Journal of Mathematical Sciences (2022) 266:675–695
https://doi.org/10.1007/s10958-022-06027-z

MODELLING OF PATHOGENS IMPACT ON THE HUMAN DISEASE TRANSMISSION WITH OPTIMAL CONTROL STRATEGIES

Abdisa Shiferaw Melese[1]

Accepted: 28 July 2022 / Published online: 1 November 2022

Abstract
This study concentrates on a nonlinear deterministic mathematical model for the impact of pathogens on human disease transmission with optimal control strategies. Both pathogen-free and coexistence equilibria are computed. The basic reproduction number R_0, which plays a vital role in mathematical epidemiology, was derived. The qualitative analysis of the model revealed the scenario for both pathogen-free and coexistence equilibria together with R_0. The local stability of the equilibria is established via the Jacobian matrix and Routh-Hurwitz criteria, while the global stability of the equilibria is proven by using an appropriate Lyapunov function. Also, the normalized sensitivity analysis has been performed to observe the impact of different parameters on R_0. The proposed model is extended into optimal control problem by incorporating three control variables, namely, preventive measure variable based on separation of susceptible from contacting the pathogens, integrated vector management based on chemical, biological control, ... etc. to kill pathogens and their carriers, and supporting infective medication variable based on the care of the infected individual in quarantine center. Optimal disease control analysis is examined using Pontryagin minimum principle. Numerical simulations are performed depending on analytical results and discussed quantitatively.

Keywords Modelling · Human pathogens · Stability analysis · Backward bifurcation analysis · Sensitivity analysis · Optimal control

1 Introduction

A human pathogen is a microorganism such as a virus, bacterium, protozoan, or fungus that causes disease in humans. Symptoms such as sneezing, coughing, fever, and vomiting are caused by viruses and bacteria [1]. These pathogens have been a great problem since the beginning of civilization and still continue to cause disease to humans. Nowadays, in a world where modern antibiotics are designed to destroy pathogens, they continue to be a primary source of disease. For example, in 2019, human infections are approximated to cause more than 8 million deaths [2]. Despite the fact that various infectious diseases have been eliminated, new problems such as antibiotic resistance have developed [3]. In combination with investigational studies, mathematical models have importantly valuable in recognizing and analyzing host-pathogen interactions (HPI) and developing optimal treatments [4–7].

✉ Abdisa Shiferaw Melese
abdisa.shiferaw@astu.edu.et

[1] Department of Applied Mathematics, Adama Science and Technology University, Adama, Ethiopia

Malaria is an infectious disease caused by a pathogen called protozoa. It is a vector-borne disease caused by parasites known as *Plasmodium* that are transmitted to people through the bites of infected female *Anopheles mosquitoes* [8]. Typhoid fever is an infectious disease caused by different species of *Salmonella* [9]. "Most of the time, typhoid fever is caused by lack of sanitation where the disease bacteria are transmitted by ingesting contaminated food or water" World Health Organization (WHO), 2003. A mathematical model is formulated and analyzed for the dynamics of water-borne disease transmission [10]. This model is extended by introducing control intervention strategies such as vaccination, treatment, and water purification. The control model is used to determine the possible benefits of these control strategies. Furthermore, the model is proposed and analyzed for the effect of contaminated materials for the spread dynamics of COVID-19 pandemic with self-protection behavior changes [11]. It illustrates that the effects of behavioral social change towards self-protective measures are crucial to stop the transmission of the virus.

There are several mechanisms for some pathogenic organism controls, such as prevention and treatment. For example, washing your hands regularly, cleaning kitchens and bathrooms, staying home when ill, avoiding insect bites, practicing safe sex, keeping up to date with recommended vaccines, and getting medical advice. A common known preventive measure for some viral pathogens is vaccines. For instance, diseases such as measles, mumps, rubella, and influenza have vaccines, whereas diseases such as AIDS, dengue, and chikungunya do not have vaccines available [12, 13]. But, vaccination is an effective control measure against any epidemic, such as the COVID-19 pandemic [14]. According to the WHO, 133 COVID-19 vaccines were in the process during 2020 and four vaccines were approved in March 2021 by Italian and European medicine agencies [15]. Also, Anthrax and pneumococcal vaccines are the vaccines of some bacterial pathogens, but various other bacteria lack vaccines as preventive measures, but infection by such bacteria can be treated by antibiotics such as amoxicillin, ciprofloxacin, and doxycycline.

In view of the above, a nonlinear deterministic mathematical model to investigate the dynamics incorporating human pathogens in the environment and interventions with optimal control is proposed, and also their qualitative analyses using the stability theory of differential equations are established.

The paper is organized as follows. In the "Model formulation" section, we derive a mathematical model. In the "Model analysis" section, we show the details of model analysis. In the "Extension of the model into optimal control" section, we propose an optimal control problem by incorporating control variables. The obtained analytical results are shown through numerical simulations in the "Numerical simulations" section. Conclusion is presented in the "Conclusion" section.

2 Model formulation

The proposed mathematical model consists of two populations: human and vector populations, with the interaction of pathogen concentration in the environmental reservoir. The total population subdivides into six compartments: susceptible human $S_h(t)$, infected human $I_h(t)$, recovered individuals $R_h(t)$, susceptible vector $S_v(t)$, infected vector $I_v(t)$, and pathogen concentration $P(t)$. The susceptible human is recruited into the population at rate φ. It can be infected at rate β_h when it contacts with infected vector. The natural death of the human population is at a rate μ_h. The infected will recover to enter into the recovered compartment at a rate γ. Recovered individuals with loss of immunity at rate δ. Recruitment of vector population with rate π. The susceptible vector can be infected in two ways: through contact with pathogens from the environment at rate β_1 and from infected humans at rate β_2. Natural death of vector population is at rate μ_v. The pathogen induced by infected humans is at rate α and its death rate θ. Some diseases cannot be transmitted from human to human without vectors. For instance, a vector-borne infectious disease like malaria is transmitted from human to human by a mosquito of the genus Anopheles. Based on the above assumptions, mathematical model is described by nonlinear systems of ordinary differential equations:

$$\begin{cases} S_h' = \varphi + \delta R_h - \beta_h I_v S_h - \mu_h S_h, \\ I_h' = \beta_h I_v S_h - (\alpha + \gamma + \mu_h) I_h, \\ R_h' = \gamma I_h - (\delta + \mu_h) R_h, \\ S_v' = \pi - (\beta_1 P + \beta_2 I_h) S_v - \mu_v S_v, \\ I_v' = (\beta_1 P + \beta_2 I_h) S_v - \mu_v I_v, \\ P' = \alpha I_h - \theta P, \end{cases} \tag{1}$$

with initial condition: $S_h(0) > 0, I_h(0) \geq 0, R_h(0) \geq 0, S_v(0) > 0, I_v(0) \geq 0, P(0) \geq 0$.

3 Model analysis

In this section, we study the invariant region, positivity of solutions, pathogen-free and coexistence equilibrium, basic reproduction number, local and global stability of equilibria, sensitivity, and bifurcation analysis of model (1).

3.1 Invariant region

Let us derive an invariant region Ω, in which the solutions of model (1) are bounded. Let $N(t) = S_h(t) + I_h(t) + R_h(t) + S_v(t) + I_v(t) + P(t)$ be the total population. Then differentiating it both sides with respect to time t and adding the equations from the system (1), we get

$$\begin{aligned} N' &= \varphi + \pi - \mu_h S_h - \mu_h I_h - \mu_h R_h - \mu_v S_v - \mu_v I_v - \theta P, \\ &\leq \varphi + \pi - \omega N, \end{aligned} \tag{2}$$

where $\omega = \min\{\mu_h, \mu_v, \theta\}$. By integrating the last inequality of Eq. (2), we obtain

$$N(t) \leq \frac{\varphi + \pi}{\omega} + ce^{-\omega t},$$

where c is constant. As $t \to \infty$, we obtain $0 \leq N(t) \leq \frac{\varphi+\pi}{\omega}$. Thus, the invariant region for the model (1) is given by

$$\Omega = \left\{ (S_h, I_h, S_v, I_v, R_h, P) \in \mathbb{R}_+^6 : 0 \leq S_h + I_h + S_v + I_v + R_h + P \leq \frac{\varphi + \pi}{\omega} \right\} \tag{3}$$

Therefore, the solution set is bounded and the model (1) is epidemiologically meaningful inside Ω.

3.2 Positivity of the solutions

The system (1) under study has non-negative solutions is of vital role. This will be stated as follows.

Theorem 1 Assume that the initial conditions in the model (1) holds. Then the solutions: $S_h(t) > 0$, $I_h(t) \geq 0$, $R_h(t) \geq 0$, $S_v(t) > 0$, $I_v(t) \geq 0$ and $P(t) \geq 0$ for all $t \geq 0$.

Proof From the first equation of model (1), we obtain the expression

$$S_h' \geq -(\beta_h I_v(t) + \mu_h) S_h(t),$$

which gives

$$S_h(t) \geq S_h(0) e^{-\int (\beta_h I_v(t) + \mu_h) dt}.$$

By similar procedure, we show that the positivity of I_h R_h, S_v, I_v, and P so that

$$\begin{aligned} I_h(t) &\geq I_h(0)e^{-(\alpha+\gamma+\mu_h)t}, \\ R_h(t) &\geq R_h(0)e^{-(\delta+\mu_h)t}, \\ S_v(t) &\geq S_v(0)e^{-\int(\beta_1 P(t)+\beta_2 I_h(t)+\mu_v)dt}, \\ I_v(t) &\geq I_v(0)e^{-\mu_v t}, \\ P(t) &\geq P(0)e^{-\theta t}. \end{aligned}$$

Therefore, all the solutions are non-negative for all $t \geq 0$ and so the model (1) is epidemiologically meaningful and well posed in Ω.

3.3 Pathogen-free equilibrium point (PFEP)

The pathogen-free equilibrium of the model is the steady-state solution of system (1) in the absence of the pathogens. To find PFEP, $E_0 = \left(S_h^0, I_h^0, R_h^0, S_v^0, I_v^0, P^0\right)$, we equated the left hand side of model (1) to zero, evaluating at $I_h^0 = 0, I_v^0 = 0, P^0 = 0$ and solving for the non-infected state variables, we get $S_h^0 = \varphi/\mu_h$ and $S_v^0 = \pi/\mu_v$. Hence, PFEP is $E_0 = (\varphi/\mu_h, 0, 0, \pi/\mu_v, 0, 0)$.

