi \neq 0, u_1 \neq 0, u_2 = 0$) to minimise the objective function J, while the other control u_2 is set to zero. On figure 7, we observe that this strategy does not have any effect on the symptomatic infectious humans (I) but it permits to reduce bacteria population (B). This is consistent with the fact that vaccination and protection, taken individually, have no significant effect on the total number of human symptomatic infected.

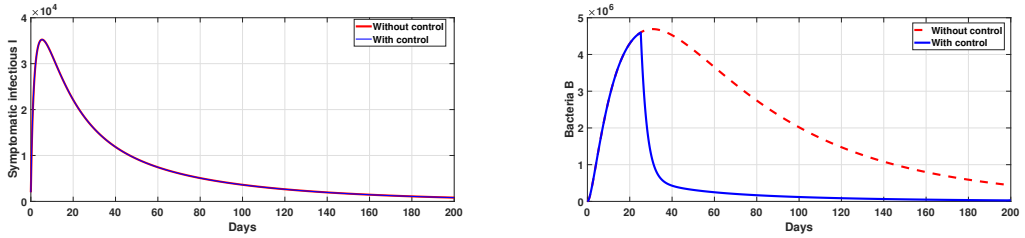

Figure 7: Simulation results of optimal control model (13) showing the effect of using optimal vaccination combined with protection like the only control strategies ($\xi \neq 0, u_1 \neq 0, u_2 = 0$).

(v) Vaccination combined with treatment We use vaccination combined with treatment like the only control strategies ($\xi \neq 0, u_2 \neq 0, u_1 = 0$) to minimise the objective function J, while the other control u_1 is set to zero. On figure 8, we observe that this strategy permits to reduce the number of symptomatic infectious humans (I) and bacteria population (B). This is consistent with the fact that treatment taken individually, is benefit to the reduction of symptomatic infected and bacteria population.

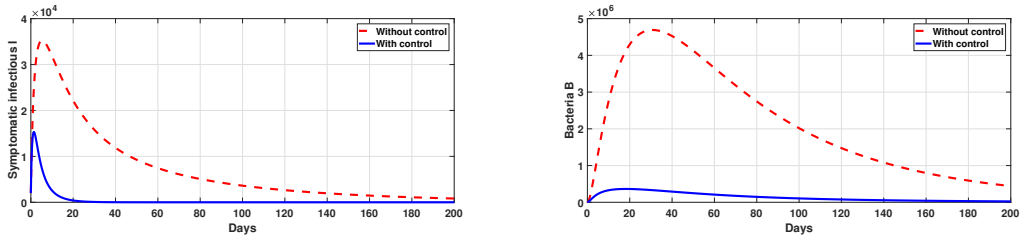

Figure 8: Simulation results of optimal control model (13) showing the effect of using optimal vaccination combined with treatment like the only control strategies ($\xi \neq 0, u_2 \neq 0, u_1 = 0$).

(vi) Protection combined with Treatment We use optimal protection combined with treatment like the only control strategies ($\xi = 0, u_1 \neq 0, u_2 \neq 0$) to minimise the objective function J, while the other control $u\xi$ is set to zero. On figure 9, we observe that this strategy permits to reduce the number of symptomatic infectious humans (I) and bacteria population (B). This is consistent with the fact that treatment taken individually, is benefit to the reduction of symptomatic infected and bacteria population.

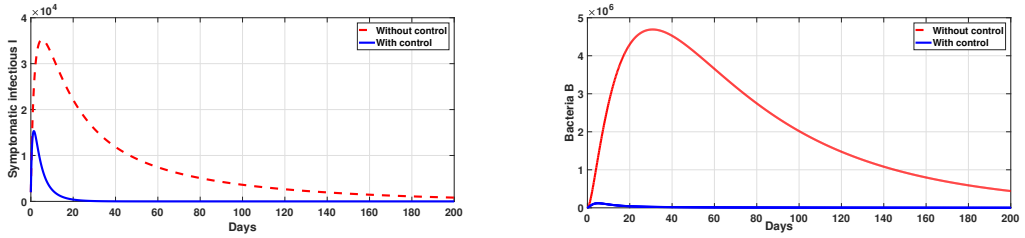

Figure 9: Simulation results of optimal control model (13) showing the effect of using optimal protection combined with treatment like the only control strategies ($\xi = 0, u_1 \neq 0, u_2 \neq 0$).

