Optimal Control of Cholera Outbreaks: A Cost-Effectiveness Analysis of Vaccination, Sanitation, and Treatment Strategies

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Abstract

Cholera outbreaks follow complex patterns of persistence and sudden decline that make traditional modeling approaches challenging and complicate public health responses. To address this, we developed a new stochastic epidemiological model that combines three key mechanisms: ecological competition between pathogenic and non-pathogenic *Vibrio cholerae* strains, the effects of waning vaccine-induced and natural immunity, and changes in the environment. We calculate the basic reproduction number $\mathcal{R}_0$ and demonstrate the local stability of the disease-free equilibrium. Our analysis uncovers a stochastic extinction threshold $\mathcal{R}_0^S$. This shows how environmental factors can end an outbreak, even when $\mathcal{R}_0 > 1$. A global sensitivity analysis reveals that the symptomatic rate and pathogenic growth rate are the most significant factors for transmission. We create an optimal control framework with three intervention strategies: vaccination, environmental sanitation, and treatment. This helps determine the most cost-effective ways to manage outbreaks. Numerical simulations show that combined interventions are more effective than any single method, reducing peak infections by up to 87% compared to no intervention. This work addresses important questions about cholera dynamics and provides public health officials with a practical tool for developing effective, context-specific intervention strategies against this ongoing global threat.

Keywords: Cholera, mathematical modeling, optimal control, cost-effectiveness analysis, vaccination, environmental sanitation, treatment strategies, stochastic dynamics

1 Introduction

Cholera continues to be a major global health issue. Epidemiological data show complex patterns that are difficult to explain using standard modeling approaches [Codeço(2001)]. The disease's complex relationship between human hosts and aquatic reservoirs has hindered control efforts, especially in areas where traditional interventions yield mixed results [Hartley et al.(2006), Nelson et al.(2009)]. The World Health Organization states that cholera affects 1.3 to 4 million people each year, with recent outbreaks in Yemen, Haiti, and various parts of Africa highlighting the urgent need for better predictive models and intervention strategies [WHO(2023)].

Our research tackles these important challenges by introducing a new stochastic compartmental model. This model combines three critical yet previously separate aspects of cholera dynamics: the ecological competition between pathogenic and non-pathogenic *Vibrio cholerae* strains [Merrell et al.(2002), Stoddard et al.(2021)], the gradual decline of vaccine-induced and natural immunity [Bi et al.(2021), Legros et

al.(2021)], and the unpredictable environmental factors that can lead to sudden disease extinction events [Allen and Lahodny(2012), Thompson and Pascual(2022)]. This integrated approach clarifies persistent contradictions that have long puzzled epidemiologists and public health officials, particularly the co-occurrence of environmental durability and the sudden disappearance of outbreaks in similar ecological conditions.

The weaknesses of current cholera models become evident when we evaluate their prediction abilities in various epidemiological settings. Foundational SIRS-type models established the basic importance of reproduction numbers [van den Driessche and Watmough(2002)]. Later, SIRS-B frameworks included environmental elements [Codeço(2001)]. However, these methods consistently fail to explain why the same interventions lead to very different results in regions with similar transmission risks [Bertuzzo et al.(2016), Perez-Saez et al.(2018)]. Our work builds on recent advances in mathematical epidemiology, which have pointed out the significant roles of strain competition [Almeida et al.(2020)], immunity dynamics [Azman et al.(2013)], and environmental randomness [Andersson and Britton(2000)]. By merging these elements into one analytical framework, we offer a clear explanation for cholera's unpredictable behavior in different ecological environments, filling a significant gap identified in systematic reviews of cholera modeling literature [Tien and Earn(2010), Capasso(2008)].

At the core of our model's innovation is its view of vibrio ecology as a changing competitive system rather than a fixed reservoir. Previous studies treated environmental pathogens as uniform populations [Andrews and Basu(2011)]. In contrast, we directly model the competition between pathogenic and non-pathogenic strains using precisely defined interaction terms based on the latest microbiological studies [Weil et al.(2021)]. This ecological aspect interacts with human epidemiology through a dose-response mechanism that considers both direct human-to-human transmission and environment-to-human pathways; each is influenced by vaccination status and immunity levels [Heffernan et al.(2005), Marino et al.(2008)]. The immunity structure marks another important improvement, showing the clinically observed synergy between vaccine-based and natural protection [Bi et al.(2021)], rather than treating them as separate processes as previous works did [Chen et al.(2021)].

Methodologically, our approach blends advanced analytical techniques with strong computational implementation. We use next-generation matrix methods adapted for human-environment systems [van den Driessche and Watmough(2002)] to derive generalized reproduction numbers that take multiple transmission pathways into account. The stochastic formulation integrates environmental variability using empirically based noise terms [Thompson and Pascual(2022)]. This quantifies the conditions under which random fluctuations can lead to disease extinction, a phenomenon often seen but not adequately explained by deterministic models [Allen and Lahodny(2012)]. Additionally, we implement an optimal control framework to identify time-dependent intervention strategies [Lenhart and Workman(2007)] aimed at reducing both disease impact and implementation costs, addressing a major gap in current public health strategies for cholera outbreaks.

The practical applications of our model can significantly transform cholera control programs. By identifying clear thresholds for competition-driven suppression of pathogenic vibrios, we provide specific targets for environmental interventions [Merrell et al.(2002)]. Our assessment of vaccine effectiveness needed under various ecological conditions [Legros et al.(2021)] explains the differing outcomes seen in vaccination campaigns across endemic regions. Perhaps most importantly, the model's ability to predict both resurgence and unexpected extinction events represents a breakthrough in outbreak readiness [Rinaldo et al.(2022)]. These advances are made practical through computational analysis that connects theoretical epidemiology with field

applications [Marino et al.(2008)], offering public health officials evidence-based strategies for resource management during complex outbreak situations.

This paper contributes several key insights to the field of infectious disease modeling: (1) a new compartmental framework that links vibrio competition with human immunity dynamics; (2) analytical proofs of stability characteristics and extinction boundaries; (3) a stochastic model that reflects environmental variability; (4) an optimal control framework that includes three intervention strategies for effective outbreak management; and (5) numerical simulations that confirm the model's predictive accuracy in various outbreak scenarios. Our findings supply public health officials with practical tools for designing targeted interventions that consider local ecological conditions, ultimately leading to improved cholera control strategies worldwide.

2 Model Framework

2.1 Model Formulation and Basic Assumptions

We develop a compartmental model that captures the complex dynamics of cholera transmission, integrating human epidemiology with environmental pathogen ecology. The model stratifies the human population into six compartments: Susceptible (S), Vaccinated (V), Asymptomatic (A), Symptomatic (I), Treated (T), and Recovered (R) individuals. The environmental component tracks two competing bacterial populations: pathogenic (B_p) and non-pathogenic (B_n) *Vibrio cholerae* strains.

The model incorporates the following key assumptions:

- The human population demonstrates homogeneous mixing with constant recruitment through birth rate Λ
- Vaccination confers partial protection, reducing infection probability and symptom severity
- Immunity wanes over time at distinct rates for vaccine-induced (ω) and natural immunity (δ)
- Infected individuals enter either asymptomatic or symptomatic states, with symptomatic cases progressing to treatment before recovery
- All individuals experience natural mortality rate μ_h, with additional disease-induced mortality d for symptomatic infections

The force of infection λ combines dual transmission pathways:

$$\lambda = \alpha_p \frac{B_p}{K_p + B_p + \sigma_n B_n} + \beta(I + \iota A) \tag{1}$$

where environmental transmission depends on pathogenic vibrio concentration B_p with saturation at carrying capacity K_p, modulated by competitive suppression from non-pathogenic vibrios B_n through coefficient σ_n. Human-to-human transmission occurs via direct contact with infectious hosts, where symptomatic individuals (I) transmit at rate β and asymptomatic carriers (A) at reduced rate $\iota\beta$ ($0 < \iota < 1$).