3.4 Basic reproduction number

The basic reproduction number R_0 is the average number of secondary infections caused by primary infections when all individuals are susceptible [16, 17]. To obtain the basic reproduction number, we used the next-generation matrix [18, 19]. In epidemiology, the next-generation matrix is a technique used to derive R_0 for a compartmental model with multiple infectious classes discussed in [20]. The model equations are rewritten beginning with newly infective groups:

$$\begin{cases} I_h' &= \beta_h I_v S_h - (\alpha+\gamma+\mu_h)I_h, \\ I_v' &= (\beta_1 P + \beta_2 I_h)S_v - \mu_v I_v, \\ P' &= \alpha I_h - \theta P. \end{cases} \tag{4}$$

The right-hand side of Eq. (4) is decomposed as $u - v$ with

$$u = \begin{bmatrix} \beta_h I_v S_h \\ (\beta_1 P + \beta_2 I_h)S_v \\ 0 \end{bmatrix}, \quad v = \begin{bmatrix} (\alpha+\gamma+\mu_h)I_h \\ \mu_v I_v \\ -\alpha I_h + \theta P \end{bmatrix}.$$

Next, by linearization approach, the associated matrices of u and v at E_0 are given by

$$U = \begin{bmatrix} 0 & \frac{\beta_h \varphi}{\mu_h} & 0 \\ \frac{\beta_2 \pi}{\mu_v} & 0 & \frac{\beta_1 \pi}{\mu_v} \\ 0 & 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \alpha+\gamma+\mu_h & 0 & 0 \\ 0 & \mu_v & 0 \\ -\alpha & 0 & \theta \end{bmatrix}.$$

Then V is an invertible and its inverse is given by

$$V^{-1} = \begin{bmatrix} \frac{1}{\alpha+\gamma+\mu_h} & 0 & 0 \\ 0 & \frac{1}{\mu_v} & 0 \\ \frac{\alpha}{(\alpha+\gamma+\mu_h)\theta} & 0 & \frac{1}{\theta} \end{bmatrix}.$$

The product of U and V^{-1} can be computed as follows.

$$UV^{-1} = \begin{bmatrix} 0 & \frac{\varphi\beta_h}{\mu_h\mu_v} & 0 \\ \frac{\pi\beta_2}{\mu_v(\alpha+\gamma+\mu_h)} + \frac{\pi\alpha\beta_1}{\theta\mu_v(\alpha+\gamma+\mu_h)} & 0 & \frac{\pi\beta_1}{\theta\mu_v} \\ 0 & 0 & 0 \end{bmatrix}.$$

Since the basic reproduction number R_0 is the dominant eigenvalue of the matrix UV^{-1}, then we obtain

$$R_0 = \sqrt{\frac{\pi\varphi\beta_h(\alpha\beta_1 + \theta\beta_2)}{\theta\mu_h\mu_v^2(\alpha+\gamma+\mu_h)}}.$$

3.5 Sensitivity of the basic reproduction number

In this section, we investigate sensitivity analysis of basic reproduction number R_0 with respect to the main parameters. This help us to check and classify parameters which extremely affect R_0 and thus determine an appropriate parameter values to minimize disease from human population. To do this, we follow similar method presented in [21–23].

Definition 1 The definition of normalized forward sensitivity indices of R_0 with respect to g is given by

$$\Delta_g^{R_0} = \frac{\partial R_0}{\partial g} \times \frac{g}{R_0}, \tag{5}$$

where R_0 is a given variable, g is differentiable parameter.

By applying the definition from Eq. (5), normalized forward sensitivity index of R_0 is computed as follows.

$$\begin{aligned}
\Delta_{\varphi}^{R_0} &= \tfrac{1}{2} > 0 \\
\Delta_{\beta_h}^{R_0} &= \tfrac{1}{2} > 0 \\
\Delta_{\pi}^{R_0} &= \tfrac{1}{2} > 0 \\
\Delta_{\beta_1}^{R_0} &= \frac{\alpha\beta_1}{2\alpha\beta_1+2\theta\beta_2} > 0 \\
\Delta_{\beta_2}^{R_0} &= \frac{\theta\beta_2}{2\alpha\beta_1+2\theta\beta_2} > 0 \\
\Delta_{\alpha}^{R_0} &= \tfrac{1}{2}\alpha\left(\frac{\beta_1}{\alpha\beta_1+\theta\beta_2} - \frac{1}{\alpha+\gamma+\mu_h}\right) > 0 \\
\Delta_{\theta}^{R_0} &= -\frac{\alpha\beta_1}{2\alpha\beta_1+2\theta\beta_2} < 0 \\
\Delta_{\mu_h}^{R_0} &= -1 + \frac{\alpha+\gamma}{2(\alpha+\gamma+\mu_h)} < 0 \\
\Delta_{\mu_v}^{R_0} &= -1 < 0 \\
\Delta_{\gamma}^{R_0} &= -\frac{\gamma}{2(\alpha+\gamma+\mu_h)} < 0
\end{aligned}$$

The sensitivity indices of R_0 at parameter values are given in Table 1.
The implication of the main parameters with positive sensitivity index is that R_0 is an increasing (or decreasing) function with respect to an increase (or decrease) in these parameter values. The parameters with negative sensitivity indices, on the other hand, lead to an increase (or decrease) in R_0 value when they are decreased (or increased). From Table 1, those parameters that have positive indices (φ, β_h, π, β_1, β_2, α) show that they have great impact on expanding the disease in the community if their values are increasing. However, those parameters in which their sensitivity indices are negative (θ, μ_h,μ_v, γ) have an effect of reducing pathogens from human population with values increase. Hence, we can eliminate the decrease from human population by decreasing the values of φ, β_h, π, β_1, and β_2, the same time, by increasing the values of α, θ, μ_h,μ_v, and γ. The bar diagram of the sensitivity indices in Table 1 is depicted in Fig. 1.

Table 1 Sensitivity indices and parameters

Model parameters	**Sensitivity indices of** $\mathcal{R}_0$
φ	0.5
β_h	0.5
π	0.5
β_1	0.4911
β_2	0.0089
α	0.0160
θ	−0.4911
μ_h	−0.5226
μ_v	−1
γ	−0.0023

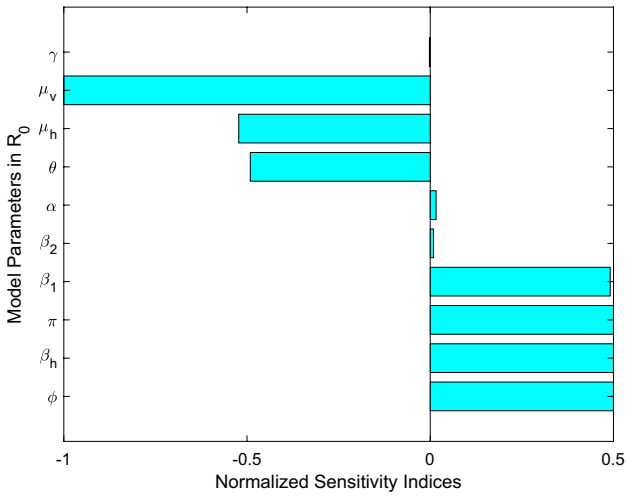


Fig. 1 Normalized sensitivity indices of $\mathcal{R}_0$ with respect to parameters of the model (1). Parameter values are taken from Table 2

3.6 Local stability of pathogen-free equilibrium

In this section, we investigate the local stability of pathogen free equilibrium E_0 based on the basic reproduction number R_0.

Theorem 2 If $R_0 < 1$, then pathogen-free equilibrium $E_0 = (\varphi/\mu_h, 0, 0, \pi/\mu_v, 0, 0)$ of the model (1) is locally asymptotically stable, and otherwise it is unstable in Ω.

Proof By linearizion approach, Jacobian matrix of model (1) at equilibria is given by

$$J = \begin{bmatrix} -(\beta_h I_v + \mu_h) & 0 & \delta & 0 & -\beta_h S_h & 0 \\ \beta_h I_v & -(\alpha+\gamma+\mu_h) & 0 & 0 & \beta_h S_h & 0 \\ 0 & \gamma & -(\delta+\mu_h) & 0 & 0 & 0 \\ 0 & -\beta_2 S_v & 0 & -(\beta_1 P + \beta_2 I_h + \mu_v) & 0 & -\beta_1 S_v \\ 0 & \beta_2 S_v & 0 & \beta_1 P + \beta_2 I_h & -\mu_v & \beta_1 S_v \\ 0 & \alpha & 0 & 0 & 0 & -\theta \end{bmatrix}. \tag{6}$$

The Jacobian matrix J at pathogen-free equilibrium E_0 becomes

$$J(E_0) = \begin{bmatrix} -\mu_h & 0 & \delta & 0 & -\frac{\varphi\beta_h}{\mu_h} & 0 \\ 0 & -(\alpha+\gamma+\mu_h) & 0 & 0 & \frac{\varphi\beta_h}{\mu_h} & 0 \\ 0 & \gamma & -(\delta+\mu_h) & 0 & 0 & 0 \\ 0 & -\frac{\pi\beta_2}{\mu_v} & 0 & -\mu_v & 0 & -\frac{\pi\beta_1}{\mu_v} \\ 0 & \frac{\pi\beta_2}{\mu_v} & 0 & 0 & -\mu_v & \frac{\pi\beta_1}{\mu_v} \\ 0 & \alpha & 0 & 0 & 0 & -\theta \end{bmatrix}. \tag{7}$$

It is clear by considering the first and fourth column eigenvalues are always negative (i.e., $-\mu_h < 0, -\mu_v < 0$), and so stability is controlled by the Jacobian corresponding to the I_h,R_h,I_v and P components:

$$J^* = \begin{bmatrix} -(\alpha+\gamma+\mu_h) & 0 & \frac{\varphi\beta_h}{\mu_h} & 0 \\ \gamma & -(\delta+\mu_h) & 0 & 0 \\ \frac{\pi\beta_2}{\mu_v} & 0 & -\mu_v & \frac{\pi\beta_1}{\mu_v} \\ \alpha & 0 & 0 & -\theta \end{bmatrix}. \tag{8}$$

The characteristic polynomial of Eq. (8) is given by

$$(\lambda+\delta+\mu_h)\left(\lambda^2 + \frac{\mu_h\mu_v(\theta+\mu_v)(\alpha+\gamma+\mu_h) - \pi\varphi\beta_2\beta_h}{\mu_h\mu_v(\alpha+\gamma+\mu_h)}\lambda + \frac{\theta\mu_h\mu_v^2(\alpha+\gamma+\mu_h) - \pi\varphi\beta_h}{\mu_h\mu_v(\alpha+\gamma+\mu_h)}\right) = 0 \tag{9}$$

Next, we obtain $\lambda = -(\lambda+\delta) < 0$, and the other characteristic equation becomes:

$$\lambda^2 + a_1\lambda + a_0 = 0, \tag{10}$$

where

$$\begin{aligned} a_1 &= \frac{\mu_h\mu_v(\theta+\mu_v)(\alpha+\gamma+\mu_h) - \pi\varphi\beta_2\beta_h}{\mu_h\mu_v(\alpha+\gamma+\mu_h)}, \\ a_0 &= \frac{\theta\mu_h\mu_v^2(\alpha+\gamma+\mu_h) - \pi\varphi\beta_h}{\mu_h\mu_v(\alpha+\gamma+\mu_h)}. \end{aligned}$$

The characteristic polynomial in Eq. (10) is degree $n = 2$, then we can find matrices:

$$M1 = \begin{bmatrix} a_{n-1} \end{bmatrix} = \begin{bmatrix} a_1 \end{bmatrix}, \quad M2 = \begin{bmatrix} a_{n-1} & a_{n-3} \\ 1 & a_{n-2} \end{bmatrix} = \begin{bmatrix} a_1 & 0 \\ 1 & a_0 \end{bmatrix}.$$

Applying Routh-Hurwitz criterion [24] on Eq. (10) shows that the two eigenvalues have negative real part, and so E_0 is local asymptotically stable if $a_0 > 0$,a_1 and $a_1a_0 > 0$ for $R_0 < 1$.