(vii) The combination of all three controls Vaccine combined with protection and treatment In this strategy, the combination of all the three controls is applied. On figure 10, we observed that combining all three controls give a better result in a decrease in the number of symptomatic infectious humans (I), as well as, the total number of bacteria population (B).

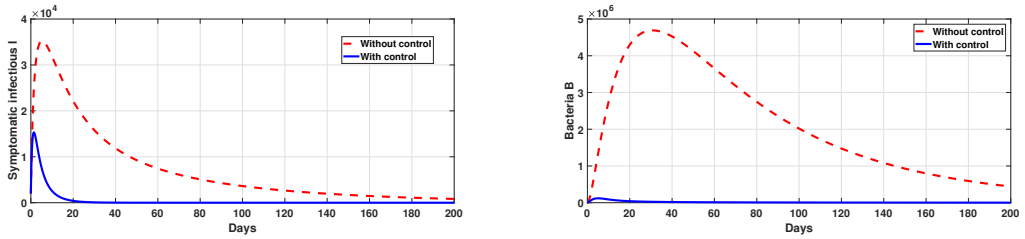

Figure 10: Simulation results of optimal control model (13) showing the effect of using optimal protection combined with treatment like the only control strategies ($\xi \neq 0, u_1 \neq 0, u_2 \neq 0$).

Since it not possible to use only figures result of simulations to say which is the best control strategy, because figures 6, 8, 9 and 10 have the same shape, we perform, in the following paragraph, an efficiency analysis to determine the best strategy in terms of efficiency.

4.2 Efficiency analysis

To compare different control strategies listed above, we perform an efficiency analysis which will allow us to determine the best control strategy, without taking into account the different costs resulting from each control strategy used [2, 14]. Efficiency analysis consist to compare the effects of possible different strategies on the reduction of the number of cases (infectious humans I_h in our case) following infection by *Salmonella typhi*, by the introduction of the efficiency index, designated by $\mathcal{E}$. Let us define the the variable $\mathcal{A}$ as the area comprised between the curve of the symptomatic infectious

Table 3: Efficiency index

Strategy	$\mathcal{A}_I^c$	$\mathcal{E}(\%)$	Strategy	$\mathcal{A}_I^c$	$\mathcal{E}(\%)$
No control	1,481,700	0	(vi)	96,088	93.5150
(iii)	96,090	93.5148	(vii)	96,088	93.5150
(v)	96,090	93.5148			

human (I) population size, for instance, and the time axis during the period of time from $t_{init} = 0$ to $T_{final} = 200$ days, as

$$\mathcal{A} = \int_{t_{init}}^{T_{final}} I(t)dt, \tag{18}$$

which permits to measure the cumulated number of symptomatic infectious humans during the time interval $[t_{init}, T_{final}]$. We define the efficiency index $\mathcal{E}$ by

$$\mathcal{E} = \left(1 - \frac{\mathcal{A}_I^c}{\mathcal{A}_I^0}\right), \tag{19}$$

where $\mathcal{A}_I^c$ and $\mathcal{A}_I^0$ are the cumulated number of symptomatic infectious human with and without the different control mechanisms, respectively. Thus, the one with the biggest efficiency index will be the best strategy.

Using the above simulation results, we obtain the table of efficiency index (Table 3) From Table 3, it follows that the combination which permit to reduce the number of cases is combination of protection with treatment or combination of three controls.

Remark 4.1. *It important to note that in the efficiency index table we only consider the strategies which include treatment, because through numerical simulations we saw that vaccination and protection do not have a significant impact on the decrease of the total number of symptomatic humans.*

5 Conclusion

In this, paper we formulated a mathematical model for the transmission dynamics of typhoid fever in human populations, which takes into account incubation period, imperfect vaccine combined with protection or environment sanitation and treatment as control mechanisms. We have began by focus on the autonomous model which take only constant vaccination as control strategy. We computed the basic reproduction number $\mathcal{R}_0$ and investigated the existence and stability of equilibria. Through Lyapunov's theory, we proved that the disease–free equilibrium is globally asymptotically stable whenever the $\mathcal{R}_0$ is less than one. When $\mathcal{R}_0$ is equal to one, we proved that our model exhibits a forward bifurcation, which mean that the phenomenon of backward bifurcation not

occurs. Hence, the condition $\mathcal{R}_0 < 1$ is sufficient to go out the disease in human populations. We proved the local stability of the unique endemic equilibrium whenever the basic reproduction number is greater than unity through the center manifold theory.