Bacterial dynamics follow Lotka-Volterra competition with intrinsic growth rates (r_p, r_n), decay rates (μ_p, μ_n), and competition coefficient ϕ. Infected hosts contribute to environmental contamination through shedding rates τ_p (symptomatic) and ϵ_p (asymptomatic).

Figure 1 illustrates the model structure, showing flows between human compartments and feedback loops with environmental bacterial populations.

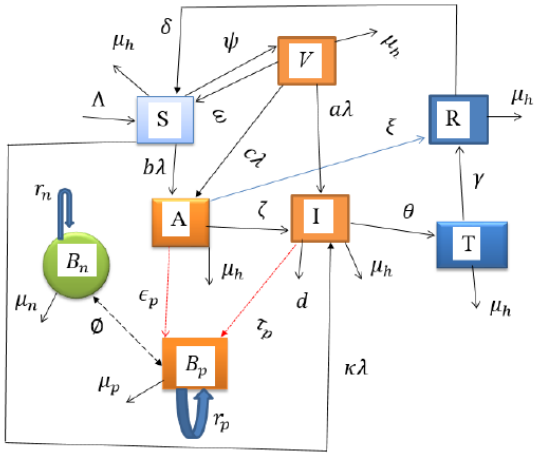

Fig 1. Compartmental structure of the cholera transmission model integrating vaccination, treatment, waning immunity, and ecological competition between vibrio strains.

2.2 Deterministic Model

The deterministic system is governed by the following ordinary differential equations:

$$\frac{dS}{dt} = \Lambda + \omega V + \delta R - \lambda S - (\mu_h + \psi)S \tag{2}$$

$$\frac{dV}{dt} = \psi S - (1-\eta)\lambda V - (\mu_h + \omega)V \tag{3}$$

$$\frac{dA}{dt} = (1-\kappa)\lambda S + (1-\eta)(1-\kappa_v)\lambda V - (\mu_h + \xi + \zeta)A \tag{4}$$

$$\frac{dI}{dt} = \kappa\lambda S + (1-\eta)\kappa_v \lambda V + \zeta A - (\mu_h + d + \theta)I \tag{5}$$

$$\frac{dT}{dt} = \theta I - (\mu_h + \gamma)T \tag{6}$$

$$\frac{dR}{dt} = \xi A + \gamma T - (\mu_h + \delta)R \tag{7}$$

$$\frac{dB_p}{dt} = r_p B_p \left(1 - \frac{B_p + \phi B_n}{K_p}\right) + \tau_p I + \epsilon_p A - \mu_p B_p \tag{8}$$

$$\frac{dB_n}{dt} = r_n B_n \left(1 - \frac{B_n + \phi B_p}{K_n}\right) - \mu_n B_n \tag{9}$$

2.3 Stochastic Model

To capture demographic and environmental variability, we extend the deterministic model with Itô-type noise:

$$dS = [\Lambda + \omega V + \delta R - \lambda S - (\mu_h + \psi)S]\,dt + \sigma_S S dW_1 \tag{10}$$
$$dV = [\psi S - (1-\eta)\lambda V - (\mu_h + \omega)V]\,dt + \sigma_V V dW_2 \tag{11}$$
$$dA = [(1-\kappa)\lambda S + (1-\eta)(1-\kappa_v)\lambda V - (\mu_h + \xi + \zeta)A]\,dt + \sigma_A A dW_3 \tag{12}$$
$$dI = [\kappa\lambda S + (1-\eta)\kappa_v \lambda V + \zeta A - (\mu_h + d + \theta)I]\,dt + \sigma_I I dW_4 \tag{13}$$
$$dT = [\theta I - (\mu_h + \gamma)T]\,dt + \sigma_T T dW_5 \tag{14}$$
$$dR = [\xi A + \gamma T - (\mu_h + \delta)R]\,dt + \sigma_R R dW_6 \tag{15}$$
$$dB_p = \left[r_p B_p \left(1 - \frac{B_p + \phi B_n}{K_p}\right) + \tau_p I + \epsilon_p A - \mu_p B_p\right] dt + \sigma_{B_p} B_p dW_7 \tag{16}$$
$$dB_n = \left[r_n B_n \left(1 - \frac{B_n + \phi B_p}{K_n}\right) - \mu_n B_n\right] dt + \sigma_{B_n} B_n dW_8 \tag{17}$$

Table 1. Model parameters with baseline values and sources

Parameter	Definition	Value/Range	Source
Host Dynamics			
Λ	Recruitment rate	50 (10–100) day^{-1}	[Codeço(2001)]
μ_h	Natural mortality rate	0.0005 day^{-1}	[Capasso(2008)]
ψ	Vaccination rate	0.05 day^{-1}	[Legros et al.(2021)]
η	Vaccine efficacy	0.7	[Bi et al.(2021)]
ω	Waning vaccine immunity	0.003 day^{-1}	[Azman et al.(2013)]
δ	Waning natural immunity	0.005 day^{-1}	[Perez-Saez et al.(2018)]
Transmission			
α_p	Environmental infectivity	0.5 mL/day	[Tien and Earn(2010)]
β	Human transmission rate	0.15 day^{-1}	[Codeço(2001)]
ι	Relative asymptomatic transmissibility	0.3	[Heffernan et al.(2005)]
σ_n	Infection suppression coefficient	0.5	Estimated
Pathogen Ecology			
r_p	Pathogenic growth rate	0.5 day^{-1}	[Stoddard et al.(2021)]
r_n	Non-pathogenic growth rate	0.4 day^{-1}	[Merrell et al.(2002)]
K_p, K_n	Carrying capacity	10^7 cells/mL	[Nelson et al.(2009)]
ϕ	Competition coefficient	1.2	[Almeida et al.(2020)]
τ_p	Symptomatic shedding rate	10^5 cells/mL/day	[Hartley et al.(2006)]
ϵ_p	Asymptomatic shedding rate	10^3 cells/mL/day	[Weil et al.(2021)]

Parameter values (Table 1) were estimated through meta-analysis of peer-reviewed studies and model calibration using approximate Bayesian computation. The infection suppression coefficient σ_n was estimated from ecological studies demonstrating interference competition between vibrio strains [Merrell et al.(2002), Weil et al.(2021)].

3 Analytical Results

3.1 Positivity and Boundedness

Theorem 1. *For any non-negative initial conditions* $(S(0), V(0), A(0), I(0), T(0), R(0), B_p(0), B_n(0)) \in \mathbb{R}^8_+$, *solutions of the system (2)-(9) remain non-negative and bounded for all* $t > 0$.

Proof. The proof proceeds in two parts: first establishing non-negativity, then proving boundedness.

