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Global stability analysis and control of leptospirosis

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Abstract: The aim of this paper is to investigate the effectiveness and cost-effectiveness of leptospirosis control measures, preventive vaccination and treatment of infective humans that may curtail the disease transmission. For this, a mathematical model for the transmission dynamics of the disease that includes preventive, vaccination, treatment of infective vectors and humans control measures are considered. Firstly, the constant control parameters' case is analyzed, also calculate the basic reproduction number and investigate the existence and stability of equilibria. The threshold condition for disease-free equilibrium is found to be locally asymptotically stable and can only be achieved when the basic reproduction number is less than unity. The model is found to exhibit the existence of multiple endemic equilibria. Furthermore, to assess the relative impact of each of the constant control parameters measures the sensitivity index of the basic reproductive number to the model's parameters are calculated. In the time-dependent constant control case, Pontryagin's Maximum Principle is used to derive necessary conditions for the optimal control of the disease. The cost-effectiveness analysis is carried out by first of all using ANOVA to check on the mean costs. Then followed by Incremental Cost-Effectiveness Ratio (ICER) for all the possible combinations of the disease control measures. Our results revealed that the most cost-effective strategy for the control of leptospirosis is the combination of the vaccination and treatment of infective livestock. Though the combinations of all control measures is also effective, however, this strategy is not cost-effective and so too costly. Therefore, more efforts from policy makers on vaccination and treatment of infectives livestock regime would go a long way to combat the disease epidemic.

Keywords: Leptospirosis, Stability analysis, Optimal control, Cost-effectiveness analysis, ANOVA

MSC: 92B05, 93A30, 93C15

1 Introduction

Leptospirosis is caused by numerous distinct serovars of a spiral-shaped bacterium known as *Leptospira interrogans* and it is a disease of animals and humans. These serovars are harboured by a wide range of animals, and all of them are capable of causing illness in humans. *Leptospira* serovars Pomona and hardjo are particularly important in livestock, however the number of other serovars of concern, detected in domestic animals and in humans, is fast growing (Alabama Cooperative Extension Systems (ANR-0858)). Leptospirosis is a cause of economic losses in the farming of animals. Many infected animals do not show signs of clinical disease.

Leptospirosis is commonly spread by the urine of infected animals and with moisture acting as an important factor of the survival of the bacteria in the environment. Livestock pick up infection by contact with pasture or water contaminated by the urine of infected livestock or wild animals. In warm, moist conditions the organisms may

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survive in the environment and cause infection for several weeks, so that under suitable climate conditions, many livestock are almost continually exposed for long periods [1].

Infections can range from asymptomatic or sub-clinical to acute and fatal. Symptoms of acute leptospirosis in animals include sudden agalactia in the lactating female, icterus and haemoglobinuria in the young, nephritis and hepatitis in dogs, and meningitis. Chronic leptospirosis can cause abortion, stillbirth, high mortality among young calves, decreased milk production, runting, and infertility. Often chronically infected animals remain as asymptomatic carriers for life with the organism localized in the kidneys and in the reproductive organs and while horses can develop periodic ophthalmia as a result of leptospirosis [2]. In humans, leptospirosis is capable of causing headaches, fever, chills, sweats and myalgia. Also other symptoms may include lethargy, aching joints, and long periods of sickness. Some highly pathogenic serovars may cause pulmonary haemorrhaging and death. While mild type leptospirosis is probably the most common form of infection, they can sometimes be chronic in nature and have a mental component to their clinical manifestations.

The disease can either be transmitted directly between animals or indirectly through the environment. Leptospirosis is of increasing importance as an occupational disease as intensive farming practices become more widely adopted. For instance, during 1999, those working in agricultural industries in Australia accounted for 35.3% of notifications while those working in livestock industries accounted for 22.9% of notifications [2].

There have been applications of optimal control methods to epidemiological models, but most of these studies focused on HIV and TB diseases dynamics. The authors in [3–6] studied the optimal chemotherapy treatment in controlling the virus reproduction in an HIV patient. In [7–10], optimal control was used to minimize the costs of both diseases and treatment. In [11, 12] the authors used optimal control to investigate the best strategy for educational campaigns during the outbreak of an epidemic and at the same time minimizing the number of infective humans. The authors in [13] also used Optimal control to study a nonlinear mathematical SIR epidemic model with a vaccination program. Optimal control was applied to study the impact of chemo-therapy on malaria disease with infective immigrants and the impact of basic amenities [14, 15], while [16] studied the effects of prevention and treatment on malaria, using an SEIR model. It was also used in a malaria model with genetically modified mosquitoes but without human population [17]. For other applications of optimal control to modelling of infectious diseases [18–21].

Very little has been done in the area of applying optimal control theory to study and analyse the dynamics of leptospirosis. Recently, the authors in [22] studied the dynamical interactions between leptospirosis infected vector and human population. While [23] considered a leptospirosis epidemic model to implement optimal campaign using multiple control variables. However, none of these studies carried out cost-effectiveness analysis of the control strategies.

In this paper, an extension of the SIR Leptospirosis model presented in [22] is considered by incorporating both human and vector populations (livestocks) and also incorporates vector vaccination, treatments and prevention strategies. The aim is to gain some insights into the best intervention for minimizing the transmission of the disease within the population and to explore the impacts of various intervention scenarios, namely, prevention, vaccination and treatment. We analyse the stability and bifurcation of the model, then we incorporate into the model appropriate cost functions in order to study and determine the possible impacts of these strategies in controlling the disease. We further carried out detailed qualitative optimal control analysis of the resulting model and give the necessary conditions for optimal control of the disease using Pontryagin's Maximum Principle, in order to determine optimal strategies for controlling the spread of the disease. The cost-effectiveness analysis of the control strategies is further considered, in order to ascertain the most cost-effective out of the strategies.

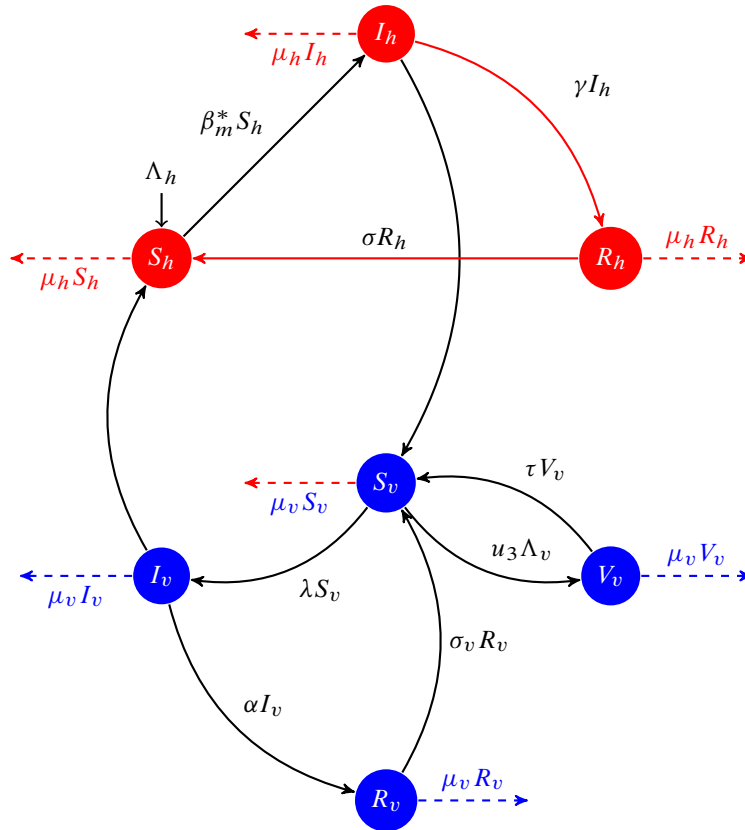
The organization of the paper is as follows, in Section 2, we derive a model consisting of ordinary differential equations that describes the interactions between humans and livestock populations and the underlying assumptions. Section 3 is devoted to the mathematical analysis of the leptospirosis model. In Section 4, the optimal control analysis of the disease is presented. In Sections 5, the simulation results are shown to illustrate the effects of preventions, vaccination and treatment. The cost-effectiveness analysis is presented in Section 6 while the conclusions are in Section 7.

2 Model formulation

The model sub-divides the total human population, denoted by N_h , into sub-populations of susceptible individuals (S_h), individuals with leptospirosis symptoms (I_h), recovered human (R_h). So that $N_h = S_h + I_h + R_h$.

The total vector (livestock) population, denoted by N_v , is sub-divided into susceptible vector (S_v), infectious vector (I_v), recovered vector (R_v) and vaccinated vector (V_v). Thus, $N_v(t) = S_v + I_v + R_v + V_v$.