We then extended the autonomous model by adding density dependent death rate of humans and three times-dependent controls (optimal vaccination, protection/environment sanitation and treatment of symptomatic infectious). Optimal control theory was used to establish conditions under which the spread of typhoid fever can be stopped and to examine the impact of a possible combination of these three controls on the disease transmission. The characterization of the optimal control was obtained by the application of the Pontryagin's maximum principle.

We performed numerical studies and the impact of different combination of controls on the reduction of human with symptomatic signs of diseases was investigated through efficiency analysis. In fact, thanks to the results of the numerical simulations and efficiency analysis, we conclude that any control strategy must take into account the treatment of the individuals who present the symptoms of the diseases.

Because of the uncertainties around the parameter values and to the availability of budget or others resources, this conclusion must be taken with caution. Also, because of constraints such as financial and material resources limited, sociological and cultural barriers that sometimes make difficult the task of health workers of developing countries, the implementation of these controls may be difficult.

In this work, factors such as climatic factors and the fact that bacteria in the environment can develop by a logistic growth rate, had not been taken into account. It would therefore be better realistic to incorporate its into the model and redo an analysis of the complete model. This is a perspective to this work.

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A useful result

We use the following result to prove the non appearance of the backward bifurcation in typhoid model (1) when the basic reproduction number $\mathcal{R}_0$ is less that one, and the local stability of the unique endemic equilibrium whenever $\mathcal{R}_0 > 1$.

Theorem A.1 (Castillo-Chavez & Song [9]). *Consider the following general system of ordinary differential equations with a parameter ϕ*

$$\frac{dz}{dt} = f(z, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \longrightarrow \mathbb{R} \quad \text{and } f \in C^2(\mathbb{R}^n, \mathbb{R}) \tag{20}$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ for all ϕ) and assume

1. $A = D_z f(0,0) = \left(\dfrac{\partial f_i}{\partial z_j}(0,0)\right)$ *is the linearization matrix of system (20) around*

the equilibrium 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

2. *Matrix A has a right eigenvector u and a left eigenvector v (each corresponding to the zero eigenvalue).*

Let f_k be the k^{th} component of f and

$$a = \sum_{k,i,j=1}^{n} v_k u_i u_j \frac{\partial^2 f_k}{\partial z_i \partial z_j}(0,0) \quad \text{and} \quad b = \sum_{k,i=1}^{n} v_k u_i \frac{\partial^2 f_k}{\partial z_i \partial \phi}(0,0),$$

then, the local dynamics of the system around the equilibrium point 0 is totally determined by the signs of a and b.

1. *$a > 0$, $b > 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, 0 is unstable and there exists a negative, locally asymptotically stable equilibrium;*

2. *$a < 0$, $b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable; when $0 < \phi \ll 1$, 0 is locally asymptotically stable equilibrium, and there exists a positive unstable equilibrium;*

3. *$a > 0$, $b < 0$. When $\phi < 0$ with $|\phi| \ll 1$, 0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, 0 is stable, and a positive unstable equilibrium appears;*

4. *$a < 0$, $b > 0$. When ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

B Proof of Proposition 2.1

The Jacobian of the model system (1), around the disease–free equilibrium point $\mathcal{Q}_0$ is

$$J(\mathcal{Q}_0) = \begin{pmatrix} -k_1 & \theta & 0 & 0 & 0 & \alpha & -\nu S_0 \\ \xi & -k_2 & 0 & 0 & 0 & 0 & -\nu\pi V_0 \\ 0 & 0 & -k_3 & 0 & 0 & 0 & \nu(S_0 + \pi V_0) \\ 0 & 0 & q\gamma_1 & -k_4 & 0 & 0 & 0 \\ 0 & 0 & q_1\gamma_1 & p_1\gamma_2 & -(k_5+\sigma) & 0 & 0 \\ 0 & 0 & 0 & p\gamma_2 & \sigma & -k_6 & 0 \\ 0 & 0 & 0 & p_c & p_i & 0 & -\mu_b \end{pmatrix}.$$

