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Modelling the dynamics of Pine Wilt Disease with asymptomatic carriers and optimal control

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Pine wilt disease is a lethal tree disease caused by nematodes carried by pine sawyer beetles. Once affected, the trees are destroyed within a few months, resulting in significant environmental and economic losses. The role of asymptomatic carrier trees in the disease dynamics remains unclear. We developed a mathematical model to investigate the effect of asymptomatic carriers on the long-term outcome of the disease. We performed a stability and sensitivity analysis to identify key parameters and used optimal control to examine several intervention options. Our model shows that, with the application of suitable controls, the disease can be eliminated in the vector population and all tree populations except for asymptomatic carriers. Of the possible controls (tree injection, elimination of infected trees, insecticide spraying), we determined that elimination of infected trees is crucial. However, if the costs of insecticide spraying increase, it can be supplemented (although not replaced entirely) by tree injection, so long as some spraying is still undertaken.

Among the vector-borne diseases of trees and plants, the most destructive are a red ring disease of palms and Pine Wilt Disease (PWD), whose causative agent is pine wood nematodes (PWNs)[1]. The vector for PWD is the pine sawyer beetle, which transfers nematodes to healthy host pine trees and usually kills host trees within a few months of infection. The lack of resin exudation of bark wounds become visible as a first symptom. The foliage become pale green in the second stage, yellow in the third stage and finally become reddish brown when the trees fail to resist against the disease. It is well-established that PWD has three different transmission paths: the first happens during maturation feeding[2]; the second during oviposition of the mature female on recently cut, dying, or dead pine trees through the oviposition wounds[3]; and the third is horizontal transmission, which happens during mating[4].

A number of epidemiological studies have been carried out to investigate the transmission dynamics of pine wilt disease[5–8]. These models investigating the spread and control of PWD are used to describe the host–vector interaction between nematode-carrying pine sawyers and pine trees. Lee[9] presented an epidemiological model of PWD and developed optimal-control strategies for the prevention of PWD. Khan *et al.*[10] introduced a dynamical model of PWD and investigates the stability of the disease with saturated incidence rate. They classified the total host tree size into three states: susceptible, exposed and infected host pine trees, while the vector size was also classified into three similar states. Ozair[11] included horizontal transmission and nonlinear incidence. The global stability of PWD in a model with nonlinear incidence rates was analyzed by Lee[5]. Optimal control has been used to study a variety of infectious disease[12–16], including plant diseases[17–19].

Asymptomatic carrier cases can play a critical role in the subsequent spread of PWD[20]. Asymptomatic infection increases the density of infected vectors, which further increases the level of infection in the host. Studies on asymptomatic infection in pine trees show that asymptomatic infected trees may remained infected for up to a year and may ultimately die[21]. Mathematical models that address pine tree dynamics with asymptomatic infections have previously been considered[22,23]. The effect of asymptomatic infection on neighboring trees has also been studied[20].

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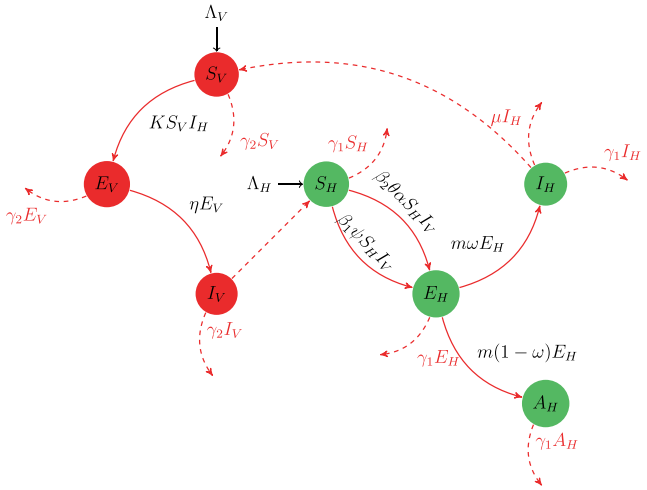

Figure 1. Flow chart for the transmission of PWD. The short dashed arrows indicate the natural and the disease-specific death rates in each compartment. The long dashed arrows represent the interaction between the vector and pine trees. The long solid arrows represent the transition between compartments due to disease. The short solid arrows represent the recruitment.

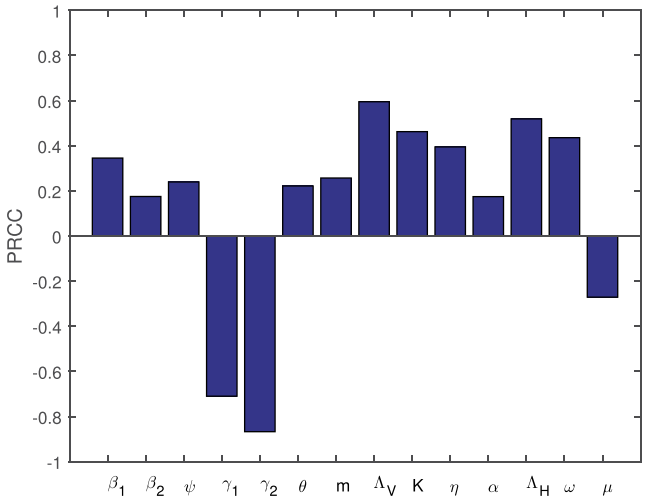

Figure 2. Sensitivity of R_0 to all input parameters.

Here, we develop a dynamic model of PWD incorporating an asymptomatic carrier class and examine control policies that minimize implementation costs while protecting forests from the disease. To the best of our knowledge, none of the previous mathematical studies used optimal control to explore the transmission dynamics of the PWD in the presence of the asymptomatic carriers.

Model formulation

The total host (pine wood trees) and vector (beetles) are represented by $N_H(t)$ and $N_V(t)$, respectively. $N_H(t)$ is further classified into four epidemiological classes: susceptible pine trees $S_H(t)$, exposed pine trees $E_H(t)$, asymptomatic carrier pine trees $A_H(t)$ and infected pine trees $I_H(t)$. $N_V(t)$ is classified into three epidemiological classes: susceptible beetles $S_V(t)$, exposed beetles $E_V(t)$ and infected beetles $I_V(t)$.

The recruitment rates of host trees and beetles are represented, respectively, by Λ_H and Λ_V, while the natural death rates of host pine trees and vector beetles are denoted by γ_1 and γ_2, and the disease mortality rate of host pine trees is represented by μ. Here, m and η are the respective rates of progression from the exposed class to the infected class in the host and vector populations. The term $\beta_1\psi S_H I_V$ denotes the incidence rate, where β_1 is the rate of transmission and ψ is the average number of daily contacts with vector adult beetles during maturation. β_2 is the rate at which an infected beetle transmits a nematode through oviposition, with the average number of oviposition contacts per day denoted by θ. The termination of oleoresin exudation in susceptible trees without infection of nematode is denoted by α. We thus interpret $\beta_2\theta\alpha$ as the transmission through oviposition, and hence $\beta_2\theta\alpha S_H I_V$ represents the number of new infections. A fraction ω $(0 \leq \omega \leq 1)$ of the exposed tree class

Parameter	Interpretation	Values	References
β_1	transmission probability during maturation	0.0016600 day^{-1}	[29]
β_2	transmission probability of nematode through oviposition	0.0004000 day^{-1}	[29]
ψ	contacts averagely made during maturation per day	0.2000000 day^{-1}	[30]
γ_1	natural death rate of host pine trees	0.0000301 day^{-1}	[31]
γ_2	natural death rate of vector beetles	0.0011764 day^{-1}	[32]
θ	contacts averagely made during oviposition per day	0.0023000 day^{-1}	assumed
m	progression rate of pine trees from E_H to I_H	0.0133000 day^{-1}	assumed
Λ_V	recruitment rate of susceptible vector	0.0132652 day^{-1}	assumed
K	the rate at which the adult beetles carry PWN when they escape from dead trees	0.00305 day^{-1}	[33]
η	progression rate of vectors from E_V to I_V	0.0100000 day^{-1}	assumed
α	probability that host susceptible cease oleoresin exudation without infected by the nematode	0.0032000 day^{-1}	assumed
Λ_H	recruitment rate of host trees	0.0020210 day^{-1}	assumed
ω	rate of symptomatic cases	0.1000000	assumed
μ	transfer rate from E_V to I_V	0.0022000 day^{-1}	assumed

Table 1. Parameter interpretations and their sample values used in numerical simulations.

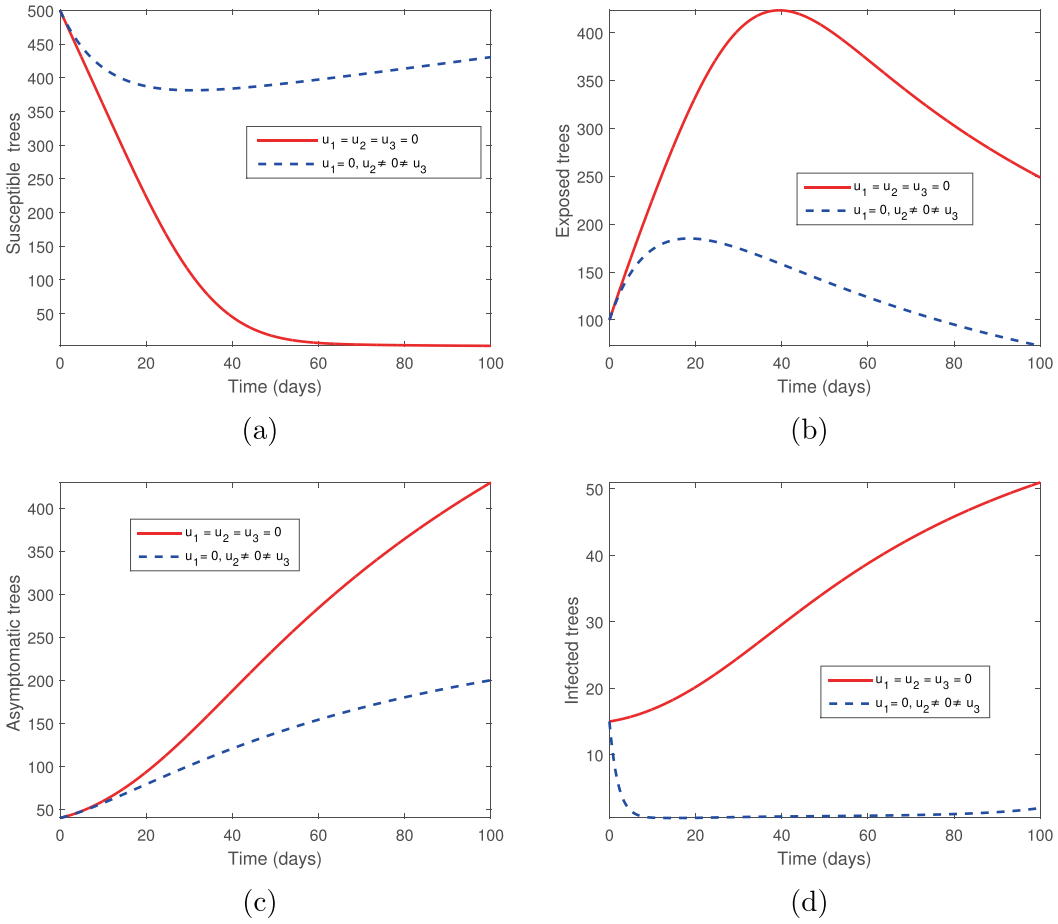

Figure 3. The behaviour of the pine-tree population for the controls u_2 and u_3; (**a**) Susceptible pine trees, (**b**) Exposed pine trees, (**c**) Asymptomatic pine trees, (**d**) Infected pine trees.

generates symptomatic infection, while the remaining fraction $(1-\omega)$ generates asymptomatic infection. The vector incidence rate is given by the term KI_HS_V[15]. The schematic diagram for the PWD model is shown in Fig. 1.