Fig. 1. Flow diagram for the disease transmission. The blue balls represent the vector population, while the red balls indicate the human population



The model is given by the following system of ordinary differential equations:

$$\begin{aligned}
 \frac{dS_h}{dt} &= \Lambda_h + \sigma_h R_h - (1 - u_1)\beta_m^* \beta S_h - \mu_h S_h \\
 \frac{dI_h}{dt} &= (1 - u_1)\beta_m^* \beta S_h - (u_2 \gamma + \mu_h + \delta_h) I_h \\
 \frac{dR_h}{dt} &= u_2 \gamma I_h - (\sigma_h + \mu_h) R_h \\
 \frac{dS_v}{dt} &= (1 - u_3)\Lambda_v - (1 - u_1)\beta_m^* \lambda S_v - \mu_v S_v + \sigma_v R_v + \tau V_v \\
 \frac{dI_v}{dt} &= (1 - u_1)\beta_m^* \lambda S_v + (1 - u_1)b\beta_m^* \lambda V_v - (u_4 \alpha + \mu_v + \delta_v) I_v \\
 \frac{dR_v}{dt} &= u_4 \alpha I_v - (\sigma_v + \mu_v) R_v \\
 \frac{dV_v}{dt} &= u_3 \Lambda_v - (\tau + \mu_v) V_v - (1 - u_1)b\lambda \beta_m^* V_v
 \end{aligned} \tag{1}$$

where $\beta_m^* = I_v + I_h$.

Susceptible individuals are recruited at a rate Λ_h . Susceptible individuals acquire leptospirosis through contact with infectious vectors and infectious humans at a rate $(I_v + I_h)\beta$. Infected individuals recovered from the disease at a rate γ . Individuals with the disease are treated under control, at a rate $u_2(t)$, while $u_1(t)$ is the control efforts on prevention. Non treated infected individuals die at a rate δ_h . Recovered individual loose immunity at a rate σ_h and become susceptible again. The term μ_h is the natural death rate.

Susceptible vector (S_v) are generated at a rate Λ_v , where a proportion $u_3 \in [0, 1]$ is successfully vaccinated individual vector. Vectors with the disease are treated under control, at a rate $u_4(t)$. Leptospirosis is acquired through contacts with infected humans and infectious vectors at a rate $(I_v + I_h)\lambda$. Leptospirosis infected livestock are assumed to suffer death due to natural causes and disease induced death rates, μ_v and δ_v respectively. The vectors recovery rate is α and due to wanning effect some vaccinated vectors will move to the infected class at a rate $b\beta_m^*\lambda$, where $(1 - b) \in [0, 1]$ is the efficacy of the vaccine or they loose their immunity completely and move to the susceptible class at a rate τ .

3 Mathematical analysis of the Leptospirosis model

3.1 Positivity and boundedness of solutions

For the leptospirosis transmission model (1) to be epidemiologically meaningful, it is important to prove that all solutions with non-negative initial data will remain non-negative for all time.

Theorem 3.1. *If $S_h(0)$, $I_h(0)$, $R_h(0)$, $S_v(0)$, $I_v(0)$, $R_v(0)$, $V_v(0)$ are non negative, then so are $S_h(t)$, $I_h(t)$, $R_h(t)$, $S_v(t)$, $I_v(t)$, $R_v(t)$ and $V_v(t)$ for all time $t > 0$. Moreover,*

$$\limsup_{t \rightarrow \infty} N_h(t) \leq \frac{\Lambda_h}{\mu_h} \text{ and } \limsup_{t \rightarrow \infty} N_v(t) \leq \frac{\Lambda_v}{\mu_v}. \quad (2)$$

Furthermore, if $N_h(0) \leq \frac{\Lambda_h}{\mu_h}$, then $N_h(t) \leq \frac{\Lambda_h}{\mu_h}$, and if $N_v(0) \leq \frac{\Lambda_v}{\mu_v}$, then $N_v(t) \leq \frac{\Lambda_v}{\mu_v}$.

The proof is omitted for simplicity. The feasible region for system (1) is therefore given by

$$\mathcal{D} = \mathcal{D}_h \times \mathcal{D}_v \subset \mathbb{R}_+^3 \times \mathbb{R}_+^4 \quad (3)$$

where,

$$\mathcal{D}_h = \{(S_h, I_h, R_h) \in \mathbb{R}_+^3 : S_h + I_h + R_h \leq \frac{\Lambda_h}{\mu_h}\}, \quad (4)$$

and

$$\mathcal{D}_v = \{(S_v, I_v, R_v, V_v) \in \mathbb{R}_+^4 : S_v + I_v + R_v + V_v \leq \frac{\Lambda_v}{\mu_v}\}. \quad (5)$$

\mathcal{D} is positively invariant.

3.2 Steady states, stability and bifurcation

The disease-free equilibrium (DFE) of the disease model (1) exists only when $u_1 = 0$ and other controls are constants, it is given by

$$\mathcal{E}_0 = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, \frac{\Lambda_v(\tau + \mu_v(1 - u_3))}{\mu_v(\tau + \mu_v)}, 0, 0, \frac{u_3\Lambda_v}{\tau + \mu_v} \right). \quad (6)$$

The basic reproduction number of the model (1), R_{hv} , is calculated by using the next generation matrix [24]. It is given by

$$R_{hv} = \frac{\beta\Lambda_h}{\mu_h(\gamma + \delta_h + \mu_h)} + \frac{\lambda\Lambda_v[\tau + (1 - (1 - b)u_3)]}{(\tau + \mu_v)(\alpha + \delta_v + \mu_v)}. \quad (7)$$

It is clear that the vaccination would results in the reduction of R_{hv} . Hence the total vaccination coverage is given as

$$u_3^* = \frac{1}{1-b} \left(\frac{R_{vq}(\tau+1) + R_{hq} - R_{hv}}{R_{vq}} \right) \quad (8)$$

where,

$$R_{hq} = \frac{\beta \Lambda_h}{\mu_h(\gamma + \delta_h + \mu_h)}, \quad R_{vq} = \frac{\lambda \Lambda_v(1+\tau)}{(\tau + \mu_v)(\alpha + \delta_v + \mu_v)}$$

Further, using Theorem 2 in [24], the following result is established.

Proposition 3.2. *The DFE of the model (1), is locally asymptotically stable if $R_{hv} < 1$, and unstable if $R_{hv} > 1$.*

3.3 Global stability of disease free

Here in this section, the global behaviour of the equilibrium system (1) is analyzed.

Theorem 3.3. *If $R_{hv} \leq 1$, the disease free equilibrium is globally asymptotically stable in the interior of Ω*

Proof. Consider the following Lyapunov function:

$$P(t) = (\alpha + \mu_v + \delta_v)I_h + (\gamma + \mu_h + \delta_h)I_v \quad (9)$$

Calculating the time derivative of P along the solutions of system (1), the following is obtain,

$$\begin{aligned} \frac{dP(t)}{dt} &= (\alpha + \mu_v + \delta_v) \frac{dI_h}{dt} + (\gamma + \mu_h + \delta_h) \frac{dI_v}{dt} \\ &= (\alpha + \mu_v + \delta_v) \left(\beta S_h(I_h + I_v) - (u_2\gamma + \mu_h + \delta_h)I_h \right) \\ &\quad + (\gamma + \mu_h + \delta_h) \left(\lambda S_v(I_h + I_v) + b(I_h + I_v)\lambda V_v - (u_4\alpha + \mu_v + \delta_v)I_v \right) \\ &\leq (\alpha + \mu_v + \delta_v) \frac{\beta \Lambda_h I_h}{\mu_h} + (\alpha + \mu_v + \delta_v) \frac{\beta \Lambda_h I_v}{\mu_h} - (\alpha + \mu_v + \delta_v)(\gamma + \mu_h + \delta_h)I_h \\ &\quad + I_h(\gamma + \mu_h + \delta_h) \left(\frac{\lambda \Lambda_v(\tau + \mu_v(1-u_3))}{\mu_v(\tau + \mu_v)} \right) + I_v(\gamma + \mu_h + \delta_h) \left(\frac{\lambda \Lambda_v(\tau + \mu_v(1-u_3))}{\mu_v(\tau + \mu_v)} \right) \\ &\quad + I_h(\gamma + \mu_h + \delta_h) \frac{bu_3\lambda\Lambda_v}{\tau + \mu_v} + I_v(\gamma + \mu_h + \delta_h) \frac{bu_3\lambda\Lambda_v}{\tau + \mu_v} - I_v(\gamma + \mu_h + \delta_h)(\alpha + \mu_v + \delta_v) \\ &\leq -I_h(\gamma + \mu_h + \delta_h)(\alpha + \mu_v + \delta_v) \left(1 - R_{hv} \right) - I_v(\gamma + \mu_h + \delta_h)(\alpha + \mu_v + \delta_v) \left(1 - R_{hv} \right) \\ &= -(I_h + I_v)(\gamma + \mu_h + \delta_h)(\alpha + \mu_v + \delta_v) \left(1 - R_{hv} \right) \end{aligned} \quad (10)$$