The eigenvalues of $J(\mathcal{Q}_0)$ are $X = -k_6$ and those of the sub-matrices

$$J_1 = \begin{pmatrix} -k_1 & \theta \\ \xi & -k_2 \end{pmatrix}$$

and

$$J_2 = \begin{pmatrix} -k_3 & 0 & 0 & \nu(S_0 + \pi V_0) \\ q\gamma_1 & -k_4 & 0 & 0 \\ q_1\gamma_1 & p_1\gamma_2 & -(k_5+\sigma) & 0 \\ 0 & p_c & p_i & -\mu_b \end{pmatrix}.$$

The characteristic polynomial of J_1 is

$$\mathcal{P}_{J_1}(X) = \det(J_1 - XI_2) = X^2 + X(k_1 + k_2) + k_1k_2 - \theta\xi$$

where $k_7 = k_1k_2 - \theta\xi = \mu_h(k_2 + \xi) > 0$. Since all coefficients of $\mathcal{P}_{J_1}(X)$ are positive, J_1 has eigenvalues with negative real parts. It remains to shows that J_2 has eigenvalues with negative real parts. The characteristic polynomial of J_2 is

$$\det(J_2 - XI_2) = \Psi(X) := X^4 + a_1X^3 + a_2X^2 + a_3X + a_4$$

with $k_8 = k_5 + \sigma$, $a_1 = k_3 + k_4 + k_8 + \mu_b$, $a_2 = \mu_b(k_3 + k_4 + k_8) + k_8(k_3 + k_4) + k_3k_4$, $a_4 = k_3k_4k_8\mu_b(1 - \mathcal{R}_0^2)$ and

$$\begin{aligned} a_3 = \frac{1}{k_4p_iq_1 + (\gamma_2p_1p_i + k_8p_c)q} \big[&(((k_4 + (1 - R_0^2)k_3)k_8 + k_3k_4)\mu_b + k_3k_4k_8)k_4p_iq_1 \\ &+(((k_4 + k_3)k_8 + k_3k_4)\mu_b + k_3k_4k_8)\gamma_2qp_1p_i + (((k_4 + k_3)k_8 + (1 - R_0^2)k_3k_4)\mu_b + k_3k_4k_8)k_8p_cq\big] \end{aligned}$$

Since $\mathcal{R}_0 < 1$, it is clear that all coefficients of $\Psi(X)$ are always positive. Now we have to verify that the Routh–Hurwitz criterion holds for polynomial $\Psi(X)$. To this aim, setting $H_1 = a_1 > 0$, consider

$$\begin{aligned} H_2 &= a_1a_2 - a_3 \\ &= \frac{1}{k_4p_iq_1 + (\gamma_2p_1p_i + k_8p_c)q} \big[((k_4k_8 + k_4^2 + k_3k_4)\mu_b^2 \\ &+(k_4k_8^2 + (2k_4^2 + (R_0^2 + 2)k_3k_4)k_8 + k_4^3 + 2k_3k_4^2 + k_3^2k_4)\mu_b \\ &+(k_4^2 + k_3k_4)k_8^2 + (k_4^3 + 2k_3k_4^2 + k_3^2k_4)k_8 + k_3k_4^3 + k_3^2k_4^2)p_iq_1 \\ &+(((\gamma_2k_8 + \gamma_2k_4 + \gamma_2k_3)\mu_b^2 + (\gamma_2k_8^2 + (2\gamma_2k_4 + 2\gamma_2k_3)k_8 + \gamma_2k_4^2 + 2\gamma_2k_3k_4 + \gamma_2k_3^2)\mu_b \\ &+(\gamma_2k_4 + \gamma_2k_3)k_8^2 + (\gamma_2k_4^2 + 2\gamma_2k_3k_4 + \gamma_2k_3^2)k_8 + \gamma_2k_3k_4^2 + \gamma_2k_3^2k_4)p_1p_i \\ &+((k_8^2 + (k_4 + k_3)k_8)\mu_b^2 + (k_8^3 + (2k_4 + 2k_3)k_8^2 + (k_4^2 + (R_0^2 + 2)k_3k_4 + k_3^2)k_8)\mu_b \\ &+(k_4 + k_3)k_8^3 + (k_4^2 + 2k_3k_4 + k_3^2)k_8^2 + (k_3k_4^2 + k_3^2k_4)k_8)p_c)q\big], \end{aligned}$$

