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Research Article

Mathematical modeling and optimal control strategies of the typhoid transmission with cost-effectiveness analysis

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Abstract

This paper presents the development of a sophisticated mathematical model aimed at optimizing the control of typhoid fever in Taiwan. The model incorporates key factors influencing transmission dynamics, including human interactions, exposure to contaminated sources, and the effectiveness of preventive measures. It is analyzed using optimal control theory and rigorous numerical simulations, enabling a comprehensive assessment of various intervention strategies. The findings highlight that a combination of awareness campaigns and vaccination programs constitutes the most effective approach to reducing disease spread. This work underscores the critical role of mathematical modeling as a decision-support tool in public health planning, providing data-driven insights to guide the prevention and control of typhoid fever.

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1 Introduction

Typhoid fever, also referred to as enteric fever, is caused by Salmonella enterica serovars Typhi and Paratyphi A, B, and C.

S. Typhi is responsible for typhoid fever, whereas S. Paratyphi can also cause enteric fever [4]. Most infections from non-typhoidal Salmonella spp. lead to diarrhea and only rarely result in bloodstream infections. Individuals affected by typhoid fever, however, typically harbor the bacteria in both their bloodstream and intestinal tract. Notably, enteric fever is exclusive to humans and is primarily transmitted through contaminated food or water.

Medical research indicates that the duration of the incubation period for typhoid fever depends on the bacterial load in the body, which is influenced by the patient's overall health and stomach acidity [9]. The infectious dose of enteric fever is estimated at 10^5 bacilli. Older individuals and those with achlorhydria—characterized by reduced stomach acid secretion and impaired cell-mediated immunity—may acquire the infection after exposure to a lower infectious dose [17].

The incubation period for typhoid fever averages 10 to 20 days (range: 3–56 days), whereas for S. Paratyphi A, it typically ranges from 1 to 10 days [13]. During the first week, symptoms are often nonspecific and may include headache, fatigue, and fever. Constipation and a mild, non-productive cough are also frequently reported. In the second week, patients generally present with lethargy, persistent fever, mild abdominal distension, and splenomegaly. The appearance of rose-colored spots, usually 2–4 mm in diameter and blanching under pressure, is considered a classic sign of typhoid fever, although such spots are uncommon and difficult to detect in individuals with darker skin tones [13].

Confirmation of typhoid infection requires the isolation of S. Typhi from blood, bone marrow, or lesion samples. Importantly, asymptomatic carriers, individuals excreting S. Typhi in their stool or urine without showing symptoms can also contribute to transmission [40]. The most widely accepted diagnostic method is blood culture, as over 80% of infected individuals have detectable bacteria in their blood. Factors such as prior antibiotic use, the volume of blood cultured, and the timing of collection can explain why some cultures fail to isolate S. Typhi [41].

In 2017, an estimated 14.3 million people were infected with enteric fever, including 11 million S. Typhi cases and 120,000 deaths, more than half occurring in children under 15 years [37]. According to [34], these numbers decreased in 2021, with 9.3 million infections and 107,500 deaths annually. Although the disease has been controlled in developed countries, it remains

endemic in regions with poor hygiene. South Asia—including India, Pakistan, and Bangladesh—continues to show particularly high incidence rates [10, 24].

The emergence of bacterial resistance to common antibiotics and the existence of multiple Salmonella strains [6, 23] indicate that improvements in sanitation and hygiene alone are insufficient. Vaccination, therefore, remains a critical strategy for disease control, especially in epidemic areas. Currently, three types of licensed typhoid vaccines are available:

Typhoid conjugate vaccines (TCVs): New-generation TCVs include two licensed types, Typbar-TCV and PedaTyph™ (the latter licensed and marketed only in India). These are Vi-TT conjugate vaccines, produced with different carrier proteins. Additional TCV candidates are currently under regulatory review [42].

Vi capsular polysaccharide (ViPS) vaccine: Purified from the S. Typhi strain Ty2, this vaccine is used in ViPS-hepatitis A non-conjugate combination vaccines, mainly for travelers. Available data indicate that seroconversion against vaccine antigens is equivalent to that obtained with monovalent ViPS and hepatitis A vaccines [42].

Ty21a vaccine: Orally administered and prepared from a live attenuated Ty2 strain of S. Typhi, this vaccine has several genes modified by chemical mutagenesis, resulting in a strain that lacks the Vi antigen [42].

Mathematically, several models have been proposed to clarify transmission dynamics and evaluate the effectiveness of different preventive strategies against typhoid fever. These include models focusing on direct human-to-human transmission [27, 21], transmission via contaminated food and water [39, 29], and hybrid models combining both routes [16, 36]. Preventive strategies against typhoid epidemics have been studied through approaches involving treatment [28, 39], sanitation [3, 38], educational campaigns [33, 26], and media coverage [25]. The outcomes of such mathematical models contribute to the development of effective strategies for controlling and preventing typhoid fever.

For instance, Tilahun, Makinde, and Malonza [38] developed an epidemic model to investigate transmission dynamics and highlight the role of public health education in reducing disease spread in Taiwan and China. Musa et al. [26] proposed a model assessing the effects of vaccination, including herd immunity, and demonstrated that vaccination provides indirect short-term protection and reduces incidence. Alharbi, Alalhareth, and Ibrahim [3] designed a model to evaluate the role of direct and indirect transmission, incorporating vaccination coverage, treatment, and water sanitation. Their results revealed that reducing typhoid prevalence depends on implementing these interventions, minimizing contact with infected patients, and protecting water sources from fecal contamination. Similarly, Abboubakar et al. [1] developed a fractional derivative model incorporating vaccination, showing that immunization significantly reduces disease spread. Abboubakar and Racke [2] analyzed a standalone model including incomplete vaccina-

tion, hygiene measures, and treatment. Based on clinical data from Mbandjock, Cameroon, they concluded that large-scale vaccination campaigns, environmental sanitation, and therapeutic interventions must be combined to effectively control typhoid fever.

This body of research highlights the importance of mathematical models for understanding the transmission dynamics of typhoid fever and their relevance to public health interventions aimed at prevention and control.

Our main contribution lies in integrating several aspects often neglected in existing models. First, we consider the impact of infected immigrants on transmission dynamics by distributing them across the different compartments of the model. Second, we account for the role of population and hospital waste in contaminating water and food, as well as the effect of government sterilization efforts. Third, we include the therapeutic behaviors of infected individuals, assuming that patients may choose between drug-based and herbal treatments, which influences recovery rates. Some patients may also discontinue treatment due to financial constraints, lack of awareness, or premature relief of symptoms. Finally, we evaluate the effectiveness of various typhoid control strategies using a cost-effectiveness framework, enabling identification of the most optimal interventions under resource constraints.

The study is organized as follows: Section 2 presents the mathematical model, including its description and fundamental properties, such as the positivity and boundedness of solutions. Section 3 formulates the optimal control problem, establishes the existence of an optimal solution, and characterizes the controls using Pontryagin's maximum principle. Section 4 provides numerical simulations along with cost-effectiveness analyses of the proposed strategies. Finally, Section 5 is devoted to interpreting the results in a public health context and concludes with perspectives for future research. This last section is structured into two subsections: A discussion of the findings in relation to existing literature, and a conclusion summarizing the main contributions of the study.

2 Mathematical model

2.1 Model description

In this paper, we propose an eight-compartment model to describe the transmission dynamics of typhoid fever. The compartment of susceptible individuals, denoted by $S(t)$, represents the population at risk of infection who have neither contracted the disease nor developed immunity. Individuals temporarily immune as a result of vaccination are grouped into the vaccinated-

susceptible compartment, $S_v(t)$ [42]. Exposed individuals in the incubation period, denoted by $E(t)$, are also considered. The incubation time varies with the infectious dose, which for enteric fever is typically around 10^5 bacilli ingested (and about 10^3 for non-typhoidal *Salmonella*) [17].

Asymptomatic infectious individuals are represented by $I_A(t)$ [40], whereas symptomatic infectious individuals are described by $I_S(t)$ [13]. Those receiving medical treatment (conventional rather than herbal), either at home or in hospital, are included in the treatment compartment $H(t)$. Recovered individuals, denoted by $R(t)$, are those who have fully recovered, either through successful medical treatment or via natural immunity, and have acquired temporary protection against typhoid fever [19].

At any time t, the total human population is defined as

$$N(t) = S(t) + S_v(t) + E(t) + I_A(t) + I_S(t) + H(t) + R(t).$$

Note that the total population is not assumed to be constant, as it evolves according to the inflow of newborns and immigrants, and the outflow due to natural and disease-related mortality. Finally, the environmental compartment $E_n(t)$ represents the density of *Salmonella* present in contaminated water and food.

The overall structure of the proposed model is illustrated in Figure 1, while its parameters are summarized in Table 1.

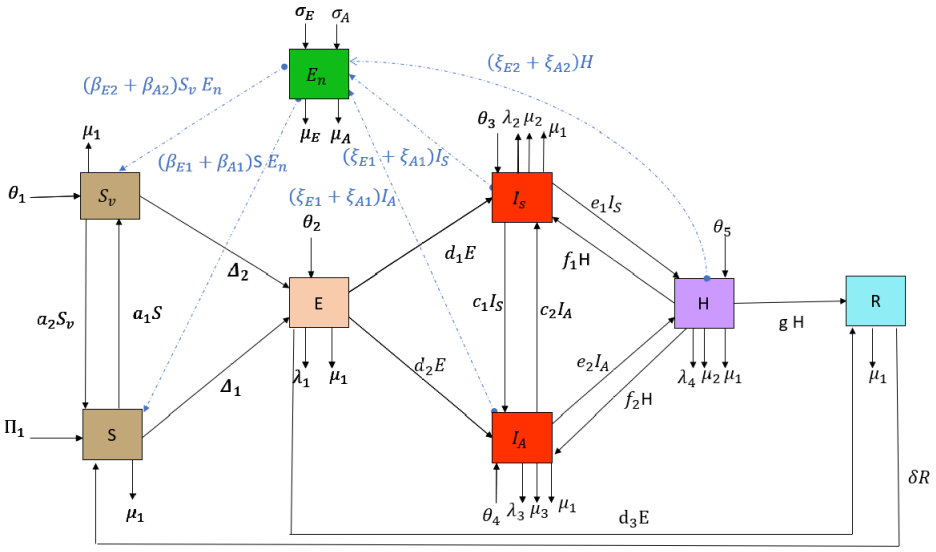

Figure 1: Model of typhoid fever

where

$$\Delta_1 = (\beta_{A1} + \beta_{E1})SE_n + (b_1 I_S + b_2 I_A)S.$$
$$\Delta_2 = (\beta_{A2} + \beta_{E2})S_v E_n + (b_1' I_S + b_2' I_A)S_v.$$