The model is thus given by

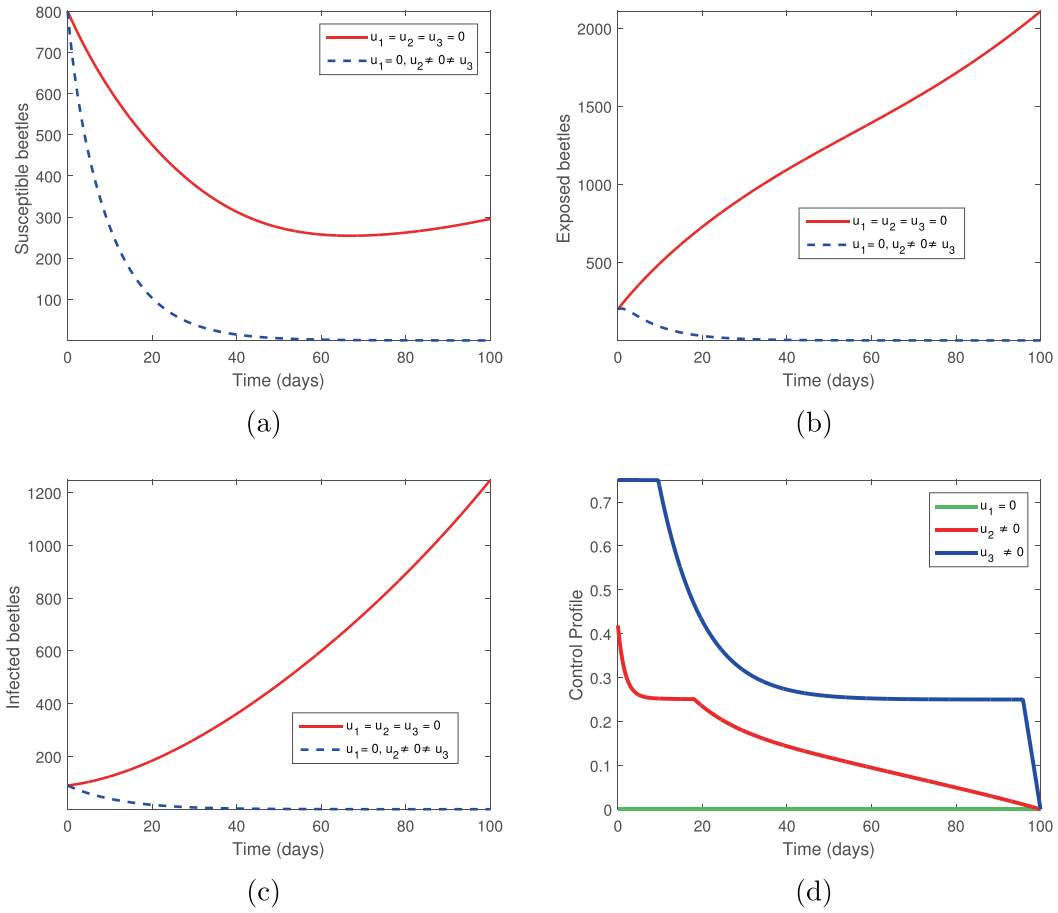

Figure 4. The behaviour of the vector (beetles) population for the controls u_2 and u_3; (**a**) Susceptible beetles, (**b**) Exposed beetles, (**c**) Infected beetles, (**d**) Control profile.

$$\begin{aligned}
S'_H &= \Lambda_H - \beta_1\psi S_H I_V - \beta_2\theta\alpha S_H I_V - \gamma_1 S_H,\\
E'_H &= \beta_1\psi S_H I_V + \beta_2\theta\alpha S_H I_V - (\gamma_1 + m)E_H,\\
A'_H &= m(1-\omega)E_H - \gamma_1 A_H,\\
I'_H &= m\omega E_H - (\gamma_1 + \mu)I_H,\\
S'_V &= \Lambda_V - KS_V I_H - \gamma_2 S_V,\\
E'_V &= KS_V I_H - (\gamma_2 + \eta)E_V,\\
I'_V &= \eta E_V - \gamma_2 I_V,
\end{aligned} \tag{1}$$

with initial conditions

$$S_H(0) \geq 0,\ E_H(0) \geq 0,\ A_H(0) \geq 0,\ I_H(0) \geq 0,\ S_V(0) \geq 0,\ E_V(0) \geq 0,\ I_V(0) \geq 0.$$

The total population sizes of host and vector are given by

$$N_H(t) = S_H(t) + E_H(t) + A_H(t) + I_H(t),\ N_V(t) = S_V(t) + E_V(t) + I_V(t).$$

For biological realism, we study the behaviour of the system (1) in the closed set

$$\Psi = \left\{(S_H, E_H, A_H, I_H, S_V, E_V, I_V) \in \mathbb{R}^7_+ | 0 \leq S_H + E_H + A_H + I_H \leq \frac{\Lambda_H}{\gamma_1},\right.$$
$$\left. 0 \leq S_V + E_V + I_V \leq \frac{\Lambda_V}{\gamma_2}\right\}.$$

Nonnegative solutions of system (1) can be easily verified for appropriate initial values. The first four equations of (1) imply that

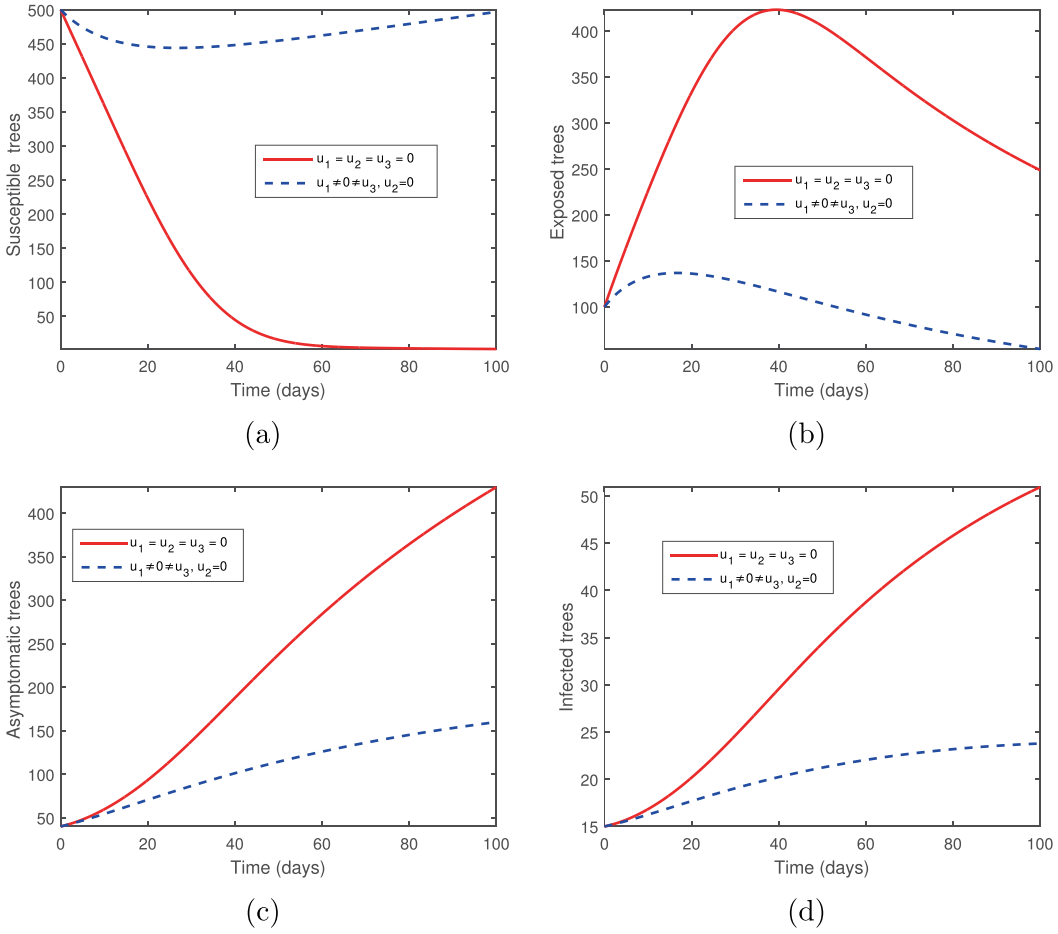

Figure 5. The behaviour of the pine-tree population for the controls u_1 and u_3; (**a**) Susceptible pine trees, (**b**) Exposed pine trees, (**c**) Asymptomatic pine trees, (**d**) Infected pine trees.

$$\frac{d(S_H + E_H + A_H + I_H)}{dt} \leq \Lambda_H - \gamma_1(S_H + E_H + A_H + I_H).$$

By comparison theorem presented in[24], there exists $t_1 > 0$, such that

$$S_H + E_H + A_H + I_H \leq \frac{\Lambda_H}{\gamma_1} \equiv N_1 \text{ for } t > t_1.$$

Similarly, adding the last three equations of the system (1), we get

$$\frac{d(S_V + E_V + I_V)}{dt} = \Lambda_V - \gamma_2(S_V + E_V + I_V).$$

Using the comparison theorem again, there exists $t_2 > t_1$, such that

$$S_V + E_V + I_V \leq \frac{\Lambda_V}{\gamma_2} \equiv N_2 \text{ for } t > t_2.$$

Hence, the solutions of the system (1) are bounded.

In the Supplementary Material, we determine $\mathcal{R}_0$ and prove that the disease-free equilibrium (DFE) is globally asymptotically stable, which also rules out the possibility of a backward bifurcation. We also show that the endemic equilibrium is globally asymptotically stable, under certain conditions.