3.7 Global stability of pathogen-free equilibrium

Theorem 3 If $R_0 < 1$, then the pathogen-free equilibrium $E_0 = (\varphi/\mu_h,0,0,\pi/\mu_v,0,0)$ of the model (1) is globally asymptotically stable in Ω.

Proof To perform the global stability of E_0, we consider Lyapunov function:

$$V = I_h + R_h + P. \tag{11}$$

The Lyapunov function V needs to satisfy the conditions: $V(S_h,I_h,R_h,S_v,I_v,P) > 0$ for all $(S_h,I_h,R_h,S_v,I_v,P) / \{E_0\}$ and $V(E_0) = 0$. By differentiating V with respect to t, we get

$$\begin{aligned} V' &= I_h' + I_v' + P' \\ &= \left(\frac{\pi\beta_2}{\mu_v} - \gamma - \mu_h\right)I_h + \left(\frac{\varphi\beta_h}{\mu_h} - \mu_v\right)I_v + \left(\frac{\pi\beta_1}{\mu_v} - \theta\right)P \\ &= (K-Q)\begin{bmatrix} I_h \\ I_v \\ P \end{bmatrix} - \begin{bmatrix} \gamma & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}\begin{bmatrix} I_h \\ I_v \\ P \end{bmatrix}, \end{aligned} \tag{12}$$

where the matrices K and Q are given by

$$K = \begin{bmatrix} \frac{\pi\beta_2}{\mu_v} & 0 & 0 \\ 0 & \frac{\varphi\beta_h}{\mu_h} & 0 \\ 0 & 0 & \frac{\pi\beta_1}{\mu_v} \end{bmatrix}, \quad Q = \begin{bmatrix} \mu_h & 0 & 0 \\ 0 & \mu_v & 0 \\ 0 & 0 & \theta \end{bmatrix}.$$

Since $\gamma > 0$, then the last inequality of Eq. (12) can be rewritten as

$$V' \le (K-Q)\begin{bmatrix} I_h \\ I_v \\ P \end{bmatrix}. \tag{13}$$

The eigenvalues of matrix $(K-Q)$ all have negative real parts if $\pi\beta_2/\mu_v < \mu_h$, $\varphi\beta_h/\mu_h < \mu_v$ and $\pi\beta_1/\mu_v < \theta$. Equation (13) is stable only if $R_0 < 1$. As a result, $(I_h, I_v, P) \to (0,\ 0,\ 0)$ as $t \to \infty$. It follows by the comparison approach from [25] that $(I_h, I_v, P) \to (0,\ 0,\ 0)$. Therefore, $(S_h, I_h, R_h, S_v, I_v, P) \to (\varphi/\mu_h, 0, 0, \pi/\mu_v, 0, 0)$ as t approaches infinity, and E_0 is globally asymptotically stable for $R_0 < 1$ in Ω.

3.8 Coexistence equilibrium point (CEP)

We consider a situation in which pathogen persist in the human populations. A coexistence equilibrium point $E^* = (S_h^*, I_h^*, R_h^*, S_v^*, I_v^*, P^*)$ can be computed as follow.

$$\begin{aligned} \varphi + \delta R_h^* - \beta_h I_v^* S_h^* - \mu_h S_h^* &= 0, \\ \beta_h I_v^* S_h^* - (\alpha + \gamma + \mu_h) I_h^* &= 0, \\ \gamma I_h^* - (\delta + \mu_h) R_h^* &= 0, \\ \pi - (\beta_1 P^* + \beta_2 I_h^*) S_v^* - \mu_v S_v^* &= 0, \\ (\beta_1 P^* + \beta_2 I_h^*) S_v^* - \mu_v I_v^* &= 0, \\ \alpha I_h^* - \theta P^* &= 0. \end{aligned} \tag{14}$$

Solving Eq. (14), we obtain $S_h^*, R_h^*, S_v^*, I_v^*$, and P^* in terms of I_h^*:

$$\begin{aligned} S_h^* &= \frac{\varphi}{\mu_h} - \left(\frac{\delta(\alpha+\mu_h)+\mu_h(\alpha+\gamma+\mu_h)}{\mu_h(\delta+\mu_h)}\right)I_h^*, \\ R_h^* &= \frac{\gamma}{\delta+\mu_h} I_h^*, \\ S_v^* &= \frac{\pi\theta\mu_v}{\mu_v(\alpha\beta_1+\theta\beta_2)I_h^* + \theta\mu_v^2}, \\ I_v^* &= \frac{\pi(\alpha\beta_1+\theta\beta_2)I_h^*}{\mu_v(\alpha\beta_1+\theta\beta_2)I_h^* + \theta\mu_v^2}, \\ P^* &= \frac{\alpha}{\theta} I_h^*, \end{aligned} \tag{15}$$

where

$$I_h^* = \frac{\theta\mu_h\mu_v^2(\delta+\mu_h)(\theta\mu_h\mu_v^2(\alpha+\gamma+\mu_h)R_0^4 - \pi\varphi\beta_h(\alpha\beta_1+\theta\beta_2))}{(\pi^2\beta_h^2\varphi(\delta+\mu_h)(\alpha\beta_1+\theta\beta_2) - \theta\mu_h\mu_v^2\pi\gamma\delta\beta_h R_0^2 + \pi\varphi\beta_h\mu_v(\delta+\mu_h)(\alpha\beta_1+\theta\beta_2))(\alpha\beta_1+\theta\beta_2)}.$$

3.9 Local stability of coexistence equilibrium

Theorem 4 If $R_0 > 1$, then the coexistence equilibrium point E^* of model (1) is locally asymptotically stable, and otherwise it is unstable in Ω.

Proof From Eq. (6) the Jacobian matrix J at $E^* = (S_h^*, I_h^*, R_h^*, S_v^*, I_v^*, P^*)$ is given by

$$J(E^*) = \begin{bmatrix} -(\beta_h I_v^* + \mu_h) & 0 & \delta & 0 & -\beta_h S_h^* & 0 \\ \beta_h I_v^* & -(\alpha+\gamma+\mu_h) & 0 & 0 & \beta_h S_h^* & 0 \\ 0 & \gamma & -(\delta+\mu_h) & 0 & 0 & 0 \\ 0 & -\beta_2 S_v^* & 0 & -(\beta_1 P^* + \beta_2 I_h^* + \mu_v) & 0 & -\beta_1 S_v^* \\ 0 & \beta_2 S_v^* & 0 & \beta_1 P^* + \beta_2 I_h^* & -\mu_v & \beta_1 S_v^* \\ 0 & \alpha & 0 & 0 & 0 & -\theta \end{bmatrix}. \tag{16}$$

The eigenvalues of matrix (16) are computed from the following equation.

$$\begin{vmatrix} b_{11}-\lambda & 0 & b_{13} & 0 & b_{15} & 0 \\ b_{21} & b_{22}-\lambda & 0 & 0 & b_{25} & 0 \\ 0 & b_{32} & b_{33}-\lambda & 0 & 0 & 0 \\ 0 & b_{42} & 0 & b_{44}-\lambda & 0 & b_{46} \\ 0 & b_{52} & 0 & b_{54} & b_{55}-\lambda & b_{56} \\ 0 & b_{62} & 0 & 0 & 0 & b_{66}-\lambda \end{vmatrix} = 0 \tag{17}$$

where . $b_{11} = -(\beta_h I_v^* + \mu_h),\ b_{13} = \delta,\ b_{15} = -\beta_h S_h^*,\ b_{21} = \beta_h I_v^*,\ b_{22} = -(\alpha+\gamma+\mu_h),\ b_{25} = \beta_h S_h^*,\ b_{31} = \gamma,$
$b_{33} = -(\delta+\mu_h),\ b_{42} = -\beta_2 S_v^*,\ b_{44} = -(\beta_1 P^* + \beta_2 I_h^* + \mu_v),\ b_{46}$
$= -\beta_1 S_v^*,\ b_{52} = \beta_2 S_v^*,\ b_{54} = \beta_1 P^* + \beta_2 I_h^*,\ b_{55} = -\mu_v,\ b_{56} = \beta_1 S_v^*,\ b_{62} = \alpha,\ b_{66} = \theta$

Then the characteristic polynomial of Eq. (16) is given by

$$\lambda^6 + B_1\lambda^5 + B_2\lambda^4 + B_3\lambda^3 + B_4\lambda^2 + B_5\lambda + B_6 = 0, \tag{18}$$

where

$$\begin{aligned}
B_1 &= -(b_{11}+b_{22}+b_{33}+b_{44}+b_{55}+b_{66}),\\
B_2 &= -b_{22}(b_{33}+b_{44}+b_{55}+b_{66}) - b_{66}(b_{44}+b_{55}) - b_{33}b_{66} - b_{11}(b_{22}+b_{33}+b_{44}\\
&\quad +b_{55}+b_{66}) + b_{33}b_{44} - b_{25}b_{52} + b_{46}b_{54} + b_{33}b_{55} + b_{44}b_{55},\\
B_3 &= b_{22}(b_{44}b_{55} - b_{46}b_{54} + b_{66}(b_{44}+b_{55})) + b_{22}b_{33}(b_{44}+b_{55}+b_{66}) + b_{66}(b_{44}b_{55}\\
&\quad -b_{25}b_{52} - b_{46}b_{54}) + b_{33}b_{66}(b_{44}+b_{55}) - b_{11}(b_{46}b_{54} + b_{25}b_{52} - b_{55}b_{66}\\
&\quad -b_{44}(b_{55}+b_{66}) - b_{22}b_{44} + b_{22}b_{55} + b_{22}b_{66} - b_{33}(b_{22}+b_{44}+b_{55}+b_{66}))\\
&\quad -(b_{13}b_{21}b_{32} + b_{15}b_{21}b_{52} - b_{25}b_{33}b_{52} - b_{25}b_{44}b_{52} + b_{25}b_{42}b_{54} - b_{33}b_{46}b_{54}\\
&\quad +b_{33}b_{44}b_{55} + b_{25}b_{56}b_{62}),\\
B_4 &= -(b_{22}b_{66}(b_{44}b_{55} - b_{46}b_{54}) + b_{22}b_{33}(b_{44}b_{55} - b_{46}b_{54} + b_{66}(b_{44}+b_{55})))\\
&\quad -b_{66}b_{13}b_{21}b_{32} + b_{66}(b_{15}b_{21}b_{52} - b_{44}b_{25}b_{52} + b_{25}b_{42}b_{54}) + b_{33}b_{66}(b_{44}b_{55}\\
&\quad -b_{25}b_{52} - b_{46}b_{54}) + b_{11}(b_{25}b_{42}b_{54} + b_{25}b_{56}b_{62} - b_{66}(b_{25}b_{52} + b_{46}b_{54})\\
&\quad +b_{44}(b_{25}b_{52} - b_{52}b_{66}) - b_{22}b_{46}b_{54} + b_{22}b_{44}b_{55} + b_{66}(b_{22}b_{44} + b_{22}b_{55})\\
&\quad -b_{33}(b_{46}b_{54} + b_{25}b_{52} - b_{55}b_{66} - b_{44}(b_{55}+b_{66}) - b_{22}b_{44} + b_{22}b_{55} + b_{22}b_{66}))\\
&\quad -b_{13}b_{21}b_{32}b_{44} - b_{15}b_{21}b_{33}b_{52} - b_{15}b_{21}b_{44}b_{52} - b_{25}b_{33}b_{44}b_{52} + b_{15}b_{21}b_{42}b_{54}\\
&\quad -b_{25}b_{33}b_{42}b_{54} - b_{13}b_{21}b_{32}b_{55} + b_{15}b_{21}b_{56}b_{62} - b_{15}b_{33}b_{56}b_{62} - b_{25}b_{44}b_{56}b_{62},\\
B_5 &= -[b_{22}b_{33}b_{66}(b_{44}b_{55} - b_{46}b_{54}) + b_{66}b_{13}b_{21}b_{32}(b_{44}+b_{55}) + b_{66}(b_{15}b_{21}b_{42}b_{54}\\
&\quad -b_{44}b_{15}b_{21}b_{52}) - b_{33}b_{66}(b_{15}b_{21}b_{52} - b_{44}b_{25}b_{52} + b_{25}b_{42}b_{54}) - b_{11}(b_{66}b_{25}b_{42}b_{54}\\
&\quad +b_{44}(b_{25}b_{56}b_{62} - b_{25}b_{52}b_{66}) + b_{66}(b_{22}b_{44} + b_{22}b_{55})) + b_{15}b_{21}b_{33}b_{44}b_{52}\\
&\quad -b_{15}b_{21}b_{33}b_{42}b_{54} - b_{13}b_{21}b_{32}b_{44}b_{55} + b_{13}b_{21}b_{44}b_{55} - b_{15}b_{21}b_{33}b_{44}b_{62}\\
&\quad +b_{25}b_{33}b_{44}b_{56}b_{62}],\\
B_6 &= -[b_{66}b_{13}b_{21}b_{32}(b_{46}b_{54} - b_{44}b_{55}) - b_{33}b_{66}(b_{15}b_{21}b_{42} - b_{44}b_{15}b_{21}b_{52})\\
&\quad +b_{11}b_{33}(b_{66}b_{25}b_{42}b_{54} + b_{44}(b_{25}b_{56}b_{52} - b_{25}b_{52}b_{66})) - b_{15}b_{21}b_{33}b_{44}b_{56}b_{62}].
\end{aligned}$$