Table 1: Model parameters (person/day)

Symbol	Description
Π_1	Birth rate (newborns entering the population).
θ_1	Integration rate of vaccinated immigrants.
θ_2	Integration rate of immigrants carrying Salmonella bacteria.
θ_3	Integration rate of symptomatic infected immigrants.
θ_4	Integration rate of asymptomatic infected immigrants.
θ_5	Integration rate of immigrants based on treatment duration.
λ_1	Exit rate of immigrants carrying Salmonella.
λ_2	Discharge rate of symptomatic infectious immigrants.
λ_3	Discharge rate of asymptomatic infectious immigrants.
λ_4	Discharge rate of immigrants under treatment.
μ_1	Natural mortality rate.
μ_2	Disease-induced mortality rate for symptomatic infected individuals.
μ_3	Disease-induced mortality rate for asymptomatic infected individuals.
μ_E	Bacterial mortality rate in water.
μ_A	Bacterial mortality rate in food.
σ_E	Water disinfection rate.
σ_A	Food disinfection rate.
β_{A1}	Contamination rate via food.
β_{E1}	Contamination rate via water.
β_{A2}	Contamination rate of vaccinated susceptibles via food.
β_{E2}	Contamination rate of vaccinated susceptibles via water.
a_1	Vaccination rate.
a_2	Vaccine immunity waning rate.
b_1	Contamination rate of susceptibles by symptomatic infected.
b_2	Contamination rate of susceptibles by asymptomatic infected.
b_1'	Contamination rate of vaccinated individuals by symptomatic infected.
b_2'	Contamination rate of vaccinated individuals by asymptomatic infected.
d_1	Rate at which a Salmonella carrier becomes symptomatic.
d_2	Rate at which a Salmonella carrier becomes asymptomatic.
d_3	Natural immunity recovery rate.
e_1	Hospitalization rate of symptomatic infected individuals.
e_2	Hospitalization rate of asymptomatic infected individuals.
f_1	Rate of treatment cessation.
f_2	Rate of treatment discontinuation or resistance.
g	Recovery rate.
δ	Immunity loss rate.
ξ_{E1}	Bacterial shedding rate in water by infected individuals.
ξ_{A1}	Bacterial shedding rate in food by infected individuals.
c_1	Rate at which symptomatic individuals become asymptomatic.
c_2	Rate at which asymptomatic individuals become symptomatic.
ξ_{E2}	Bacterial shedding rate in water by hospitalized individuals.
ξ_{A2}	Bacterial shedding rate in food by hospitalized individuals.

As a result, the model of Figure 1 can be expressed by the following nonlinear system:

$$
\begin{cases}
\dfrac{dS(t)}{dt} &= \Pi_1 + a_2 S_v(t) + \delta R(t) - (\mu_1 + a_1) S(t) \\
&\quad -[b_1 I_S(t) + b_2 I_A(t) + (\beta_{E1} + \beta_{A1}) E_n(t)] S(t), \\
\dfrac{dS_v(t)}{dt} &= \theta_1 - (a_2 + \mu_1) S_v(t) + a_1 S(t) \\
&\quad -[b_1^{'} I_S(t) + b'_2 I_A(t) + (\beta_{E2} + \beta_{A2}) E_n(t)] S_v(t), \\
\dfrac{dE(t)}{dt} &= \theta_2 - (\mu_1 + \lambda_1 + d_1 + d_2 + d_3) E(t) \\
&\quad +[b_1 I_S(t) + b_2 I_A(t) + (\beta_{E1} + \beta_{A1}) E_n(t)] S(t) \\
&\quad +[b_1^{'} I_S(t) + b'_2 I_A(t) + (\beta_{E2} + \beta_{A2}) E_n(t)] S_v(t), \\
\dfrac{dI_S(t)}{dt} &= \theta_3 + d_1 E(t) + c_2 I_A(t) - (c_1 + e_1 + \lambda_2 + \mu_1 + \mu_2) I_S(t) + f_1 H(t), \\
\dfrac{dI_A(t)}{dt} &= \theta_4 + d_2 E(t) + c_1 I_S(t) - (c_2 + e_2 + \lambda_3 + \mu_1 + \mu_3) I_A(t) + f_2 H(t), \\
\dfrac{dH(t)}{dt} &= \theta_5 + e_1 I_S(t) + e_2 I_A(t) - (g + \lambda_4 + \mu_1 + \mu_2 + f_2 + f_1) H(t), \\
\dfrac{dR(t)}{dt} &= g H(t) + d_3 E(t) - (\mu_1 + \delta) R(t), \\
\dfrac{dE_n(t)}{dt} &= (-\sigma_E - \sigma_A - \mu_E - \mu_A) E_n(t) + (\xi_{E1} + \xi_{A1})(I_A(t) + I_S(t)) \\
&\quad +(\xi_{E2} + \xi_{A2}) H(t).
\end{cases}
\tag{1}
$$

Under the following initial conditions:

$S(0) = S^0 \geqslant 0$, $S_v(0) = S_v^0 \geqslant 0$, $E(0) = E^0 \geqslant 0$, $E_n(0) = E_n^0 \geqslant 0$, $I_A(0) = I_A^0 \geqslant 0$, $I_S(0) = I_S^0 \geqslant 0$, $H(0) = H^0 \geqslant 0$ and $R(0) = R^0 \geqslant 0$.

2.2 Model properties

The proposed model describes the evolution of typhoid fever within a population. To ensure the mathematical rigor of system (1), it is essential to investigate and establish fundamental properties, such as the existence, positivity, and boundedness of solutions. These properties guarantee that the model is well-posed and that the solutions remain biologically meaningful over time.

2.2.1 Positivity of solutions

Theorem 1. If $S^0 \geqslant 0$, $S_v^0 \geqslant 0$, $E^0 \geqslant 0$, $I_A^0 \geqslant 0$, $I_S^0 \geqslant 0$, $H^0 \geqslant 0$, $R^0 \geqslant 0$, $E_n^0 \geqslant 0$, then the solutions $S(t)$, $S_v(t)$, $E(t)$, $I_A(t)$, $I_S(t)$, $H(t)$, $R(t)$, and $E_n(t)$ of system (1) are positive for all $t \geqslant 0$.

Proof. It follows from the first equation of system (1) that

$$\frac{dS(t)}{dt} = \Pi_1 + a_2 S_v(t) + \delta R(t) - (\mu_1 + a_1 + (\beta_{A1} + \beta_{E1})E_n(t) + (b_1 I_S(t) + b_2 I_A(t))S(t).$$

Then

$$\frac{dS(t)}{dt} \geqslant -[\mu_1 + a_1 + (\beta_{A1} + \beta_{E1})E_n(t) + (b_1 I_S(t) + b_2 I_A(t))]S(t).$$

Let

$$F(t) = b_1 I_S(t) + b_2 I_A(t) + \mu_1 + a_1 + (\beta_{E1} + \beta_{A1})E_n(t).$$

Then

$$\frac{dS(t)}{dt} \geqslant -F(t)S(t).$$

By applying Gronwall's Lemma [12] and following the approach of Davarian et al. [11], we obtain

$$S(t) \geqslant S(0)\exp\left(-\int_0^t F(s)ds\right) \geqslant 0.$$

Similarly, we prove that $S_v(t) \geqslant 0, E(t) \geqslant 0, I_A(t) \geqslant 0, I_S(t) \geqslant 0, H(t) \geqslant 0,$ $R(t) \geqslant 0$ and $E_n(t) \geqslant 0$. □

2.2.2 Boundedness of the solutions

Theorem 2. The set $\Omega = \{(S, S_v, \ldots, R, E_n) \in \mathbb{R}_+^8 /$ $0 \leq S(t) + \cdots + R(t) \leq N(0) + \frac{Z}{\mu_1}$ and $0 \leq E_n(t) \leq E_n(0) + \frac{C}{q_{10}}\}$ is positively invariant under system with initial conditions $S^0 \geqslant 0$, $S_v^0 \geqslant 0$, $E^0 \geqslant 0$, $E_n^0 \geqslant 0$, $I_A^0 \geqslant 0$, $I_S^0 \geqslant 0$, $H^0 \geqslant 0$ and $R^0 \geqslant 0$,

where

$$\begin{aligned} Z &= \Pi_1 + \theta_1 + \theta_2 + \theta_3 + \theta_4 + \theta_5. \\ q_{10} &= \sigma_E + \sigma_A + \mu_E + \mu_A. \\ C &= \frac{Z}{\mu_1}(\xi_{E2} + \xi_{A2} + 2\xi_{E1} + 2\xi_{A1}). \end{aligned}$$

Proof. From system (1), the total population satisfies

$$\frac{dN(t)}{dt} = \frac{dS(t)}{dt} + \frac{dS_v(t)}{dt} + \cdots + \frac{dR(t)}{dt}.$$

We replace each derivative with its corresponding expression in system (1) to obtain

$$\frac{dN(t)}{dt} = Z - \mu_1 N(t) - \big[\lambda_1 E(t) + (\mu_2 + \lambda_2)I_S(t) + (\mu_3 + \lambda_3)I_A(t) + (\mu_2 + \lambda_3)H(t)\big].$$

Since all state variables $E(t), I_S(t), I_A(t), H(t)$ are non-negative, the last term is always non-negative. Hence,

$$\frac{dN(t)}{dt} \leq Z - \mu_1 N(t).$$

we rewrite

$$\frac{dN(t)}{dt} + \mu_1 N(t) \leq Z.$$

Multiplying by the integrating factor $e^{\mu_1 t}$ gives

$$\frac{d}{dt}\big(e^{\mu_1 t} N(t)\big) \leq Z e^{\mu_1 t}.$$

Integrating from 0 to t, we obtain

$$e^{\mu_1 t} N(t) - N(0) \leq Z \int_0^t e^{\mu_1 s}\, ds = \frac{Z}{\mu_1}\big(e^{\mu_1 t} - 1\big).$$

Thus,

$$N(t) \leq N(0) e^{-\mu_1 t} + \frac{Z}{\mu_1}\big(1 - e^{-\mu_1 t}\big).$$

The coefficients $e^{-\mu_1 t}$ and $1 - e^{-\mu_1 t}$ both lie in $[0, 1]$ and sum to 1. Therefore, the right-hand side is a convex combination of $N(0)$ and $\frac{Z}{\mu_1}$ [20], which implies

$$\min\left(N(0), \frac{Z}{\mu_1}\right) \leq N(t) \leq \max\left(N(0), \frac{Z}{\mu_1}\right), \qquad \text{for all } \ t \geq 0.$$