Thus $\frac{dP(t)}{dt}$ is negative whenever $R_{hv} < 1$. $\frac{dP(t)}{dt} = 0$ if and only if $I_h + I_v = 0$ or in the case when $R_{hv} = 1$. Hence, the largest compact invariant set in $S_h, I_h, I_v \in \Omega$, $\frac{dP(t)}{dt} = 0$, whenever $R_{hv} \leq 1$, is the singleton \mathcal{E}_0 . Therefore, LaSalle's invariance principle [26] implies that \mathcal{E}_0 is globally asymptotically stable in Ω . This completes the proof. \square

3.4 Endemic Equilibrium

Next we calculate the endemic steady states. Solving system (1) at the equilibrium we obtain $\beta_m^* = 0$ (which corresponds to the DFE) or

$$\Omega_0\beta_m^{*3} + \Omega_1\beta_m^{*2} + \Omega_2\beta_m^* + \Omega_3 = 0 \quad (11)$$

$$\begin{aligned}
\Omega_0 &= 1 \\
\Omega_1 &= \frac{Z_*}{E} (1 - R_w) \\
\Omega_2 &= \frac{G_1}{E} (1 - R_f) \\
\Omega_3 &= \chi [1 - R_{hv}],
\end{aligned} \tag{12}$$

where

$$\begin{aligned}
R_{hv}^2 &= R_{hq} + R_{vq} = \frac{\beta \Lambda_h}{\mu_h(\gamma + \delta_h + \mu_h)} + \frac{\lambda \Lambda_v[\tau + (1 - (1 - b)u_3)]}{(\tau + \mu_v)(\alpha + \delta_v + \mu_v)}, \\
E &= b\beta\lambda^2[\mu_v(\alpha + \delta_v + \mu_v) + (\delta_v + \mu_v)\sigma_v][\mu_h(\gamma + \delta_h + \mu_h) + (\delta_h + \mu_h)\sigma_h], \\
Q_1 &= b\lambda^2\mu_h(\gamma + \delta_h + \mu_h)(\mu_h + \sigma_h)[\mu_v(\alpha + \delta_v + \mu_v) + (\delta_v + \mu_v)\sigma_v], \\
Q_2 &= \frac{\beta\lambda[\mu_h(\gamma + \delta_h + \mu_h) + (\delta_h + \mu_h)\sigma_h]F_3b(\mu_v + \delta_v)(\tau + \mu_v)(\alpha + \delta_v + \mu_v)}{(\tau + (1 - (1 - b)u_3))}, \\
Z_* &= Q_1 + Q_2 \\
R_w^2 &= \frac{Q_1 R_{hq} + Q_2 R_{vq}}{Z_*} \\
F_1 &= \lambda\mu_h(\mu_h + \sigma_h)(\gamma + \delta_h + \mu_h)(\tau + (1 + b)\mu_v)[\mu_v(\alpha + \delta_v + \mu_v) + (\delta_v + \mu_v)\sigma_v], \\
F_2 &= \beta\mu_h(\alpha + \delta_v + \mu_v)(\tau + \mu_v)(\mu_v + \sigma_v)[\mu_h(\gamma + \delta_h + \mu_h) + (\delta_h + \mu_h)\sigma_h], \\
F_3 &= [(\tau + (1 + b)\mu_v)[\mu_v(\alpha + \delta_v + \mu_v) + (\delta_v + \mu_v)\sigma_v] + b\alpha\mu_v] \\
G_1 &= \lambda[\mu_h(\mu_h + \sigma_h)(\gamma + \delta_h + \mu_h)(\tau + \mu_v)[\mu_v(\alpha + \delta_v + \mu_v) + (\delta_v + \mu_v)\sigma_v] \\
&\quad - b[\Lambda_v(\mu_v + \sigma_v) + \beta\Lambda_h\alpha\mu_v\sigma_v(\mu_h + \sigma_h)] + b\mu_v(\alpha + \delta_v + \mu_v)(\mu_v + \sigma_v)], \\
\chi &= \frac{\mu_v\mu_h(\mu_v + \sigma_v)(\mu_h + \sigma_h)(\tau + \mu_v)(\alpha + \delta_v + \mu_v)(\gamma + \delta_h + \mu_h)}{b\beta\lambda^2[\mu_v(\alpha + \delta_v + \mu_v) + (\delta_v + \mu_v)\sigma_v][\mu_h(\gamma + \delta_h + \mu_h) + (\delta_h + \mu_h)\sigma_h]}, \\
R_f^2 &= \frac{F_1^2 R_{hq} + F_2^2 R_{vq}}{G_1}.
\end{aligned} \tag{13}$$

Table 1. Number of possible positive real roots of $P(\beta_m^*)$ for $R_{hv} > 1$ and $R_{hv} < 1$

Cases	Ω_0	Ω_1	Ω_2	Ω_3	R_{hv}	Number of sign change	Number of positive real roots
1	+	+	+	+	$R_{hv} < 1$	0	0
	+	+	+	-	$R_{hv} > 1$	1	1
2	+	+	-	+	$R_{hv} < 1$	2	0, 2
	+	+	-	-	$R_{hv} > 1$	1	1
3	+	-	-	+	$R_{hv} < 1$	2	0, 2
	+	-	-	-	$R_{hv} > 1$	1	1
4	+	-	+	+	$R_{hv} < 1$	2	0, 2
	+	-	+	-	$R_{hv} > 1$	3	1, 3

Remark. The system (1) has a unique endemic equilibrium E^* if $R_{hv} > 1$ and Cases 1-3 (as declared in Table 1) are satisfied. It could have more than one endemic equilibrium if $R_{hv} > 1$ and Case 4 is satisfied; it could have 2 endemic equilibria if $R_{hv} < 1$ and Cases 2-4 are satisfied.

3.4.1 Global stability of endemic equilibrium

Theorem 3.4. The model equations has a unique positive endemic equilibrium whenever $R_{hv} > 1$ and its globally asymptotically stable.

Letting $R_{hv} > 1$ so that the endemic equilibrium exists. We consider the non-linear Lyapunov function

$$\begin{aligned} L = & S_h^{**} \left(\frac{S_h}{S_h^{**}} - \ln \frac{S_h}{S_h^{**}} \right) + I_h^{**} \left(\frac{I_h}{I_h^{**}} - \ln \frac{I_h}{I_h^{**}} \right) + \frac{g_1 R_h^{**}}{\gamma} \left(\frac{R_h}{R_h^{**}} - \ln \frac{R_h}{R_h^{**}} \right) \\ & + S_v^{**} \left(\frac{S_v}{S_v^{**}} - \ln \frac{S_v}{S_v^{**}} \right) + I_v^{**} \left(\frac{I_v}{I_v^{**}} - \ln \frac{I_v}{I_v^{**}} \right) + R_v^{**} \left(\frac{R_v}{R_v^{**}} - \ln \frac{R_v}{R_v^{**}} \right) \\ & + V_v^{**} \left(\frac{V_v}{V_v^{**}} - \ln \frac{V_v}{V_v^{**}} \right) \end{aligned} \quad (14)$$

where $g_1 = (u_2\gamma + \mu_h + \delta_h)$, $g_2 = (\sigma_2 + \mu_h)$, $g_3 = (u_4\alpha + \mu_v + \delta_v)$, $g_4 = (\sigma_v + \mu_v)$. Differentiating the above equation (14), we have

$$\begin{aligned} \frac{dL}{dt} = & \left(1 - \frac{S_h^{**}}{S_h} \right) \frac{dS_h}{dt} + \left(1 - \frac{I_h^{**}}{I_h} \right) \frac{dI_h}{dt} + \frac{g_1}{\gamma} \left(1 - \frac{R_h^{**}}{R_h} \right) \frac{dR_h}{dt} + \left(1 - \frac{S_v^{**}}{S_v} \right) \frac{dS_v}{dt} \\ & + \left(1 - \frac{I_v^{**}}{I_v} \right) \frac{dI_v}{dt} + \left(1 - \frac{R_v^{**}}{R_v} \right) \frac{dR_v}{dt} + \left(1 - \frac{V_v^{**}}{V_v} \right) \frac{dV_v}{dt} \end{aligned} \quad (15)$$