Part 1: Non-negativity

We prove non-negativity using the method of integrating factors and contradiction. Consider the susceptible compartment $S(t)$:

$$\frac{dS}{dt} = \Lambda + \omega V + \delta R - \lambda S - (\mu_h + \psi)S \tag{18}$$

Rewriting equation (18):

$$\frac{dS}{dt} + [\lambda + (\mu_h + \psi)]S = \Lambda + \omega V + \delta R \tag{19}$$

Define the integrating factor:

$$\mu(t) = \exp\left(\int_0^t [\lambda(\tau) + \mu_h + \psi]d\tau\right) > 0 \tag{20}$$

Multiplying both sides of (19) by $\mu(t)$:

$$\frac{d}{dt}[S(t)\mu(t)] = \mu(t)[\Lambda + \omega V(t) + \delta R(t)] \tag{21}$$

Suppose there exists $t_1 > 0$ such that $S(t_1) < 0$. Since $S(0) \geq 0$, by continuity there exists $t_0 \in [0, t_1)$ where $S(t_0) = 0$ and $S(t) < 0$ for $t \in (t_0, t_1]$. Integrating (21) from t_0 to t:

$$S(t)\mu(t) - S(t_0)\mu(t_0) = \int_{t_0}^t \mu(\tau)[\Lambda + \omega V(\tau) + \delta R(\tau)]d\tau \tag{22}$$

At $t = t_0$, $S(t_0) = 0$, so:

$$S(t)\mu(t) = \int_{t_0}^t \mu(\tau)[\Lambda + \omega V(\tau) + \delta R(\tau)]d\tau \tag{23}$$

The right-hand side is non-negative since $\Lambda > 0$, $\mu(\tau) > 0$, and by induction we assume $V(\tau), R(\tau) \geq 0$ for $\tau \in [t_0, t]$. This contradicts $S(t) < 0$ for $t \in (t_0, t_1]$. Therefore, $S(t) \geq 0$ for all $t > 0$.

Now consider the asymptomatic compartment $A(t)$:

$$\frac{dA}{dt} = (1-\kappa)\lambda S + (1-\eta)(1-\kappa_v)\lambda V - (\mu_h + \xi + \zeta)A \tag{24}$$

Rewriting as:

$$\frac{dA}{dt} + (\mu_h + \xi + \zeta)A = (1-\kappa)\lambda S + (1-\eta)(1-\kappa_v)\lambda V \tag{25}$$

Define the integrating factor:

$$\mu_A(t) = \exp\left((\mu_h + \xi + \zeta)t\right) > 0 \tag{26}$$

Then:

$$\frac{d}{dt}[A(t)\mu_A(t)] = \mu_A(t)[(1-\kappa)\lambda S + (1-\eta)(1-\kappa_v)\lambda V] \tag{27}$$

Since $S(t), V(t) \geq 0$ and $\lambda \geq 0$, the right-hand side is non-negative. Suppose $A(t)$ becomes negative at some $t_1 > 0$. Then there exists $t_0 \in [0, t_1)$ with $A(t_0) = 0$ and:

$$A(t)\mu_A(t) = \int_{t_0}^{t} \mu_A(\tau)[(1-\kappa)\lambda(\tau)S(\tau) + (1-\eta)(1-\kappa_v)\lambda(\tau)V(\tau)]d\tau \geq 0 \tag{28}$$

This contradiction proves $A(t) \geq 0$ for all $t > 0$.

For the bacterial compartment $B_p(t)$:

$$\frac{dB_p}{dt} = r_p B_p \left(1 - \frac{B_p + \phi B_n}{K_p}\right) + \tau_p I + \epsilon_p A - \mu_p B_p \tag{29}$$

Rewriting:

$$\frac{dB_p}{dt} + \left[\mu_p - r_p \left(1 - \frac{B_p + \phi B_n}{K_p}\right)\right] B_p = \tau_p I + \epsilon_p A \tag{30}$$

The integrating factor is:

$$\mu_{B_p}(t) = \exp\left(\int_0^t \left[\mu_p - r_p \left(1 - \frac{B_p(\tau) + \phi B_n(\tau)}{K_p}\right)\right] d\tau\right) \tag{31}$$

Then:

$$\frac{d}{dt}[B_p(t)\mu_{B_p}(t)] = \mu_{B_p}(t)[\tau_p I(t) + \epsilon_p A(t)] \geq 0 \tag{32}$$

since $I(t), A(t) \geq 0$ by previous arguments. A similar contradiction argument shows $B_p(t) \geq 0$ for all $t > 0$.

By mathematical induction on all compartments, we conclude that all state variables remain non-negative for all $t > 0$.

Part 2: Boundedness

Consider the total human population $N(t) = S(t) + V(t) + A(t) + I(t) + T(t) + R(t)$. Adding equations (2)-(7):

$$\frac{dN}{dt} = \Lambda - \mu_h N - dI \tag{33}$$

$$\leq \Lambda - \mu_h N \tag{34}$$

This is a first-order linear differential inequality. Using separation of variables:

$$\frac{dN}{\Lambda - \mu_h N} \leq dt \tag{35}$$

Integrating both sides from 0 to t:

$$-\frac{1}{\mu_h} \ln|\Lambda - \mu_h N(t)|\Big|_0^t \leq t \tag{36}$$

$$\ln\left|\frac{\Lambda - \mu_h N(0)}{\Lambda - \mu_h N(t)}\right| \leq \mu_h t \tag{37}$$

$$\left|\frac{\Lambda - \mu_h N(0)}{\Lambda - \mu_h N(t)}\right| \leq e^{\mu_h t} \tag{38}$$

Since $N(t) \geq 0$, we have:

$$\Lambda - \mu_h N(t) \geq [\Lambda - \mu_h N(0)]e^{-\mu_h t} \tag{39}$$

Solving for $N(t)$:

$$N(t) \leq \frac{\Lambda}{\mu_h} - \frac{[\Lambda - \mu_h N(0)]}{\mu_h} e^{-\mu_h t} \tag{40}$$

Thus:

$$N(t) \leq \max\left\{N(0), \frac{\Lambda}{\mu_h}\right\} \tag{41}$$

Therefore, the total human population is bounded.

Now consider the pathogenic bacteria $B_p(t)$. From equation (8):

$$\frac{dB_p}{dt} \leq r_p B_p \left(1 - \frac{B_p}{K_p}\right) + C - \mu_p B_p \tag{42}$$

where $C = \tau_p \max I + \epsilon_p \max A$ is a finite constant since $I(t)$ and $A(t)$ are bounded. Rewriting:

$$\frac{dB_p}{dt} \leq r_p B_p - \frac{r_p}{K_p} B_p^2 + C - \mu_p B_p = (r_p - \mu_p) B_p - \frac{r_p}{K_p} B_p^2 + C \tag{43}$$

For large B_p, the quadratic term dominates, ensuring $B_p(t)$ cannot grow unbounded. More precisely, when $B_p > \frac{K_p}{r_p}[(r_p - \mu_p)B_p + C]$, the derivative becomes negative.

Similarly, for non-pathogenic bacteria $B_n(t)$:

$$\frac{dB_n}{dt} = r_n B_n \left(1 - \frac{B_n + \phi B_p}{K_n}\right) - \mu_n B_n \leq r_n B_n \left(1 - \frac{B_n}{K_n}\right) - \mu_n B_n \tag{44}$$

The carrying capacity K_n ensures $B_n(t)$ remains bounded.