Since, by Theorem 1, $N(t) \geq 0$, for all $t \geq 0$, the total population satisfies the following boudedness condition:

$$0 \leq N(t) \leq \max\left(N(0), \tfrac{Z}{\mu_1}\right).$$

Finally, by the elementary inequality $\max(a, b) \leq a + b$ for $a, b \geq 0$, we deduce the weaker but simpler estimate

$$0 \leq N(t) \leq N(0) + \frac{Z}{\mu_1}, \qquad \text{for all } \ t \geq 0.$$

On the other hand, we have

$$\frac{dE_n(t)}{dt} = -(\sigma_E + \sigma_A + \mu_E + \mu_A) E_n(t) + (\xi_{E1} + \xi_{A1})(I_A(t) + I_S(t)) + (\xi_{E2} + \xi_{A2}) H(t).$$

Since $\quad 0 \leq I_A(t) \leq N(0) + \dfrac{Z}{\mu_1}, \quad 0 \leq I_S(t) \leq N(0) + \dfrac{Z}{\mu_1} \quad$ and $\quad 0 \leq H(t) \leq N(0) + \dfrac{Z}{\mu_1}.$

Then

$$\begin{aligned}\frac{dE_n(t)}{dt} \leq\ & -(\sigma_E+\sigma_A+\mu_E+\mu_A)E_n(t)\\ & +(\xi_{E1}+\xi_{A1})(N(0)+\frac{Z}{\mu_1}+N(0)+\frac{Z}{\mu_1})\\ & +(\xi_{E2}+\xi_{A2})(N(0)+\frac{Z}{\mu_1}).\end{aligned}$$

We put

$$\begin{aligned}q_{10} =\ & \sigma_E+\sigma_A+\mu_E+\mu_A.\\ C\ =\ & \frac{Z}{\mu_1}(\xi_{E2}+\xi_{A2}+2\xi_{E1}+2\xi_{A1}+2N(0)).\end{aligned}$$

Then

$$\frac{dE_n(t)}{dt} \leq -q_{10}E_n(t)+C,$$

Proceeding in the same way, using the proof of the previous inequality, we can derive the following result:

$$0 \leq E_n(t) \leq E_n(0)+\frac{C}{q_{10}}, \quad \text{for all } t \geq 0.$$

Hence, we prove that the region Ω is a positively invariant set for the system (1). □

2.2.3 Existence of solutions:

Theorem 3. The system (1) that satisfies a given initial condition $(S^0, S_v^0, \ldots, E_n^0)$ has an unique solution.

Proof. Let $Y=[S, S_v, \ldots, E_n]^T$ and $\varphi(Y)=\left(\frac{dS(t)}{dt}, \frac{dS_v(t)}{dt}, \ldots, \frac{dE_n(t)}{dt}\right)$. Then the system (1) can be rewritten in the following form:

$$\varphi(Y)=AY+B(Y),$$

where

$$A=\begin{pmatrix} -q_1 & a_2 & 0 & 0 & 0 & 0 & \delta & 0\\ a_1 & -q_2 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & -q_3 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & d_1 & -q_4 & c_2 & f_1 & 0 & 0\\ 0 & 0 & d_2 & c_1 & -q_5 & f_2 & 0 & 0\\ 0 & 0 & 0 & e_1 & e_2 & -q_6 & 0 & 0\\ 0 & 0 & d_3 & 0 & 0 & g & -q_7 & 0\\ 0 & 0 & 0 & q_8 & q_8 & q_9 & 0 & -q_{10} \end{pmatrix},$$

such that

$$\begin{aligned}
q_1 &= a_1 + \mu_1, & q_2 &= a_2 + \mu_1,\\
q_3 &= \mu_1 + \lambda_1 + d_1 + d_2 + d_3, & q_4 &= c_1 + e_1 + \lambda_2 + \mu_1 + \mu_2,\\
q_5 &= c_2 + e_2 + \lambda_3 + \mu_1 + \mu_3, & q_6 &= g + \lambda_4 + \mu_1 + \mu_2 + f_1 + f_2,\\
q_7 &= \mu_1 + \delta, & q_8 &= \xi_{E1} + \xi_{A1},\\
q_9 &= \xi_{E2} + \xi_{A2}, & q_{10} &= \sigma_E + \sigma_A + \mu_E + \mu_A,
\end{aligned}$$

and

$$B(Y) = \left[\Psi_1\ \Psi_2\ \Psi_3\ \theta_3\ \theta_4\ \theta_5\ 0\ 0\right]^T,$$

where

$$\begin{aligned}
\Psi_1 &= \Pi_1 - [(b_1 I_S(t) + b_2 I_A(t))S(t) + (\beta_{E1} + \beta_{A1})S(t)E_n(t)],\\
\Psi_2 &= \theta_1 - [(b_1^{'} I_S(t) + b'_2 I_A(t))S_v(t) + (\beta_{E2} + \beta_{A2})S_v(t)E_n(t)],\\
\Psi_3 &= \theta_2 + (b_1 I_S(t) + b_2 I_A(t))S(t) + (\beta_{E1} + \beta_{A1})S(t)E_n(t)\\
&\quad +(b_1^{'} I_S(t) + b'_2 I_A(t))S_v(t) + (\beta_{E2} + \beta_{A2})S_v(t)E_n(t).
\end{aligned}$$

The second term of system (1) satisfies

$$\begin{aligned}
|B(Y_1) - B(Y_2)| = 2|&(b_1 I_{S1}(t) + b_2 I_{A1}(t))S_1(t) + (\beta_{E1} + \beta_{A1})S_1(t)E_{n1}(t)\\
&+(b_1^{'} I_{S1}(t) + b'_2 I_{A1}(t))S_{v1}(t) + (\beta_{E2} + \beta_{A2})S_{v1}(t)E_{n1}(t)\\
&-[(b_1 I_{S2}(t) + b_2 I_{A2}(t))S_2(t) + (\beta_{E1} + \beta_{A1})S_2(t)E_{n2}(t)]\\
&-[(b_1^{'} I_{S2}(t) + b'_2 I_{A2}(t))S_{v2}(t) + (\beta_{E2} + \beta_{A2})S_{v2}(t)E_{n2}(t)]|,
\end{aligned}$$

then

$$\begin{aligned}
|B(Y_1) - B(Y_2)| \le 2|&b_1 I_{S1}(t)(S_1(t) - S_2(t)) + b_1 S_2(t)(I_{S1}(t) - I_{S2}(t))\\
&+b_2 I_{A1}(t)(S_1(t) - S_2(t)) + b_2 S_2(t)(I_{A1}(t) - I_{A2}(t))\\
&+(\beta_{E1} + \beta_{A1})S_1(t)(E_{n1}(t) - E_{n2}(t))\\
&+(\beta_{E1} + \beta_{A1})E_{n2}(t)(S_1(t) - S_2(t))\\
&+b_1^{'} I_{S1}(t)(S_{v1}(t) - S_{v2}(t)) + b'_1 S_{v2}(t)(I_{S1}(t) - I_{S2}(t))\\
&+b_2^{'} I_{A1}(t)(S_{v1}(t) - S_{v2}(t)) + b'_2 S_{v2}(t)(I_{A1}(t) - I_{A2}(t))\\
&+(\beta_{E2} + \beta_{A2})S_{v1}(t)(E_{n1}(t) - E_{n2}(t))\\
&+(\beta_{E2} + \beta_{A2})E_{n2}(t)(S_{v1}(t) - S_{v2}(t))|.
\end{aligned}$$

We have $0 \le N(t) \le N(0) + Z^{'}$, where $Z^{'} = \dfrac{\Pi_1 + \theta_1 + \theta_2 + \theta_3 + \theta_4 + \theta_5}{\mu_1}$.
Then

$$\begin{aligned}|B(Y_1) - B(Y_2)| \leq 2|&(b_1 + b_2 + \beta_{E1} + \beta_{A1})(N(0) + Z^{'})(S_1(t) - S_2(t))\\ &+(b_1 + b_1^{'})(N(0) + Z^{'})(I_{S1}(t) - I_{S2}(t))\\ &+(b_2 + b_2^{'})(N(0) + Z^{'})(I_{A1}(t) - I_{A2}(t))\\ &+(\beta_{E1} + \beta_{A1} + \beta_{E2} + \beta_{A2})(N(0) + Z^{'})(E_{n1}(t) - E_{n2}(t))\\ &+(b_1^{'} + b_2^{'} + \beta_{E2} + \beta_{A2})(N(0) + Z^{'})(S_{v1}(t) - S_{v2}(t))|\\ \leq K[&|S_1(t) - S_2(t)| + |S_{v1}(t) - S_{v2}(t)| + |I_{S1}(t) - I_{S2}(t)|\\ &+|I_{A1}(t) - I_{A2}(t)| + |E_{n1}(t) - E_{n2}(t)|],\end{aligned}$$

where

$$\begin{aligned}K = 2\max(&b_1 + b_2 + \beta_{E1} + \beta_{A1}, b_1^{'} + b_2^{'} + \beta_{E2} + \beta_{A2}, b_1 + b_1^{'}, b_2 + b_2^{'},\\ &\beta_{E1} + \beta_{A1} + \beta_{E2} + \beta_{A2}).\end{aligned}$$

Then $||\varphi(Y_1) - \varphi(Y_2)|| \leq W||Y_1 - Y_2||$, which $W = \max(K, ||A||) < \infty$.

Therefore the function φ is uniformly Lipschitz continuous, from the restriction on $S(t) \geqslant 0$, $S_v(t) \geqslant 0$, $E(t) \geqslant 0$, $I_A(t) \geqslant 0$, $I_S(t) \geqslant 0$, $H(t) \geqslant 0$, $R(t) \geqslant 0$ and $E_n(t) \geqslant 0$, we conclude the existence of the solution of the our system (1) [4, 22]. □

3 Optimal control problem

3.1 Problem formulation

Given the significant health risks posed by the spread of typhoid fever, particularly antimicrobial-resistant Salmonella Typhi, it is crucial to implement control strategies capable of limiting or reducing its transmission. In this context, we have formulated an optimal control problem aimed at decreasing the incidence of symptomatic and asymptomatic infections, increasing recovery rates, and reducing the bacterial load in the environment. To achieve these objectives, six control measures are considered:

Control $\mathbf{u_1}$: Promotes awareness of hygiene practices, including the use of protective bibs, avoiding close contact with potentially contaminated objects, proper cleaning of supplies and water, and correct food packaging. This control targets the reduction of infection rates among susceptible individuals, both vaccinated and unvaccinated, as well as those already affected.