so

$$\left\{ \begin{aligned} \frac{dL}{dt} = & \left(1 - \frac{S_h^{**}}{S_h} \right) [\Lambda_h + \sigma_h R_h^{**} + (1 - u_1) \beta \beta_m^{**} S_h^{**} + \mu_h S_h^{**} - \Lambda_h \\ & - \sigma R_h - (1 - u_1) \beta \beta_m S_h - \mu_h S_h] \\ & + \left(1 - \frac{I_h^{**}}{I_h} \right) [(1 - u_1) \beta \beta_m S_h - g_1 I_h] + \frac{g_1}{\gamma} \left(1 - \frac{R_h^{**}}{R_h} \right) [u_2 \gamma I_h - g_2 R_h] \\ & + \left(1 - \frac{S_v^{**}}{S_v} \right) [(1 - u_3) \Lambda_v + (1 - u_1) \lambda \beta_m^{**} S_v^{**} + \mu_v S_v^{**} + \sigma_v R_v^{**} + \tau V_v^{**} - (1 - u_3) \Lambda_v \\ & - (1 - u_1) \lambda \beta_m S_v - \mu_v S_v - \sigma_v R_v - \tau V_v] \\ & + \left(1 - \frac{I_v^{**}}{I_v} \right) [(1 - u_1) \lambda \beta_m S_v + (1 - u_1) b \lambda \beta_m V_v - g_3 I_v] + \frac{g_3}{\alpha} \left(1 - \frac{R_v^{**}}{R_v} \right) [u_4 \alpha I_v - g_4 R_v] \\ & + \left(1 - \frac{V_v^{**}}{V_v} \right) [u_3 \Lambda_v + (1 - u_1) b \lambda \beta_m^{**} V_v^{**} + (\tau + \mu_v) V_v^{**} - u_3 \Lambda_v \\ & - (1 - u_1) b \lambda \beta_m V_v - (\tau + \mu_v) V_v] \end{aligned} \right. \quad (16)$$

Therefore, simplifying further, we have,

$$\begin{aligned}
 & \mu_h S^{**} \left(2 - \frac{S_h^{**}}{S_h} - \frac{S_h}{S_h^{**}} \right) + \sigma R_h^{**} \left(1 - \frac{R_h}{R_h^{**}} \right) + \frac{R_h S_h^{**}}{S_h} \left(1 - \frac{R_h^{**}}{R_h} - \frac{g_1 g_2 S_h}{\gamma S_h^{**}} \left(1 - \frac{R_h^{**}}{R_h} \right) \right) \\
 & + (1 - u_1) \beta \beta_m^{**} S_h^{**} \left(1 - \frac{\beta_m}{\beta_m^{**}} - \frac{S_h^{**}}{S_h} - \frac{S_h \beta_m I^{**}}{S_h^{**} \beta_m^{**} I_h} \right) + g_1 I_h^{**} \left(1 - \frac{I_h}{I_h^{**}} - \frac{u_2 I_h}{I_h^{**}} \left(1 - \frac{R_h^{**}}{R_h} \right) \right) \\
 & + \mu_v S_v^{**} \left(2 - \frac{S_v^{**}}{S_v} - \frac{S_v}{S_v^{**}} \right) + \sigma_v R_v^{**} \left(1 - \frac{S_v^{**}}{S_v} - \frac{R_v}{R_v^{**}} + \frac{R_v S_v^{**}}{R_v^{**} S_v} \right) \\
 & + \tau V_v^{**} \left(1 - \frac{S_v^{**}}{S_v} - \frac{V_v}{V_v^{**}} - \frac{V_v S_v^{**}}{V_v^{**} S_v} \right) + (1 - u_1) \lambda \beta_m^{**} S_v^{**} \left(1 - \frac{S_v^{**}}{S_v} + \frac{\beta_m}{\beta_m^{**}} - \frac{S_v \beta_m I_v^{**}}{S_v^{**} \beta_m^{**} I_v} \right) \\
 & + \frac{g_3 I_v^{**}}{I_v} \left(1 - \frac{I_v}{I_v^{**}} - g_3 u_4 \frac{I_v}{I_v^{**}} - g_3 u_4 \frac{I_v R_v^{**}}{I_v^{**} R_v} \right) + \frac{g_3 g_4 R_v^{**}}{\alpha} \left(1 - \frac{R_v}{R_v^{**}} \right) \\
 & + (\tau + \mu_v) V_v^{**} \left(2 - \frac{V_v^{**}}{V_v} - \frac{V_v}{V_v^{**}} \right) + b(1 - u_1) \lambda \beta_m^{**} V_v^{**} \left(1 - \frac{V_v^{**}}{V_v} + \frac{\beta_m}{\beta_m^{**}} - \frac{V_v \beta_m I_v^{**}}{V_v^{**} \beta_m^{**} I_v} \right)
 \end{aligned} \tag{17}$$

since the arithmetic mean exceeds the geometric mean value [25], it follows that

$$\begin{aligned}
 & 2 - \frac{S_h^{**}}{S_h} - \frac{S_h}{S_h^{**}} \leq 0 \\
 & 1 - \frac{R_h}{R_h^{**}} \leq 0 \\
 & 1 - \frac{R_h^{**}}{R_h} - \frac{g_1 g_2 S_h}{\gamma S_h^{**}} \left(1 - \frac{R_h^{**}}{R_h} \right) \leq 0 \\
 & 1 - \frac{\beta_m}{\beta_m^{**}} - \frac{S_h^{**}}{S_h} - \frac{S_h \beta_m I^{**}}{S_h^{**} \beta_m^{**} I_h} \leq 0 \\
 & 1 - \frac{I_h}{I_h^{**}} - \frac{u_2 I_h}{I_h^{**}} \left(1 - \frac{R_h^{**}}{R_h} \right) \leq 0 \\
 & 2 - \frac{S_v^{**}}{S_v} - \frac{S_v}{S_v^{**}} \leq 0 \\
 & 1 - \frac{S_v^{**}}{S_v} - \frac{R_v}{R_v^{**}} + \frac{R_v S_v^{**}}{R_v^{**} S_v} \leq 0 \\
 & 1 - \frac{S_v^{**}}{S_v} - \frac{V_v}{V_v^{**}} - \frac{V_v S_v^{**}}{V_v^{**} S_v} \leq 0 \\
 & 1 - \frac{S_v^{**}}{S_v} + \frac{\beta_m}{\beta_m^{**}} - \frac{S_v \beta_m I_v^{**}}{S_v^{**} \beta_m^{**} I_v} \leq 0 \\
 & 1 - \frac{I_v}{I_v^{**}} - g_3 u_4 \frac{I_v}{I_v^{**}} - g_3 u_4 \frac{I_v R_v^{**}}{I_v^{**} R_v} \leq 0
 \end{aligned} \tag{18}$$

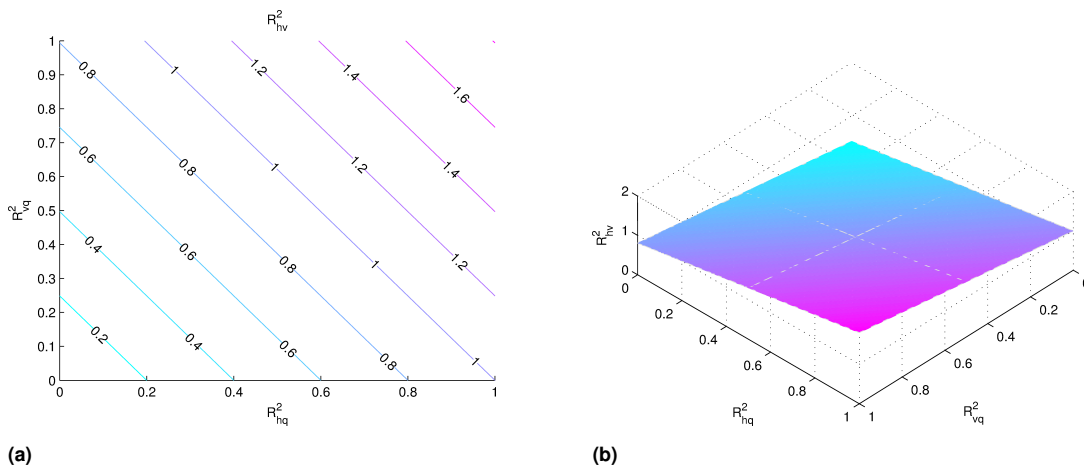
$$1 - \frac{R_v}{R_v^{**}} \leq 0$$

$$2 - \frac{V_v^{**}}{V_v} - \frac{V_v}{V_v^{**}} \leq 0$$

$$1 - \frac{V_v^{**}}{V_v} + \frac{\beta_m}{\beta_m^{**}} - \frac{V_v \beta_m I_v^{**}}{V_v^{**} \beta_m^{**} I_v} \leq 0$$

Since all the model parameters are non-negative, it follows that $\dot{L} \leq 0$ for $R_{hv} > 1$. Hence, by LaSalle's Invariance Principle [26], every solution of the equation in the model approaches the endemic equilibrium point as $t \rightarrow \infty$ whenever $R_{hv} > 1$.

Fig. 2. Simulations of the leptospirosis model showing the effect of the optimal strategies: Prevention of humans and vaccination of vectors.