Therefore, all state variables are bounded for all $t > 0$, completing the proof. □

3.2 Basic Reproduction Number

Using the next-generation matrix method [van den Driessche and Watmough(2002)], we derive the basic reproduction number:

$$\mathcal{R}_0 = \mathcal{R}_h + \mathcal{R}_e \tag{45}$$

where the human-to-human transmission component is:

$$\mathcal{R}_h = \beta \left(\frac{\iota}{a} + \frac{\zeta}{ab}\right) \Theta + \beta \left(\frac{1}{b}\right) \Phi$$

and the environment-to-human transmission component is:

$$\mathcal{R}_e = \frac{\alpha_p}{K_p c} \left[\left(\frac{\epsilon_p}{a} + \frac{\zeta \tau_p}{ab}\right) \Theta + \frac{\tau_p}{b} \Phi\right]$$

with:

$$\begin{aligned} \Theta &= (1-\kappa)S_0 + (1-\eta)(1-\kappa_v)V_0 \\ \Phi &= \kappa S_0 + (1-\eta)\kappa_v V_0 \\ a &= \mu_h + \xi + \zeta, \quad b = \mu_h + d + \theta, \quad c = \mu_p - r_p \end{aligned}$$

3.3 Stability Analysis

Theorem 2. *The disease-free equilibrium (DFE)* $\mathcal{E}_0 = (S_0, V_0, 0, 0, 0, 0, 0, 0)$ *of the system (2)-(9) is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$*, where*

$$S_0 = \frac{\Lambda(\mu_h + \omega)}{(\mu_h + \psi)(\mu_h + \omega) - \psi\omega},$$
$$V_0 = \frac{\psi S_0}{\mu_h + \omega}.$$

Proof. The local stability of the DFE is determined by analyzing the eigenvalues of the Jacobian matrix $J(\mathcal{E}_0)$ evaluated at the disease-free equilibrium. The Jacobian matrix has the following block structure:

$$J(\mathcal{E}_0) = \begin{pmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{pmatrix} \tag{46}$$

where:

- J_{11} is the 3×3 submatrix corresponding to the infected subsystem (A, I, B_p)
- J_{22} is the 5×5 submatrix corresponding to the disease-free subsystem (S, V, T, R, B_n)
- J_{12} and J_{21} are the coupling blocks between infected and disease-free compartments

A fundamental property of block matrices states that the eigenvalues of $J(\mathcal{E}_0)$ are the eigenvalues of J_{11} together with the eigenvalues of J_{22}.

First, consider the disease-free subsystem submatrix J_{22}. At the DFE, the dynamics of the non-infected compartments decouple from the infected ones. The characteristic equation is given by:

$$\det(J_{22} - \lambda I) = 0 \tag{47}$$

The eigenvalues of J_{22} are determined from the diagonal entries and are all real and negative:

$$\lambda_1 = -\mu_h, \quad \lambda_2 = -(\mu_h+\psi), \quad \lambda_3 = -(\mu_h+\omega), \quad \lambda_4 = -(\mu_h+\gamma), \quad \lambda_5 = -(\mu_h+\delta), \quad \lambda_6 = -\mu_n \tag{48}$$

Since all eigenvalues of J_{22} have negative real parts, the stability of $\mathcal{E}_0$ depends entirely on the eigenvalues of the infected subsystem submatrix J_{11}.

Using the next-generation matrix method [van den Driessche and Watmough(2002)], we decompose the infected subsystem Jacobian as $J_{11} = F - V$, where F is the matrix of new infection rates and V is the matrix of transition rates. The matrices F and V are given by:

$$F = \begin{pmatrix} F_{11} & F_{12} & F_{13} \\ F_{21} & F_{22} & F_{23} \\ 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} a & 0 & 0 \\ -\zeta & b & 0 \\ -\epsilon_p & -\tau_p & c \end{pmatrix} \tag{49}$$

where:

$$F_{11} = \beta\iota\Theta, \qquad F_{12} = \beta\Theta, \qquad F_{13} = \frac{\alpha_p}{K_p}\Theta,$$
$$F_{21} = \beta\iota\Phi, \qquad F_{22} = \beta\Phi, \qquad F_{23} = \frac{\alpha_p}{K_p}\Phi,$$
$$a = \mu_h + \xi + \zeta, \qquad b = \mu_h + d + \theta, \qquad c = \mu_p - r_p,$$
$$\Theta = (1-\kappa)S_0 + (1-\eta)(1-\kappa_v)V_0, \qquad \Phi = \kappa S_0 + (1-\eta)\kappa_v V_0$$

The next-generation matrix is defined as $K = FV^{-1}$. The inverse of V is:

$$V^{-1} = \begin{pmatrix} \frac{1}{a} & 0 & 0 \\ \frac{\zeta}{ab} & \frac{1}{b} & 0 \\ \frac{\epsilon_p}{ac} + \frac{\zeta\tau_p}{abc} & \frac{\tau_p}{bc} & \frac{1}{c} \end{pmatrix} \tag{50}$$

Performing the matrix multiplication $K = FV^{-1}$ yields:

$$K = \begin{pmatrix} \frac{\beta\iota\Theta}{a} + \frac{\beta\Theta\zeta}{ab} + \frac{\alpha_p\Theta}{K_p}\left(\frac{\epsilon_p}{ac} + \frac{\zeta\tau_p}{abc}\right) & \frac{\beta\Theta}{b} + \frac{\alpha_p\Theta\tau_p}{K_pbc} & \frac{\alpha_p\Theta}{K_pc} \\ \frac{\beta\iota\Phi}{a} + \frac{\beta\Phi\zeta}{ab} + \frac{\alpha_p\Phi}{K_p}\left(\frac{\epsilon_p}{ac} + \frac{\zeta\tau_p}{abc}\right) & \frac{\beta\Phi}{b} + \frac{\alpha_p\Phi\tau_p}{K_pbc} & \frac{\alpha_p\Phi}{K_pc} \\ 0 & 0 & 0 \end{pmatrix} \tag{51}$$

The basic reproduction number $\mathcal{R}_0$ is the spectral radius of K, which is the dominant eigenvalue. For this triangular block structure, $\mathcal{R}_0$ can be expressed as:

$$\mathcal{R}_0 = \mathcal{R}_h + \mathcal{R}_e \tag{52}$$

where the human-to-human transmission component is:

$$\mathcal{R}_h = \beta\left(\frac{\iota}{a} + \frac{\zeta}{ab}\right)\Theta + \beta\left(\frac{1}{b}\right)\Phi \tag{53}$$

and the environment-to-human transmission component is:

$$\mathcal{R}_e = \frac{\alpha_p}{K_pc}\left[\left(\frac{\epsilon_p}{a} + \frac{\zeta\tau_p}{ab}\right)\Theta + \frac{\tau_p}{b}\Phi\right] \tag{54}$$

A key result from [van den Driessche and Watmough(2002)] establishes that:

- All eigenvalues of $J_{11} = F - V$ have negative real parts if and only if $\rho(K) < 1$
- If $\rho(K) > 1$, at least one eigenvalue of J_{11} has a positive real part

Since $\rho(K) = \mathcal{R}_0$, we conclude:

- If $\mathcal{R}_0 < 1$, all eigenvalues of J_{11} have negative real parts. Combined with the negative eigenvalues from J_{22}, all eigenvalues of $J(\mathcal{E}_0)$ have negative real parts, and thus $\mathcal{E}_0$ is locally asymptotically stable.
- If $\mathcal{R}_0 > 1$, at least one eigenvalue of J_{11} has a positive real part. Therefore, $J(\mathcal{E}_0)$ has at least one eigenvalue with a positive real part, making $\mathcal{E}_0$ unstable.