Sensitivity analysis of threshold dynamic

Due to uncertainties in experimental data, determining accurate outcomes from an epidemiological system is difficult[25]. To compensate for these uncertainties, we use partial rank correlation coefficients (PRCCs) to identify the impact of all parameters on $\mathcal{R}_0$. This technique measures the degree of the relationship between inputs and output of the system. Positive PRCCs indicate parameters that increase $\mathcal{R}_0$ when they are increased, while nega-

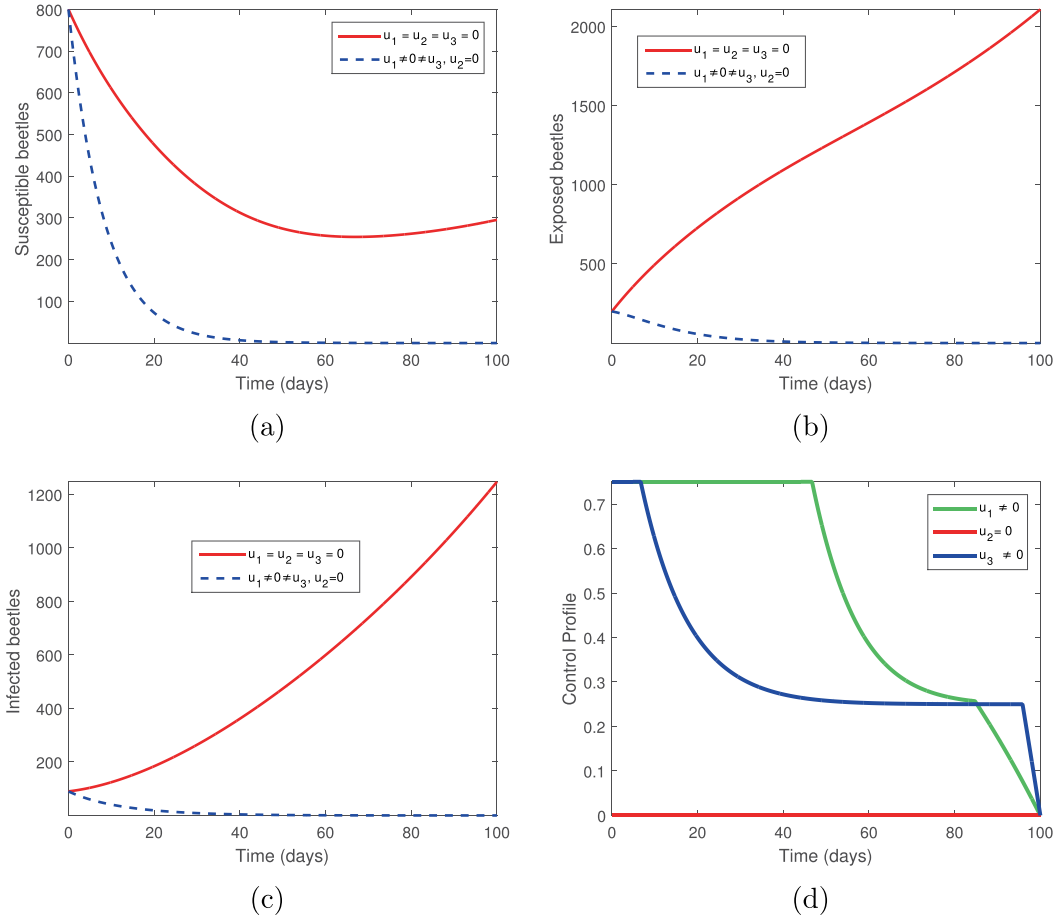

Figure 6. The behaviour of the vector (beetles) population for the controls u_1 and u_3; (**a**) Susceptible beetles, (**b**) Exposed beetles, (**c**) Infected beetles, (**d**) Control profile.

tive PRCCs indicate parameters that decrease $\mathcal{R}_0$ when they are increased. Parameters with PRCCs values greater than 0.4 in magnitude have a significant effect on the outcome.

Figure 2 illustrates the effect of parameter variations on $\mathcal{R}_0$ for all fourteen parameters. Clearly, $\mathcal{R}_0$ is most sensitive to γ_1 and γ_2, the natural death rates of pine trees and beetles, respectively; the latter can be controlled using insecticide (u_3), while the former can be partially controlled by eliminating infected trees (u_2). $\mathcal{R}_0$ is also sensitive to the birth rates of pine trees and beetles, the latter of which can be controlled using insecticide (u_3). The transmission rate K is also a sensitive parameter, which can be controlled by nematicide-injection and vaccination (u_1).

Optimal control strategies

In this section, we introduce u_1, u_2 and u_3 as three control measures that can affect PWD. The force of infection in the pine-tree population is reduced by $(1-u_1)$, where precautionary measures efforts are denoted by u_1; for example nematicide injection and vaccination. To keep the host tree population safe and to prevent infection, the nematicide-injection preventative control measure is used. We use the control variable u_2 to describe elimination of infected host trees. Supplementary infections are extremely reduced by demolition and elimination of infected host trees. The removal of these infected trees guarantees that eggs, larvae and pupa that are occupying the host pines are devasted. Our third control variable represents spraying of insecticide and larvacide to kill adult insects and reduce the vector birth rate.

Model (1) is modified for optimal control as follows:

$$\begin{aligned}
S'_H &= \Lambda_H + cN_H - \beta_1\psi S_H I_V(1-u_1) - \beta_2\theta\alpha S_H I_V(1-u_1) - \gamma_1 S_H,\\
E'_H &= \beta_1\psi S_H I_V(1-u_1) + \beta_2\theta\alpha S_H I_V(1-u_1) - (\gamma_1+m)E_H,\\
A'_H &= m(1-\omega)E_H - \gamma_1 A_H,\\
I'_H &= m\omega E_H - (\gamma_1+\mu)I_H - u_2 b_1 I_H,\\
S'_V &= \Lambda_V(1-u_3) - KS_V I_H(1-u_1) - \gamma_2 S_V - b_0 u_3 S_V,\\
E'_V &= KS_V I_H(1-u_1) - (\gamma_2+\eta)E_V - b_0 u_3 E_V,\\
I'_V &= \eta E_V - \gamma_2 I_V - b_0 u_3 I_V,
\end{aligned} \tag{2}$$

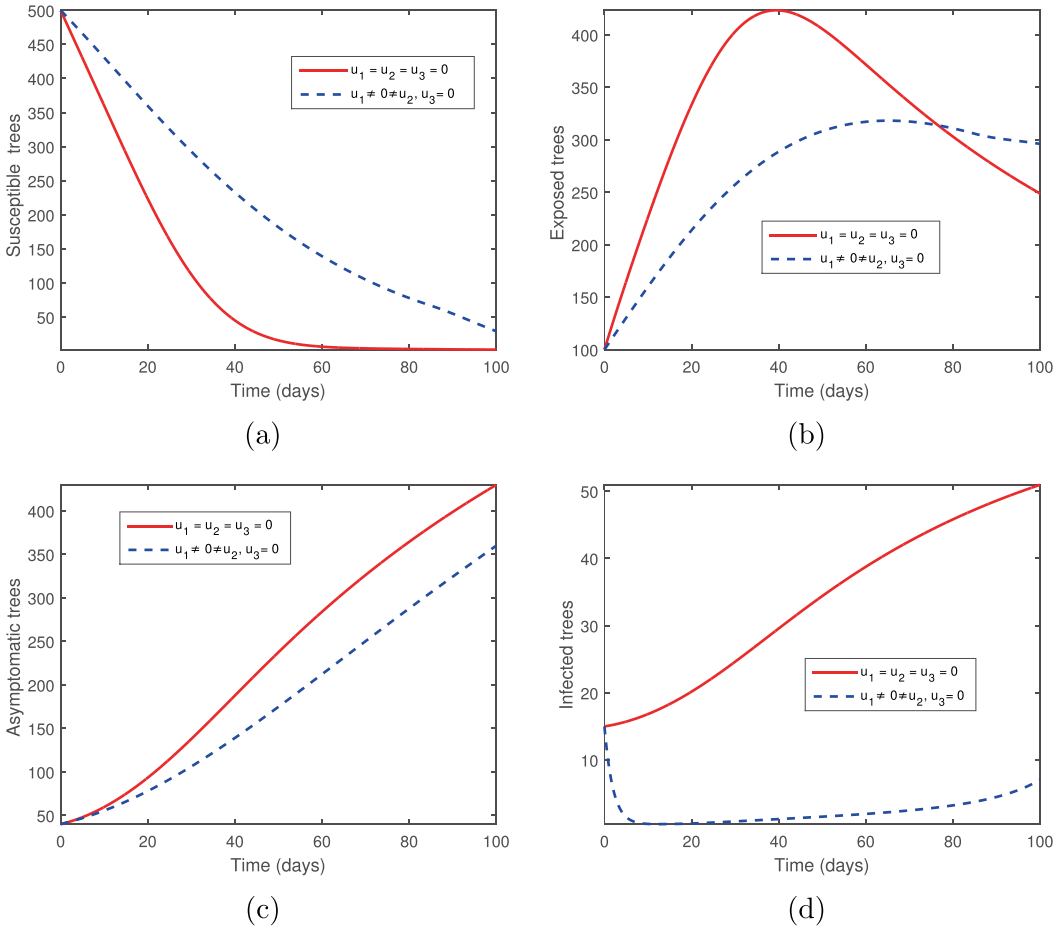

Figure 7. The behaviour of the pine-tree population for the controls u_1 and u_2; (**a**) Susceptible pine trees, (**b**) Exposed pine trees, (**c**) Asymptomatic pine trees, (**d**) Infected pine trees.

with nonnegative initial conditions. The control functions $u(t) = (u_1, u_2, u_3) \in U$ associated to the variables S_H, E_H, A_H, I_H, S_V, E_V and I_V satisfy

$$U(t) = \{(u_1, u_2, u_3) \textit{ are Lebesgue measurable}, 0 \leq u_i \leq 1, t \in [0, T], i = 1, 2, 3\}. \tag{3}$$

The constants b_0 and b_1 are removal-rate constants whose inverses correspond to the average time spent in the relevant compartment. Since it is unlikely that infected trees will be removed within one day of infection, we set $b_1 = 1$; hence the range $0 \leq u_2 \leq 1$ corresponds to a removal time between 1 day and infinite time. The objective functional for the optimal-control problem is

$$\begin{aligned} J(u_1, u_2, u_2) &= \int_0^T [L_1 E_H + L_2 A_H + L_3 I_H + L_4 N_V \\ &\quad + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2)]dt, \end{aligned} \tag{4}$$

subject to the control system (2). The constants L_1, L_2, L_3, L_4, B_1, B_2 and B_3 are the weight or balancing constants, which measure the relative cost of interventions over the interval $[0, T]$. We seek optimal controls u_1^*, u_2^*, u_3^*, such that

$$J(u_1^*, u_2^*, u_3^*) = \min_U \{u_1, u_2, u_3\}. \tag{5}$$

Clearly, the equations in the control system (2) are bounded above, and thus we can apply the results in[26] to model (2). Moreover, the set of control variables and the state variables is nonempty, and the set of control variables denoted by U is closed and convex. In the control problem (2), the right-hand side is continuous and bounded above by state variables and a sum of the bounded control, and can be expressed as a linear function of U having state- and time-dependent coefficients. Hence there exists constants $m > 1$ and $l_1, l_2 > 0$ such that the integrand $L(y, u, t)$ of the objective functional J is convex and satisfies