3.5 Sensitivity analysis of model parameters

The sensitivity analysis to determine the model robustness to parameter values is investigated. This is in order to help us know the parameters that have a high impact on the reproduction number (R_{hv}). Adopting the approach in ([14, 27]), we analyzed the reproduction number to determine whether or not vaccination, treatment of infectives and mortality can lead to the effective elimination or control of the disease in the population.

Definition. The normalized forward sensitivity index of a variable, h , that depends differentially on a parameter, l , is defined as:

$$\Upsilon_l^h := \frac{\partial h}{\partial l} \times \frac{l}{h}. \quad (19)$$

3.5.1 Sensitivity indices of R_{hv}

We therefore derive the sensitivity of R_{hv} to each of the thirteen different parameters of the model. Using the parameter values in Table 3, the detail sensitivity indices of R_{hv} resulting from the evaluation with respect to the parameters of the model are shown below.

Table 2. Sensitivity indices of model parameters to R_{hv}

Parameter	Description	Sensitivity index
μ_v	livestock death rate	-1.1057
β	human transmission rate	0.9906
Λ_h	humans recruitment rate	0.9906
γ	human rate of recovery	-0.5887
δ_h	humans disease induced death rate	-0.2867
μ_h	death rate in humans	-0.0147
λ	livestocks transmission rate	0.00944
Λ_v	recruitment rate of livestock	0.00944
α	livestocks recovery rate	-0.003825
u_3	proportion vaccinated	-0.003059
δ_v	livestocks disease induced death	-0.001913
τ	waning rate from	0.00152
b	vaccine efficacy	0.0003398

Table 2, above, implies that an increase in human treatment γ , livestock treatment α or increase in the mosquito mortality μ_v have positive impact in controlling leptospirosis in the community. The parameters are arranged from the most sensitive to least, the most sensitive parameters are proportion of mosquito biting and contact rates μ_v , β , Λ_h . Increasing (or decreasing) the transmission rate β by 10%, increases (or decreases) the R_{hv} by 9.9%, similarly increasing (or decreasing) the humans recruitment rate, Λ_h , by 10%, increases (or decreases) the R_{hv} by 9.9%. In the same way, increasing (or decreasing) the human recovery rate γ , decreases (or increases) R_{hv} , by 5.89% and in like manner increasing (or decreasing) the livestock recovery rate α decreases (or increases) R_{hv} , by 0.03%.

In the next section, we apply optimal control method using Pontryagin's Maximum Principle to determine the necessary conditions for the optimal control of the impact of control measures on leptospirosis disease.

4 Optimal control analysis of the Leptospirosis model

We seek here to minimize the number of infective individuals and the cost of applying prevention, treatment and vaccination controls. The objective functional that we consider is given by

$$J = \min_{u_1, u_2, u_3, u_4} \int_0^{t_f} \left(w_1 I_v + w_2 I_h + w_3 u_1^2 + w_4 u_2^2 + w_5 m u_3^2 + w_6 u_4^2 \right) dt \quad (20)$$

subject to differential equations system (1).

Here $w_1 I_v$ and $w_2 I_h$ are the cost associated with a number I_v of infected vectors and I_h of infected individuals. The term $w_5 m u_3^2$ is the cost associated with vaccination, where m is the number of vectors vaccinated and $w_4 u_2^2$, $w_6 u_4^2$ are the costs associated with human and vector treatments respectively. The cost associated with preventive measure is $w_3 u_1^2$, while t_f is the time period of the intervention and the coefficients, $w_1, w_2, w_3, w_4, w_5, w_6$ are the balancing cost factors due to scales and importance of the ten parts of the objective function. In line with [3–5, 15, 28], a linear function for the cost on infection, $w_1 I_v$, $w_2 I_h$, and quadratic forms for the cost on the controls $w_3 u_1^2$, $w_4 u_2^2$, $w_5 m u_3^2$ and $w_6 u_4^2$.

We seek an optimal control $u_1^\#, u_2^\#, u_3^\#, u_4^\#$ such that

$$J(u_1^\#, u_2^\#, u_3^\#, u_4^\#) = \min_{u_1, u_2, u_3, u_4 \in \mathcal{U}} J(u_1, u_2, u_3, u_4) \quad (21)$$

where $\mathcal{U} = \{u : u \text{ is measurable and } 0 \leq u_i(t) \leq 1 \text{ for } t \in [0, t_f], i = 1, 2, 3, 4\}$ is the control set.

The necessary conditions that an optimal control must satisfy come from the Pontryagin's Maximum Principle [29]. This principle converts (1) and (20) into a problem of minimizing pointwise a Hamiltonian H , with respect to (u_1, u_2, u_3, u_4)

$$\begin{aligned}
 H = & w_1 I_v + w_2 I_h + w_3 u_1^2 + w_4 u_2^2 + w_5 m u_3^2 + w_6 u_4^2 \\
 & + M_{S_h} \{ \Lambda_h + \sigma_h R_h - (1 - u_1) \beta (I_v + I_h) S_h - \mu_h S_h \} \\
 & + M_{I_h} \{ (1 - u_1) \beta (I_v + I_h) S_h - (u_2 \gamma_1 + \delta_h + \mu_h) I_h \} \\
 & + M_{R_h} \{ u_2 \gamma I_h - (\sigma_h + \mu_h) R_h \} \\
 & + M_{S_v} \{ (1 - u_3) \Lambda_v - (1 - u_1) \lambda (I_v + I_h) S_v - \mu_v S_v + \sigma_v R_v + \tau V_v \} \\
 & + M_{I_v} \{ (1 - u_1) \lambda (I_v + I_h) S_v + (1 - u_1) b \lambda (I_v + I_h) V_v - (u_4 \alpha + \delta_v + \mu_v) I_v \} \\
 & + M_{R_v} \{ u_4 \alpha I_v - (\sigma_v + \mu_v) R_v \} \\
 & + M_{V_v} \{ u_3 \Lambda_v - (\tau + \mu_v) V_v - (1 - u_1) b \lambda (I_v + I_h) V_v \}
 \end{aligned} \tag{22}$$

where $M_{S_h}, M_{I_h}, M_{R_h}, M_{S_v}, M_{I_v}, M_{R_v}$ and M_{V_v} are the adjoint variables or co-state variables solutions of the following adjoint system:

$$\begin{aligned}
 -\frac{dM_{S_h}}{dt} &= ((1 - u_1)(I_v + I_h) \beta (M_{S_h} - M_{I_h}) + \mu_h M_{S_h} \\
 -\frac{dM_{I_h}}{dt} &= -w_2 + (1 - u_1) \beta S_h (M_{S_h} - M_{I_h}) + (u_2 \gamma + \mu_h + \delta_h) M_{I_h} - u_2 \gamma M_{R_h} \\
 &\quad + (1 - u_2) \lambda S_v (M_{S_v} - M_{I_v}) + b \lambda (M_{V_v} - M_{I_v}) \\
 -\frac{dM_{R_h}}{dt} &= -\sigma_h M_{S_h} + (\sigma_h + \mu_h) M_{R_h} \\
 -\frac{dM_{S_v}}{dt} &= (1 - u_1) \lambda (I_v + I_h) (M_{S_v} - M_{I_v}) + \mu_v M_{S_v} \\
 -\frac{dM_{I_v}}{dt} &= -w_1 + (1 - u_1) \beta (M_{S_h} - M_{I_h}) S_h + (1 - u_1) \lambda (M_{S_v} - M_{I_v}) S_v \\
 &\quad + b \lambda (M_{V_v} - M_{I_v}) V_v + (u_4 \alpha + \mu_v + \delta_v) M_{I_v} - u_4 \alpha M_{R_v} \\
 -\frac{dM_{R_v}}{dt} &= -\sigma_v M_{S_v} + (\sigma_v + \mu_v) M_{R_v} \\
 -\frac{dM_{V_v}}{dt} &= -\tau M_{S_v} + (1 - u_1) b \lambda (I_v + I_h) (M_{V_v} - M_{I_v}) + (\tau + \mu_v) M_{V_v}
 \end{aligned} \tag{23}$$

satisfying the transversality conditions

$$M_{S_h}(t_f) = M_{I_h}(t_f) = M_{R_h}(t_f) = M_{S_v}(t_f) = M_{I_v}(t_f) = M_{R_v}(t_f) = M_{V_v}(t_f) = 0. \tag{24}$$

By applying Pontryagin's Maximum Principle [29] and the existence result for the optimal control from [30], we obtain

Theorem 4.1. The optimal control vector $(u_1^\#, u_2^\#, u_3^\#, u_4^\#)$ that minimizes J over \mathcal{U} is given by

$$\begin{aligned}
 u_1^\# &= \max \left\{ 0, \min \left(1, \frac{\beta(M_{I_h} - M_{S_h})(I_v + I_h) S_h^* + \lambda(M_{I_v} - M_{S_v})(I_v + I_h) S_v^* + b \lambda(M_{I_v} - M_{V_v})(I_v + I_h) V_v^*}{2w_3} \right) \right\} \\
 u_2^\# &= \max \left\{ 0, \min \left(1, \frac{\gamma(M_{R_h} - M_{I_h}) I_h^*}{2w_4} \right) \right\} \\
 u_3^\# &= \max \left\{ 0, \min \left(1, \frac{\Lambda_v(M_{V_v} - M_{S_v})}{2w_5} \right) \right\} \\
 u_4^\# &= \max \left\{ 0, \min \left(1, \frac{\alpha(M_{R_v} - M_{I_v}) I_v^*}{2w_6} \right) \right\}
 \end{aligned} \tag{25}$$

where $M_{S_h}, M_{I_h}, M_{R_h}, M_{S_v}, M_{I_v}, M_{R_v}$ and M_{V_v} are the solutions of (23)-(24).