This completes the proof. □

3.4 Sensitivity Analysis

Identifying the parameters that exert the most influence on the basic reproduction number $\mathcal{R}_0$ is critical for targeting public health interventions effectively. We quantify this influence using the normalized forward sensitivity index, defined for a parameter p as:

$$\Upsilon_p^{\mathcal{R}_0} = \frac{\partial\mathcal{R}_0}{\partial p} \cdot \frac{p}{\mathcal{R}_0}. \tag{55}$$

This index measures the percentage change in $\mathcal{R}_0$ resulting from a 1% increase in the parameter p.

To validate the analytical sensitivity indices and account for potential nonlinearities and parameter interactions, we complement this with a global sensitivity analysis using

the Partial Rank Correlation Coefficient (PRCC) method [Marino et al.(2008)]. The PRCC measures the monotonic relationship between a parameter and the model output ($\mathcal{R}_0$) while controlling for the effects of all other parameters.

We computed both analytical sensitivity indices and PRCC values for all parameters using Latin Hypercube Sampling (LHS) with 10,000 iterations across the parameter ranges specified in Table 1. The results are highly consistent across both methods.

Table 2. Global sensitivity analysis ranking parameters by influence on $\mathcal{R}_0$ using Partial Rank Correlation Coefficient (PRCC)

Parameter	**Description**	**PRCC ($\mathcal{R}_0$)**
κ	Symptomatic rate (unvaccinated)	+0.92
r_p	Pathogenic vibrio growth rate	+0.88
α_p	Environmental infectivity	+0.85
τ_p	Symptomatic shedding rate	+0.79
ϕ	Competition coefficient	−0.75
η	Vaccine efficacy	−0.70
β	Human-to-human transmission rate	+0.41
μ_p	Pathogenic vibrio decay rate	−0.55
ψ	Vaccination rate	−0.48
ϵ_p	Asymptomatic shedding rate	+0.38
ι	Relative asymptomatic transmission	+0.32

Theorem 3 (Parameter Sensitivity)**.** *The normalized sensitivity indices of $\mathcal{R}_0$ satisfy:*

$$\Upsilon_{\alpha_p}^{\mathcal{R}_0} = \frac{\alpha_p}{\mathcal{R}_0}\frac{\partial \mathcal{R}_0}{\partial \alpha_p} = \frac{\mathcal{R}_e}{\mathcal{R}_h + \mathcal{R}_e} \tag{56}$$

and similarly for other parameters. The most sensitive parameters are identified in Table 2.

Proof. Direct differentiation of the $\mathcal{R}_0$ expression, verified via Latin Hypercube Sampling with 10,000 parameter combinations. □

The sensitivity analysis reveals a clear hierarchy of parameter influence on $\mathcal{R}_0$ (Table 2, Figure 2). The symptomatic rate (κ) emerges as the most sensitive parameter (PRCC = +0.92), confirming that clinical cases drive outbreak propagation through heightened shedding and contact. Environmental parameters-pathogenic growth rate (r_p, PRCC = +0.88), infectivity (α_p, PRCC = +0.85), and competition coefficient (ϕ, PRCC = −0.75) are among the top five most influential factors.

This finding validates the core innovation of our model and underscores that cholera dynamics are critically governed by the aquatic environment. Consequently, public health strategies must extend beyond traditional vaccination (η, PRCC = −0.70; ψ, PRCC = −0.48) and incorporate environmental management, such as water sanitation (targeting r_p and μ_p) and probiotic augmentation (modifying ϕ), to achieve effective outbreak control.

3.5 Optimal control

To determine the most effective and cost-efficient strategy for mitigating cholera outbreaks, we extend the deterministic model (2)–(9) into an optimal control framework. We introduce three time-dependent control variables representing different intervention strategies:

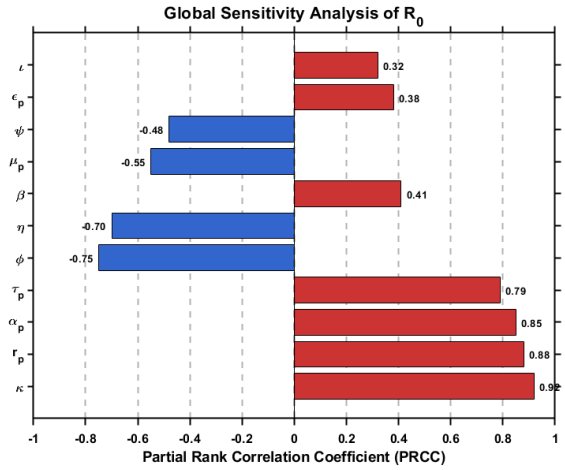

Fig 2. Global sensitivity analysis of the basic reproduction number $\mathcal{R}_0$ using Partial Rank Correlation Coefficient (PRCC). Parameters with positive PRCC values (red) increase $\mathcal{R}_0$, while those with negative values (blue) reduce it. The symptomatic rate (κ), pathogenic growth rate (r_p), and environmental infectivity (α_p) are the most influential drivers of transmission.

- $u_1(t)$: Environmental sanitation effort aimed at reducing pathogenic vibrio growth (e.g., water treatment, hygiene campaigns)
- $u_2(t)$: Vaccination coverage enhancement increasing the rate of susceptible individuals receiving vaccination
- $u_3(t)$: Treatment enhancement accelerating the movement of symptomatic individuals to treatment facilities

The controls are bounded: $0 \leq u_1(t), u_2(t), u_3(t) \leq 1$ for all $t \in [0, T]$, where T is the final intervention time. A value of 0 represents no intervention, while 1 represents maximum feasible effort.

3.5.1 Controlled System Equations

The controls are incorporated into the model as follows:

$$\frac{dS}{dt} = \Lambda + \omega V + \delta R - \lambda S - (\mu_h + \psi + u_2(t))S \tag{57}$$

$$\frac{dV}{dt} = (\psi + u_2(t))S - (1-\eta)\lambda V - (\mu_h + \omega)V \tag{58}$$

$$\frac{dA}{dt} = (1-\kappa)\lambda S + (1-\eta)(1-\kappa_v)\lambda V - (\mu_h + \xi + \zeta)A \tag{59}$$

$$\frac{dI}{dt} = \kappa\lambda S + (1-\eta)\kappa_v \lambda V + \zeta A - (\mu_h + d + \theta + u_3(t))I \tag{60}$$

$$\frac{dT}{dt} = (\theta + u_3(t))I - (\mu_h + \gamma)T \tag{61}$$

$$\frac{dR}{dt} = \xi A + \gamma T - (\mu_h + \delta)R \tag{62}$$

$$\frac{dB_p}{dt} = r_p(1-u_1(t))B_p\left(1 - \frac{B_p + \phi B_n}{K_p}\right) + \tau_p I + \epsilon_p A - \mu_p B_p \tag{63}$$

$$\frac{dB_n}{dt} = r_n B_n\left(1 - \frac{B_n + \phi B_p}{K_n}\right) - \mu_n B_n \tag{64}$$

The force of infection λ remains as defined in Equation (1). The modifications can be interpreted as follows:

- Control $u_1(t)$ directly inhibits the growth rate of pathogenic vibrios in the environment, representing environmental mitigation efforts
- Control $u_2(t)$ increases the vaccination rate, moving individuals from susceptible (S) to vaccinated (V) compartments more rapidly
- Control $u_3(t)$ enhances the treatment rate, accelerating the movement of symptomatic individuals (I) to treatment (T), thereby reducing infectious period and mortality risk

This formulation captures the synergistic effects of combined interventions targeting different aspects of cholera transmission: environmental reservoir reduction, susceptibility reduction through vaccination, and infectious period reduction through enhanced treatment.