$$
\begin{aligned}
H_3 &= a_1a_2a_3 - a_1^2a_4 - a_3^3 \\
&= \frac{1}{k_4^2p_i^2q_1^2 + (2\gamma_2k_4p_1p_i^2 + 2k_4k_8p_cp_i)qq_1 + (\gamma_2^2p_1^2p_i^2 + 2\gamma_2k_8p_1p_cp_i + k_8^2p_c^2)q^2} \times ... \\
&\times \big[(((k_4^3 + (1-R_0^2)k_3k_4^2)k_8^2 + (k_4^4 + 2k_3k_4^3 + (1-R_0^2)k_3^2k_4^2)k_8 + k_3k_4^4 + k_3^2k_4^3)\mu_b^3 \\
&+((k_4^3 + (1-R_0^2)k_3k_4^2)k_8^3 + (2k_4^4 + (R_0^2+4)k_3k_4^3 + (-R_0^4 - R_0^2 + 2)k_3^2k_4^2)k_8^2 \\
&+(k_4^5 + (R_0^2+4)k_3k_4^4 + (R_0^2+4)k_3^2k_4^3 + (1-R_0^2)k_3^3k_4^2)k_8 + k_3k_4^5 + 2k_3^2k_4^4 + k_3^3k_4^3)\mu_b^2 \\
&+((k_4^4 + 2k_3k_4^3 + (1-R_0^2)k_3^2k_4^2)k_8^3 + (k_4^5 + (R_0^2+4)k_3k_4^4 + (R_0^2+4)k_3^2k_4^3 + (1-R_0^2)k_3^3k_4^2)k_8^2 \\
&+((R_0^2+2)k_3k_4^5 + (R_0^2+4)k_3^2k_4^4 + 2k_3^3k_4^3)k_8 + k_3^2k_4^5 + k_3^3k_4^4)\mu_b + (k_3k_4^4 + k_3^2k_4^3)k_8^3 \\
&+(k_3k_4^5 + 2k_3^2k_4^4 + k_3^3k_4^3)k_8^2 + (k_3^2k_4^5 + k_3^3k_4^4)k_8)p_i^2q_1^2 + ((((2\gamma_2k_4^2 + (2\gamma_2 - \gamma_2R_0^2)k_3k_4)k_8^2 \\
&+(2\gamma_2k_4^3 + (\gamma_2R_0^2 + 4\gamma_2)k_3k_4^2 + (2\gamma_2 - \gamma_2R_0^2)k_3^2k_4)k_8 + 2\gamma_2k_3k_4^3 + 2\gamma_2k_3^2k_4^2)\mu_b^3 \\
&+((2\gamma_2k_4^2 + (2\gamma_2 - \gamma_2R_0^2)k_3k_4)k_8^3 + (4\gamma_2k_4^3 + (3\gamma_2R_0^2 + 8\gamma_2)k_3k_4^2 + (4\gamma_2 - \gamma_2R_0^2)k_3^2k_4)k_8^2 \\
&+(2\gamma_2k_4^4 + (3\gamma_2R_0^2 + 8\gamma_2)k_3k_4^3 + (3\gamma_2R_0^2 + 8\gamma_2)k_3^2k_4^2 + (2\gamma_2 - \gamma_2R_0^2)k_3^3k_4)k_8 \\
&+2\gamma_2k_3k_4^4 + 4\gamma_2k_3^2k_4^3 + 2\gamma_2k_3^3k_4^2)\mu_b^2 + ((2\gamma_2k_4^3 + (\gamma_2R_0^2 + 4\gamma_2)k_3k_4^2 + (2\gamma_2 - \gamma_2R_0^2)k_3^2k_4)k_8^3 \\
&+(2\gamma_2k_4^4 + (3\gamma_2R_0^2 + 8\gamma_2)k_3k_4^3 + (3\gamma_2R_0^2 + 8\gamma_2)k_3^2k_4^2 + (2\gamma_2 - \gamma_2R_0^2)k_3^3k_4)k_8^2 \\