Using the Routh-Hurwitz criterion [24], the coexistence equilibrium E^* is locally asymptotically stable for $R_0 > 1$ if $B_i > 0$, $i = 1,2,\cdot,6$,

$$
\begin{aligned}
&B_1 > 0,\ \ B_1B_2 - B_3 > 0,\ \ B_1(B_2B_3 - B_1B_4) - B_3^2 + B_5B_1 > 0,\\
&B_1B_2(B_3B_4 - B_2B_5) - B_1^2(B_4^2 - B_2B_6) + B_1(B_4B_5 - B_3B_6) - B_5 + B_4(B_3^2 - B_1B_5) > 0,\\
&B_1B_6B_2(B_3B_4 - B_1B_5) - B_1B_6(B_4^2 - B_1B_6) - B_1B_5B_2(B_3B_4 - B_2B_5) + B_1^2B_5(B_4^2 -\\
&B_2B_6) - B_1B_5(B_4B_5 - B_3B_6) - B_6B_3(B_3B_4 - B_1B_5) + B_6B_1B_3B_5 + B_5B_3(B_4^2 - B_2B_5) - B_5^2(B_1B_4 - B_5) > 0,\\
&B_1B_6^2B_2(B_3^2 - B_1B_5) - B_1^2B_6^2(B_3B_4 - B_2B_5) + B_1^2B_5B_6(B_4^2 - B_2B_6) - B_1B_5B_6(B_4B_5 - B_3B_6) -\\
&B_6^2B_3(B_3^2 - B_1B_5) + B_6^2B_1B_3B_5 + B_5B_6B_3(B_3B_4 - B_2B_3) - B_5B_6B_1B_4B_5 + B_5^2B_6 > 0.
\end{aligned}
$$

3.10 Global stability of coexistence equilibrium

Theorem 5 If $R_0 > 1$, then the coexistence equilibrium E^* of the model (1) is globally asymptotically stable in Ω.

Proof To establish the global stability of the coexistence equilibrium point $E^*=(S_h^*, I_h^*, R_h^*, S_v^*, I_v^*, P^*)$, we consider Lyapunov function:

$$
V = \epsilon_1\frac{(S_h - S_h^*)^2}{2} + \epsilon_2\frac{(I_h - I_h^*)^2}{2} + \epsilon_3\frac{(R_h - R_h^*)^2}{2} + \epsilon_4\frac{(S_v - S_v^*)^2}{2} + \epsilon_5\frac{(I_v - I_v^*)^2}{2} + \epsilon_6\frac{(P - P^*)^2}{2}, \tag{19}
$$

where ϵ_1, ϵ_2, ϵ_3, ϵ_4, ϵ_5, $\epsilon_6 > 0$ are to be chosen appropriately such that

$$
\begin{aligned}
\epsilon_1 &= \tfrac{S_h}{(\beta_h I_v + \mu_h)S_h - \varphi - \delta R_h},\\
\epsilon_2 &= \tfrac{I_h}{(\alpha+\gamma+\mu_h)I_h - \beta_h I_v S_h},\\
\epsilon_3 &= \tfrac{R_h}{(\delta+\mu_h)R_h - \gamma I_h},\\
\epsilon_4 &= \tfrac{S_v}{(\beta_1 P + \beta_2 I_h + \mu_v)S_v - \pi},\\
\epsilon_5 &= \tfrac{I_v}{\mu_v I_v - (\beta_1 P + \beta_2 I_h)S_v},\\
\epsilon_6 &= \tfrac{P}{\theta P - \alpha I_h}.
\end{aligned}
$$

The Lyapunov function V needs to satisfy the conditions: $V(S_h,I_h,R,S_v,I_v,P) > 0$ for all $(S_h,I_h,R,S_v,I_v,P) / \{E^*\}$ and $V(E^*) = 0$. Applying derivative of V with respect to t, we find that

$$
V' = (S_h - S_h^*)S_h' + (I_h - I_h^*)I_h' + (R_h - R_h^*)R_h' + S_v - S_v^*)S_v' + (I_v - I_v^*)I_v' + (P - P^*)P' \tag{20}
$$

By substituting corresponding equations of the model (1) into Eq. (20), we obtain that

$$
\begin{aligned}
V' &= \epsilon_1(S_h - S_h^*)[\varphi + \delta R_h - \beta_h I_v S_h - \mu_h S_h] + \epsilon_2(I_h - I_h^*)[\beta_h I_v S_h - (\alpha + \gamma + \mu_h)I_h]\\
&+ \epsilon_3(R_h - R_h^*)[\gamma I_h - (\delta + \mu_h)R_h] + \epsilon_4(I_v - I_v^*)[\pi - (\beta_1 P + \beta_2 I_h)S_v - \mu_v S_v]\\
&+ \epsilon_5(R_h - R_h^*)[(\beta_1 P + \beta_2 I_h)S_v - \mu_v I_v] + \epsilon_6(P - P^*)[\alpha I_h - \theta P].
\end{aligned}
$$

Next, rearranging this equation, we obtain

$$
\begin{aligned}
V' &= \epsilon_1(S_h - S_h^*)\left\{\tfrac{\varphi}{S_h} + \tfrac{\delta R_h}{S_h} - \beta_h I_v - \mu_h\right\}\{S_h - S_h^*\} + \epsilon_2(I_h - I_h^*)\left\{\tfrac{\beta_h I_v S_h}{I_h} - \alpha - \gamma - \mu_h\right\}\{I_h - I_h^*\}\\
&+ \epsilon_3(R_h - R_h^*)\left\{\tfrac{\gamma I_h}{R_h} - \delta - \mu_h\right\}\{R_h - R_h^*\} + \epsilon_4(S_v - S_v^*)\left\{\tfrac{\pi}{S_v} - \beta_1 P - \beta_2 I_h - \mu_v\right\}\{S_v - S_v^*\}\\
&+ \epsilon_5(I_v - I_v^*)\left\{\tfrac{(\beta_1 P + \beta_2 I_h)S_v}{I_v} - \mu_v\right\}\{I_v - I_v^*\} + \epsilon_6(P - P^*)\left\{\tfrac{\alpha I_h}{P} - \theta\right\}\{P - P^*\},\\
&= -\epsilon_1(S_h - S_h^*)^2[-\tfrac{\varphi}{S_h} - \tfrac{\delta R_h}{S_h} + \beta_h I_v + \mu_h] - \epsilon_2(I_h - I_h^*)^2[-\tfrac{\beta_h I_v S_h}{I_h} + \alpha + \gamma + \mu_h]\\
&- \epsilon_3(R_h - R_h^*)^2[-\tfrac{\gamma I_h}{R_h} + \delta + \mu_h] - \epsilon_4(S_v - S_v^*)^2[-\tfrac{\pi}{S_v} + \beta_1 P + \beta_2 I_h + \mu_v]\\
&- \epsilon_5(I_v - I_v^*)^2[-\tfrac{(\beta_1 P + \beta_2 I_h)S_v}{I_v} + \mu_v] - \epsilon_6(P - P^*)^2[-\tfrac{\alpha I_h}{P} + \theta].
\end{aligned}
$$

Thus, $V'(S_h, I_h, R, S_v, I_v, P) \leq 0$ and a coexistence equilibrium point E^* is globally asymptotically stable with possible setting ϵ_1, ϵ_2, ϵ_3, ϵ_4, ϵ_5, ϵ_6. Hence, the maximum compact invariant set in $\{(S_h, I_h, R, S_v, I_v, P) \in \Omega : V' = 0\}$ is the singleton E^*. Therefore, by LaSalle's invariant principle [26], as $t \to \infty$, all the solutions of the system (1) approaches E^* in Ω for $R_0 > 1$.

3.11 Backward bifurcation analysis

We investigated the existence of bifurcation analysis at $R_0 = 1$ by the concept of center manifold theory [27]. Then the next theorem can be obtained.

Theorem 6 If $R_0 < 1$, then the model (1) shows that backward bifurcation at $R_0 = 1$.