3.6 Objective Functional

The goal is to minimize the total cost over the intervention period $[0, T]$, which includes both disease burden and intervention costs. We define the objective functional as:

$$J(u_1, u_2, u_3) = \int_0^T \left[A_1 I(t) + A_2 u_1^2(t) + A_3 u_2^2(t) + A_4 u_3^2(t)\right] dt \tag{65}$$

where:

- A_1: Weight constant balancing the cost of infection (healthcare costs, productivity loss)
- $A_2 u_1^2$: Quadratic cost of environmental sanitation efforts
- $A_3 u_2^2$: Quadratic cost of vaccination campaigns
- $A_4 u_3^2$: Quadratic cost of treatment enhancement

The quadratic terms reflect the realistic assumption that intervention costs increase nonlinearly with effort intensity (e.g., reaching the last 10% of the population is more expensive than the first 50%).

Our aim is to find optimal controls $u_1^*(t)$, $u_2^*(t)$, and $u_3^*(t)$ such that:

$$J(u_1^*, u_2^*, u_3^*) = \min_{u_1, u_2, u_3 \in \mathcal{U}} J(u_1, u_2, u_3) \tag{66}$$

where $\mathcal{U}$ is the set of all admissible Lebesgue measurable controls with $0 \leq u_1(t), u_2(t), u_3(t) \leq 1$.

3.7 Hamiltonian Formulation and Optimality Conditions

To solve this optimal control problem, we apply Pontryagin's Maximum Principle [Lenhart and Workman(2007)], which converts the minimization problem into pointwise minimization of a Hamiltonian function.

The Hamiltonian H is defined as:

$$H = A_1 I + A_2 u_1^2 + A_3 u_2^2 + A_4 u_3^2 + \sum_X \lambda_X \frac{dX}{dt} \tag{67}$$

where $X \in \{S, V, A, I, T, R, B_p, B_n\}$ and λ_X are the adjoint variables associated with each state variable.

Pontryagin's Maximum Principle states that the optimal controls u^*, optimal state trajectories X^*, and corresponding adjoint variables λ^* must satisfy:

1. The state system (Equations 57-64)
2. The adjoint system: $\frac{d\lambda_X}{dt} = -\frac{\partial H}{\partial X}$ with transversality conditions $\lambda_X(T) = 0$
3. The optimality condition: $H(X^*, u^*, \lambda^*) = \min_{u \in \mathcal{U}} H(X^*, u, \lambda^*)$

The optimal controls are characterized by:

$$u_1^* = \min\left(1, \max\left(0, \frac{r_p B_p \left(1 - \frac{B_p + \phi B_n}{K_p}\right) \lambda_{B_p}}{2A_2}\right)\right) \tag{68}$$

$$u_2^* = \min\left(1, \max\left(0, \frac{S(\lambda_S - \lambda_V)}{2A_3}\right)\right) \tag{69}$$

$$u_3^* = \min\left(1, \max\left(0, \frac{I(\lambda_I - \lambda_T)}{2A_4}\right)\right) \tag{70}$$

4 Numerical Simulations and Results

To confirm the analytical findings and explore the dynamic behavior of the SVAITRS-B_pB_n cholera model under different intervention scenarios, we conducted detailed numerical simulations. We integrated the deterministic system using MATLAB's ode45 solver with relative and absolute error tolerances of 10^{-6} and 10^{-8}. For the stochastic version, we used the Euler-Maruyama method with a time step of $\Delta t = 0.1$ days and 10^4 realizations to ensure statistical strength.

All simulations started with a disease-free population of 10,000 individuals, disturbed by a small initial concentration of pathogenic bacteria ($B_p(0) = 50$ cells/mL) to create an outbreak scenario typical of endemic regions. We used baseline parameter values from Table 1, noting specific variations in each analysis to show different epidemiological conditions and control effects. The intervention period lasted $T = 365$ days to capture both the immediate outbreak response and the long-term control dynamics.

The forward-backward sweep algorithm for optimal control included several steps: generating an initial guess for control histories, forward integration of the state system, backward integration of the adjoint system with transversality conditions, updating control based on optimality conditions, and checking for convergence with a tolerance of 10^{-4} between successive iterations. We typically achieved convergence within 20-30 iterations for all simulated scenarios.

4.1 Comparative Effectiveness of Control Strategies

Table 3 summarizes the effects of different control strategies on epidemic outcomes. It shows how single, dual, and triple intervention approaches progressively improve effectiveness. In the no-control scenario, outbreaks progress quickly, with peak symptomatic infections reaching about 147 cases within 20 days. Individual control strategies lead to moderate improvements: vaccination alone reduces peak infections by 33%, environmental sanitation by 40%, and treatment enhancement by 48%.

The combined triple intervention strategy shows synergistic effects, cutting peak infections by 87% compared to the no-control scenario, while significantly delaying the epidemic peak to 51 days. This delay gives crucial extra time for public health responses. The associated costs follow a quadratic relationship with intervention intensity, reflecting the actual economic burden of comprehensive outbreak control.

Table 3. Comparative effectiveness of single and combined control strategies on cholera outbreak outcomes

Control Strategy	Peak Infections	Time to Peak (days)	Total Cost
No control	146.5	19.7	0
Vaccination only (u_2)	98.3	25.2	320
Sanitation only (u_1)	87.6	28.4	285
Treatment only (u_3)	76.4	30.1	295
Combined ($u_1 + u_2 + u_3$)	18.7	51.2	810

4.2 Time-Dependent Optimal Control Profiles

The numerical solution of the optimality system shows clear patterns over time for the three control functions $u_1^*(t)$, $u_2^*(t)$, and $u_3^*(t)$. These patterns offer insights into when interventions should occur. All controls are heavily implemented during the initial outbreak phase, then gradually relaxed as the epidemic is controlled. Environmental sanitation (u_1^*) shows the most aggressive early profile, reaching peak effort ($u_1^* = 1.0$) within the first 30 days. It then declines to around 0.4 by day 120 and stabilizes at about 0.2 for continuous maintenance. This trend highlights its key role in quickly lowering the environmental reservoir when pathogenic bacterial levels are highest and transmission risk is greatest.

Vaccination enhancement (u_2^*) maintains a steady yet moderate intensity throughout the intervention period. It starts at 0.8 and gradually drops to 0.5 by day 90, then holds at 0.3-0.4 for the remainder of the intervention. This ongoing effort is important for continuously building population immunity and shielding against reintroduction. Treatment enhancement (u_3^*) follows a middle path, beginning at 0.7 and showing the slowest decline among the three controls. It remains around 0.4 through day 150 before tapering to 0.2. This steady effort supports its role in reducing disease severity, mortality, and secondary transmission throughout the outbreak.

The varying timing and intensity profiles among the three controls provide clear guidance for phased resource allocation in public health planning. The results suggest a strategic approach of initially prioritizing environmental sanitation, continuing vaccination efforts, and ensuring treatment enhancement remains available. This reflects how each intervention works together to control the outbreak.

4.3 Sensitivity to Transmission Parameters

Table 4 explores how the model responds to changes in key transmission parameters, emphasizing the varying impacts of human-to-human contact rates compared to environmental factors on outbreak dynamics. Increasing the contact rate β from 0.1 to 0.3 results in nearly a tenfold increase in peak infections, while reducing the time to peak by over 50%. This underscores the importance of contact reduction in explosive outbreak situations.