&+((2\gamma_2R_0^2 + 4\gamma_2)k_3k_4^4 + (3\gamma_2R_0^2 + 8\gamma_2)k_3^2k_4^3 + (\gamma_2R_0^2 + 4\gamma_2)k_3^3k_4^2)k_8 + 2\gamma_2k_3^2k_4^4 + 2\gamma_2k_3^3k_4^3)\mu_b \\
&+(2\gamma_2k_3k_4^3 + 2\gamma_2k_3^2k_4^2)k_8^3 + (2\gamma_2k_3k_4^4 + 4\gamma_2k_3^2k_4^3 + 2\gamma_2k_3^3k_4^2)k_8^2 + (2\gamma_2k_3^2k_4^4 + 2\gamma_2k_3^3k_4^3)k_8)p_1p_i^2 \\
&+(((2k_4^2 + (2-R_0^2)k_3k_4)k_8^3 + (2k_4^3 + 4k_3k_4^2 + (2-R_0^2)k_3^2k_4)k_8^2 \\
&+((2-R_0^2)k_3k_4^3 + (2-R_0^2)k_3^2k_4^2)k_8)\mu_b^3 + ((2k_4^2 + (2-R_0^2)k_3k_4)k_8^4 \\
&+(4k_4^3 + (2R_0^2+8)k_3k_4^2 + (4-R_0^2)k_3^2k_4)k_8^3 + (2k_4^4 + (2R_0^2+8)k_3k_4^3 \\
&+(-2R_0^4 + 2R_0^2 + 8)k_3^2k_4^2 + (2-R_0^2)k_3^3k_4)k_8^2 + ((2-R_0^2)k_3k_4^4 + (4-R_0^2)k_3^2k_4^3 \\
&+(2-R_0^2)k_3^3k_4^2)k_8)\mu_b^2 + ((2k_4^3 + (R_0^2+4)k_3k_4^2 + (2-R_0^2)k_3^2k_4)k_8^4 + (2k_4^4 + (2R_0^2+8)k_3k_4^3 \\
&+(2R_0^2+8)k_3^2k_4^2 + (2-R_0^2)k_3^3k_4)k_8^3 + ((R_0^2+4)k_3k_4^4 + (2R_0^2+8)k_3^2k_4^3 + 4k_3^3k_4^2)k_8^2 \\
&+((2-R_0^2)k_3^2k_4^4 + (2-R_0^2)k_3^3k_4^3)k_8)\mu_b + (2k_3k_4^3 + 2k_3^2k_4^2)k_8^4 + (2k_3k_4^4 + 4k_3^2k_4^3 + 2k_3^3k_4^2)k_8^3 \\
&+(2k_3^2k_4^4 + 2k_3^3k_4^3)k_8^2)p_cp_i)qq_1 + ((((\gamma_2^2k_4 + \gamma_2^2k_3)k_8^2 + (\gamma_2^2k_4^2 + (\gamma_2^2R_0^2 + 2\gamma_2^2)k_3k_4 + \gamma_2^2k_3^2)k_8 \\
&+\gamma_2^2k_3k_4^2 + \gamma_2^2k_3^2k_4)\mu_b^3 + ((\gamma_2^2k_4 + \gamma_2^2k_3)k_8^3 + (2\gamma_2^2k_4^2 + (2\gamma_2^2R_0^2 + 4\gamma_2^2)k_3k_4 + 2\gamma_2^2k_3^2)k_8^2 \\
&+(\gamma_2^2k_4^3 + (2\gamma_2^2R_0^2 + 4\gamma_2^2)k_3k_4^2 + (2\gamma_2^2R_0^2 + 4\gamma_2^2)k_3^2k_4 + \gamma_2^2k_3^3)k_8 + \gamma_2^2k_3k_4^3 + 2\gamma_2^2k_3^2k_4^2 + \gamma_2^2k_3^3k_4)\mu_b^2 + \Phi\big]
\end{aligned}
$$