Proof Using center manifold theory [27], we perform back bifurcation analysis of system (1) at $R_0 = 1$. Let us consider change of variables: $S_h = x_1$, $I_h = x_2$, $R_h = x_3$, $S_v = x_4$, $I_v = x_5$, $P = x_6$. Then the model (1) can be rewritten in the form $X' = (f_1, f_2, f_3, f_4, f_5, f_6)^T$ as:

$$\begin{cases} x_1' = \varphi + \delta x_3 - \beta_h x_5 x_1 - \mu_h x_1, \\ x_2' = \beta_h x_5 x_1 - (\alpha + \gamma + \mu_h) x_2, \\ x_3' = \gamma x_2 - (\delta + \mu_h) x_3, \\ x_4' = \pi - (\beta_1 x_6 + \beta_2 x_2) x_4 - \mu_v x_4, \\ x_5' = (\beta_1 x_6 + \beta_2 x_2) x_4 - \mu_v x_5, \\ x_6' = \alpha x_2 - \theta x_6, \end{cases} \tag{21}$$

Let us use the contact rate β_h as bifurcation coefficient at $R_0 = 1$ if

$$\beta_h = \beta_h^* = \frac{\theta \mu_h \mu_v^2 (\alpha + \gamma + \mu_h)}{\pi \varphi (\alpha \beta_1 + \theta \beta_2)}. \tag{22}$$

By linearization method, Jacobian matrix of (21) at pathogen-free equilibrium E_0 is obtained:

$$J(E_0) = \begin{bmatrix} -\mu_h & 0 & \delta & 0 & -\frac{\varphi \beta_h^*}{\mu_h} & 0 \\ 0 & -(\alpha + \gamma + \mu_h) & 0 & 0 & \frac{\varphi \beta_h^*}{\mu_h} & 0 \\ 0 & \gamma & -(\delta + \mu_h) & 0 & 0 & 0 \\ 0 & -\frac{\pi \beta_2}{\mu_v} & 0 & -\mu_v & 0 & -\frac{\pi \beta_1}{\mu_v} \\ 0 & \frac{\pi \beta_2}{\mu_v} & 0 & 0 & -\mu_v & \frac{\pi \beta_1}{\mu_v} \\ 0 & \alpha & 0 & 0 & 0 & -\theta \end{bmatrix}. \tag{23}$$

The right eigenvector, $u = (u_1, u_2, u_3, u_4, u_5, u_6)^T$ are computed from $Ju = 0$ as follows.

$$Ju = \begin{cases} -\mu_h u_1 + \delta u_3 - \frac{\varphi \beta_h^*}{\mu_h} u_5 = 0 \\ -(\alpha + \gamma + \mu_h) u_2 + \frac{\varphi \beta_h^*}{\mu_h} u_5 = 0, \\ \gamma u_2 - (\delta + \mu_h) u_3 = 0, \\ -\frac{\pi \beta_2}{\mu_v} u_2 - \mu_v u_4 + \frac{\pi \beta_1}{\mu_v} u_6 = 0, \\ \frac{\pi \beta_2}{\mu_v} u_2 - \mu_v u_5 + \frac{\pi \beta_1}{\mu_v} u_6 = 0, \\ \alpha u_2 - \theta u_6 = 0. \end{cases} \tag{24}$$

Next, from Eq. (24), we get

$$\begin{aligned} u_1 &= \frac{\theta}{\alpha+\mu_h}\left(\frac{\delta\gamma}{\delta+\mu_h} - \alpha - \gamma - \mu_h\right)u_6, \\ u_2 &= \frac{\theta}{\alpha}u_6, \\ u_3 &= \frac{\gamma\theta}{\alpha(\delta+\mu_h)}u_6, \\ u_4 &= \frac{\pi}{\mu_v}\left(\beta_1 - \frac{\beta_2\theta}{\alpha}\right)u_6, \\ u_5 &= \frac{\pi}{\mu_v^2}\left(\frac{\beta_2\theta}{\alpha} + \beta_1\right)u_6, \end{aligned}$$

where $u_6 = u_6 > 0$. Also the left eigenvector, $v = (v_1, v_2, v_3, v_4, v_5, v_6)$ are computed from $vJ = 0$ as follows.

$$vJ = \begin{cases} -\mu_h v_1 = 0 \\ -(\alpha+\gamma+\mu_h)v_2 + \gamma v_3 - \frac{\pi\beta_2}{\mu_v}v_4 + \frac{\pi\beta_2}{\mu_v}v_5 + \alpha v_6 = 0, \\ \delta v_1 - (\delta+\mu_h)v_3 = 0, \\ -\mu_v v_4 = 0, \\ -\frac{\varphi\beta_h^*}{\mu_h}v_1 + \frac{\varphi\beta_h^*}{\mu_h}v_2 - \mu_v v_5 = 0, \\ -\frac{\pi\beta_1}{\mu_v}v_4 + \frac{\pi\beta_1}{\mu_v}v_5 - \theta v_6 = 0. \end{cases} \tag{25}$$

Solving (25) and then we obtain

$$v_1 = v_3 = v_4 = 0,\ v_2 = \frac{\mu_h\mu_v}{\varphi\beta_h^*}v_5,\ v_6 = \frac{\pi\beta_1}{\theta\mu_v}v_5,$$

where $v_5 = v_5 > 0$. Based on [27], the bifurcation coefficients a and b are given by

$$\begin{aligned} a &= \sum_{i,j,k=1}^{6} v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0), \\ b &= \sum_{i,k=1}^{6} v_k u_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_h^*}(E_0). \end{aligned} \tag{26}$$

The nonzero second partial derivatives of f_1, f_2, f_4, and f_5 at E_0 are given as follows:

$$\begin{aligned} \frac{\partial^2 f_1}{\partial x_1 \partial x_5} &= \frac{\partial^2 f_1}{\partial x_5 \partial x_1} = -\beta_h^*, \\ \frac{\partial^2 f_2}{\partial x_1 \partial x_5} &= \frac{\partial^2 f_2}{\partial x_5 \partial x_1} = \beta_h^*, \\ \frac{\partial^2 f_4}{\partial x_2 \partial x_4} &= \frac{\partial^2 f_4}{\partial x_4 \partial x_2} = -\beta_2, \\ \frac{\partial^2 f_4}{\partial x_4 \partial x_6} &= \frac{\partial^2 f_4}{\partial x_6 \partial x_4} = -\beta_1, \\ \frac{\partial^2 f_5}{\partial x_2 \partial x_4} &= \frac{\partial^2 f_5}{\partial x_4 \partial x_2} = \beta_2, \\ \frac{\partial^2 f_5}{\partial x_4 \partial x_6} &= \frac{\partial^2 f_5}{\partial x_6 \partial x_4} = \beta_1, \\ \frac{\partial^2 f_1}{\partial x_5 \partial \beta_h^*} &= \frac{\partial^2 f_1}{\partial \beta_h^* \partial x_5} = x_1^* = -\frac{\varphi}{\mu_h}, \\ \frac{\partial^2 f_2}{\partial x_5 \partial \beta_h^*} &= \frac{\partial^2 f_2}{\partial \beta_h^* \partial x_5} = x_1^* = \frac{\varphi}{\mu_h}. \end{aligned} \tag{27}$$

All the others second partial derivatives of f_i, $i = 1,...,6$ are zero. By using Eq. (25), we get

$$\begin{aligned} a &= 2v_1u_1u_5\frac{\partial^2 f_1}{\partial x_1\partial x_5} + 2v_2u_1u_5\frac{\partial^2 f_2}{\partial x_1\partial x_5} + 2v_4u_2u_4\partial^2 f_4\partial x_2\partial x_4 + 2v_4u_2u_6\frac{\partial^2 f_4}{\partial x_2\partial x_6} + 2v_5u_2u_4\frac{\partial^2 f_5}{\partial x_2\partial x_4} \\ &+ 2v_5u_4u_6\frac{\partial^2 f_5}{\partial x_4\partial x_6} \\ &= \left(-\frac{\mu_h\mu_v\theta^2((\delta+\mu_h)(\alpha+\mu_h)+\gamma\mu_h)}{\varphi\alpha(\alpha+\mu_h)(\delta+\mu_h)} + \frac{\pi(\alpha^2\beta_1^2-\theta^2\beta_2^2)}{\mu_v\alpha^2}\right)u_6^2v_5, \end{aligned} \tag{28}$$

and

$$\begin{aligned} b &= 2v_1u_5\frac{\partial^2 f_1}{\partial x_5\partial\beta_h^*} + 2v_2u_5\frac{\partial^2 f_2}{\partial x_5\partial\beta_h^*} \\ &= \frac{\pi}{\mu_v\beta_h^*}\left(\frac{\theta\beta_2}{\alpha}+\beta_1\right)u_6v_5. \end{aligned} \tag{29}$$

The coefficients a and b are evaluated at the parameter values so that $a = 0.1998u_6^2v_5 > 0$ and $b = 0.1677u_6v_5 > 0$ for $u_6 > 0$ and $v_5 > 0$. Therefore, the model (1) has a backward bifurcation with stable coexistence equilibrium when $R_0 < 1$.

4 Extension of the model into optimal control

In this section, we extend the model (1) into optimal control problem by including control variables. This helped us to choose appropriate control strategies that used to eliminate pathogens from human populations at the end of control strategy implemented. The following three control strategies are introduced.

(i) Prevention: personal and environmental sanitation. By this case, we aimed to separate susceptible human population from pathogens contact.
(ii) Integrated vector management: using chemical, biological control, ...etc. to kill pathogens and their carriers.
(iii) Diagnosis and treatment: supporting infected individuals in isolation center with medication.

At time t, $u_1(t)$, $u_2(t)$, and $u_3(t)$ denote prevention, integrated vector management, and treatment control variables, respectively. After incorporating those controls into the model (1), we obtain the corresponding state system:

$$\begin{cases} S_h' = \varphi + \delta R_h - (1-u_1)\beta_h I_v S_h - \mu_h S_h, \\ I_h' = (1-u_1)\beta_h I_v S_h - (\alpha+\gamma+\mu_h)I_h, \\ R_h' = \gamma I_h - (\delta+\mu_h)R_h, \\ S_v' = \pi - (\beta_1 P + (1-u_2)\beta_2 I_h)S_v - \mu_v S_v, \\ I_v' = (\beta_1 P + (1-u_2)\beta_2 I_h)S_v - \mu_v I_v, \\ P' = \alpha I_h - (1+u_3)\theta P, \end{cases} \tag{30}$$

with initial condition: $S_h(0) > 0, I_h(0) \geq 0, R_h(0) \geq 0, S_v(0) > 0, I_v(0) \geq 0$, $P(0) \geq 0$.
The objective function J is given as similar form presented in [28] as follows.

$$J(u_1(.),\ u_2(.),\ u_3(.)) = \underset{u_1, u_2, u_3}{min} \int_0^{t_f} \left(a_1I_h + a_2I_v + a_3P + \frac{1}{2}\sum_{i=1}^{3} b_iu_i^2\right)dt, \tag{31}$$

where t_f is the final time, while a_i, $b_i > 0$. The term $0.5b_1u_1^2$, $0.5b_2u_2^2$, and $0.5b_3u_3^2$ represent cost functions which are corresponding to the control u_1, u_2, and u_3, respectively. The objective of this study is to find the optimal control set $(u_1^*,\ u_2^*,\ u_3^*)$ such that

$$J(u_1^*,\ u_2^*,\ u_3^*) = min\left\{J(u_1,\ u_2,\ u_3) :\ u_i \in U\right\}, \tag{32}$$

where

$$U = \left\{u(t) = (u_1(t),\ u_2(t),\ u_3(t)) : 0 \le u_i(t) \le 1,\ 0 \le t \le t_f,\ i = 1,2,3\right\}.$$

4.1 Characterization of the optimal control function

Pontryagin's minimum principle [29] helps to reduces problems (30)–(32) to a problem of minimizing the Hamiltonian H given by

$$H = J' + \lambda_1 S_h' + \lambda_2 I_h' + \lambda_3 R_h' + \lambda_4 S_v' + \lambda_5 I_v' + \lambda_6 P'. \tag{33}$$

That is,

$$\begin{aligned} H(\Phi, u, \lambda) &= a_1 I_h + a_2 I_v + a_3 P + \frac{1}{2}\sum_{i=1}^{3} b_i u_i^2 + \lambda_1(\varphi + \delta R_h - (1-u_1)\beta_h I_v S_h - \mu_h S_h) \\ &+ \lambda_2((1-u_1)\beta_h I_v S_h - (\alpha+\gamma+\mu_h)I_h) + \lambda_3(\gamma I_h - (\delta+\mu_h)R_h) \\ &+ \lambda_4(\pi - (\beta_1 P + (1-u_2)\beta_2 I_h)S_v - \mu_v S_v) + \lambda_5((\beta_1 P + (1-u_2)\beta_2 I_h)S_v - \mu_v I_v) \\ &+ \lambda_6(\alpha I_h - (1+u_3)\theta P), \end{aligned} \tag{34}$$

where $\Phi = (S_h, I_h, R_h, S_v, I_v, P)$ which is state variables.
Based on [30], if the control u^* and corresponding state Φ^* are an optimal pair, there is a non-zero adjoint vector $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6)$ such that

$$\begin{cases} \Phi' = \frac{\partial H(\Phi,u,\lambda)}{\partial \lambda}, \\ \lambda' = -\frac{\partial H(\Phi,u,\lambda)}{\partial \Phi}, \\ \frac{\partial H(\Phi,u,\lambda)}{\partial u} = 0. \end{cases} \tag{35}$$

From the boundedness of u_i^* on [0,1] and the third equation of Eq. (35) (i.e., minimality condition), we have

$$\begin{cases} u_i^* = 0, & \frac{\partial H}{\partial u_i} > 0, \\ 0 < u_i^* < 1, & \frac{\partial H}{\partial u_i} = 0, \\ u_i^* = 1, & \frac{\partial H}{\partial u_i} < 0. \end{cases}$$

To obtain the adjoint variables λ_i, $i = 1,...,6$, we follow the classical result of [29]. So the following theorem can be established.