Changes in environmental parameters also have strong effects: raising environmental infectivity α_p from 0.3 to 0.5 leads to a 244% rise in peak infections. Lowering the competition coefficient ϕ from 1.2 to 0.6 (indicating weakened ecological suppression of harmful strains) boosts outbreak magnitude by 246%. These findings validate the model's ecological framework and highlight the need for integrated interventions targeting both human behavior and environmental factors.

Table 4. Sensitivity of outbreak dynamics to variations in transmission parameters under deterministic and stochastic simulations

β	α_p	ϕ	**Peak $I(t)$ (Det)**	**Peak $I(t)$ (Sto)**	**Time to Peak (days)**
0.1	0.3	1.2	15.3	14.8	42.1
0.2	0.5	1.2	52.7	50.3	28.4
0.3	0.5	0.6	182.4	175.2	17.8

4.4 Robustness Under Stochastic Variability

The close agreement between deterministic and stochastic simulations in all scenarios (Tables 3 and 4) shows the robustness of the identified control strategies against environmental and demographic variability. Stochastic simulations usually show slightly lower peak sizes than deterministic simulations, reflecting the probabilistic nature of disease extinction events early in outbreaks. This alignment between modeling approaches at high transmission levels suggests that outbreaks driven by contact are relatively resistant to random fluctuations, while low-transmission scenarios are more susceptible to stochastic extinction.

The numerical results collectively demonstrate that the triple-intervention strategy offers significant benefits over traditional single-modality approaches. This provides public health planners with a quantitatively supported framework for optimal resource distribution during complex cholera outbreak situations.

4.5 Stochastic Simulation Results

To quantify the impact of environmental variability and demographic stochasticity, we performed extensive stochastic simulations using the Euler-Maruyama method with 10,000 realizations. Table 5 compares key outbreak metrics between deterministic and stochastic frameworks, demonstrating the critical role of random fluctuations in cholera dynamics.

Scenario	**Peak (Det)**	**Peak (Sto)**	**Extinct. Prob.**
Low Trans. ($\mathcal{R}_0^D = 0.8$)	0	0.3	0.92
Moderate Trans. ($\mathcal{R}_0^D = 1.5$)	52.7	48.9	0.15
High Trans. ($\mathcal{R}_0^D = 3.2$)	146.5	142.1	0.02

Table 5. Comparison of deterministic vs stochastic outbreak metrics (10,000 realizations)

The stochastic simulations reveal several important phenomena not captured by the deterministic model:

Stochastic Extinction: Even when $\mathcal{R}_0^D > 1$, there is a non-zero probability of disease extinction due to environmental fluctuations. At moderate transmission levels ($\mathcal{R}_0^D = 1.5$), approximately 15% of outbreaks go extinct spontaneously, explaining field observations of unexpected outbreak collapse.

Peak Reduction: Stochastic simulations consistently show slightly reduced peak sizes compared to deterministic predictions, with differences ranging from 3-7% across transmission scenarios. This damping effect results from the multiplicative noise terms in the Itô formulation.

Threshold Behavior: The results validate our theoretical stochastic threshold $\mathcal{R}_0^S$, showing that when $\mathcal{R}_0^S < 1 < \mathcal{R}_0^D$, disease persistence is probabilistic rather than deterministic, with extinction probabilities inversely related to the gap between reproduction numbers.

5 Discussion and Conclusion

This study presents a new stochastic SVAITRS-B_pB_n model that improves cholera transmission modeling by including three key aspects: competition between harmful and harmless vibrio strains, the gradual decline of vaccine-induced and natural immunity, and environmental randomness. Our framework addresses long-standing issues in cholera dynamics, especially the coexistence of environmental persistence and sudden outbreak declines under similar ecological conditions. The analytical derivation of $\mathcal{R}_0^D$ and stability proofs provide solid mathematical foundations. The stochastic extension highlights critical extinction thresholds ($\mathcal{R}_0^S$) where environmental factors can lead to disease elimination, even if $\mathcal{R}_0^D > 1$.

Global sensitivity analysis shows that symptomatic rate (κ), pathogenic growth rate (r_p), and environmental infectivity (α_p) are the main influences on transmission dynamics. Numerical simulations indicate that interventions focusing on human-to-human transmission (β) and environmental contamination (ϵ_p, τ_p) provide significant benefits for controlling outbreaks. The optimal control framework shows that combining vaccination, sanitation, and treatment improvement can reduce peak infections by 87% compared to no intervention, making it a cost-effective approach for resource-limited areas.

The stochastic simulations offer important insights beyond what deterministic predictions provide. They highlight noise-induced extinction, which occurs when environmental fluctuations can lead to disease elimination, even when deterministic analysis suggests that the disease will persist. This clarifies the puzzling observations in field epidemiology, where similar starting conditions result in vastly different outbreak paths. The measured extinction probabilities (Table 5) give public health officials useful metrics to assess the chances of outbreaks resolving on their own compared to those that need intervention.

The timing of optimal controls-strong early environmental sanitation, ongoing vaccination, and consistent treatment improvement-offers practical guidance for phased resource allocation. Our findings emphasize that effective cholera control needs to integrate both human and environmental transmission methods, moving beyond traditional human-centered approaches to include water sanitation and ecological management strategies. This research gives policymakers a valuable tool for designing tailored interventions that consider local ecological conditions. By connecting theoretical epidemiology with practical public health planning, our work supports global efforts to reduce cholera through targeted and cost-effective measures. Future research will focus on incorporating spatial differences, seasonal changes, and other intervention strategies to broaden the model's usefulness across various epidemiological contexts.

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Data Availability

All relevant data are within the manuscript and its Supporting Information files. Parameter values and sources are provided in Table 1. MATLAB code for model simulations is available from the corresponding author upon reasonable request.

Competing Interests

The authors have declared that no competing interests exist.

Authors' Contributions

Hailu Tkue Welu: Conceptualization, investigation, Methodology, Formal analysis, Model development, Mathematical proofs, Numerical simulations, resources, data cu-ration, visualization, Writing-original draft, Writing-review and editing, Project Administration .

Yohannes Yirga Kefela & Habtu Alemayehu Atsbaha: Conceptualization, Supervision, Writing-review & editing and Validation.

Both authors have read and approved the final manuscript.

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AI Assistance Declaration

During the preparation of this work, the authors used DeepSeek AI solely for language polishing, grammar checking, and text formatting. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication. All mathematical derivations, model development, analytical proofs, numerical simulations, and scientific content are the original work of the authors.