Control $\mathbf{u_2}$: Aims to reduce Salmonella contamination in environmental water sources by treating wastewater before it is discharged into the environment.

Control $\mathbf{u_3}$: Focuses on food sterilization to lower contamination rates and bacterial load in food, through proper packaging and the enforcement of sanitary protocols among food-handling personnel.

Control $\mathbf{u_4}$: Encourages booster vaccination among previously vaccinated individuals, emphasizing the importance of revaccination every three years to decrease contamination rates via person-to-person transmission, food, or water.

Control $\mathbf{u_5}$: Involves symptom screening of infected individuals to differentiate typhoid cases from other diseases such as malaria, helminthiases, leptospirosis, or murine typhoid [18, 30]. The primary objective is to reduce the environmental contribution of asymptomatic carriers, who remain contagious long after symptoms subside [37].

Control $\mathbf{u_6}$: Represents treatment-related efforts, including the provision of free medication, ambulance transport, patient care, monitoring during treatment, and isolation of infected patients in hospitals. This control aims to minimize treatment failures among hospitalized and infected individuals.

By integrating these six controls into the typhoid fever model (1), the resulting controlled system can be formally defined as follows:

$$
\begin{cases}
\dfrac{dS(t)}{dt} &= \Pi_1 + a_2 S_v(t) + \delta R(t) - (\mu_1 + a_1 + u_4(t))S(t) \\
&\quad -(1-u_1(t))[b_1 I_S(t) + b_2 I_A(t) + (\beta_{E1} + \beta_{A1})E_n(t)]S(t), \\
\dfrac{dS_v(t)}{dt} &= \theta_1 - (a_2 + \mu_1)S_v(t) + (a_1 + u_4(t))S(t) \\
&\quad -(1-u_1(t))[b_1^{'} I_S(t) + b'_2 I_A(t) + (\beta_{E2} + \beta_{A2})E_n(t)]S_v(t), \\
\dfrac{dE(t)}{dt} &= \theta_2 - (\mu_1 + \lambda_1 + d_1 + d_2 + d_3)E(t) \\
&\quad +(1-u_1(t))[(b_1 I_S(t) + b_2 I_A(t))S(t) + (\beta_{E1} + \beta_{A1})S(t)E_n(t) \\
&\quad +(b_1^{'} I_S(t) + b'_2 I_A(t))S_v(t) + (\beta_{E2} + \beta_{A2})S_v(t)E_n(t)], \\
\dfrac{dI_S(t)}{dt} &= \theta_3 + d_1 E(t) + c_2 I_A(t) + (1-u_6(t))f_1 H(t) \\
&\quad -[c_1 + e_1 + \lambda_2 + \mu_1 + \mu_2 + u_5(t) + u_6(t)]I_S(t), \\
\dfrac{dI_A(t)}{dt} &= \theta_4 + d_2 E(t) + c_1 I_S(t) - [c_2 + e_2 + \lambda_3 + \mu_1 + \mu_3]I_A(t) \\
&\quad +(1-u_6(t))f_2 H(t), \\
\dfrac{dH(t)}{dt} &= \theta_5 + (e_1 + u_5(t) + u_6(t))I_S(t) + e_2 I_A(t) \\
&\quad -[g + \lambda_4 + \mu_1 + \mu_2 + (1-u_6(t))(f_1 + f_2)]H(t), \\
\dfrac{dR(t)}{dt} &= gH(t) + d_3 E(t) - (\mu_1 + \delta)R(t), \\
\dfrac{dE_n(t)}{dt} &= [-\sigma_E - \sigma_A - (1+u_2(t))\mu_E - (1+u_3(t))\mu_A]E_n(t) \\
&\quad +(\xi_{E1} + \xi_{A1})(I_A(t) + I_S(t)) + (\xi_{E2} + \xi_{A2})H(t),
\end{cases}
\tag{2}
$$

where $S_v^0 \geqslant 0$, $S^0 \geqslant 0$, $E^0 \geqslant 0$, $E_n^0 \geqslant 0$, $I_A^0 \geqslant 0$, $I_S^0 \geqslant 0$, $H^0 \geqslant 0$, and $R^0 \geqslant 0$ are the given initial states.

Our aim is to minimize the number of carriers, both symptomatic and asymptomatic, while maintaining our environment on sanitation without bacteria. For that we search to minimize the following objective function:

$$J(u) = E(T_e) + I_A(T_e) + I_S(T_e) + \int_0^{T_e} [E(t) + I_A(t) + I_S(t) + \sum_{i=1}^{6} \frac{A_i}{2} u_i^2(t)]dt. \tag{3}$$

Here, A_i for $i = 1, 2, \ldots, 6$ represent the cost coefficients, which are chosen to evaluate the relative significance of $u = (u_1, u_2, \ldots, u_6)$ at time t, where T_e denotes the final time. In other words, our objective is to find the optimal control $u^* = (u_1^*, \ldots, u_6^*)$ such that

$$J(u^*) = \min_{u \in U_{ad}} J(u),$$

where U_{ad} is the set of admissible controls defined by

$$U_{ad} = \{u = (u_1, u_2, \ldots, u_6) : 0 \leq u_{i,\min} \leq u_i(t) \leq u_{i,\max} \leq 1 \text{ for } i \in \{1, 2, \ldots, 6\} \text{ and } t \in [0, T_e]\}.$$

3.2 Existence of an optimal control

Before studying the characterization of optimal control, we will use Fleming and Rishel [14, Corollary 4.1] to confirm its existence.

Theorem 4. Let us contemplate the optimal control problem stated in equations (2)–(3). It is established that there exists an optimal control $u^* \in U_{ad}$ for which

$$J(u^*) = \min_{u \in U_{ad}} J(u).$$

Proof. The existence of an optimal control $u^* \in U_{ad}$ can be established using in [14, Corollary 4.1]. To apply this result, we verify the following conditions:

1. The set of admissible controls and the corresponding state variables is nonempty.
2. The control set U_{ad} is convex and closed.
3. The right-hand side of the state system is bounded by a linear function of the state and control variables.

4. The integrand $L(E, I_A, I_S, u)$ of the objective functional is convex on U_{ad}, and there exist constants $\Upsilon_1, \Upsilon_2 \geq 0$ and $\rho \geq 1$ such that

$$L(E, I_A, I_S, u) \geq -\Upsilon_1 + \Upsilon_2 \left(|u_1|^2 + \cdots + |u_6|^2\right)^{\frac{\rho}{2}}.$$

Step 1: Non-emptiness of the control and state set. Using Theorem 7.1.1 of Boyce and DiPrima [8], consider $X = (S, S_v, \ldots, E_n)$ and the system

$$\dot{S} = G_S(t, X), \quad \dot{S}_v = G_{S_v}(t, X), \quad \ldots, \quad \dot{E}_n = G_{E_n}(t, X),$$

where $G_S, G_{S_v}, \ldots, G_{E_n}$ are the right-hand sides of system (2). Taking $u_i(t) = c_i$ for constants c_i, and noting that all parameters are constant and X is continuous, it follows that $G_S, \ldots, G_{E_n}$ are continuous along with their partial derivatives. By the Cauchy-Lipschitz Theorem, there exists a unique solution $X(t)$ satisfying the initial conditions. Therefore, the set of admissible controls and corresponding states is nonempty.

Step 2: Convexity and closure of the control set. By the definition, we have

$$0 \leq \Gamma v_1 + (1 - \Gamma) v_2 \leq 1,$$

showing that U_{ad} is convex.

Step 3: Boundedness of the right-hand side.

For the total population $N(t)$ in system (2), as proved in Theorem 1, we have

$$0 \leq N(t) \leq N(0) + \frac{Z}{\mu_1}.$$

Writing the system in vector form $Y = [S, S_v, \ldots, E_n]^T$, we have

$$\varphi(Y) = AY + B(Y),$$

with

$$A = \begin{pmatrix} -q_1' & a_2 & 0 & 0 & 0 & 0 & \delta & 0 \\ q_2' & -q_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -q_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & d_1 & -q_4' & c_2 & q_5' & 0 & 0 \\ 0 & 0 & d_2 & c_1 & -q_5 & q_7' & 0 & 0 \\ 0 & 0 & 0 & q_8' & e_2 & q_9' & 0 & 0 \\ 0 & 0 & d_3 & 0 & 0 & g & -q_7 & 0 \\ 0 & 0 & 0 & q_8 & q_8 & q_9 & 0 & -q_{10}' \end{pmatrix},$$

where

$$\begin{aligned} q_1^{'} &= a_1 + \mu_1 + u_4(t) & q_2^{'} &= a_1 + u_4(t), \\ q_4^{'} &= c_1 + e_1 + \lambda_2 + \mu_1 + \mu_2 + u_5(t) + u_6(t), & q_2 &= a_2 + \mu_1, \\ q_3 &= \mu_1 + \lambda_1 + d_1 + d_2 + d_3, & q_5 &= c_2 + e_2 + \lambda_3 + \mu_1 + \mu_3, \\ q_5^{'} &= (1 - u_6(t))f_1, & q_7^{'} &= (1 - u_6(t))f_2, \\ q_7 &= \mu_1 + \delta, & q_8 &= \xi_{E1} + \xi_{A1}, \\ q_9^{'} &= -(g + \lambda_4 + \mu_1 + \mu_2 + (1 - u_6(t))(f_1 + f_2)), & q_9 &= \xi_{E2} + \xi_{A2}, \\ q_{10}^{'} &= \sigma_E + \sigma_A + (1 + u_2(t))\mu_E + (1 + u_3(t))\mu_A, & q_8^{'} &= e_1 + u_5(t) + u_6(t). \end{aligned}$$

and

$$B(Y) = \left[\Psi_1^{'}\ \Psi_2^{'}\ \Psi_3^{'}\ \theta_3\ \theta_4\ \theta_5\ 0\ 0\right]^t,$$

where

$$\begin{aligned} \Psi_1^{'} &= \Pi_1 - (1 - u_1(t))[(b_1 I_S(t) + b_2 I_A(t))S(t) + (\beta_{E1} + \beta_{A1})S(t)E_n(t)], \\ \Psi_2^{'} &= \theta_1 - (1 - u_1(t))[(b_1^{'} I_S(t) + b'_2 I_A(t))S_v(t) + (\beta_{E2} + \beta_{A2})S_v(t)E_n(t), \\ \Psi_3^{'} &= \theta_2 + (1 - u_1(t))[(b_1 I_S(t) + b_2 I_A(t))S(t) + (\beta_{E1} + \beta_{A1})S(t)E_n(t)] \\ &\quad + (1 - u_1(t))[(b_1^{'} I_S(t) + b'_2 I_A(t))S_v(t) + (\beta_{E2} + \beta_{A2})S_v(t)E_n(t)]. \end{aligned}$$

Next, for any Y_1, Y_2, we estimate

$$|B(Y_1) - B(Y_2)| \leq K \sum |Y_1 - Y_2|,$$

where

$$K = 2|1 - u_1(t)| \max\left(b_1 + b_2 + \beta_{E1} + \beta_{A1}, b_1' + b_2' + \beta_{E2} + \beta_{A2}, b_1 + b_1', b_2 + b_2', \beta_{E1} + \beta_{A1} + \beta_{E2} + \beta_{A2}\right).$$

Hence, φ is uniformly Lipschitz continuous and Condition 3 is satisfied.