with

$$\begin{aligned}\Phi = &((\gamma_2^2k_4^2+(\gamma_2^2R_0^2+2\gamma_2^2)k_3k_4+\gamma_2^2k_3^2)k_8^3+(\gamma_2^2k_4^3+(2\gamma_2^2R_0^2+4\gamma_2^2)k_3k_4^2+(2\gamma_2^2R_0^2+4\gamma_2^2)k_3^2k_4+\gamma_2^2k_3^3)k_8^2\\
&+((\gamma_2^2R_0^2+2\gamma_2^2)k_3k_4^3+(2\gamma_2^2R_0^2+4\gamma_2^2)k_3^2k_4^2+(\gamma_2^2R_0^2+2\gamma_2^2)k_3^3k_4)k_8+\gamma_2^2k_3^2k_4^3+\gamma_2^2k_3^3k_4^2)\mu_b\\
&+(\gamma_2^2k_3k_4^2+\gamma_2^2k_3^2k_4)k_8^3+(\gamma_2^2k_3k_4^3+2\gamma_2^2k_3^2k_4^2+\gamma_2^2k_3^3k_4)k_8^2+(\gamma_2^2k_3^2k_4^3+\gamma_2^2k_3^3k_4^2)k_8)p_1^2p_i^2\\
&+(((2\gamma_2k_4+2\gamma_2k_3)k_8^3+(2\gamma_2k_4^2+(\gamma_2R_0^2+4\gamma_2)k_3k_4+2\gamma_2k_3^2)k_8^2\\
&+((2\gamma_2-\gamma_2R_0^2)k_3k_4^2+(2\gamma_2-\gamma_2R_0^2)k_3^2k_4)k_8)\mu_b^3+((2\gamma_2k_4+2\gamma_2k_3)k_8^4+(4\gamma_2k_4^2+(3\gamma_2R_0^2+8\gamma_2)k_3k_4\\
&+4\gamma_2k_3^2)k_8^3+(2\gamma_2k_4^3+(3\gamma_2R_0^2+8\gamma_2)k_3k_4^2+(3\gamma_2R_0^2+8\gamma_2)k_3^2k_4+2\gamma_2k_3^3)k_8^2+((2\gamma_2-\gamma_2R_0^2)k_3k_4^3\\
&+(4\gamma_2-\gamma_2R_0^2)k_3^2k_4^2+(2\gamma_2-\gamma_2R_0^2)k_3^3k_4)k_8)\mu_b^2+((2\gamma_2k_4^2+(2\gamma_2R_0^2+4\gamma_2)k_3k_4+2\gamma_2k_3^2)k_8^4\\
&+(2\gamma_2k_4^3+(3\gamma_2R_0^2+8\gamma_2)k_3k_4^2+(3\gamma_2R_0^2+8\gamma_2)k_3^2k_4+2\gamma_2k_3^3)k_8^3+((\gamma_2R_0^2+4\gamma_2)k_3k_4^3\\
&+(3\gamma_2R_0^2+8\gamma_2)k_3^2k_4^2+(\gamma_2R_0^2+4\gamma_2)k_3^3k_4)k_8^2+((2\gamma_2-\gamma_2R_0^2)k_3^2k_4^3+(2\gamma_2-\gamma_2R_0^2)k_3^3k_4^2)k_8)\mu_b\\
&+(2\gamma_2k_3k_4^2+2\gamma_2k_3^2k_4)k_8^4+(2\gamma_2k_3k_4^3+4\gamma_2k_3^2k_4^2+2\gamma_2k_3^3k_4)k_8^3+(2\gamma_2k_3^2k_4^3+2\gamma_2k_3^3k_4^2)k_8^2)p_1p_cp_i\\
&+(((k_4+k_3)k_8^4+(k_4^2+2k_3k_4+k_3^2)k_8^3+((1-R_0^2)k_3k_4^2+(1-R_0^2)k_3^2k_4)k_8^2)\mu_b^3+((k_4+k_3)k_8^5\\
&+(2k_4^2+(R_0^2+4)k_3k_4+2k_3^2)k_8^4+(k_4^3+(R_0^2+4)k_3k_4^2+(R_0^2+4)k_3^2k_4+k_3^3)k_8^3+((1-R_0^2)k_3k_4^3\\
&+(-R_0^4-R_0^2+2)k_3^2k_4^2+(1-R_0^2)k_3^3k_4)k_8^2)\mu_b^2+((k_4^2+(R_0^2+2)k_3k_4+k_3^2)k_8^5+(k_4^3+(R_0^2+4)k_3k_4^2\\
&+(R_0^2+4)k_3^2k_4+k_3^3)k_8^4+(2k_3k_4^3+(R_0^2+4)k_3^2k_4^2+2k_3^3k_4)k_8^3+((1-R_0^2)k_3^2k_4^3+(1-R_0^2)k_3^3k_4^2)k_8^2)\mu_b\\
&+(k_3k_4^2+k_3^2k_4)k_8^5+(k_3k_4^3+2k_3^2k_4^2+k_3^3k_4)k_8^4+(k_3^2k_4^3+k_3^3k_4^2)k_8^3)p_c^2)q^2\end{aligned}$$

and $H_4 = a_4H_3$.

We always have $H_1 > 0$, $H_2 > 0$, $H_3 > 0$ and $H_4 > 0$ if $\mathcal{R}_0 < 1$. Thus, the disease–free equilibrium $\mathcal{Q}_0$ is locally asymptotically stable whenever $\mathcal{R}_0 < 1$.

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