Theorem 7 Let u^* be the solution to the optimal control problem Eqs. (30)–(32) and $(S_h^*, I_h^*, R_h^*, S_v^*, I_v^*, P^*)$ be the corresponding optimal state variables. Then there exist adjoint variables λ_i, $i = 1,...,6$ that satisfy the adjoint system:

$$\begin{cases} \lambda_1' = \lambda_1((1-u_1)\beta_h I_v + \mu_h) - \lambda_2(1-u_1)\beta_h I_v, \\ \lambda_2' = -a_1 + \lambda_2(\alpha+\gamma+\mu_h) - \lambda_3\gamma + \lambda_4(1-u_2)\beta_2 S_v - \lambda_5(1-u_2)\beta_2 S_v, \\ \lambda_3' = -\lambda_1\delta + \lambda_3(\delta+\mu_h), \\ \lambda_4' = \lambda_4(\beta_1 P + (1-u_2)\beta_2 I_h + \mu_v) - \lambda_5(\beta_1 P + (1-u_2)\beta_2 I_h), \\ \lambda_5' = -a_2 + \lambda_1(1-u_1)\beta_h S_h - \lambda_2(1-u_1)\beta_h S_h + \lambda_5\mu_v, \\ \lambda_6' = -a_3 + \lambda_4\beta_1 S_v - \lambda_5\beta_1 S_v + \lambda_6(1+u_3)\theta. \end{cases} \tag{36}$$

Together with transversality condition: $\lambda_i(t_f) = 0$, $i = 1,...,6$.
Also, we get optimal controls: $u_1^*(t)$, $u_2^*(t)$, and $u_3^*(t)$ which are characterized by

$$\begin{aligned} u_1^*(t) &= \min\left\{\max\left\{0, \frac{(\lambda_2-\lambda_1)\beta_h I_v S_h}{b_1}\right\}, 1\right\}, \\ u_2^*(t) &= \min\left\{\max\left\{0, \frac{(\lambda_5-\lambda_4)\beta_2 I_h S_v}{b_2}\right\}, 1\right\}, \\ u_3^*(t) &= \min\left\{\max\left\{0, \frac{\theta P \lambda_6}{b_3}\right\}, 1\right\}. \end{aligned} \tag{37}$$

Proof We find that the adjoint equations by taking the negative of $\partial H/\partial(S_h,I_h,R_h,S_v,I_v,P)$ as follows. That is,

$$\begin{cases} \lambda_1' = -\frac{\partial H}{\partial S_h} = \lambda_1((1-u_1)\beta_h I_v + \mu_h) - \lambda_2(1-u_1)\beta_h I_v, \\ \lambda_2' = -\frac{\partial H}{\partial I_h} = -a_1 + \lambda_2(\alpha+\gamma+\mu_h) - \lambda_3\gamma + \lambda_4(1-u_2)\beta_2 S_v - \lambda_5(1-u_2)\beta_2 S_v, \\ \lambda_3' = -\frac{\partial H}{\partial R_h} = -\lambda_1\delta + \lambda_3(\delta+\mu_h), \\ \lambda_4' = -\frac{\partial H}{\partial S_v} = \lambda_4(\beta_1 P + (1-u_2)\beta_2 I_h + \mu_v) - \lambda_5(\beta_1 P + (1-u_2)\beta_2 I_h), \\ \lambda_5' = -\frac{\partial H}{\partial I_v} = -a_2 + \lambda_1(1-u_1)\beta_h S_h - \lambda_2(1-u_1)\beta_h S_h + \lambda_5\mu_v, \\ \lambda_6' = -\frac{\partial H}{\partial P} = -a_3 + \lambda_4\beta_1 S_v - \lambda_5\beta_1 S_v + \lambda_6(1+u_3)\theta. \end{cases}$$

We assume that $S_h(t_f)$, $I_h(t_f)$, $R_h(t_f)$, $S_v(t_f)$, $I_v(t_f)$, and $P(t_f)$ are free, then we obtain the transversality condition: $\lambda_i(t_f) = 0$. We find that the optimal controls $u_1^*(t)$, $u_2^*(t)$, and $u_3^*(t)$ from the third equation of (27) as follows.

$$\begin{aligned} \frac{\partial H}{\partial u_1} &= b_1 u_1 + (\lambda_1-\lambda_2)\beta_h I_v S_h = 0 \Rightarrow u_1^*(t) = \frac{(\lambda_2-\lambda_1)\beta_h I_v S_h}{b_1}, \\ \frac{\partial H}{\partial u_2} &= b_2 u_2 + (\lambda_4-\lambda_5)\beta_2 I_h S_v = 0 \Rightarrow u_2^*(t) = \frac{(\lambda_5-\lambda_4)\beta_2 I_h S_v}{b_2}, \\ \frac{\partial H}{\partial u_3} &= b_3 u_3 - \theta P \lambda_6 = 0 \qquad\qquad \Rightarrow u_3^*(t) = \frac{\theta P \lambda_6}{b_3}. \end{aligned}$$

Since u_i^* is bounded on [0,1], then $u_i^*(t)$ can be written in compact form as (37).

The second partial derivative of Hamiltonian H with respect to (u_1,u_2,u_3) at (u_1^*, u_2^*, u_3^*) is positive definite. This shows that the optimal control (u_1^*, u_2^*, u_3^*) is a minimizer.

5 Numerical simulations

In this section, we provide numerical simulations obtained from the application of analytical results, as given in previous sections. The state system (30) with the impact of controls: preventive measure (u_1), integrated vector management (u_1), and supporting infective by medication (u_3) on human population is illustrated numerically. Since the optimal system under investigation is a two point boundary value problem with separated boundary conditions at times $t = 0$ and $t = t_f$, we use the forward-backward iterative scheme [31].

In order to find numerical solutions of the optimality system, first the state system (30) is computed forward with the given initial condition and controls' initial guess in time by using a Runge-Kutta method of fourth order. Next, the adjoint system (36) is computed backward with the transversality condition in time by using Runge-Kutta algorithm of fouth order. Each control variable value is modified by averaging the new value and old value arising from the characteristic control (37). This step continues many times upto successive iterations are close enough to each other [31].

To study the behavior of the model (1), we performed numerical simulations with the set of parameter values and initial data, which are assumed for illustrative purposes. Accordingly, parameters values are given in Table 2, and with initial data: $S_h(0) = 6$, $I_h(0) = 4$, $R_h(0) = 1$, $S_v(0) = 2$, $I_h(0) = 2$, $P(0) = 1$.

To achieve optimal control strategies, the weight constants of the objective function are assumed: $a_1 = 600$, $a_2 = 80$, $a_3 = 40$, $b_1 = 6$, $b_2 = 100$, $b_3 = 80$ and the adjoint system with terminal condition: $\lambda_i(t_f) = 0$, $i = 1,\ldots,6$ for the final implementation time $t_f = 50$ months. So that those strategies are given below:

Table 2 Description of model parameters and their values

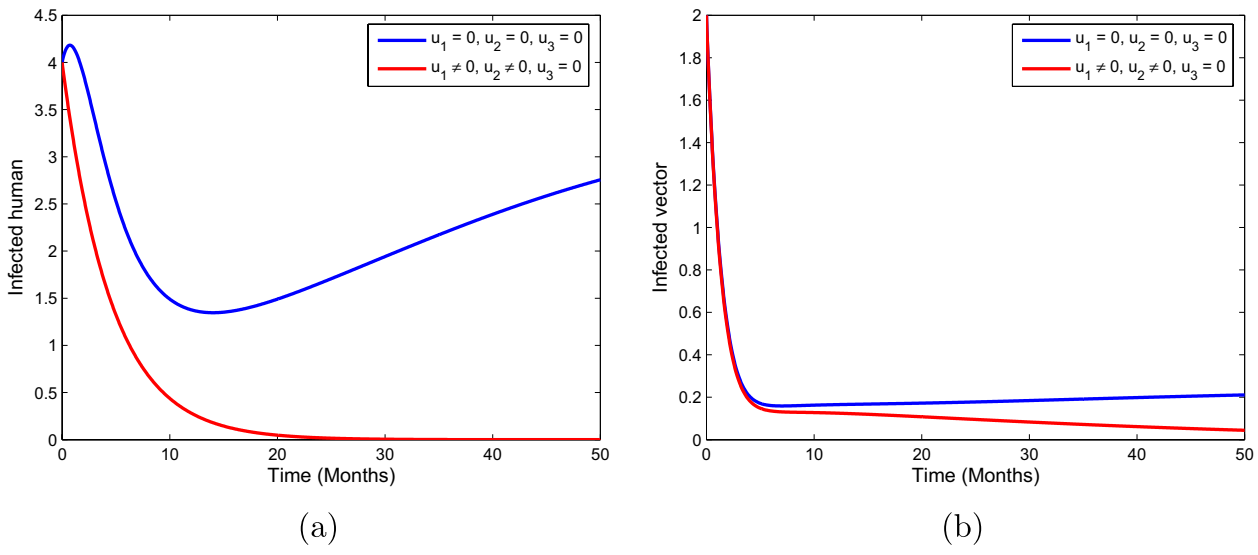
Parameters	Description	Values
φ	Recruitment rate of human population	0.99
β_h	Contact rate of susceptible with infected human	0.12
β_1	Primary contact rate of susceptible vector with infected human	0.21
β_2	Secondary contact rate of susceptible vector with pathogen	0.02
μ_h	Natural death rate of human	0.01
γ	Induced mortality rate by infected human	0.001
δ	Recovered individuals rate	0.85
α	Induced rate of pathogens by infected human	0.21
π	Recruitment rate of vector population	0.3
θ	Decay rate of pathogens	0.04
μ_v	Natural death rate of vector	0.98

- Strategy A: $u_1 \neq 0$, $u_2 \neq 0$ and $u_3 = 0$.
- Strategy B: $u_1 \neq 0$, $u_3 \neq 0$ and $u_2 = 0$.
- Strategy C: $u_2 \neq 0$, $u_3 \neq 0$ and $u_1 = 0$.
- Strategy D: $u_1 \neq 0$, $u_2 \neq 0$ and $u_3 \neq 0$.