Proof. From Corollary 4.1, [30], the existence of optimal control results from the convexity of the integrand of J with respect to u_1, u_2, u_3 and u_4 , a priori boundedness of the state solutions, and the Lipschitz property of the

state system with respect to the state variables. System (23) is obtained by differentiating the Hamiltonian function, evaluated at the optimal control. Furthermore, by equating to zero the derivatives of the Hamiltonian with respect to the controls, we obtain (see [31])

$$u_1 = \tilde{u}_1 := \frac{\beta(M_{I_h} - M_{S_h})(I_v + I_h)S_h^* + \lambda(M_{I_v} - M_{S_v})(I_v + I_h)S_v^* + b\lambda(M_{I_v} - M_{V_v})(I_v + I_h)V_v^*}{2w_3},$$

$$u_2 = \tilde{u}_2 := \frac{\gamma(M_{R_h} - M_{I_h})I_h^*}{2w_4}, u_3 = \tilde{u}_3 := \frac{\Lambda_v(M_{V_v} - M_{S_v})}{2w_5} \text{ and } u_4 = \tilde{u}_4 := \frac{\alpha(M_{R_v} - M_{I_v})I_v^*}{2w_6}.$$

By standard control arguments involving the bounds on the controls, we conclude

$$u_1^\# = \begin{cases} 0 & \text{if } \tilde{u}_1 \leq 0 \\ \tilde{u}_1 & \text{if } 0 < \tilde{u}_1 < 1, \\ 1 & \text{if } \tilde{u}_1 \geq 1, \end{cases} u_2^\# = \begin{cases} 0 & \text{if } \tilde{u}_2 \leq 0 \\ \tilde{u}_2 & \text{if } 0 < \tilde{u}_2 < 1, \\ 1 & \text{if } \tilde{u}_2 \geq 1 \end{cases} \quad (26)$$

$$u_3^\# = \begin{cases} 0 & \text{if } \tilde{u}_3 \leq 0 \\ \tilde{u}_3 & \text{if } 0 < \tilde{u}_3 < 1 \\ 1 & \text{if } \tilde{u}_3 \geq 1 \end{cases} \text{ and } u_4^\# = \begin{cases} 0 & \text{if } \tilde{u}_4 \leq 0 \\ \tilde{u}_4 & \text{if } 0 < \tilde{u}_4 < 1 \\ 1 & \text{if } \tilde{u}_4 \geq 1 \end{cases} \quad (27)$$

which leads to (25). Due to the a priori boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ODEs, we obtain the uniqueness of the optimal control for small t_f . The uniqueness of the optimal control quadruple follows from the uniqueness of the optimality system, which consists of (1), (23), (24) and (25). \square

There is a restriction on the length of time interval in order to guarantee the uniqueness of the optimality system. This is due to the opposite time orientations of the optimality system; the state problem has initial values and the adjoint problem has final values. This restriction is very common in control problems (see [6, 28, 32, 33]).

Next we discuss the numerical solutions of the optimality system and the corresponding optimal control pair, the parameter choices, and the interpretations from various cases.

5 Numerical results

In this section, we show the numerical simulations of the impacts of the optimal control strategies on leptospirosis transmission. The optimal control is obtained by solving the optimality system that consists of the state system (1) and adjoint system (23), (24) and (25). We use an iterative scheme to solve the optimality system. We first solve the state equations with a guess for the controls over the simulated time using fourth order Runge-Kutta scheme. Then, we use the current iterations solutions of the state equation to solve the adjoint equations by a backward fourth order Runge-Kutta scheme. Finally, we update the controls by using a convex combination of the previous controls and the value from the characterizations (25). This process is repeated and iterations are stopped if the values of the unknowns at the previous iterations are very close to the ones at the present iterations ([31]).

Due to space, the results for the best four (4) most effective control strategies out of the following control strategies considered are presented.

- Strategy A: Combination of treatment of humans and vaccination of vectors
- Strategy B: Combination of prevention control on humans and vaccination of vectors
- Strategy C: Combination of prevention control on humans, treatment of infective humans and vaccination
- Strategy D: Combination of prevention control on humans and treatment of infective humans
- Strategy E: Combination of vaccination of vectors and treatment of infective vectors
- Strategy F: Combination of prevention control on humans, vaccination and treatment of infective vectors
- Strategy G: Combination of prevention control on humans and treatment of infective vectors
- Strategy H: Combination of treatment of humans, vaccination and treatment of infective vectors
- Strategy I: Combination of treatment of humans and treatment of infective vectors

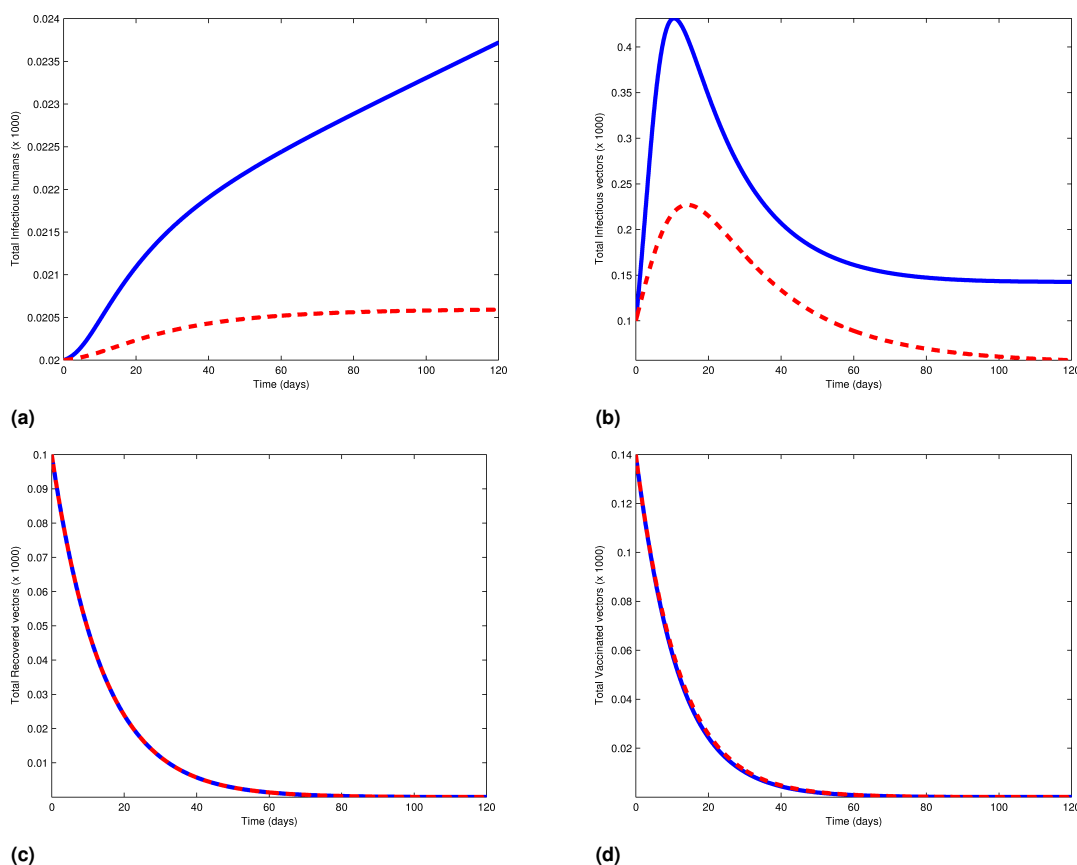
Table 3. Description of Variables and Parameters of the Leptospirosis Model (1). The units of $\mu_h, \mu_v, \alpha, \Lambda_h, \Lambda_v, \tau, \delta_h, \delta_v$ are day^{-1} , the other parameters are without units.