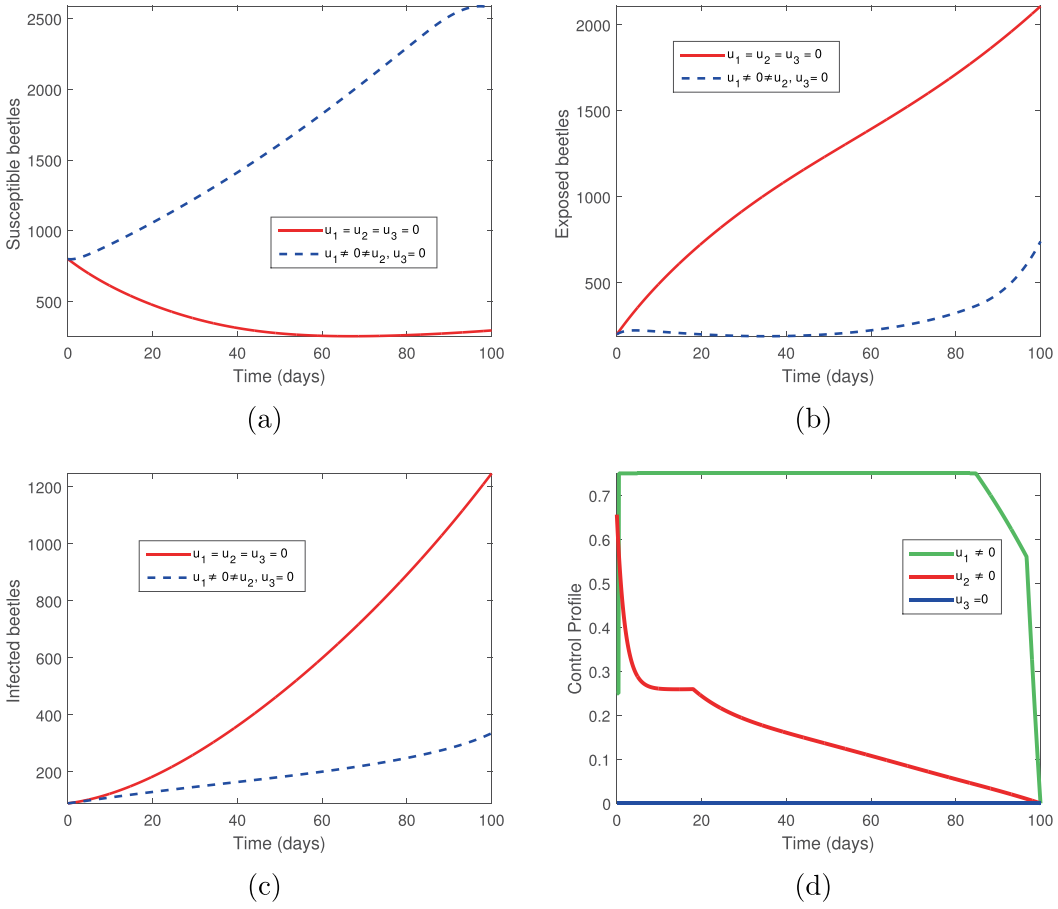

Figure 8. The behaviour of the vector (beetles) population for the controls u_1 and u_2; (**a**) Susceptible beetles, (**b**) Exposed beetles, (**c**) Infected beetles, (**d**) Control profile.

$$L(y, u, t) \geq l_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{m}{2}} - l_2.$$

We apply the results presented in[27] to justify the existence of (2) and to obey the above conditions. Clearly, the set of control and state variables are bounded and nonempty. The solutions are bounded and convex. Therefore the system is bilinear in the control variables. We verify the last condition:

$$\begin{aligned} &L_1E_H + L_2A_H + L_3I_H + L_4N_V + \frac{1}{2}(B_1u_1^2 + B_2u_2^2 + B_3u_3^2) \\ &\geq l_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\frac{m}{2}} - l_2, \end{aligned}$$

where $L_1, L_2, L_3, L_4, B_1, B_2, B_3, l_1, l_2 > 0$ and $m > 1$. We have thus proved the following theorem.

Theorem 1. *For the objective functional* (4) *and the control set* (3) *subject to the control system* (2), *there exists an optimal control* $u^* = (u_1^*, u_2^*, u_3^*)$ *such that* $(u_1^*, u_2^*, u_3^*) = \min_U J(u_1, u_2, u_3)$.

In order to get the solution of the control problem, it is necessary to obtain the Lagrangian and the Hamiltonian of (2). The Lagrangian L is expressed as

$$\begin{aligned} L(E_H, A_H, I_H, N_V, u_1, u_2, u_3) &= L_1E_H + L_2A_H + L_3I_H + L_4N_V \\ &\quad + \frac{1}{2}(B_1u_1^2 + B_2u_2^2 + B_3u_3^2). \end{aligned}$$

By choosing $X = (S_H, E_H, I_H, S_H, E_H, I_H)$, $U = (u_1, u_2, u_3)$ and $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7)$, the Hamiltonian can be written

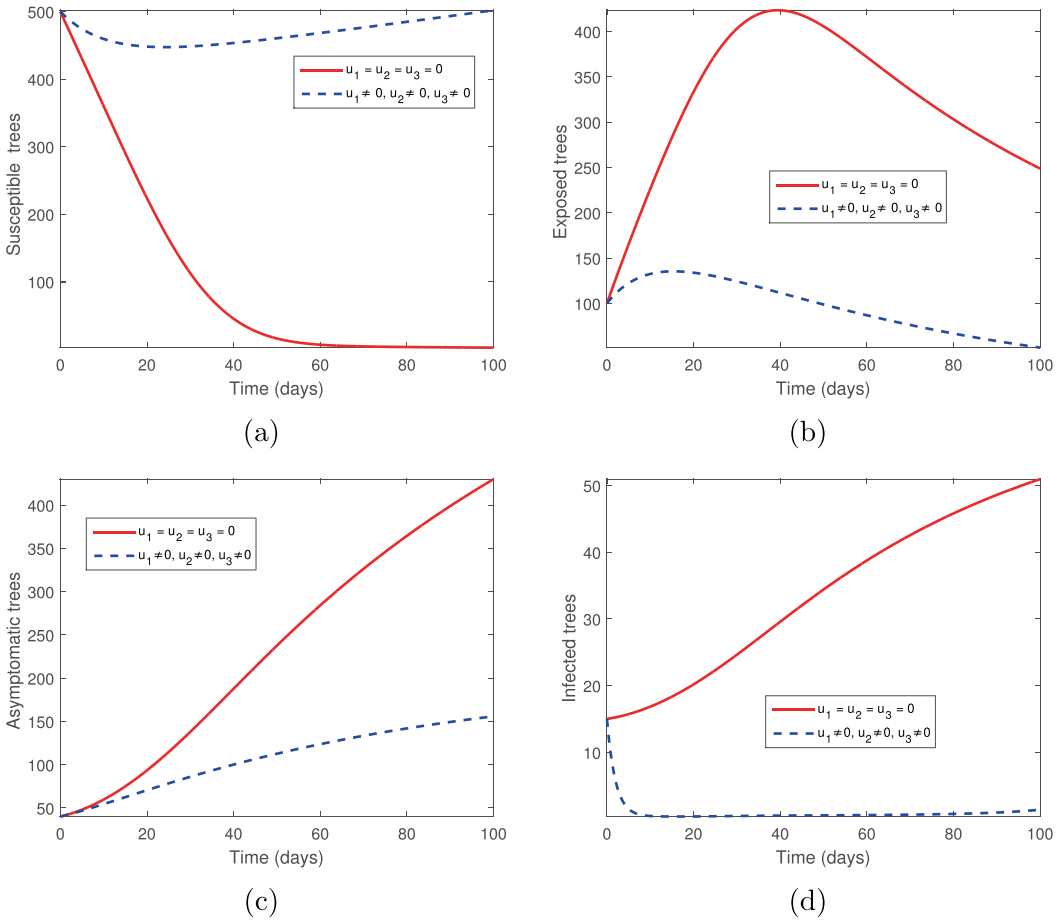

Figure 9. The behaviour of the pine-tree population for the controls u_1, u_2 and u_3; (**a**) Susceptible pine trees, (**b**) Exposed pine trees, (**c**) Asymptomatic pine trees, (**d**) Infected pine trees.

$$\begin{aligned} H(X, U, \lambda) &= L(E_H, A_H, I_H, N_V, u_1, u_2, u_3) + \lambda_1[\Lambda_H + cN_H - \beta_1\psi S_H I_V(1-u_1) \\ &\quad - \beta_2\theta\alpha S_H I_V(1-u_1) - \gamma_1 S_H] \\ &\quad + \lambda_2[\beta_1\psi S_H I_V(1-u_1) + \beta_2\theta\alpha S_H I_V(1-u_1) \\ &\quad - (\gamma_1 + m)E_H] + \lambda_3[m(1-\omega)E_H - \gamma_1 A_H] \\ &\quad + \lambda_4[m\omega E_H - (\gamma_1 + \mu)I_H - u_2 I_H] \\ &\quad + \lambda_5[\Lambda_V N_V(1-u_3) - KS_V I_H(1-u_1) - \gamma_2 S_V - b_0 u_3 S_V] \\ &\quad + \lambda_6[KS_V I_H(1-u_1) \\ &\quad - (\gamma_2 + \eta)E_V - b_0 u_3 E_V] + \lambda_7[\eta E_V - \gamma_2 I_V - b_0 u_3 I_V]. \end{aligned} \tag{6}$$

We use Pontryagin's Maximum Principle[28] to obtain the optimal solution of the control system (2). Since u_1^*, u_2^* and u_3^* are solutions to the control problem (2), there exist adjoint variables λ_i $(i = 1, 2, 3, 4, 5, 6, 7)$ satisfying the following conditions:

$$\begin{aligned} \frac{dx}{dt} &= \frac{\partial H(t, u_1^*, u_2^*, u_3^*, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7)}{\partial \lambda}, \\ 0 &= \frac{\partial H(t, u_1^*, u_2^*, u_3^*, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7)}{\partial \lambda}, \\ \frac{d\lambda}{dt} &= \frac{\partial H(t, u_1^*, u_2^*, u_3^*, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7)}{\partial x}. \end{aligned} \tag{7}$$

Theorem 2. *For the optimal-control measures u_1^*, u_2^*, u_3^* and the state solutions S_H^*, E_H^*, A_H^*, I_H^*, S_V^*, E_V^*, I_V^* of* system (2), there exist adjoint variables λ_i $(i = 1, 2, 3, 4, 5, 6, 7)$ such that

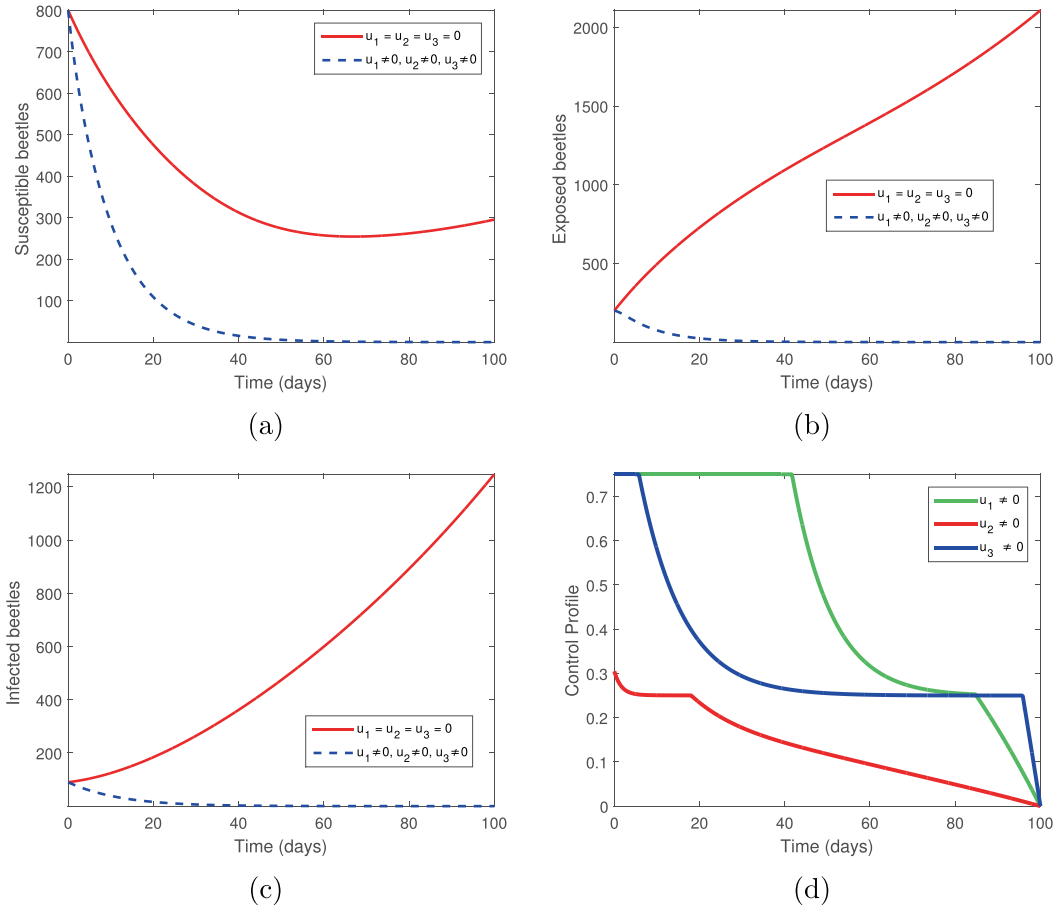

Figure 10. The behaviour of the vector (beetles) population for the controls u_1, u_2 and u_3; (**a**) Susceptible beetles, (**b**) Exposed beetles, (**c**) Infected beetles, (**d**) Control profile.