Step 4: Convexity and growth of the integrand. The integrand of the objective functional is

$$L(E, I_S, I_A, u) = E(t) + I_A(t) + I_S(t) + \sum_{i=1}^{6} \frac{A_i}{2} u_i^2(t),$$

which is convex on U_{ad}. Since $A_i > 0$ and E, I_A, I_S are bounded, one can choose

$$\Upsilon_1 = 3 \inf_{t\in[0,T_e]} (E + I_S + I_A), \quad \Upsilon_2 = \inf_i \frac{A_i}{2}, \quad \rho = 2,$$

ensuring

$$L(E, I_S, I_A, u) \geq -\Upsilon_1 + \Upsilon_2 \sum_{i=1}^{6} |u_i|^2.$$

By steps 1–4 and Fleming and Rishel [14], there exists an optimal control u^* such that

$$J(u^*) = \min_{u\in U_{ad}} J(u).$$

□

3.3 Characterization of optimal controls

In this section, we apply Pontryagin's Maximum Principle [35] to derive the necessary conditions for optimality. To this end, we construct the Hamiltonian function, denoted by $\mathcal{H}$, which links the objective functional to the controlled dynamical system. This framework provides a rigorous characterization of the optimal controls.

The Hamiltonian function is defined at time t, by

$$\mathcal{H}(t) = E(t) + I_A(t) + I_S(t) + \sum_{i=1}^{6} \frac{A_i}{2} u_i^2(t) + \sum_{i=1}^{8} \phi_i g_i(X),$$

where g_i is the right side of the difference equation of the ith state variable and

$$X = (S, S_v, \ldots, E_n).$$

Theorem 5. Given the optimal control $u^* = (u_1^*, u_2^*, \ldots, u_6^*)$ and the solution S^*, S_v^*, E^*, I_a^*, I_s^*, H^*, R^* and E_n^*, of the corresponding state system (2), there exists adjoins variables ϕ_1, ϕ_2, …, ϕ_8 satisfying

$$
\begin{aligned}
\dot{\phi_1} &= -\phi_1[-\mu_1 - a_1 - u_4(t) - (1-u_1(t))(b_1 I_S(t) \\
&\quad + b_2 I_A(t) + (\beta_{E1} + \beta_{A1})E_n(t))] \\
&\quad - \phi_2[a_1 + u_4(t)] - \phi_3[(1-u_1(t))(b_1 I_S(t) + b_2 I_A(t) + (\beta_{E1} + \beta_{A1})E_n(t))] \\
&\quad + \phi_8(\beta_{E1} + \beta_{A1}), \\
\dot{\phi_2} &= -\phi_1[a_2] \\
&\quad - \phi_2[-a_2 - \mu_1 - (1-u_1(t))(b_1^{'} I_S(t) + b_2^{'} I_A(t) + (\beta_{E2} + \beta_{A2})E_n(t))] \\
&\quad - \phi_3[(1-u_1(t))(b_1^{'} I_S(t) + b_2^{'} I_A(t) + (\beta_{E2} + \beta_{A2})E_n(t))] - \phi_8[\beta_{E2} + \beta_{A2}], \\
\dot{\phi_3} &= -1 + \phi_3[\mu_1 + \lambda_1 + d_1 + d_2 + d_3] - \phi_4[d_1] - \phi_5[d_2] - \phi_7 d_3, \\
\dot{\phi_4} &= -1 + \phi_1[(1-u_1(t))b_1 S(t)] + \phi_2[(1-u_1(t))b_1^{'} S_v(t)] - \phi_8[\xi_{E1} + \xi_{A1}] \\
&\quad - \phi_3[(1-u_1(t))(b_1 S(t) + b_1^{'} S_v(t))] - \phi_5[c_1] - \phi_6[e_1 + u_5(t) + u_6(t)] \\
&\quad - \phi_4[-c_1 - e_1 - \lambda_2 - \mu_1 - \mu_2 - u_5(t) - u_6(t)],
\end{aligned}
$$

$$
\begin{aligned}
\dot{\phi_5} &= -1 + \phi_1[(1-u_1(t))b_2 S(t)] + \phi_2[(1-u_1(t))b_2^{'} S_v(t)] \\
&\quad - \phi_3[(1-u_1(t))(b_2 S(t) + b_2^{'} S_v(t))] - \phi_4[c_2] \\
&\quad - \phi_5[-c_2 - e_2 - \lambda_3 - \mu_1 - \mu_3] - \phi_6[e_2] - \phi_8[\xi_{E1} + \xi_{A1}], \\
\dot{\phi_6} &= -\phi_4[(1-u_6(t))f_1] - \phi_5[(1-u_6(t))f_2] \\
&\quad - \phi_6[-g - \lambda_4 - \mu_1 - \mu_2 - (1-u_6(t))(f_1 + f_2)] - \phi_7[g] - \phi_8[\xi_{E2} + \xi_{A2}], \\
\dot{\phi_7} &= -\phi_1[\delta] - \phi_7[-\mu_1 + \delta], \\
\dot{\phi_8} &= \phi_1[(1-u_1(t))(\beta_{E1} + \beta_{A1})S(t)] + \phi_2[(1-u_1(t))(\beta_{E2} + \beta_{A2})S_v(t)] \\
&\quad - \phi_3[(1-u_1(t))((\beta_{E1} + \beta_{A1})S(t) + (\beta_{E2} + \beta_{A2})S_v(t))] \\
&\quad - \phi_8[-\sigma_A - \sigma_E - (1+u_2(t))\mu_E - (1+u_3(t))\mu_A],
\end{aligned}
$$

with the transversal conditions at finally time T_e,

$$
\begin{aligned}
&\phi_1(T_e) = 0, \quad \phi_3(T_e) = -1, \quad \phi_5(T_e) = -1, \quad \phi_7(T_e) = 0, \\
&\phi_2(T_e) = 0, \quad \phi_4(T_e) = -1, \quad \phi_6(T_e) = 0, \quad \phi_8(T_e) = 0.
\end{aligned}
$$

Furthermore, for $t \in [0, T_e]$, the optimal control $u^* = (u_1^*, u_2^*, \ldots, u_6^*)$ is given by

$$
u_1^* = \min(1, \max(0, \frac{1}{A_1}[-\phi_1\Delta_1 - \phi_2\Delta_2 + \phi_3\Delta_3])), \tag{4}
$$

$$
u_2^* = \min(1, \max(0, \frac{1}{A_2}[\phi_8\mu_E E_n(t)])), \tag{5}
$$

$$
u_3^* = \min(1, \max(0, \frac{1}{A_3}[\phi_8\mu_A E_n(t)])), \tag{6}
$$

$$u_4^* = \min(1, \max(0, \frac{1}{A_4}[\phi_1 + \phi_2]S(t))), \tag{7}$$

$$u_5^* = \min(1, \max(0, \frac{1}{A_5}[\phi_4 - \phi_6]I_S(t))), \tag{8}$$

$$u_6^* = \min(1, \max(0, \frac{1}{A_6}[\phi_4(I_S(t) + f_1 H(t)) + \phi_5 f_2 H(t) - \phi_6((f_1 + f_2)H(t) + I_S(t))])), \tag{9}$$

where

$$\Delta_1 = (b_1 I_S(t) + b_2 I_A(t))S(t) + (\beta_{E1} + \beta_{A1})S(t)E_n(t),$$

$\Delta_2 = (b_1^{'} I_S(t) + b'_2 I_A(t))S_v(t) + (\beta_{E2} + \beta_{A2})S_v(t)E_n(t)$, and $\Delta_3 = \Delta_1 + \Delta_2$.

Proof. The Hamiltonian H_m is defined as follows:

$$\mathcal{H}(t) = [E(t) + I_A(t) + I_S(t) + \sum_{i=1}^{6} \frac{A_i}{2} u_i^2(t) + \sum_{i=1}^{8} \phi_i g_i(X),$$

where g_i is the right side of the difference equation of the ith state variable and

$$X = (S, S_v, \ldots, E_n).$$

For $t \in [0, T_e]$, we can obtain the adjoint equations and transversality conditions by using Pontryagin's maximum principle [35] such that

$$\begin{aligned}
\dot{\phi_1} = -\frac{\partial \mathcal{H}}{\partial S} &= -\phi_1[-\mu_1 - a_1 - u_4(t) \\
&\quad - (1 - u_1(t))(b_1 I_S(t) + b_2 I_A(t) + (\beta_{E1} + \beta_{A1})E_n(t))] \\
&\quad - \phi_2[a_1 + u_4(t)] - \phi_3[(1 - u_1(t))(b_1 I_S(t)a + b_2 I_A(t) \\
&\quad + (\beta_{E1} + \beta_{A1})E_n(t))] + \phi_8(\beta_{E1} + \beta_{A1}), \\
\dot{\phi_2} = -\frac{\partial \mathcal{H}}{\partial S_v} &= -\phi_1[a_2] - \phi_2[-a_2 - \mu_1 - (1 - u_1(t))(b_1^{'} I_S(t) + b_2^{'} I_A(t) \\
&\quad + (\beta_{E2} + \beta_{A2})E_n(t))] - \phi_3[(1 - u_1(t))(b_1^{'} I_S(t) + b_2^{'} I_A(t) \\
&\quad + (\beta_{E2} + \beta_{A2})E_n(t))] - \phi_8[\beta_{E2} + \beta_{A2}], \\
\dot{\phi_3} = -\frac{\partial \mathcal{H}}{\partial E} &= -1 + \phi_3[\mu_1 + \lambda_1 + d_1 + d_2 + d_3] - \phi_4[d_1] - \phi_5[d_2] - \phi_7 d_3,
\end{aligned}$$