In the simulations, we present that the infected human and vector population with control and without control. The blue curve represents the uncontrolled population case while the red curve shows the controlled population.

5.1 Strategy A: Control strategy with preventive measures and integrated vector management

In Fig. 2, we present that the infected human and infected vector population with control ($u_1 \neq 0$, $u_2 \neq 0$, $u_3 = 0$) and without control (i.e., $u_1 = u_2 = u_3 = 0$). The simulation results from Fig. 2a shows that infected human goes to zero due to control u_1 is at a maximum level for 50 months (Fig. 3a). Therefore, applying this control strategy is effective to eradicate disease from the population with minimum cost 1.5813×10^4 (Fig. 3).



(a) (b)

Fig. 2 Impact of preventive measures and integrated vector management on human (**a**) and vector (**b**) population

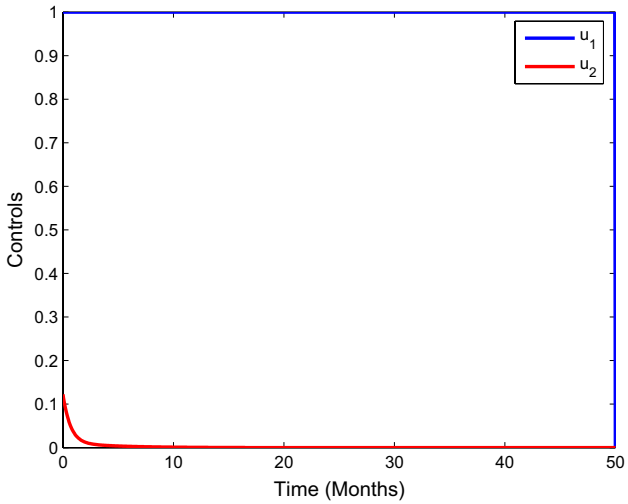


Fig. 3 Profile of control functions (u_1, u_2) when $u_3 = 0$

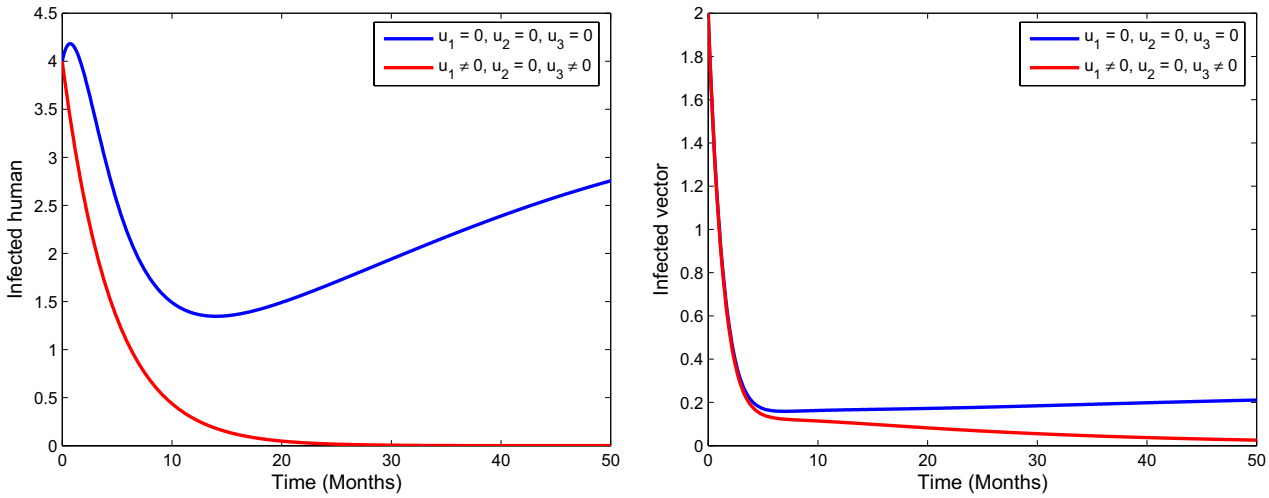


Fig. 4 Impact of preventive measures and supporting infectives by medication human (**a**) and vector (**b**) population

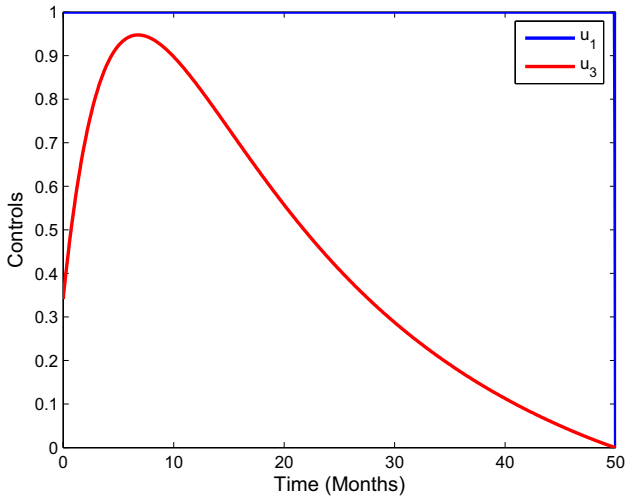


Fig. 5 Profile of control functions (u_1, u_3) when $u_2 = 0$

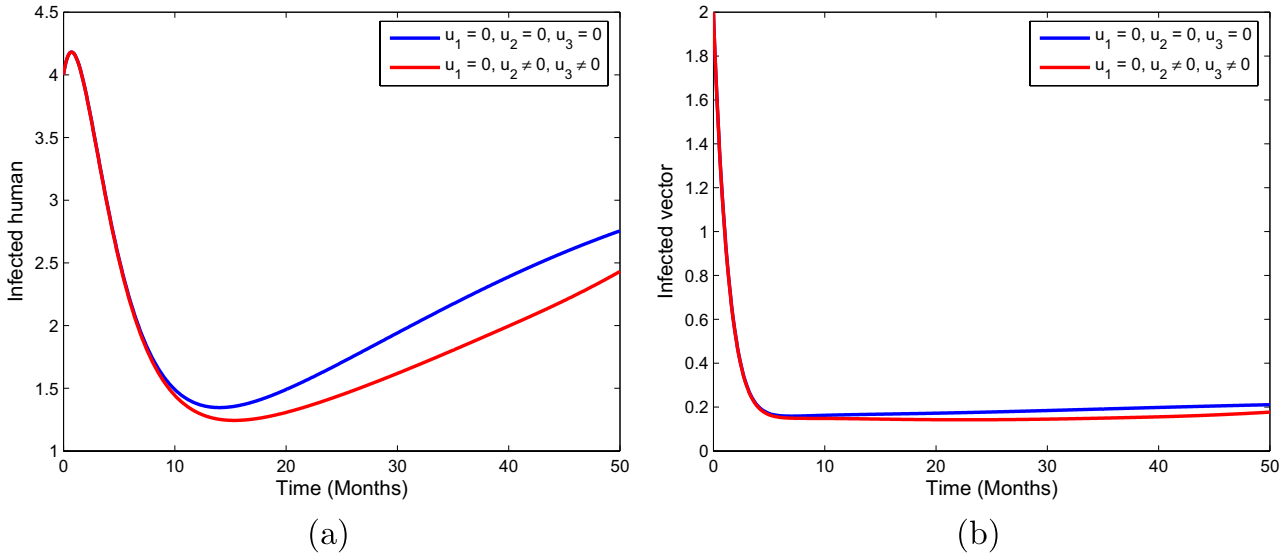
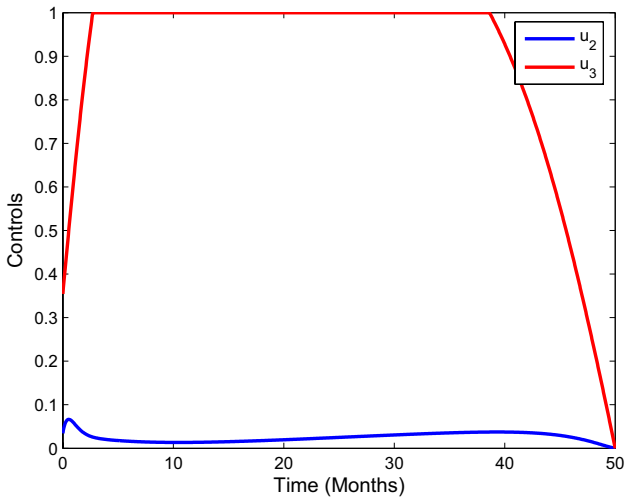


Fig. 6 Impact of integrated vector management and supporting infectives by medication on human (**a**) and vector (**b**) population

Fig. 7 Profile of control functions (u_2, u_3) when $u_1 = 0$



5.2 Strategy B: Control strategy with preventive measures and supporting infectives by medication

Figure 4a and b show that infected human and infected vector decrease. To achieve this, the control profiles u_1 and u_3 are implemented at a maximum rate for the whole period. The control u_1 is at a maximum level for 50 months, but u_2 declines after 10 months toward zero (Fig. 5).

5.3 Strategy C: Control strategy with integrated vector management and supporting infectives by medication

We observe that from Fig. 6a and b, infected human and infected vector population do not approach to zero at end of strategy. The control u_3 is at a maximum level for 40 months and declines afterwards to zero (Fig. 7). Hence, only the

control strategy with integrated vector management and supporting infectives by medication are not enough for pathogen control.

5.4 Strategy D: Control strategy with all controls

In this case, we discuss how all controls affect the pathogen spread in the human population. Figure 8a and b show that infected human and infected vector approach to zero at the end the period. Furthermore, Fig. 8c shows that the number of pathogen decreases at the end of the strategy. Hence, applying this control strategy is the best effective to eradicate pathogen from the system at end of 50 months.
From Fig. 9, we observe that control u_1 is at a maximum level for 50 months, but u_3 declines after 10 months toward zero.