$$\begin{aligned}
\lambda'_1 &= -\lambda_1 c + \lambda_1\gamma_1 + (\lambda_1 - \lambda_2)\beta_1\psi I_V(1-u_1) + (\lambda_1 - \lambda_2)\beta_2\theta\alpha I_V(1-u_1)\\
\lambda'_2 &= -L_1 - \lambda_1 c - \lambda_4 m\omega + \lambda_2(\gamma_1 + m) - \lambda_3 m(1-\omega)\\
\lambda'_3 &= -L_2 - \lambda_1 c + \lambda_3\gamma_1\\
\lambda'_4 &= -L_3 - \lambda_1 c + (\lambda_5 - \lambda_6)kS_V(1-u_1) + \lambda_4 u_2 + \lambda_4(\gamma_1 + \mu)\\
\lambda'_5 &= -L_4 - \lambda_5\Lambda_V(1-u_3) + (\lambda_5 - \lambda_6)kI_H(1-u_1) + \lambda_5 b_0 u_3\\
\lambda'_6 &= -L_4 - \lambda_5\Lambda_V(1-u_3) + \lambda_6(\gamma_2 + \eta) + \lambda_6 b_0 u_3 - \lambda_7\eta\\
\lambda'_7 &= -L_4 + (\lambda_1 - \lambda_2)\beta_1\psi S_H(1-u_1) + (\lambda_1 - \lambda_2)\beta_2\theta\alpha S_H(1-u_1)\\
&\quad -\lambda_5\Lambda_V(1-u_3) + \lambda_7(\gamma_2 + b_0 u_3),
\end{aligned} \tag{8}$$

with the transversally conditions

$$\lambda_1(T_f) = \lambda_2(T_f) = \lambda_3(T_f) = \lambda_4(T_f) = \lambda_5(T_f) = \lambda_6(T_f) = \lambda_7(T_f) = 0.$$

Furthermore, the controls u_1^*, u_2^*, u_3^* are given by

$$\begin{aligned}
u_1^* &= \max\left\{\min\left\{1, \frac{(\lambda_2 - \lambda_1)[\beta_1\psi + \beta_2\theta\alpha]S_H^* I_V^* + (\lambda_6 - \lambda_5)KS_V^* I_V^*}{B_1}\right\}, 0\right\},\\
u_2^* &= \max\left\{\min\left\{1, \frac{\lambda_4 I_H^*}{B_2}\right\}, 0\right\},\\
u_3^* &= \max\left\{\min\left\{1, \frac{\lambda_5(\Lambda_V N_V^* + b_0 S_V^*) + b_0(\lambda_6 E_V^* + \lambda_7 I_V^*)}{B_3}\right\}, 0\right\}.
\end{aligned} \tag{9}$$

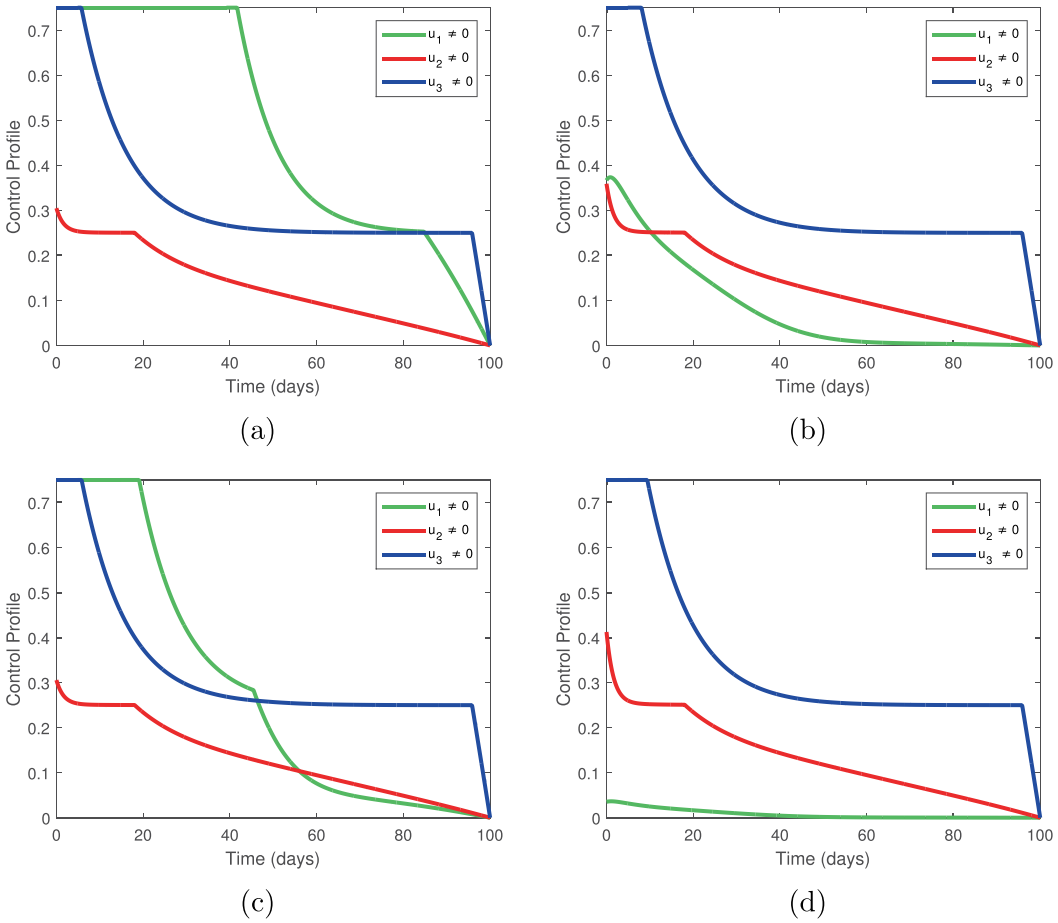

Figure 11. Temporal variation of the control profile for $L_1 = 0.01$, $L_2 = 0.002$, $L_3 = 0.0020$, $L_4 = 0.003$, $B_2 = B_3 = 10$; (**a**) $B_1 = 0.10$, (**b**) $B_1 = 1$, (**c**) $B_1 = 10$, (**d**) $B_1 = 100$.

Proof. To determine the required adjoint system (8) and the transversality conditions mentioned in (9), we utilize the Hamiltonian in (6). By applying the third condition of (7), we get (8). Applying the second condition of (7), we get (9).

Numerical Results

Unless mentioned otherwise, we use the fourth-order Runge–Kutta method over a timescale of 100 days. The input parameters for our simulations are $L_1 = 0.01$, $L_2 = 0.002$, $L_3 = 0.0020$, $L_4 = 0.003$, $B_1 = 0.10$, $B_2 = B_3 = 10$, $c = 0.001241$, $b_0 = 0.21$; all other parameter values are shown in Table 1.

Elimination of infected trees (u_2) and spraying of insecticides (u_3). We considered two controls: the elimination of infected trees (u_2) and the spraying of insecticides (u_3) in the absence of tree injection and vaccination. Figures 3 and 4 show the outcomes in both the absence and presence of control. Figure 3 shows the dynamics of the pine-tree population, while Fig. 4 shows the dynamics of the vector population. With these controls, we see a rapid increase in the population of susceptible trees (Fig. 3(a)) and eventual elimination of exposed and infected trees (Fig. 3(b,d)), with only the asymptomatic carriers remaining in the infected classes (Fig. 3(c)). The vector population is eventually depleted (Fig. 4(a–c)) in the presence of these two controls. The two control profiles u_2 and u_3 are bounded up to 0.4 and 0.8 (Fig. 4(d)). Biologically, u_2 is the additional elimination rate of only infected trees, while u_3 acts to simultaneously increase the removal rate of all vectors, while also decreasing the birth rate. Since all interventions range between 0 (no control) and 1 (complete control), this suggests that our objective can be achieved with only partial controls. Hence if infected trees are removed 2.5 days or later after infection or if insecticides/larvacides are up to 80% effective, the infection can be controlled.

Tree injection (u_1) and spraying of insecticides (u_3). We next examine the combination of tree injection (u_1) and insecticide spraying (u_3). The results are shown in Figs. 5 and 6. With these two controls, there is a significant increase in the population of susceptible and exposed pine trees, while the population of asymptomatic carriers and infected pine trees are reduced but not eliminated (Fig. 5). This suggests that the elimination of infected pine trees has a significant impact on the disease. Note that the vector population is eliminated using these controls (Fig. 6).