$$
\begin{aligned}
\dot{\phi_4} &= -\frac{\partial \mathcal{H}}{\partial I_S} = -1 + \phi_1[(1-u_1(t))b_1 S(t)] + \phi_2[(1-u_1(t))b_1^{'} S_v(t)] \\
&\quad - \phi_8[\xi_{E1} + \xi_{A1}] - \phi_3[(1-u_1(t))(b_1 S(t) + b_1^{'} S_v(t))] - \phi_5[c_1] \\
&\quad - \phi_6[e_1 + u_5(t) + u_6(t)] \\
&\quad - \phi_4[-c_1 - e_1 - \lambda_2 - \mu_1 - \mu_2 - u_5(t) - u_6(t)], \\
\dot{\phi_5} &= -\frac{\partial \mathcal{H}}{\partial I_A} = -1 + \phi_1[(1-u_1(t))b_2 S(t)] + \phi_2[(1-u_1(t))b_2^{'} S_v(t)] \\
&\quad - \phi_4[c_2] - \phi_6[e_2] - \phi_3[(1-u_1(t))(b_2 S(t) + b_2^{'} S_v(t))] \\
&\quad - \phi_5[-c_2 - e_2 - \lambda_3 - \mu_1 - \mu_3] - \phi_8[\xi_{E1} + \xi_{A1}], \\
\dot{\phi_6} &= -\frac{\partial \mathcal{H}}{\partial H} = -\phi_4[(1-u_6(t))f_1] - \phi_5[(1-u_6(t))f_2] - \phi_7[g] - \phi_8[\xi_{E2} + \xi_{A2}] \\
&\quad - \phi_6[-g - \lambda_4 - \mu_1 - \mu_2 - (1-u_6(t))(f_1 + f_2)], \\
\dot{\phi_7} &= -\frac{\partial \mathcal{H}}{\partial R} = -\phi_1[\delta] - \phi_7[-\mu_1 + \delta], \\
\dot{\phi_8} &= -\frac{\partial \mathcal{H}}{\partial E_n} = \phi_1[(1-u_1(t))(\beta_{E1} + \beta_{A1})S(t)] \\
&\quad + \phi_2[(1-u_1(t))(\beta_{E2} + \beta_{A2})S_v(t)] \\
&\quad - \phi_3[(1-u_1(t))((\beta_{E1} + \beta_{A1})S(t) + (\beta_{E2} + \beta_{A2})S_v(t))] \\
&\quad - \phi_8[-\sigma_A - \sigma_E - (1+u_2(t))\mu_E - (1+u_3(t))\mu_A].
\end{aligned}
$$

So

$$
\begin{aligned}
\dot{\phi_1} &= -\frac{\partial \mathcal{H}}{\partial S}, \phi_1(T_e) = 0, & \dot{\phi_5} &= -\frac{\partial \mathcal{H}}{\partial I_A}, \phi_5(T_e) = -1, \\
\dot{\phi_2} &= -\frac{\partial \mathcal{H}}{\partial S_v}, \phi_2(T_e) = 0, & \dot{\phi_6} &= -\frac{\partial \mathcal{H}}{\partial H}, \phi_6(T_e) = 0, \\
\dot{\phi_3} &= -\frac{\partial \mathcal{H}}{\partial E}, \phi_3(T_e) = -1, & \dot{\phi_7} &= -\frac{\partial \mathcal{H}}{\partial R}, \phi_7(T_e) = 0, \\
\dot{\phi_4} &= -\frac{\partial \mathcal{H}}{\partial I_S}, \phi_4(T_e) = -1, & \dot{\phi_8} &= -\frac{\partial \mathcal{H}}{\partial E_n}, \phi_8(T_e) = 0.
\end{aligned}
$$

For $t \in [0, T_e]$, the optimal control u^* can be solved from the optimality conditions,

$$
\frac{\partial \mathcal{H}(t)}{\partial u_1(t)} = 0, \frac{\partial \mathcal{H}(t)}{\partial u_2(t)} = 0, \ \ldots, \ \frac{\partial \mathcal{H}(t)}{\partial u_6(t)} = 0.
$$

With further simplification of the optimality condition and by taking account the bounds in U_{ad} of the controls, we can easily obtain $u_1^*, \ldots, u_6^*$ in the form (4)–(9). □

4 Numerical simulations and cost-effectiveness analysis

4.1 Numerical simulations

To illustrate the effectiveness of the various controls previously proposed to reduce the impact of typhoid fever in Taiwan, we present in this section the numerical simulation using MATLAB.

The optimality system of our control problem is solved iteratively by first solving the forward state system under the following initial conditions: $S^0 = 8{,}050{,}000$, $S_v^0 = 2{,}300{,}000$, $E^0 = 4{,}600{,}000$, $I_A^0 = 3{,}450{,}000$, $I_S^0 = 2{,}300{,}000$, $H^0 = 1{,}150{,}000$, $R^0 = 1{,}150{,}000$, $E_n^0 = 1{,}000$, then solving the backward adjoint system with the final conditions. Both state and adjoint systems are discretized using the explicit Euler method.

In contrast to approaches that monitor convergence via a tolerance criterion, our implementation uses a fixed number of iterations K, which is sufficient to ensure stable and accurate approximations of the states and controls. This avoids unnecessary computational overhead while guaranteeing the reliability of the results.

The numerical procedure can be summarized by the following pseudo-code:

Algorithm 1 Iterative scheme for solving the optimal control problem

```
Initialize parameters and initial state values.
Initialize all control variables u_i(t).
for k = 1 to K do
    Solve the state equations forward in time using the current controls (Euler method).
    Solve the adjoint equations backward in time with terminal conditions (Euler method).
    Update the controls u_i^{(k+1)}(t) using the explicit expressions from the Hamiltonian.
end for
```

Due to the limited availability of complete epidemiological data for typhoid fever in Taiwan, not all parameter values could be directly obtained from observational data. Where possible, we used reported values from published studies conducted in Taiwan. For parameters lacking local data, we selected values from the literature on similar settings or estimated reasonable ranges based on epidemiological knowledge and prior modeling studies. This approach ensures that the model remains biologically and epidemiologically plausible while enabling meaningful exploration of control strategies.

In this simulation, we used data and statistics mostly related to the Taiwan region: $f_1 = f_2 = 0.01$ [7], $\xi_{A1} = \xi_{E1} = 0.78$, $\delta = 0.054$, $c_2 = 0.0635$, $e_1 = 0.375$, $e_2 = 0.064$, $d_1 = 0.3402$, $d_2 = 0.0378$, $b_1 = b_2 = 10^{-8}$, $a_1 = 0.054$, $a_2 = 0.0292$, $\beta_{A1} = \beta_{E1} = 10^{-9}$, $\mu_2 = \mu_3 = 0.079$,

$\mu_E = \mu_A = 0.1085$, and $\mu_1 = 3.42 \times 10^{-5}$ [3]. We also provided approximate values for the other parameters: $\Pi_1 = 1{,}034{,}602$, $\theta_1 = \theta_4 = 79{,}670$, $\theta_2 = 159{,}340$, $\theta_3 = \theta_5 = 39{,}835$, $\lambda_i = 0.001868$ for $i = 1, \ldots, 4$, $\sigma_E = \sigma_A = 0.01$, $\beta_{A2} = \beta_{E2} = b_1' = b_2' = 25 \times 10^{-9}$, $d_3 = 0.1$, $c_1 = 0.008$, $g = 0.0512$, $\xi_{A2} = \xi_{E2} = 0.05$.

Note that graphs with control are represented by dotted lines and graphs without control are represented by solid lines in future.

4.2 Strategy A: Sterilization of the water and food

In this strategy, we investigate the evolution of typhoid fever under the implementation of controlled water treatment and food sterilization measures. The results presented in Figure 2 indicate a reduction of approximately 134,000 carriers and 91,000 symptomatic individuals, while the number of asymptomatic individuals remains nearly unchanged. The bacterial load in the environment decreases by nearly 2 million germs by the end of the second week. The decline in carriers and symptomatic cases is most pronounced in the first week, highlighting the rapid effect of sterilization. However, the stability of asymptomatic individuals suggests that additional interventions, such as screening or vaccination, may be required to fully control transmission. Overall, this strategy effectively reduces environmental contamination, which indirectly contributes to lowering infection rates in humans.

4.3 Strategy B: Screening and treatment

This strategy focuses on the impact of screening and treatment interventions (controls u_5 and u_6); see Figure 3. Starting from the first week, symptomatic infected individuals decrease significantly by approximately 2,308,000, while carriers decline by about 404,000. By the second week, approximately 333,300 carriers and 835,000 germs in the environment are reduced. These results indicate that active identification and treatment of infected individuals rapidly lowers disease prevalence, particularly among symptomatic cases. Compared to Strategy A, this approach shows a more substantial and direct effect on reducing human infections, emphasizing the importance of timely screening and therapeutic management.

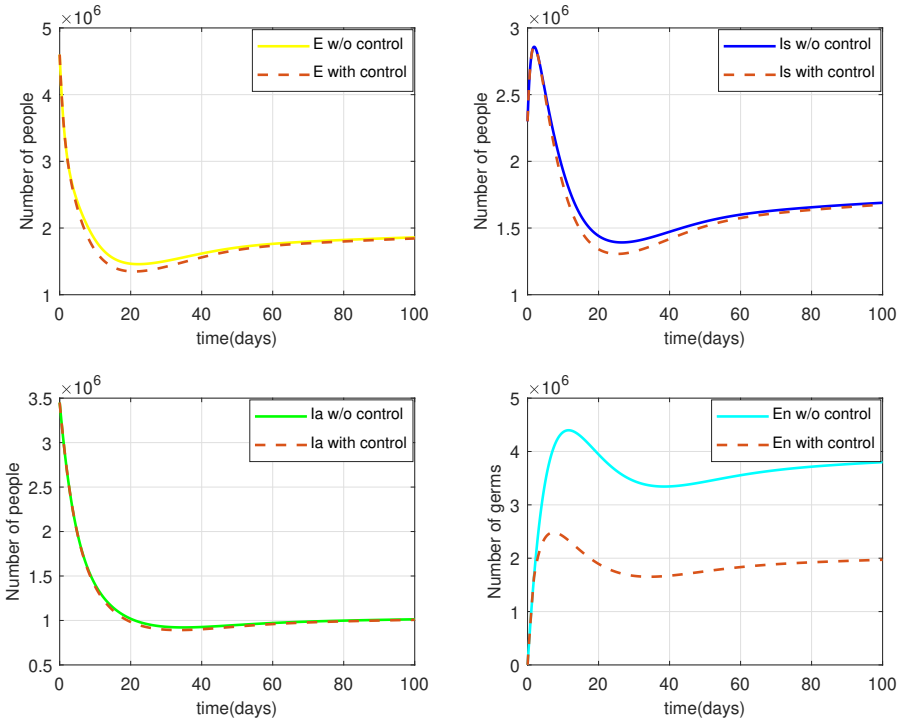

Figure 2: Illustration of the impact of sterilization of the water and food.