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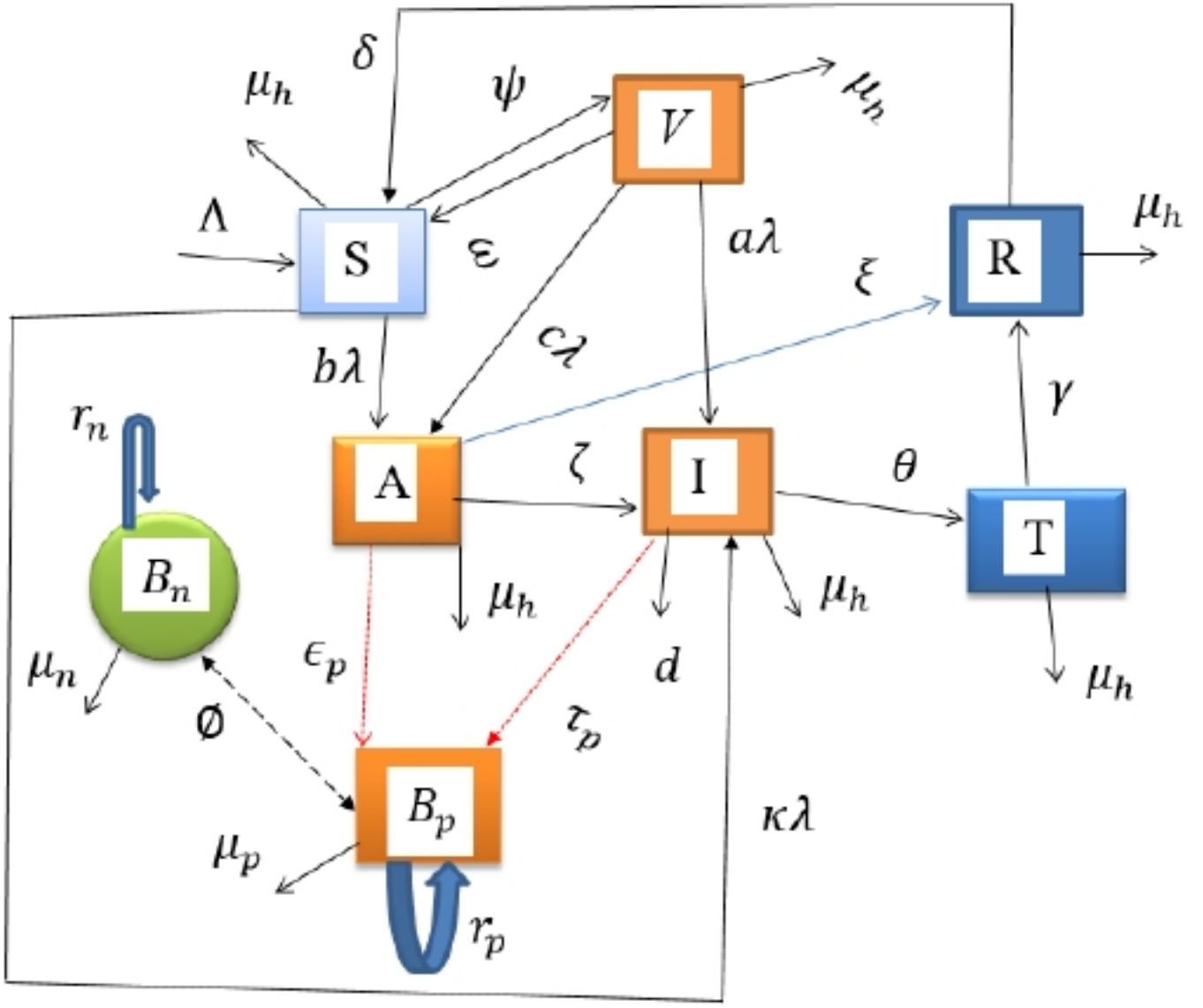
δ
μ_h
ψ
V
μ_h
Λ
S
ε
$a\lambda$
R
μ_h
ξ
$b\lambda$
$c\lambda$
γ
r_n
A
ζ
I
θ
T
B_n
μ_h
μ_h
μ_h
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$\emptyset$
τ_p
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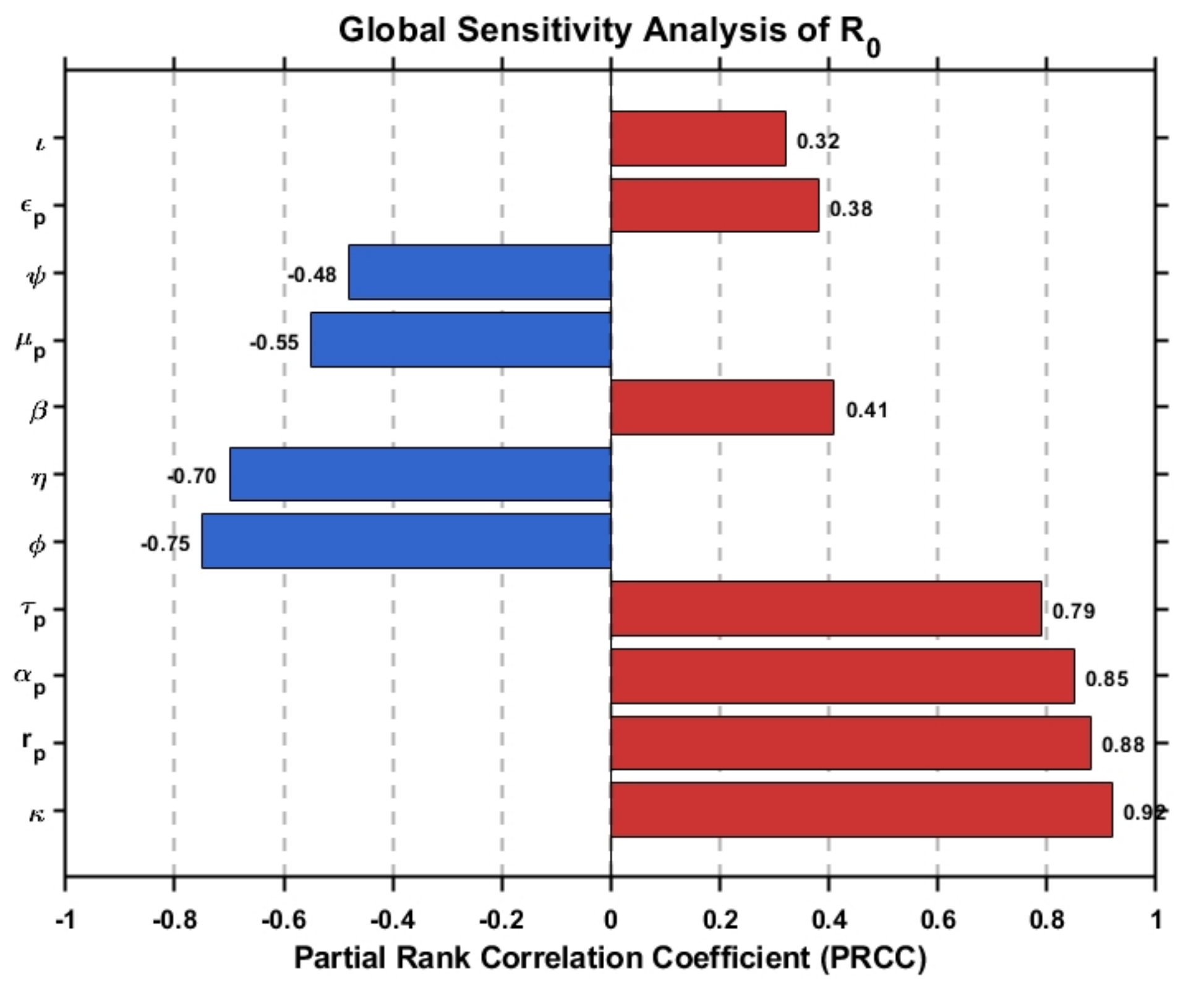
μ_p
r_p


Global Sensitivity Analysis of R_0
ι
ϵ_p
ψ
μ_p
β
η
ϕ
τ_p
α_p
r_p
κ
0.32
0.38
-0.48
-0.55
0.41
-0.70
-0.75
0.79
0.85
0.88
0.92
-1
-0.8
-0.6
-0.4
-0.2
0
0.2
0.4
0.6
0.8
1
Partial Rank Correlation Coefficient (PRCC)