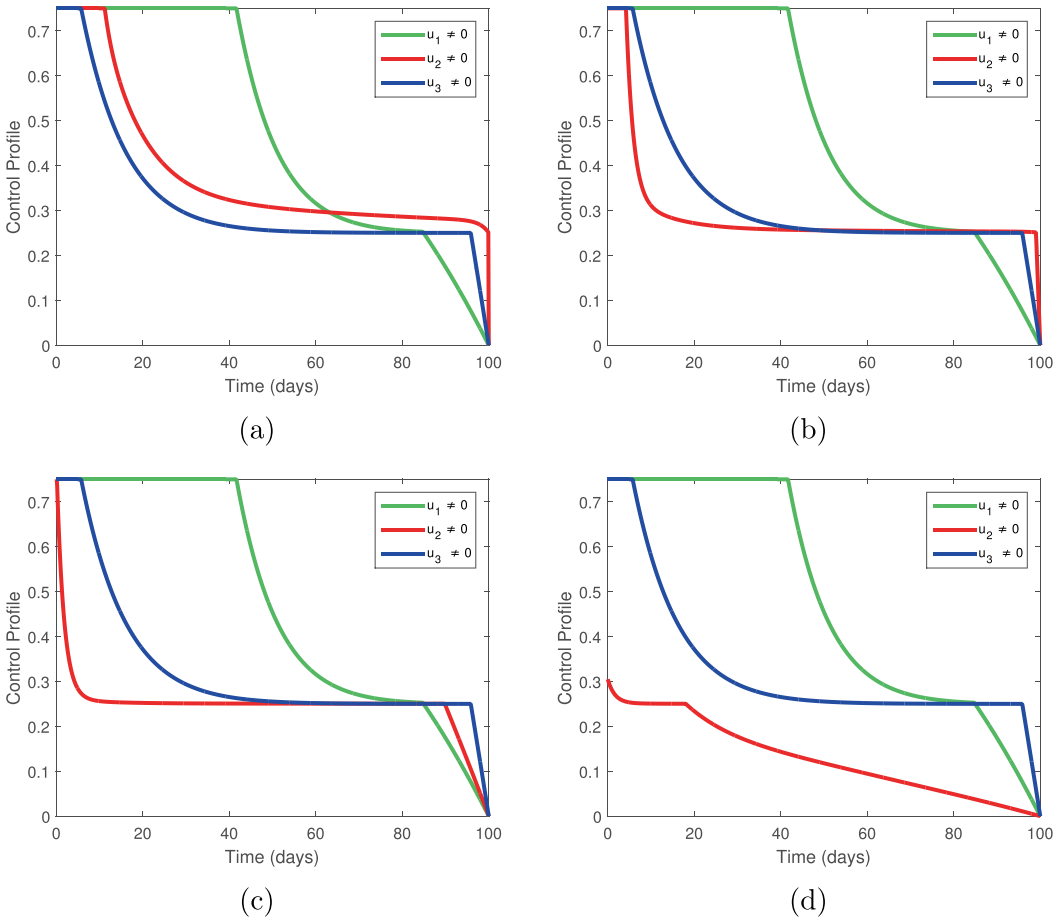

Figure 12. Temporal variation of the control profile for $L_1 = 0.01$, $L_2 = 0.002$, $L_3 = 0.0020$, $L_4 = 0.003$, $B_1 = 0.1$, $B_3 = 10$; (**a**) $B_2 = 0.010$, (**b**) $B_2 = 0.10$, (**c**) $B_2 = 1$, (**d**) $B_2 = 10$.

Tree injection (u_1) and elimination of infected trees (u_2). Considering u_1 and u_2 in combination, Figs. 7 and 8 illustrate that, without insecticide spraying, the control (minimization and/or elimination) of infection in the pine trees is not possible. While the population of susceptible pine trees has a slower decline with these control (Fig. 7(a)), the infection eventually takes over. Likewise, although the susceptible beetle population is recovered using these controls, the infection nevertheless eventually dominates (Fig. 8). It follows that, without insecticide spraying, the control of infection is not possible.

Complete control. We now apply all three controls in order to determine the ideal outcome (Figs. 9 and 10). Comparing Fig. 9 to Fig. 3, we see that susceptible pine trees recover faster and the disease is eliminated quicker, except for asymptomatic carriers. We thus see that the most effective strategy is to apply all three controls, although similar results can be achieved by applying only two controls: elimination of the infected pine trees (u_2) and the spraying of insecticides (u_3).

Temporal variation of control profiles. Next, we investigate the control profiles and their relationships to the weight constants. In Fig. 11, we fix the weight constants $L_1 = 0.01$, $L_2 = 0.002$, $L_3 = 0.0020$, $L_4 = 0.003$, $B_2 = B_3 = 10$ and allow B_1 to vary. In Fig. 12, we fix the weight constants $L_1 = 0.01$, $L_2 = 0.002$, $L_3 = 0.0020$, $L_4 = 0.003$, $B_1 = 0.1$, $B_3 = 10$ and allow B_2 to vary. In Fig. 13, we fix $L_1 = 0.01$, $L_2 = 0.002$, $L_3 = 0.0020$, $L_4 = 0.003$, $B_1 = 0.1$, $B_2 = 10$ and allow B_3 to vary. These variations represent fluctuating costs of implementing our controls.

From Fig. 11, we see that, as the cost of u_1 increases, the control profile is dominated by u_3. That is, if tree injection becomes prohibitively expensive, the procedure can be replaced by increased insecticide spraying.

Figure 12 shows little variation in the control profiles as the cost B_2 increases unless the cost is prohibitive. This suggests that the control u_2 is worth implementing, even at high cost. The combination of u_1 and u_3 alone does not eliminate infection, so it follows that elimination of infected trees is essential to disease control. This may hinder disease eradication if the costs of elimination become prohibitively expensive.

Figure 13 shows that if the cost of insecticide spraying increases, the control profile is dominated by tree injection. Interestingly, while the combination of u_2 and u_3 produced superior results to the combination of u_1 and u_2, the latter combination can still produce effective results if supplemented by a small amount of insecticide spraying.

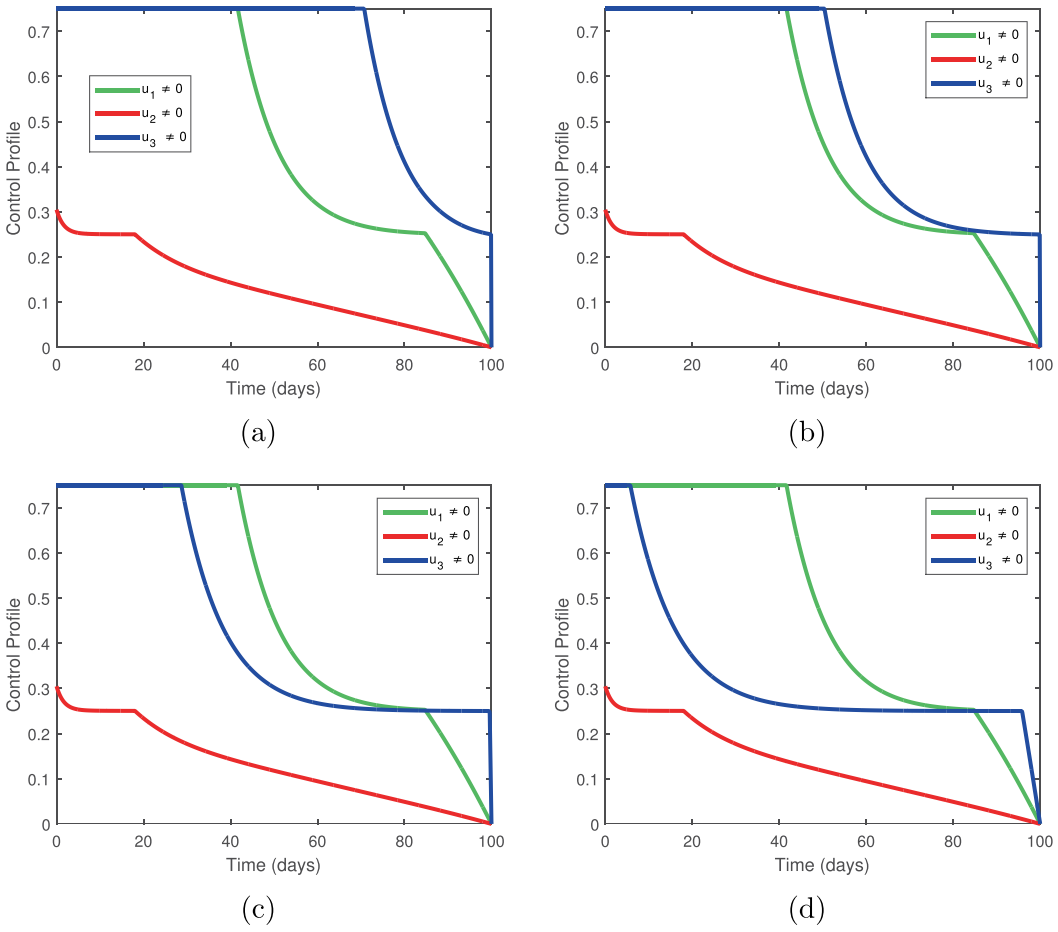

Figure 13. Temporal variation of the control profile for $L_1 = 0.01$, $L_2 = 0.002$, $L_3 = 0.0020$, $L_4 = 0.003$, $B_1 = 0.1$, $B_2 = 10$; (**a**) $B_3 = 0.010$, (**b**) $B_3 = 0.1$, (**c**) $B_3 = 1$, (**d**) $B_3 = 10$.

Discussion

We developed a mathematical model to examine the effect of asymptomatic carriers of Pine Wilt Disease (PWD) on the long-term course of disease. We showed that the disease-free equilibrium was globally asymptotically stable and that the endemic equilibrium was globally asymptotically stable under some conditions. A sensitivity analysis identified key parameters: natural death rates in trees and beetles; birth rates in both trees and beetles; and transmission rates from trees to beetles.

We applied several controls to our system: tree injection, insecticide spraying and elimination of infected trees. These were chosen in conjunction with the most sensitive parameters except for the natural birth and death rates of trees, since our ultimate goal is the preservation of trees. We showed that the disease can be eliminated using suitable controls, except for the asymptomatic carriers. By including this class, our model showed that the disease may remain endemic, requiring permanent control, even in the best-case scenario.

Examining the controls in detail, we found that elimination of infected trees is critical, especially when used in conjunction with insecticide spraying. If the cost of insecticide spraying becomes prohibitive, it can be partially replaced by tree injection. However, if the costs of elimination of infected trees becomes prohibitive, there is no simple replacement, which may result in runaway costs.

It follows that we can control the disease using suitable interventions, but it will not be eliminated due to the presence asymptomatic carriers. The presence of infection in these carriers suggests that infection can restart in nearby healthy trees. It follows that our control measures must be undertaken continually unless such asymptomatic carriers can be identified and removed. This has long-term implications for disease management and economic investment.

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References

1. Mamiya, Y. Pathology of the pine wilt disease caused by Bursaphelenchus xylophilus. *Annual Review of Phytopathology.* **21**(1), 201–220 (1983).
2. Mamiya, Y. & Enda, N. Transmission of Bursaphelenchus lignicolus (Nematoda: Aphelenchoididae) by Monochamus alternatus (Coleoptera: Cerambycidae). *Nematolog.* **18**, 159–162 (1972).