4.4 Strategy C: Awareness campaign and vaccination program

In this strategy, we analyze the combined effect of awareness campaigns and vaccination programs; see Figure 4. During the first week, carriers decrease by approximately 1,531,800 individuals. In the second week, symptomatic cases are reduced by about 1,131,000, asymptomatic cases by 344.500, and environmental germs by 1,541,000. The results highlight that public education and vaccination contribute to a progressive reduction in both human infections and environmental contamination. The strategy shows a slower initial impact compared to direct treatment but has a broader effect over multiple compartments, demonstrating the value of preventive measures in sustaining long-term control of typhoid fever.

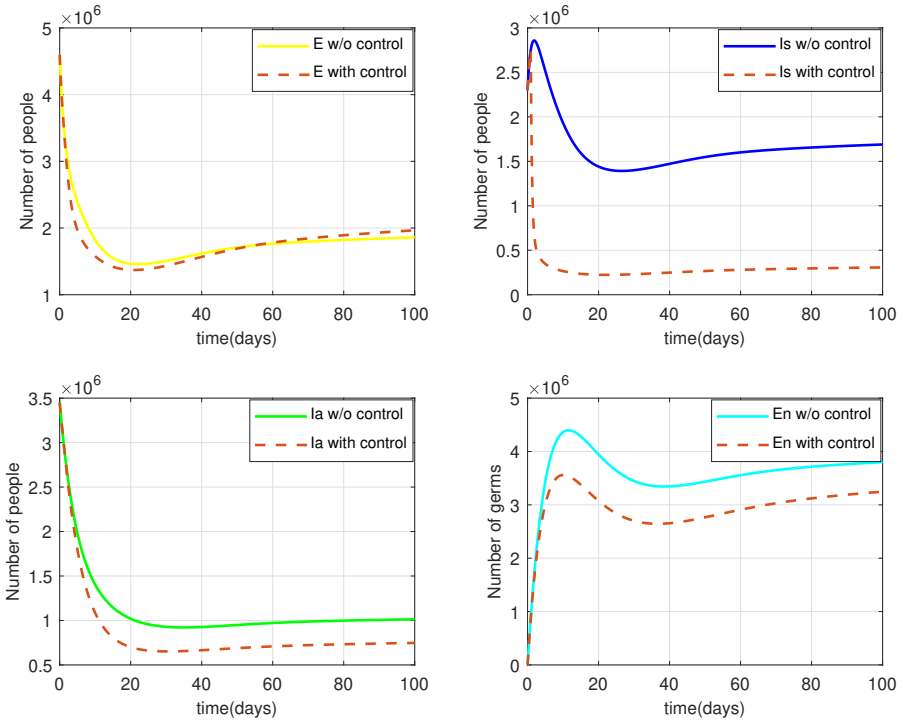

Figure 3: Illustration of the impact of treatment and symptom screening of infected.

4.5 Strategy D: Awareness program with sterilization of water and food

This strategy evaluates the combined effect of an awareness campaign and water/food sterilization; see Figure 5. The first week shows a reduction of approximately 1,626,400 carriers. By the second week, symptomatic cases decrease by about 1,183,400, asymptomatic cases by 329,500, and environmental germs by 2,289,000. Compared to previous strategies, this approach achieves substantial reductions across all compartments, demonstrating synergistic effects of preventive awareness and environmental control. The results suggest that this strategy is highly effective in reducing both human infections and environmental contamination, making it a promising candidate for cost-effective intervention.

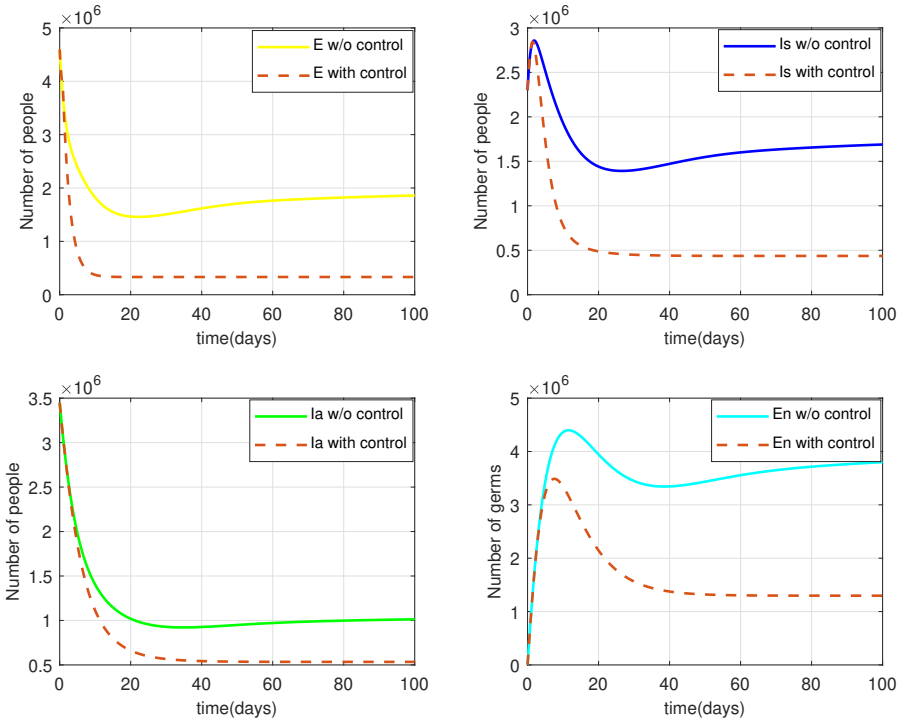

Figure 4: Illustration of the impact of awareness campaign with vaccination program.

4.6 Strategy E: Combination of all previous strategies

Here, we simultaneously implement all six controls to assess their collective impact; see Figure 6. From the first week, carriers decrease by approximately 1,578,800, symptomatic cases by 2,436,600, and environmental germs by 1,640,000. Asymptomatic individuals show a decline of about 520,500 from the second week. While this comprehensive strategy produces the greatest overall reduction in infections, the results indicate diminishing returns in certain compartments compared to Strategy D, particularly for carriers. These findings highlight that combining multiple interventions can maximize reductions but may not always proportionally improve efficiency. Strategy D remains highly effective while potentially being more cost-efficient.

Remark 1. The six controls mentioned earlier can be used to create hundreds of different strategies. The selection of these five strategies was based not only on the outcomes of previous studies using these controls but also on practical criteria such as operational feasibility, estimated

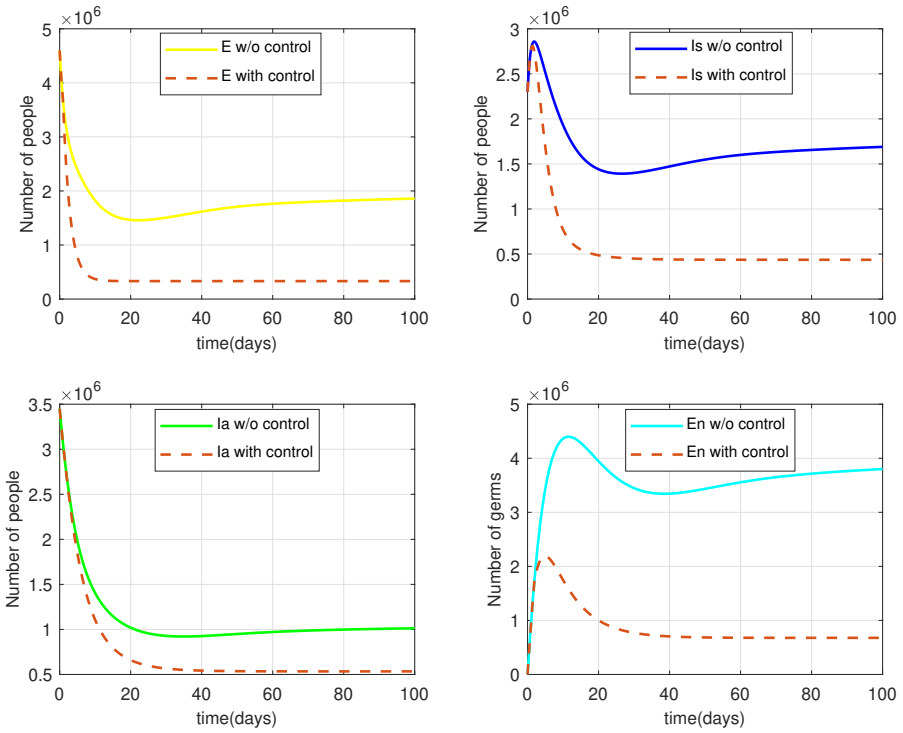

Figure 5: Illustration of the impact of awareness campaign with sterilization of the water and food.

cost, and contextual relevance, ensuring that the analysis focuses on the most realistic and potentially effective interventions.

4.7 Cost-effectiveness analysis

In this section, we identify the most cost-effective strategy by comparing the cost-effectiveness ratios of the five intervention scenarios. To this end, we use the incremental cost-effectiveness ratio (ICER), a standard measure in health economics [15, 31, 32, 5].