Parameter	Estimated value	Ref
μ_h	4.6×10^{-5}	[34]
δ_h	0.4×10^{-3}	[35]
μ_v	1.8×10^{-3}	[34]
β	0.03	assumed
λ	0.23	[22]
α	2.7×10^{-3}	[35]
Λ_h	1.34	assumed
Λ_v	1.71	assumed
τ	0.013	[22]
δ_v	0.01	assumed
b	0.002	assumed

- Strategy J: Combination of prevention control on humans, treatment of humans, vaccination and treatment of infective vectors
- Strategy K: Combination of prevention control on humans, treatment of humans and treatment of infective vectors

From the results the best four (4) strategies are Strategies *B*, *E*, *G* and *I*. These are shown below.

Fig. 3. Simulations of the leptospirosis model showing the effect of the optimal strategies: Prevention of humans and vaccination of vectors. The blue lines represent the cases without control, while the red lines indicate the cases with optimal control.



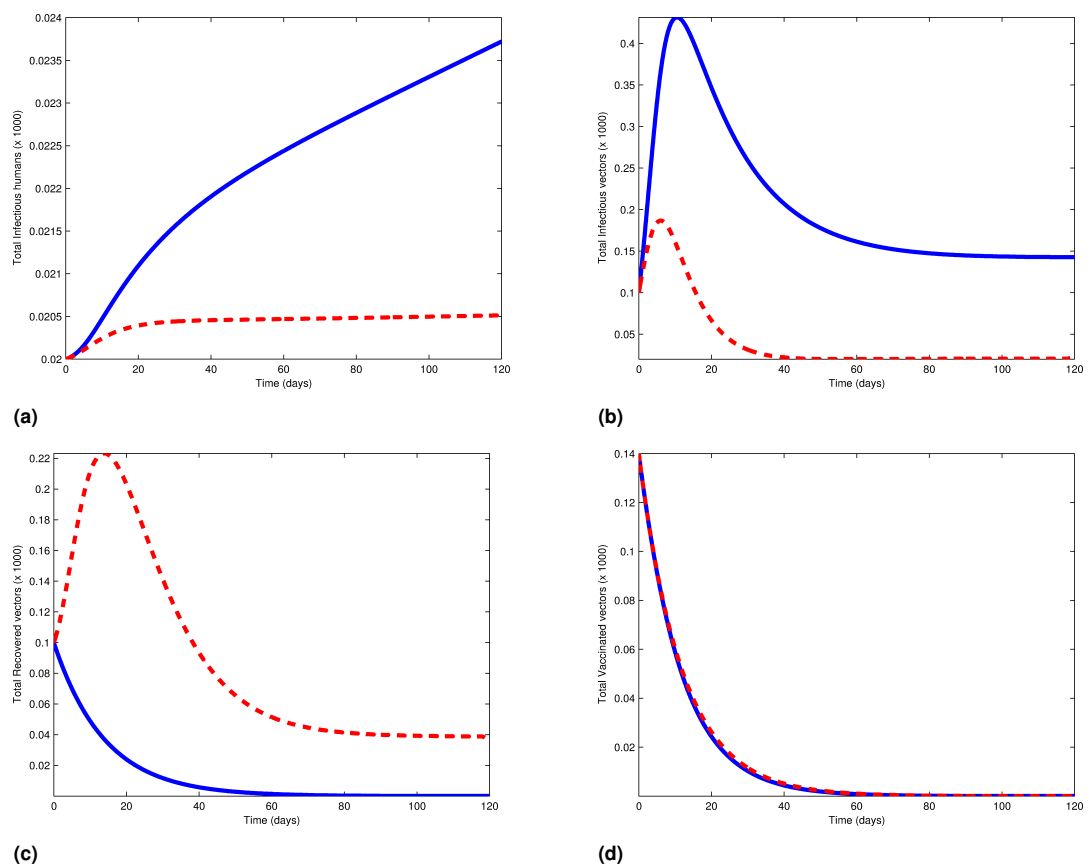
Strategy B: Optimal prevention of humans and vaccination of vectors

The prevention of humans control u_1 and the vaccination control u_3 of vectors are used to optimize the objective function J while we set other controls u_2 and u_4 to zero. We observed in Figure 3(a) and 3(b) that due to the control strategy, the number of infected humans (I_h) and infected vectors (I_v) decreases in the community. This shows that the spread of the disease can be controlled through effective prevention of humans and vaccination of vectors strategy. This strategy further shows no significant impact on the total recovered vectors and the total vectors vaccinated, Figure 3(c) and 3(d).

Strategy E: Optimal vaccination and treatment of infectives vectors

The vaccination control u_3 of vectors and treatment of infectives vectors are used to optimize the objective function J while we set other controls u_1 and u_2 to zero. We observed in Figure 4(a) and 4(b) that due to the control strategy, the number of infected humans (I_h) and infected vectors (I_v) decreases in the community. This shows that the spread of the disease can also be controlled through effective vaccination of vectors and treatment of vectors strategy. Also due to this strategy as shown in Figure 4(c), there is increase in recovered vectors.

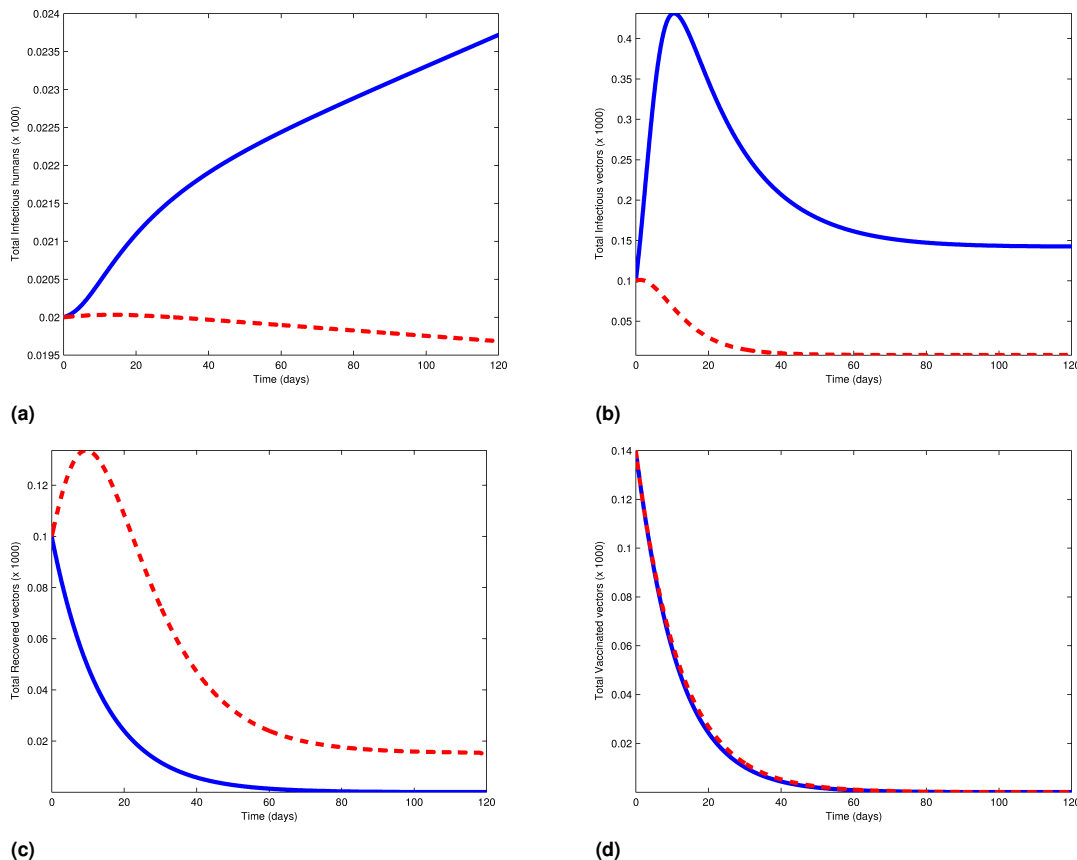
Fig. 4. Simulations of the leptospirosis model showing the effect of the optimal strategies: Vaccination and treatment of infectives vectors. The blue lines represent the cases without control, while the red lines indicate the cases with optimal control.



Strategy G: Optimal prevention of humans and treatment of infectives vectors

We optimize the objective function J using the prevention of humans control u_1 and treatment of infectives vectors control u_4 while other controls u_2 and u_3 are set to zero. We observed in Figure 5(a) and 5(b) that due to the control strategy, the number of infected humans (I_h) and infected vectors (I_v) decreases in the community. This shows that the spread of the disease can be controlled through effective prevention of humans and treatment of vectors strategy. Due to this strategy as shown in Figure 5(c), there is increase in recovered vectors.