3. Wingfield, M. J. & Blanchette, R. B. The pine-wood nematode, Bursaphelenchus xylophilus, in.Minnesota andWisconsin: insect associates and transmission studies. *Canad. Jour. For. Res.* **13**, 1068–1076 (1983).
4. Arakawa, Y. & Togashi, K. Newly discovered transmission pathway of Bursaphelenchus xylophilus from males of the beetle Monochamus alternatus to Pinus densiflora trees via oviposition wounds. *Jour. Nematol.* **34**, 396–0404 (2002).
5. Lee, K. S. & Kim, D. Global dynamics of a pine wilt disease transmission model with nonlinear incidence rates. *App. Math. Model.* **37**, 4561–4569 (2013).
6. Khan, M. A. *et al*. Mathematical modeling and stability analysis of Pine Wilt Disease with optimal control. *Scient. Rep*. **7**, Article number: 3115 (2017).
7. Khan, M. A., Khan, R., Khan, Y. & Islam, S. A mathematical analysis of Pine Wilt disease with variable population size and optimal control strategies. *Chaos, Solitons & Fractals.* **108**, 205–217 (2018).
8. Shi, X. & Song, G. Analysis of the mathematical model for the spread of pine wilt disease. *Jour. App. Math*. **2013**, Article ID184054, 10 pages, (2013).
9. Lee, K. S. Stability Analysis and Optimal Control Strategy for Prevention of Pine Wilt Disease. *Abs. App. Ana.* **2014**, 1–15 (2014).
10. Khan, M. A., Shah, K., Khan, Y. & Islam, S. Mathematical modeling approach to the transmission dynamics of pine wilt disease with saturated incidence rate. *Internat. Jour. of Biomat* **11**, 1850035 (2018).
11. Ozair, M. Analysis of Pine Wilt Disease Model with Nonlinear Incidence and Horizontal Transmission. *Jour. Appl. Math*. 1–9 (2014).
12. Okosun, K. O. & Smith?, R. Optimal control analysis of malaria-schistosomiasis co-infection dynamics. *Math. Biosci.* **35**, 250–270 (2016).
13. Okosun, K. O. & Makinde, O. D. A. Co-infection model of malaria and cholera diseases with optimal control. *Math. Biosci.* **231**, 234–255 (2014).
14. Khan, M. A. *et al*. Prevention of Leptospirosis infected vector and human population by multiple control variables. *Abs. App. Anal.* **2014**, 1–10 (2014).
15. Farasat, S. S. *et al*. Optimal Control of an Epidemic Model of Leptospirosis with Nonlinear Saturated Incidences. *Ann. Rev. Res. Bio.* **4**, 1–16 (2014).
16. Blayneh, K. W., Gumel, A. B., Lenhart, S. & Clayton, T. Backward bifurcation and optimal control in transmission dynamics of West Nile virus. *Bull. Math. Biol.* **72**, 1006–1028 (2010).
17. Cunniffe, N. & Gilligan, C. A. Invasion, persistence and control in epidemic models for plant pathogens: The effect of host demography. *J. R. Soc. Int.* **7**, 439–51 (2009).
18. Cunniffe, N. J., Stutt, R. O. J. H., DeSimone, R. E., Gottwald, T. R. & Gilligan, C. A. Optimising and Communicating Options for the Control of Invasive Plant Disease When There Is Epidemiological Uncertainty. *PLo. Compu. Bio.* **11**, e1004211 (2015).
19. Cunniffe, N. J., Laranjeira, F. F., Neri, F. M., DeSimone, R. E. & Gilligan, C. A. Cost-Effective Control of Plant Disease When Epidemiological Knowledge Is Incomplete: Modelling Bahia Bark Scaling of Citrus. *Plo.Compu.Bio.* **10**, e1003753 (2014).
20. Futai, K. Role of asymptomatic carrier trees in epidemic spread of pine wilt disease. *Jour.For.Res.* **8**, 253–260 (2003).
21. Takeuchi, Y. & Futai, K. Asymptomatic carrier trees in pine stands naturally infected with Bursaphelenchus xylophilus. *Nematology.* **9**, 243–250 (2007).
22. Futai, K. & Takeuchi, Y. Field Diagnosis of the Asymptomatic Carrier of Pinewood Nematode. In: Mota, M.M. & Viera, P. (eds) *Pine Wilt Disease: A Worldwide Threat to Forest Ecosystems*. Springer: Dordrecht 279–290 (2008).
23. Lashari, A. A. & Lee, K. S. Stability analysis of a host-vector transmission model for pine wilt disease with asymptomatic carrier trees. *J. Korean Math. Soc.* **54**(3), 987–997 (2017).
24. Smith, H. L. & Waltman, P. *The Theory of the Chemostat*, Cambridge University Press: Cambridge (1995).
25. Marino, S., Hogue, I. B., Ray, C. J. & Kirschner, D. A methodology for performing global uncertainty and sensitivity analysis in systems biology. *J. Theor. Biol.* **254**, 178–196 (2008).
26. Fleming, W. H. & Rishel, R. W. *Deterministic and Stochastic Optimal Control*, Springer Verlag: New York (1975).
27. Lukes, D. L. *Differential equations: Classical to Controlled, Mathematics in Science and Engineering*. Academic Press: New York (1982).
28. Lenhart, S. & Workman, J. T. *Optimal control applied to biological models: Mathematical and Computational Biology Series*, Chapman & Hall/CRC Press: London (2007).
29. Kobayashi, F., Yamane, A. & Ikeda, T. The Japanese pine sawyer beetle as the vector of pine wilt disease. *Ann. Rev. Ent.* **29**, 115–135 (1984).
30. Kim, D. S. *et al*. Movement of Monochamus altermatushope (Coleoptera: Cerambycidae) adults among young black pine trees in a screen cage. *Kor. Jour. Appl. Ent.* **50**, 1–6 (2011).
31. Monserud, R. A. & Sterba, H. Modeling individual tree mortality for Austrian forest species. *For. Ecol. Manag.* **113**, 109–123 (1999).
32. Togashi, K. Population density of Monochamus alternatus adults (Coleoptera: Cerambycidae) and incidence of pine wilt disease caused by Bursaphelenchus xylophilus (Nematoda: Aphelenchoididae). *Res. Pop. Ecol.* **30**, 177–192 (1988).
33. Kim, D. S. *et al*. Escape of pine wood Nematode, Bursaphelenchus xylophilus, through feeding and oviposition behaviour of Monochamus alternatus and M. saltuarius (Coleoptera: Cerambycidae) adults. *Kor. Jour. Appl. Ent.* **48**, 527–533 (2009).

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Author contributions

M.A.K. and L.A. wrote the original manuscript and performed the numerical simulations. P.K.M. and M.H. reviewed the mathematical results. R.S.? revised and restructured the manuscript. All authors are agreed on the final draft of the submission file.

Competing interests

The authors declare no competing interests.

Additional information

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Modelling the dynamics of Pine Wilt Disease with asymptomatic carriers and optimal control: Supplementary Material

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Stability analysis of the model

There are two biologically meaningful equilibria of the PWD model: the disease-free equilibrium (DFE) and the endemic equilibrium (EE). The former is given by

$$E_0 = \left(\frac{\Lambda_H}{\gamma_1}, 0, 0, 0, \frac{\Lambda_V}{\gamma_2}, 0, 0\right).$$

Using the next-generation method [1], we find the repoduction number is

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\frac{mK\omega\Lambda_V\Lambda_H\eta(\beta_2\theta\alpha + \beta_1\psi)}{\gamma_1\gamma_2^2(m+\gamma_1)(\mu+\gamma_1)(\eta+\gamma_2)}}.$$

Note that this value is a threshold for disease emergence, not necessarily the average number of secondary infections [2].

Global stability of the DFE

Here, we prove the global stability of the DFE E_0 using the approach from Castillo-Chavez and Huang [3]. We rewrite our model as follows:

$$\begin{aligned} \frac{dY}{dt} &= F(Y,Z), \\ \frac{dZ}{dt} &= M(Y,Z), \quad M(Y,0)=0, \end{aligned} \tag{1}$$

where $Y = (S_H, S_V) \in \mathbb{R}^2_+$, represent the number of uninfected compartments and $Z = (E_H,\ A_H,\ I_H,\ E_V,\ I_V) \in \mathbb{R}^5_+$, represent the infected tree and vector classes. The DFE is $(Y^0,\ 0)$, where $Y^0 = \left(\frac{\Lambda_H}{\gamma_1}, \frac{\Lambda_V}{\gamma_2}\right)$. For global stability of the DFE, the following two conditions need to be satisfied:

$$(C_1)\ \text{For } \frac{dY}{dt} = F(Y,0) = 0,\ Y^0 \text{ is globally asymptotically stable}$$

$$(C_2)\ M(Y,Z) = AZ - \widehat{G}(Y,Z),\ \text{where } \widehat{G}(Y,Z) \geq 0,\ \text{for } (Y,Z) \in \Omega,$$

and where $A = D_z M(Y^0, 0)$ is an M-matrix and Ω is the biological feasible region.

Lemma 1. *If $\mathcal{R}_0 < 1$, then the fixed point denoted by $(Y^0, 0)$ of system (1) is globally asymptotically stable if (C_1) and (C_2) are satisfied.*

For the proof of Lemma 1 where the conditions are proved in general, see [3], but in particular case, these conditions are proven in below theorem.

Theorem 1. *If $\mathcal{R}_0 < 1$ and assumptions (C_1) and (C_2) are satisfied, then the DFE E_0 is gobally asymptotically stable.*

Proof. Let

$$F(X,0) = \begin{pmatrix} \Lambda_H - \gamma_1 S_H^0 \\ \Lambda_V - \gamma_2 S_V^0 \end{pmatrix}.$$

As $t \to \infty$, and $Y \to Y^0$, $Y = Y^0 = (S_H^0, S_V^0)$ is globally asymptotically stable. To ensure condition (C_2), let

$$A = \begin{pmatrix} -\tau_1 & 0 & 0 & 0 & \tau_4 S_H^0 \\ m(1-\omega) & -\gamma_1 & 0 & 0 & 0 \\ m\omega & 0 & -\tau_2 & 0 & 0 \\ 0 & 0 & KS_V^0 & -\tau_3 & 0 \\ 0 & 0 & 0 & \eta & -\gamma_2 \end{pmatrix},$$

$$Z = \begin{pmatrix} E_H \\ A_H \\ I_H \\ E_V \\ I_V \end{pmatrix} \text{ and } \widehat{G}(Y,Z) = \begin{pmatrix} \tau_4 S_H^0 (1 - \frac{S_H}{S_H^0}) \\ 0 \\ 0 \\ KS_V^0 I_H (1 - \frac{S_V}{S_V^0}) \\ 0 \end{pmatrix}.$$

where $\tau_4 = \alpha\beta_2\theta + \beta_1\psi$. Then $M(Y,Z)$ can be written as $M(Y,Z) = AZ - \widehat{G}(Y,Z)$. Clearly, $\widehat{G}(Y,Z) \geq 0$ and A is an M-matrix with negative diagonals. Hence conditions (C_1) and (C_2) are fulfilled. Thus, by Lemma 1, E_0 is globally asymptotically stable. □

Note that the global stability of the DFE implies local stability and also that no backward bifurcation is possible.