The ICER is calculated as the ratio of the difference in costs to the difference in infections averted between two competing strategies i and j, where $i, j \in \{1, \ldots, 5\}$,

$$ICER(i,j) = \frac{C(i) - C(j)}{TA(i) - TA(j)},$$

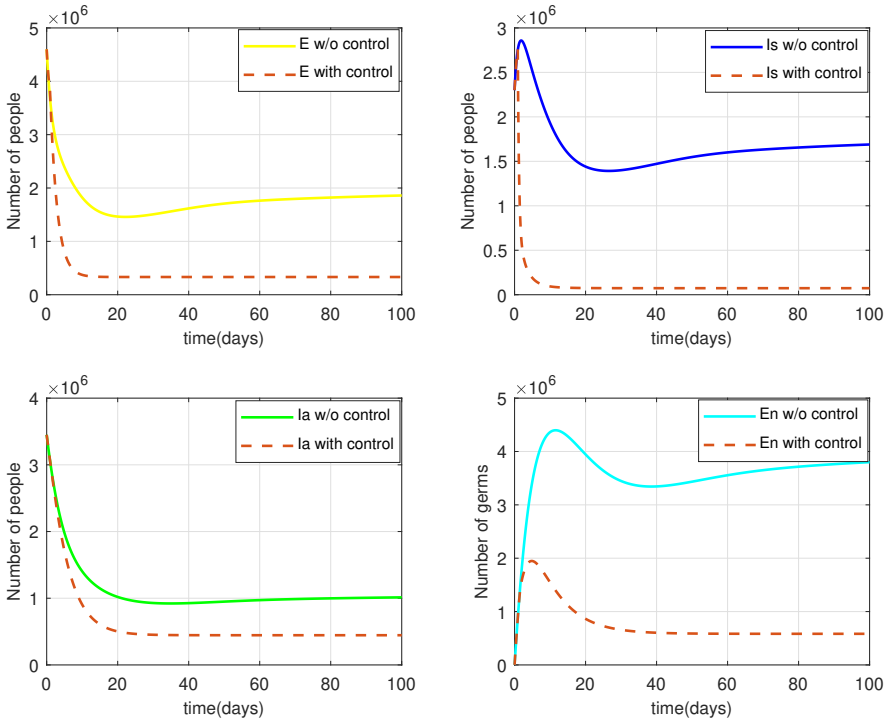

Figure 6: Illustration of the impact of combination of all strategies.

with $C(\cdot)$ denoting the total cost and $TA(\cdot)$ the total infections averted. When comparing two strategies **M** and **N**, if $TA(N) > TA(M)$, then the ICER expresses the additional cost required to avert one extra infection by adopting **N** over **M**.

The total costs and infections averted for each strategy are summarized in Table 2.

Table 2: Total costs and infections averted for strategies S_1–S_5.

Strategy	Total averted infections (TA)	Total cost (TC)
$S_1 : u_2u_3$	3.6270×10^4	980
$S_2 : u_5u_6$	1.5420×10^6	989
$S_3 : u_1u_4$	3.2588×10^6	542.5536
$S_4 : u_1u_2u_3$	3.2650×10^6	1473.5
$S_5 : u_1u_2u_3u_4u_5u_6$	3.7103×10^6	2514.8

Step 1: S_1 **vs.** S_2

$$ICER(1) = \frac{TC(1)}{TA(1)} = 2.70 \times 10^{-2},$$

$$ICER(2) = \frac{TC(2) - TC(1)}{TA(2) - TA(1)} = 5.977 \times 10^{-6}.$$

Result: S_2 dominates S_1 (lower ICER, greater effectiveness), which implies that S_1 is excluded.

Step 2: S_2 **vs.** S_3

$$ICER(2) = \frac{TC(2)}{TA(2)} = 6.41 \times 10^{-4},$$

$$ICER(3) = \frac{TC(3) - TC(2)}{TA(3) - TA(2)} = -2.60 \times 10^{-4}.$$

Result: S_3 strongly dominates S_2 (negative ICER indicates lower cost with higher effectiveness), which implies that S_2 is excluded.

Step 3: S_3 **vs.** S_4

$$ICER(3) = \frac{TC(3)}{TA(3)} = 1.66 \times 10^{-4},$$

$$ICER(4) = \frac{TC(4) - TC(3)}{TA(4) - TA(3)} = 0.1501.$$

Result: S_3 is more cost-effective than S_4, since the additional cost of S_4 per infection averted is disproportionately high, which implies that S_4 is excluded.

Step 4: S_3 **vs.** S_5

$$ICER(3) = \frac{TC(3)}{TA(3)} = 1.66 \times 10^{-4},$$

$$ICER(5) = \frac{TC(5) - TC(3)}{TA(5) - TA(3)} = 4.36 \times 10^{-3}.$$

Result: Although S_5 averts the largest number of infections, its ICER is higher than that of S_3, which implies that S_5 is excluded.

Interpretation: Awareness campaigns combined with vaccination (S_3) offer the highest cost-effectiveness by simultaneously reducing transmission and increasing population immunity, effectively controlling typhoid fever.

5 Discussion and conclusion

5.1 Discussion

The inclusion of immigration in our model provides important insights into typhoid fever dynamics that are rarely captured in previous studies. Our simulations indicate that immigrants

can substantially increase the number of exposed and infected individuals, as well as the environmental pathogen load, highlighting their potential role as a source of infection. Figures 7 and 8 illustrate these differences, emphasizing that immigration can amplify both the burden and the transmission potential of typhoid fever within the population.

Among the five control strategies proposed in this study, the combination of awareness campaigns with food and water sterilization is used here to illustrate the influence of immigration on disease dynamics. This example shows how such interventions can mitigate the effects of increased exposure and environmental contamination associated with population movement. These findings underline the importance of designing targeted preventive measures that address both resident and immigrant populations. Overall, incorporating immigration dynamics enhances the realism of the model and provides actionable guidance for public health planning.

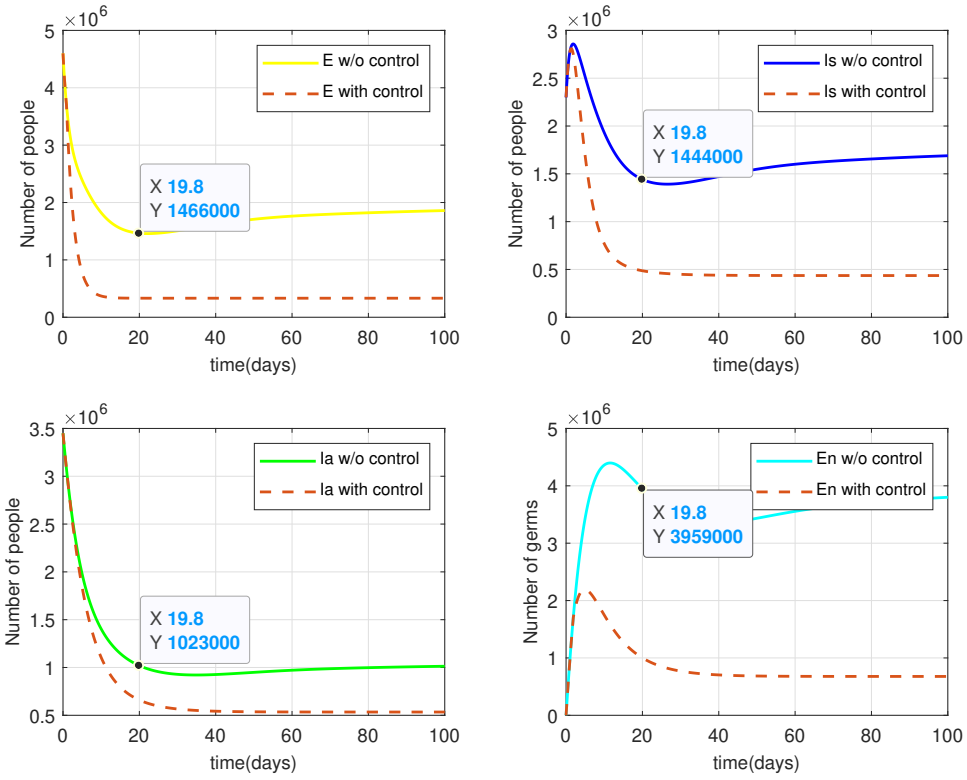

Figure 7: Projected dynamics of typhoid fever with immigration

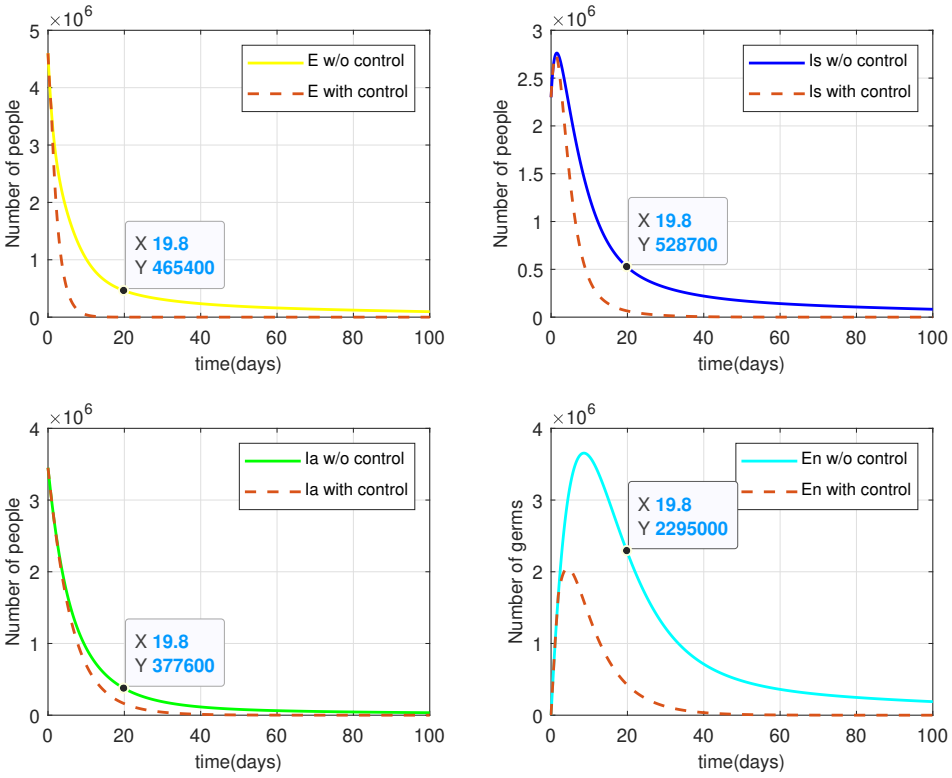

Figure 8: Projected dynamics of typhoid fever without immigration

5.2 Conclusion

In this study, we developed a deterministic mathematical model to minimize the spread of typhoid fever in Taiwan, explicitly incorporating the effects of immigrants from other endemic countries on local transmission dynamics, vaccine unreliability, assessment of government interventions, treatment of hospitalized patients, and contamination from population and hospital waste. Importantly, we proposed six control measures: Increasing awareness, sterilizing food and water, promoting vaccinations, screening, and managing treatment.

Through the application of optimal control strategies, we successfully demonstrated a reduction in the disease burden, as evidenced by numerical simulations. Furthermore, using cost-effectiveness analysis, we identified that the most efficient strategy combines Awareness campaign and vaccination program.

Despite these insights, our model has inherent limitations, such as the assumption of homogeneous population mixing, constant parameter values, and the exclusion of additional environmental or spatial heterogeneities. Future research could address these limitations by integrating more detailed epidemiological data, exploring alternative combinations of control measures, considering spatial dynamics, or extending the modeling framework to other pathogens or regions. In particular, studying the spatial spread of typhoid fever may provide further insights into designing effective and targeted intervention strategies.

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Conflicts of Interest

The author declares no conflicts of interest.

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