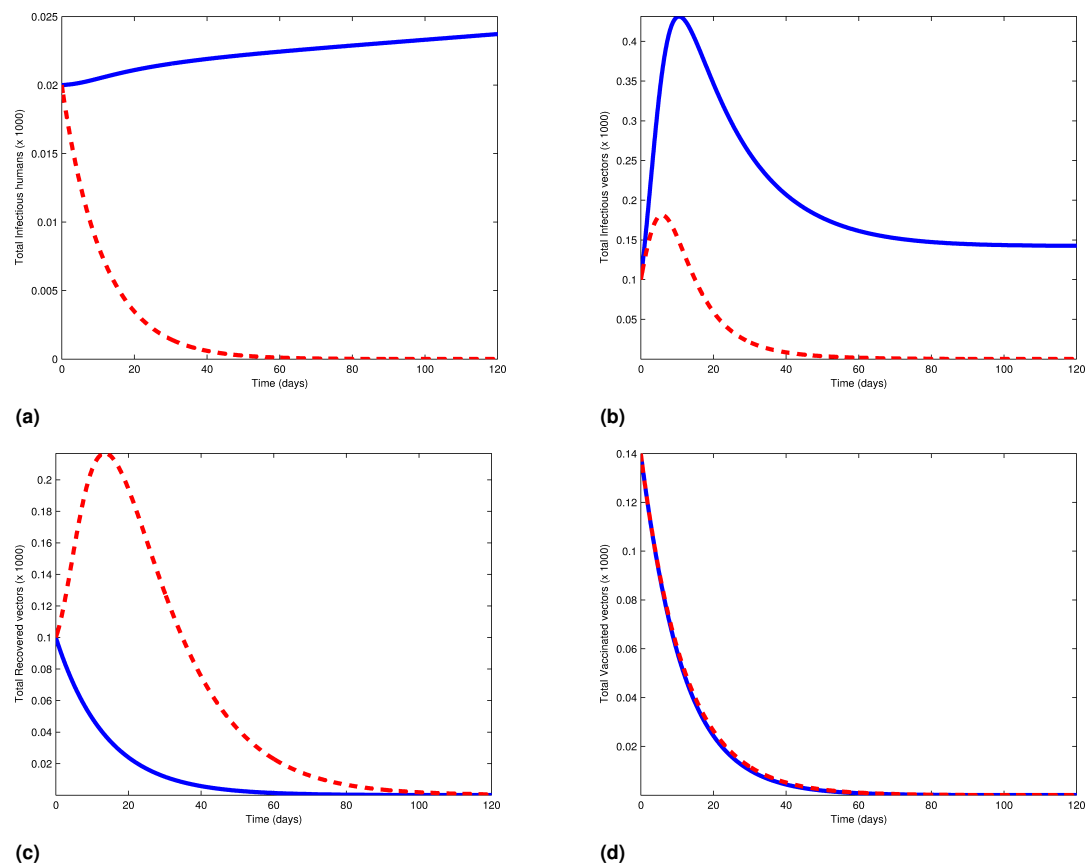
Fig. 5. Simulations of the leptospirosis model showing the effect of the optimal strategies: Prevention of humans and treatment of infectives vectors. The blue lines represent the cases without control, while the red lines indicate the cases with optimal control.



Strategy I: Optimal treatment of humans and treatment of infectives vectors

We optimize the objective function J using the treatment of humans control u_2 and treatment of infectives vectors control u_4 while other controls u_1 and u_3 are set to zero. We observed in Figure 6(a) and 6(b) that due to the control strategy, the number of infected humans (I_h) and infected vectors (I_v) decreases in the community. This shows that the spread of the disease can be controlled through effective treatment of humans and treatment of vectors strategy. It is obvious that from the selected best effective strategies one can not conclude which of the control strategy give optimal results. The four selected strategies however produce similar pattern and effect. Hence, there is need to further ascertain which of these strategies is most cost-effective and efficient. In the next section, the cost-effectiveness analysis is carried out.

Fig. 6. Simulations of the leptospirosis model showing the effect of the optimal strategies: Treatment of humans and treatment of infectives vectors. The blue lines represent the cases without control, while the red lines indicate the cases with optimal control.



6 Cost effectiveness analysis

Carrying out the cost effectiveness analysis, the most cost-effective strategy to use in the control of leptospirosis disease is determined. Doing this, the differences between the costs and health outcomes of these interventions are compared (see [21]).

Based on the model simulation results, these strategies are ranked in increasing order of effectiveness. Based on the four most effective strategies observed from the numerical results, namely prevention efforts in humans and vaccination of vectors only (strategy $B=u_1, u_3$), vaccination and treatment of vectors only (strategy $E=u_3, u_4$), prevention efforts in humans and treatment of vectors only (strategy $G=u_1, u_4$) and the treatments of both humans and vectors only (strategy $I=u_2, u_4$), an ANOVA analysis on the mean costs was initially conducted.

A one - way ANOVA between the mean costs was conducted to compare the strategies. The analysis was significant, $[F(429, 1290)= 1.29, p=0.000441]$. A post hoc comparison using Tukey HSD test indicated that the following pairs E-G, B-E and I-E were significantly different. However, G-B, G-I and B-I were not significantly different. Specifically, the results show that strategy E is recommended for cost effectiveness.

The cost-effectiveness analysis is shown below:

The difference between the total infectious individuals without control and the total infectious individuals with control was used to determine the “total number of infection averted” used in the table of cost-effectiveness analysis

Strategy	Total infection averted	Total cost (\$)
Strategy B	114.0869	\$1795.9
Strategy E	198.8027	\$1780.8

$$\begin{aligned} \text{ICER(B)} &= \frac{1795.9}{114.0869} = 15.74 \\ \text{ICER(E)} &= \frac{1780.8 - 1795.9}{198.8027 - 114.0869} = -0.17824 \end{aligned} \quad (28)$$

The comparison between ICER(B) and ICER(E) shows a cost saving of \$0.17824 for strategy E over strategy B. The negative ICER for strategy E indicates the strategy B is “strongly dominated”. That is, strategy B is more costly and less effective than strategy E. Therefore, strategy B, the strongly dominated is excluded from the set of alternatives so it does not consume limited resources.

We exclude strategy B and compare strategy E with G. From the numerical results we have

Strategy	Total infection averted	Total cost (\$)
Strategy E	198.8027	\$1780.8
Strategy G	226.5642	\$3573.6

This leads to the following values for the ICER,

$$\begin{aligned} \text{ICER(E)} &= \frac{198.8027}{1780.8} = 8.9576 \\ \text{ICER(G)} &= \frac{3573.6 - 1780.8}{226.5642 - 198.8027} = 64.5786 \end{aligned} \quad (29)$$

The comparison between ICER(E) and ICER(G) shows a cost saving of \$8.9576 for strategy E over strategy G. There is an additional \$64.57 per infection averted as we move from strategy E to G. The small value ICER for strategy E indicates the strategy G is “strongly dominated”. That is, strategy G is more costly and less effective than strategy E. Therefore, strategy G, the strongly dominated is excluded. Exclude strategy G, we now compare strategy E with I. From the numerical results we have

Strategy	Total infection averted	Total cost (\$)
Strategy E	198.8027	\$1780.8
Strategy I	239.4994	\$3194.7

This leads to the following values for the ICER,

$$\begin{aligned} \text{ICER(E)} &= \frac{198.8027}{1780.8} = 8.9576 \\ \text{ICER(I)} &= \frac{3194.7 - 1780.8}{239.4994 - 198.8027} = 34.7424 \end{aligned} \quad (30)$$

The comparison between ICER(E) and ICER(I) shows a cost saving of \$8.9576 for strategy E over strategy I. There is an additional \$34.74 per infection averted as we move from strategy E to I. Similarly, the small value ICER for strategy E indicates the strategy I is “strongly dominated”. That is, strategy I is more costly and less effective than strategy E. Therefore, strategy I, the strongly dominated is excluded.

With this result therefore, it is found that strategy E (combination of vaccination u_3 with treatment of infective vectors (u_4)) is most cost-effective of all the strategies for leptospirosis disease control.

7 Conclusion

In this paper, a deterministic model for the transmission of leptospirosis disease that includes treatment and vaccination with waning immunity is derived and analyzed. The basic reproduction number is calculated and investigated the existence and stability of equilibria as well as performed optimal control analysis of the model.

The model is found to exhibit the existence of multiple endemic equilibria. The epidemiological implication of this is that for effective control of the disease, the basic reproductive number, R_{hv} , should be less than a critical value less than one. The necessary conditions for the optimal control of the disease are derived and analyzed. Furthermore, the cost-effectiveness of the controls to determine the most effective strategy to curtail the spread of leptospirosis with minimum costs is carried out. Where there are limited resources, the model suggests that policy makers may adopt strategy E over other strategies which includes additional cost of preventions and treatments of humans. In conclusion, according to our model, the most cost-effective of all is the combination of vaccination and treatment of vectors only.

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