Global stability of the endemic equilibrium

Next, we will prove global stability of EE^* [4, 5, 6]. At the EE, the PWD model at steady state satisfies

$$\begin{aligned}
\Lambda_H &= \tau_4 S_H^* I_V^* + \gamma_1 S_H^*, & \tau_1 E_H^* &= \tau_4 S_H^* I_V^* \\
m(1-\omega)E_H^* &= \gamma_1 A_H^* & mE_H^* &= \tau_2 I_H^*, \\
\frac{\tau_1\tau_2}{m} I_H^* &= \tau_4 S_H^* I_V^* & \Lambda_V &= K S_V^* I_H^* + \gamma_2 S_V^* \\
K S_V^* I_H^* &= \tau_3 E_V^*, & \eta E_V^* &= \gamma_2 I_V^*, \\
K S_V^* I_H^* &= \frac{\tau_3\gamma_2 I_V^*}{\eta}
\end{aligned}$$

Theorem 2. *If* $\mathcal{R}_0 > 1$ *and*

$$\left(7 - \frac{S_H^*}{S_H} - \frac{S_H I_V E_H^*}{S_H^* I_V^* E_H} - \frac{A_H}{A_H^*} - \frac{E_H A_H^*}{A_H E_H^*} - \frac{E_H I_H^*}{I_H E_H^*} + \frac{E_H}{E_H^*} - \frac{S_V^*}{S_V} - \frac{S_V I_H E_V^*}{S_V^* E_V I_H^*} - \frac{E_V I_V^*}{I_V E_V^*}\right) \leq 0,$$

then the endemic equilibrium EE^* *is globally asymptotically stable*

Proof. Consider the Lyapunov function

$$\begin{aligned}
L \;=\; & K S_V^* I_H^* \left[\int_{S_H^*}^{S_H} \left(1 - \frac{S_H^*}{x}\right) dx + \int_{E_H^*}^{E_H} \left(1 - \frac{E_H^*}{x}\right) dx + \frac{\tau_4 S_H^* I_V^*}{m(1-\omega)E_H^*} \int_{A_H^*}^{A_H} \left(1 - \frac{A_H^*}{x}\right) dx \right. \\
& \left. + \frac{\tau_4 S_H^* I_V^*}{m\omega E_H^*} \int_{I_H^*}^{I_H} \left(1 - \frac{I_H^*}{x}\right) dx \right] + \tau_4 S_H^* I_V^* \left[\int_{S_V^*}^{S_V} \left(1 - \frac{S_V^*}{x}\right) dx + \int_{E_V^*}^{E_V} \left(1 - \frac{E_V^*}{x}\right) dx \right. \\
& \left. + \frac{K S_V^* I_H^*}{\eta E_V^*} \int_{I_V^*}^{I_V} \left(1 - \frac{I_V^*}{x}\right) dx \right].
\end{aligned}$$

We have

$$\begin{aligned}
L' \;=\; & K S_V^* I_H^* \left[\left(1 - \frac{S_H^*}{S_H}\right) \acute{S_H} + \left(1 - \frac{E_H^*}{E_H}\right) \acute{E_H} + \frac{\tau_4 S_H^* I_V^*}{m(1-\omega)E_H^*} \left(1 - \frac{A_H^*}{A_H}\right) \acute{A_H} \right. \\
& \left. + \frac{\tau_4 S_H^* I_V^*}{m\omega E_H^*} \left(1 - \frac{I_H^*}{I_H}\right) \acute{I_H} \right] + \tau_4 S_H^* I_V^* \left[\left(1 - \frac{S_V^*}{S_V}\right) \acute{S_V} + \left(1 - \frac{E_V^*}{E_V}\right) \acute{E_V} + \frac{K S_V^* I_H^*}{\eta E_V^*} \left(1 - \frac{I_V^*}{I_V}\right) \acute{I_V} \right].
\end{aligned}$$

Simplifying, we get the following results:

$$\begin{aligned}
\left(1-\frac{S_H^*}{S_H}\right)S_H' &= \left(1-\frac{S_H^*}{S_H}\right)[\Lambda_H-\tau_4 S_H I_V-\gamma_1 S_H]\\
&= \left(1-\frac{S_H^*}{S_H}\right)[\tau_4 S_H^* I_V^*+\gamma_1 S_H^*-\tau_4 S_H I_V-\gamma_1 S_H]\\
&= \gamma_1 S_H^*\left(2-\frac{S_H}{S_H^*}-\frac{S_H^*}{S_H}\right)+\left(1-\frac{S_H^*}{S_H}\right)[\tau_4 S_H^* I_V^*-\tau_4 S_H I_V]\\
&= \gamma_1 S_H^*\left(2-\frac{S_H}{S_H^*}-\frac{S_H^*}{S_H}\right)+\tau_4 S_H^* I_V^*\Big(1-\frac{S_H^*}{S_H}-\frac{S_H I_V}{S_H^* I_V^*}+\frac{I_V}{I_V^*}\Big),\\
\left(1-\frac{E_H^*}{E_H}\right)E_H' &= \left(1-\frac{E_H^*}{E_H}\right)[\tau_4 S_H I_V-\tau_1 E_H]\\
&= \left(1-\frac{E_H^*}{E_H}\right)\left[\tau_4 S_H I_V-\frac{\tau_4 S_H^* I_V^*}{E_H^*}E_H\right]\\
&= \tau_4 S_H^* I_V^*\Big(1-\frac{E_H}{E_H^*}-\frac{S_H I_V E_H^*}{S_H^* I_V^* E_H}+\frac{S_H I_V}{S_H^* I_V^*}\Big),\\
\frac{\tau_4 S_H^* I_V^*}{m(1-\omega)E_H^*}\left(1-\frac{A_H^*}{A_H}\right)A_H' &= \frac{\tau_4 S_H^* I_V^*}{m(1-\omega)E_H^*}\left(1-\frac{A_H^*}{A_H}\right)[m(1-\omega)E_H-\gamma_1 A_H]\\
&= \frac{\tau_4 S_H^* I_V^*}{E_H^*}\left(1-\frac{A_H^*}{A_H}\right)\left[E_H-\frac{E_H^*}{A_H^*}A_H\right]\\
&= \tau_4 S_H^* I_V^*\left(1-\frac{A_H}{A_H^*}-\frac{E_H A_H^*}{E_H^* A_H}+\frac{E_H}{E_H^*}\right),\\
\frac{\tau_4 S_H^* I_V^*}{m\omega E_H^*}\left(1-\frac{I_H^*}{I_H}\right)I_H' &= \frac{\tau_4 S_H^* I_V^*}{m\omega E_H^*}\left(1-\frac{I_H^*}{I_H}\right)[m\omega E_H-\tau_2 I_H]\\
&= \frac{\tau_4 S_H^* I_V^*}{E_H^*}\left(1-\frac{I_H^*}{I_H}\right)\left[E_H-\frac{E_H^*}{I_H^*}I_H\right],\\
&= \tau_4 S_H^* I_V^*\left(1-\frac{I_H}{I_H^*}-\frac{E_H I_H^*}{I_H E_H^*}+\frac{E_H}{E_H^*}\right),\\
\left(1-\frac{S_V^*}{S_V}\right)S_V' &= \left(1-\frac{S_V^*}{S_V}\right)[\Lambda_V-K S_V I_H-\gamma_2 S_V]\\
&= \left(1-\frac{S_H^*}{S_H}\right)[K S_V^* I_H^*+\gamma_2 S_V^*-K S_V-\gamma_2 S_V]\\
&= \gamma_2 S_V^*\left(2-\frac{S_V}{S_V^*}-\frac{S_V^*}{S_V}\right)+K S_V^* I_H^*\left(1-\frac{S_V I_H}{S_V^* I_H^*}-\frac{S_V^*}{S_V}+\frac{I_H}{I_H^*}\right),\\
\left(1-\frac{E_V^*}{E_V}\right)E_V' &= \left(1-\frac{E_V^*}{E_V}\right)[K S_V I_H-\tau_3 E_V]\\
&= \left(1-\frac{E_V^*}{E_V}\right)\left[K S_V I_H-\frac{K S_V^* I_H^* E_V}{E_V^*}\right]\\
&= K S_V^* I_H^*\Big(1-\frac{E_V}{E_V^*}-\frac{S_V I_H E_V^*}{E_V S_V^* I_H^*}+\frac{S_V I_H}{S_V^* I_H^*}\Big),
\end{aligned}$$

and

$$\left(1-\frac{I_V^*}{I_V}\right)\frac{KS_V^*I_H^*}{\eta E_V^*}I_V' = \frac{KS_V^*I_H^*}{\eta E_V^*}\left(1-\frac{I_V^*}{I_V}\right)[\eta E_V-\gamma_2 I_V]$$
$$= \frac{KS_V^*I_H^*}{E_V^*}\left(1-\frac{I_V^*}{I_V}\right)[E_V-\frac{E_V^*}{I_V^*}I_V]$$
$$= KS_V^*I_H^*\left(1-\frac{I_V}{I_V^*}-\frac{E_VI_V^*}{I_VE_V^*}+\frac{E_V}{E_V^*}\right).$$

It follows from the above equations that

$$\begin{aligned} L'(t) &= \tau_4 KS_H^*I_V^*S_V^*I_H^*\left[7-\frac{S_H^*}{S_H}-\frac{S_HI_VE_H^*}{S_H^*I_V^*E_H}-\frac{A_H}{A_H^*}-\frac{E_HA_H^*}{A_HE_H^*}-\frac{E_HI_H^*}{I_HE_H^*}+\frac{E_H}{E_H^*}\right. \\ &\quad \left.-\frac{S_V^*}{S_V}-\frac{S_VI_HE_V^*}{S_V^*E_VI_H^*}-\frac{E_VI_V^*}{I_VE_V^*}\right]+\gamma_1 KS_H^*S_V^*I_H^*\left(2-\frac{S_H}{S_H^*}-\frac{S_H^*}{S_H}\right) \\ &\quad +\tau_4\gamma_2 S_H^*I_V^*S_V^*\left(2-\frac{S_V}{S_V^*}-\frac{S_V^*}{S_V}\right). \end{aligned}$$

in which

$$\left(2-\frac{S_H}{S_H^*}-\frac{S_H^*}{S_H}\right)\le 0,$$
$$\left(2-\frac{S_V}{S_V^*}-\frac{S_V^*}{S_V}\right)\le 0,$$

and if

$$\left[7-\frac{S_H^*}{S_H}-\frac{S_HI_VE_H^*}{S_H^*I_V^*E_H}-\frac{A_H}{A_H^*}-\frac{E_HA_H^*}{A_HE_H^*}-\frac{E_HI_H^*}{I_HE_H^*}+\frac{E_H}{E_H^*}-\frac{S_V^*}{S_V}-\frac{S_VI_HE_V^*}{S_V^*E_VI_H^*}-\frac{E_VI_V^*}{I_VE_V^*}\right]\le 0,$$

then the largest invariant subset for which $L'=0$ is EE^*. By LaSalle's Invariance Principle [7], EE^* is globally asymptotically stable whenever $\mathcal{R}_0>1$. □

References

[1] Driessche, P.V.D. & Watmough, J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math. Biosci.* **180**, 29–48 (2002).

[2] Heffernan, J.M., Smith, R.J. & Wahl, L.M. Perspectives on basic reproduction ratio. *J. R. Soc. Inter.* **2**, 281–293 (2005).

[3] Castillo-Chavez, C., Feng, Z. & Huang, W. On the computation of R0 and its role on global stability. *Mathematical Approaches for Emerging and Re-Emerging Infection Diseases: An Introduction. The IMA Volumes in Mathematics and Its Applications.* **125**, 31–65 (2002).

[4] Gui-Quan, S., Xie, S.H., Jin, Z, *et al.* Transmission Dynamics of Cholera: Mathematical Modeling and Control Strategies. *Comm. Nonl. Sci. Num. Sim.*,**45**, 235–244 (2017).

[5] Ming-Tao, L., Zhen, J., Gui-Quan, S. & Juan, Z. Modeling direct and indirect disease transmission using multi-group mode. *J. Math. Anal. Appl.* **446**(2), 1292–1309 (2017).

[6] Guo, H., Li, M.Y. & Shuai, Z. A graph-theoretic approach to the method of global Lyapunov functions. *Proc. Am. Math. Soc.* **136**, 2793–2802 (2008).

[7] Lasalle, J.P. Stability theory for difference equations. In: Hale, J. K. (Ed.) *Studies in Ordinary Differential Equations.* Washington DC: Math. Assoc. of America (1977).