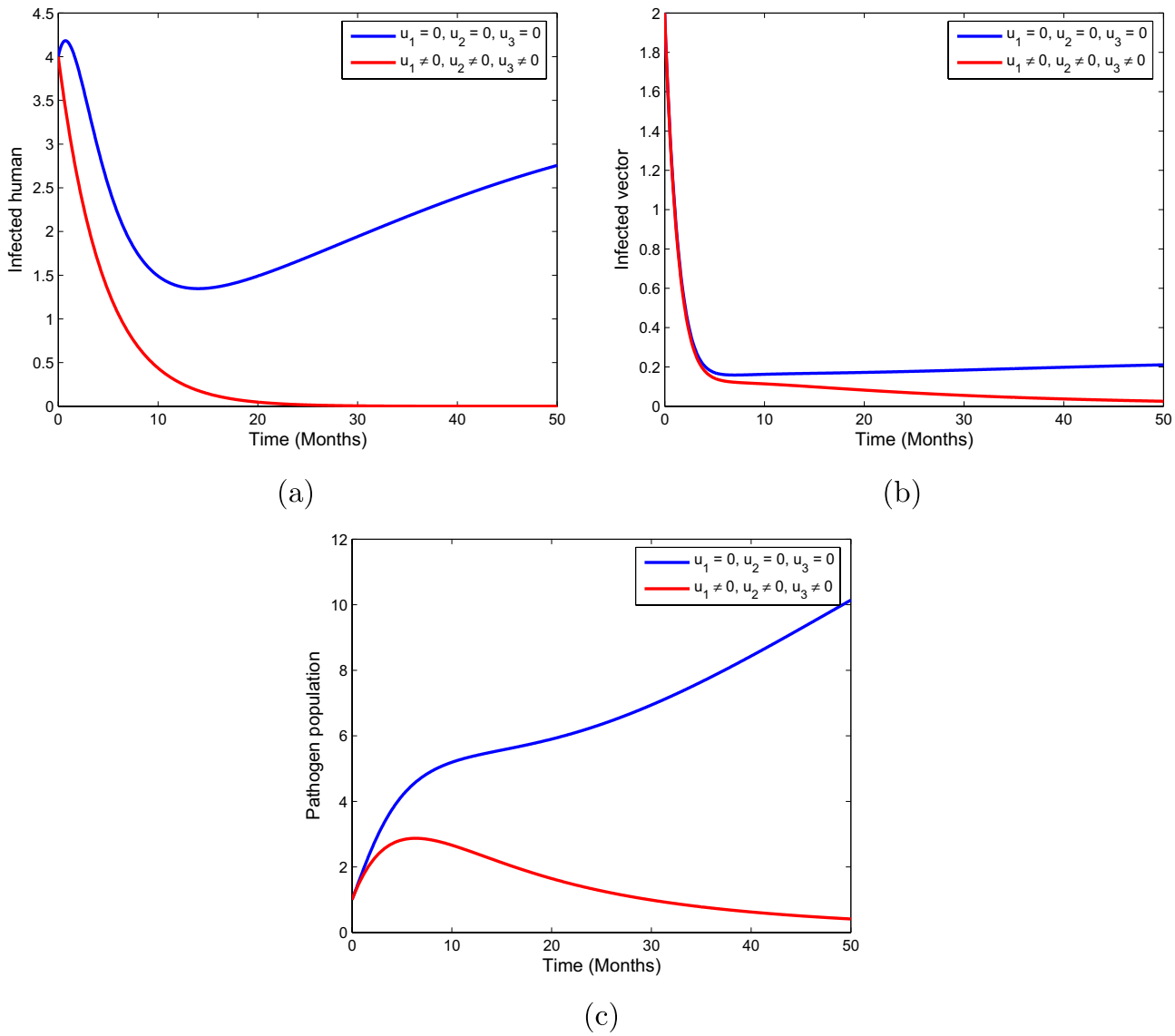


Fig. 8 Impact of all controls on human (**a**), vector (**b**), and pathogen (**c**) population

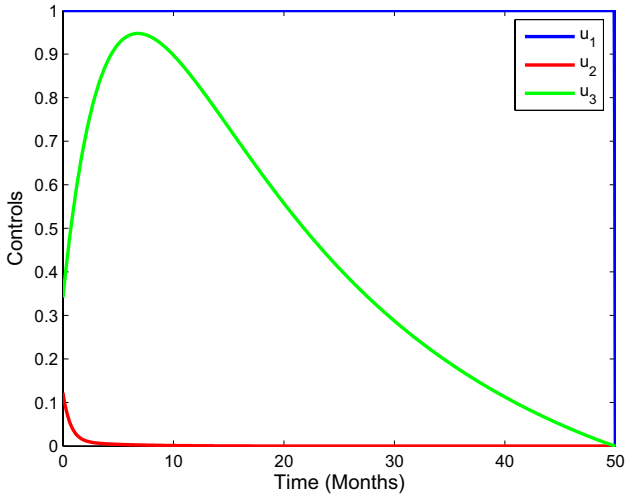


Fig. 9 Profile of control functions (u_1, u_2, u_3) when $u_1 \neq 0$, $u_2 \neq 0$, $u_3 \neq 0$

6 Conclusion

In this paper, an optimal control theory was applied to the pathogens' impact on human disease transmission model governed by a system of nonlinear ordinary differential equations. Then it was analyzed for equilibrium points, which are locally and globally proved by Routh-Hurwitz criterion and Lyapunov function, respectively. The results of the model reveal that when the basic reproductive number, R_0 is greater than unity (for instance, $R_0 = 4.3415$), more pathogens are highly spread in the environment, as well as in human population. Thus, in order to reduce more pathogens from the systems, the proposed model is extended into optimal control problems by incorporating three control variables such as u_1, u_2, and u_3. The Hamiltonian function and adjoint variables are investigated. The necessary optimality condition is formulated and analyzed by using Pontryagin's minimum principle. The simulation results showed that the combined effect of prevention via personal and environmental sanitation, integrated vector management, and continuous supervision during the treatment period helps to reduce the pathogen in the community. Therefore, the results of this study show that the optimal control is sufficient to decrease pathogen from the human population at the end of the fifth month.

Acknowledgements The author thanks Adama Science and Technology University for its hospitality and support during this work.

Data availability No data were used to support this study.

Declarations

Competing interests The author declares no competing interests.

REFERENCES

1. Alberts, B., Johnson, A., Lewis, J., Raff, M., Roberts, K., Walter, P.: (2002). Introduction to pathogens. *In Molecular Biology of the Cell. 4th edition*, Garland Science.
2. Organization, W.H., et al: (2018) Mortality and global health estimates: Causes of death; projections for 2015-2030; projection of death rates.
3. Ventola, C. L.: (2015). The antibiotic resistance crisis: part 1: causes and threats. *Pharmacy and Therapeutics*, 40(4), 277–283.
4. Kwuimy, C. A. K., Tewa, J. J., Nyabadza, F., Bildik, N.: (2015). Computational and theoretical analysis of human diseases associated with infectious pathogens. *BioMed Research International*, 2.
5. Blickensdorf, M., Timme, S., Figge, M. T.: (2019). Comparative assessment of aspergillosis by virtual infection modeling in murine and human lung. *Frontiers in Immunology*, 10, 142.

6. Duhring, S., Germerodt, S., Skerka, C., Zipfel, P. F., Dandekar, T., Schuster, S.: (2015). Host-pathogen interactions between the human innate immune system and Candida albicans-understanding and modeling defense and evasion strategies. *Frontiers in Microbiology*, 6, 625.
7. Schleicher, J., Conrad, T., Gustafsson, M., Cedersund, G., Guthke, R., Linde, J.: (2017). Facing the challenges of multiscale modelling of bacterial and fungal pathogen-host interactions. *Briefings in Functional Genomics*, 16(2), 57–69.
8. Traore, B., Sangare, B., Traore, S.: (2017). A mathematical model of malaria transmission with structured vector population and seasonality. *Journal of Applied Mathematics*, 2017.
9. World Health Organization: "Typhoid fever fact sheet," 2000, http://www.who.int/mediacentre/factsheets/.
10. Collins, O. C., Duffy, K. J.: (2018). Analysis and optimal control intervention strategies of a waterborne disease model: A realistic case study. *Journal of Applied Mathematics*, 2018.
11. Mekonen, K. G., Balcha, S. F.: (2020). Modeling the effect of contaminated objects for the transmission dynamics of COVID-19 pandemic with self protection behavior changes. *Results in Applied Mathematics*, 100134.
12. Orenstein, W. A., Bernier, R. H., Dondero, T. J., Hinman, A. R., Marks, J. S., Bart, K. J., Sirotkin, B.: (1985). Field evaluation of vaccine efficacy. *Bulletin of the World Health Organization*, 63(6), 1055.
13. "List of Vaccines: CDC".: www.cdc.gov. 2019-04-15. Retrieved 2019-11-06.
14. Khan, A. A., Ullah, S., Amin, R.: (2022). Optimal control analysis of COVID-19 vaccine epidemic model: a case study. *The European Physical Journal Plus*, 137(1), 1–25.
15. Giordano, G., Colaneri, M., Di Filippo, A., Blanchini, F., Bolzern, P., De Nicolao, G., Bruno, R.: (2021). Modeling vaccination rollouts, SARS-CoV-2 variants and the requirement for non-pharmaceutical interventions in Italy. *Nature Medicine*, 27(6), 993–998.
16. Diekmann, O., Heesterbeek, J. A. P., Metz, J. A.: (1990). On the definition and the computation of the basic reproduction ratio R 0 in models for infectious diseases in heterogeneous populations. Journal of *Mathematical Biology*, 28(4), 365–382.
17. Khan, M. A., Wahid, A., Islam, S., Khan, I., Shafie, S., Gul, T.: (2015). Stability analysis of an SEIR epidemic model with nonlinear saturated incidence and temporary immunity. *International Journal of Advances in Applied Mathematics and Mechanics*, 2(3), 1–14.
18. Van den Driessche, P., Watmough, J.: (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences,* 180(1-2), 29–48.
19. Ghosh, M., Olaniyi, S., Obabiyi, O. S.: (2020). Mathematical analysis of reinfection and relapse in malaria dynamics. *Applied Mathematics and Computation*, 373, 125044.
20. Heffernan, J. M., Smith, R. J., Wahl, L. M.: (2005). Perspectives on the basic reproductive ratio. *Journal of the Royal Society Interface*, 2(4), 281–293.
21. Chitnis, N., Cushing, J. M., Hyman, J. M.: (2006). Bifurcation analysis of a mathematical model for malaria transmission. *SIAM Journal on Applied Mathematics*, 67(1), 24–45.
22. Iddi, A. J., Massawe, E.S., Makinde, O.D.: (2012). Modelling the impact of infected immigrants on vector-borne diseases with direct transmission. *ICASTOR Journal of Mathematical Sciences*, 6(2), 143–157.
23. Makinde, O. D., Okosun, K. O.: (2011). Impact of chemo-therapy on optimal control of malaria disease with infected immigrants. *BioSystems*, 104(1), 32–41.
24. Mojeeb, A., Osman, E., Isaac, A. k.: (2017). Simple mathematical model for malaria transmission. *Journal of Advances in Mathematics and Computer Science*, 25(6), 1–24.
25. Diekmann, O., Heesterbeek, J. A. P., Metz, J. A.: (1990). On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28(4), 365–382.
26. La Salle, J. P.: (1976). *The stability of dynamical systems*. Society for Industrial and Applied Mathematics.
27. Castillo-Chavez, C., Song, B.: (2004). Dynamical models of tuberculosis and their applications. *Mathematical Biosciences & Engineering*, 1(2), 361.
28. Takaidza, I., Makinde, O. D., Okosun, O. K.: (2017). Computational modelling and optimal control of Ebola virus disease with non-linear incidence rate. *In Journal of Physics: Conference Series*, 818(1), 012003.
29. Pontryagin, L. S., Boltyanskij, V. G., Gamkrelidze, R. V., Mishchenko, E. F.: (1962). *The Mathematical Theory of Optimal Processes*, John Wiley & Sons. New York.
30. Pang, L., Ruan, S., Liu, S., Zhao, Z., Zhang, X.: (2015). Transmission dynamics and optimal control of measles epidemics. *Applied Mathematics and Computation*, 256, 131–147.
31. Lenhart, S., Workman, J. T.: (2007). *Optimal control applied to biological models*, 274. CRC Press.